27 June 2024
EMA/346655/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lynparza - EMEA/H/C/003726

Imfinzi - EMEA/H/C/004771

Medicinal products authorised through the centralised procedure

Invented name:	International non-proprietary name/Common name:	Product-specific application number
Lynparza	Olaparib	EMEA/H/C/003726/WS2463/0066
Imfinzi	Durvalumab	EMEA/H/C/004771/WS2463/0063

Procedure No. EMEA/H/C/WS2463

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA	Anti-drug antibodies
ADR	Adverse drug reaction
AE(s)	Adverse event(s)
AEPI	Adverse event of potential interest
AESI	Adverse event of special interest
AIHA	Autoimmune haemolytic anaemia
AML	Acute myeloid leukaemia
ASCO	American Society of Clinical Oncology
Bd	Twice daily
BICR	Blinded independent central review
BRCA	Breast cancer susceptibility gene
BRCAm	*BRCA* mutation
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CR	Complete response
CRF	Case report form
CSR	Clinical study report
CSP	Clinical study protocol
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Common Technical Document
CTX	Chemotherapy
D	Durvalumab
DAE	AEs leading to discontinuation
DCO	Data cut-off
DoR	Duration of Response
dMMR	Mismatch repair deficient
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
FAS	Full Analysis Set
FDA	Food and Drug Administration

FIGO	Federation Internationale de Gynecologie et d'Obstetrique;
G	Grade
H	Half
HGR	Human genetic resources
HR	Hazard ratio
HRD	Homologous recombination deficiency
HRQoL	Health related quality of life
HRR	Homologous recombination repair
HRRm	Homologous recombination repair gene mutation
ICH	International Council for Harmonisation
IHC	immunohistochemistry
imAE	Immune-mediated adverse event
ITT	Intention-to-treat
IV	Intravenous
IVRS	Interactive voice response system
KM	Kaplan-Meier
MDS	Myelodysplastic syndrome
MMR	Mismatch repair
MSI-H	High microsatellite instability
MSS	Microsatellite stable
MTP	Multiple testing procedure
N	Number of patients in treatment
n	Number of patients analysed
NA	Not applicable
nAb	Neutralising antibody
NC	Not calculated
NCCN	National Comprehensive Cancer Network
NGS	Next generation sequencing
NPM	New primary malignancy
NR	Not reached
O	Olaparib
ORR	Objective response rate
OS	Overall survival

PARP	Polyadenosine 5’diphosphoribose polymerase
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Progressive disease
PD-L1	Programmed cell death-ligand 1
PD-1/L1	Programmed cell death protein-1 /-ligand 1
PFS	Progression free survival
PFS2	Time from randomisation to second progression or death
PK	Pharmacokinetic
pMMR	Mismatch repair proficient
PR	Partial response
PRCA	Pure red cell aplasia
Q3W	Every 3 weeks
Q4W	Every 4 weeks
RECIST	Response Evaluation Criteria in Solid Tumours
RoW	Rest of world
SAE	Serious adverse event
SAP	Statistical analysis plan
SoC	Standard of care
TDT	Time from randomisation to discontinuation of treatment or death
TFST	Time from randomisation to start of first subsequent therapy or death
TSST	Time from randomisation to start of second subsequent therapy or death
US	United States
Vs	Versus

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 10 October 2023 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication for Lynparza in combination with Imfinzi for the maintenance treatment of adult patients with newly diagnosed advanced or recurrent endometrial cancer following treatment with Imfinzi and platinum-based chemotherapy, based on results from pivotal Phase III study, D9311C00001 (DUO-E). This was a phase III, randomised, double-blind, placebo-controlled, multicentre study evaluating the efficacy and safety of durvalumab in combination with platinum-based chemotherapy (paclitaxel + carboplatin) followed by maintenance durvalumab with or without olaparib for patients with newly diagnosed advanced or recurrent endometrial cancer. As a consequence, sections 4.1, 4.2, 4.4, 4,5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 30 of the RMP has also been submitted.

The worksharing procedure requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0301/2023 for Imfinzi and P/0321/2023 for Lynparza on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0301/2023 for Imfinzi was completed and the PIP P/0321/2023 for Lynparza was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the WSA did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The WSA received Scientific Advice from the CHMP on 17 October 2019 (EMEA/H/SA/3310/3/2019/II). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

Appointed Rapporteurs for the WS procedure:

CHMP Rapporteur: Carolina Prieto Fernandez PRAC Rapporteur: Amelia Cupelli

Timetable	Actual dates
Submission date	10 October 2023
Start of procedure:	28 October 2023
CHMP Rapporteur Assessment Report	31 December 2023
PRAC Rapporteur Assessment Report	4 January 2024
PRAC members comments	8 January 2024
Updated PRAC Rapporteur Assessment Report	8 January 2024
PRAC Outcome	11 January 2024
CHMP members comments	15 January 2024
Updated CHMP Rapporteur Assessment Report	20 January 2024
Request for supplementary information (RSI)	25 January 2024
WSA's responses submitted to the CHMP on	22 February 2024
Re-start of procedure	26 February 2024
CHMP Rapporteur Assessment Report	07 April 2024
PRAC Rapporteur Assessment Report	27 March 2024
PRAC members comments	3 April 2024
Updated PRAC Rapporteur Assessment Report	N/A
PRAC endorsed relevant sections of the assessment report[3]	11 April 2024
CHMP members comments	15 April 2024
Updated CHMP Rapporteur Assessment Report	19 April 2024
2nd Request for supplementary information	25 April 2024
WSA's responses submitted to the CHMP on	17 May 2024
Re-start of procedure	29 May 2024
CHMP Rapporteur Assessment Report	14 June 2024
CHMP members comments	17 June 2024
Updated CHMP Rapporteur Assessment Report	21 June 2024
Opinion	27 June 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

The scope of this variation is to extend the existing therapeutic indication for Imfinzi in combination with carboplatin and paclitaxel for first-line treatment of adults with primary advanced or recurrent endometrial cancer followed by Imfinzi alone or in combination with olaparib as maintenance treatment, and for Lynparza in combination with durvalumab for the maintenance treatment of pMMR primary advanced or recurrent endometrial cancer, based on the IA1 results of phase III study DUO-E.

Disease or condition

Advanced or recurrent endometrial cancer.

The initially proposed indications were:

Imfinzi

IMFINZI in combination with platinum-based chemotherapy, followed by maintenance with IMFINZI as monotherapy or in combination with olaparib, is indicated for the first-line treatment of adults with advanced or recurrent endometrial cancer.

Lynparza

Lynparza in combination with durvalumab is indicated for the maintenance treatment of adult patients with advanced or recurrent endometrial cancer whose disease has not progressed on first-line treatment with durvalumab in combination with platinum-based chemotherapy.

Epidemiology and risk factors

Endometrial cancer (EC) is the second most common gynaecological malignancy worldwide, the first in developed countries, with over 417 000 new cases and 97 000 deaths estimated in 2020 (Sung et al. 2021). EC's incidence has been increasing globally in the past two decades and is projected to continue rising in the next 15 years, a trend partially attributed to the prevalence of obesity and declining fertility rates (IARC 2020, Gu et al. 2021).

The main risk factor for EC's development is the exposure to increased unopposed levels of oestrogen associated with obesity, diabetes, tamoxifen use, and reproductive factors (early menarche, late menopause and nulliparity). The increased aging population may also have a role in the increased incidence. Genetic factors, such as Lynch syndrome, Cowden syndrome and pathogenic variants in *BRCA1* and *BRCA2* genes are also associated with an increased risk (Crosbie et al. 2022).

Biologic features

ECs have been historically classified according to their histopathological characteristics into Type I and Type II tumours, which have prognostic implications. Type I tumours account for approximately 65% of cases and include oestrogen-induced endometrioid carcinomas, which are associated with a favourable prognosis. Type II tumours are represented by high-grade, clinically aggressive histologies, including serous, clear cell, and undifferentiated carcinomas and carcinosarcomas, which are associated with a poor prognosis (Bokhman 1983, Colombo et al. 2015).

In 2013, The Cancer Genome Atlas (TCGA) Research Network proposed a molecular classification categorising endometrial cancers into four molecular subtypes with distinct prognosis: (1) polymerase epsilon (POLE)-ultramutated (POLEmut), which are associated with endometrioid histology and have an excellent prognosis; (2) MSI-hypermutated, which are characterised by microsatellite instability, endometrioid histology, and present an intermediate prognosis; (3) Copy-number high, which are associated with frequent somatic copy number alterations, TP53 mutations, serous and serous-like endometrioid histology, and have a poor prognosis; (4) Copy-number low, which are microsatellite-stable, associated with low-grade endometrioid histology, and have an intermediate prognosis (Cancer Genome Atlas Research Network 2013). To increase clinical utility of this classification, a categorisation based on immunohistochemistry (IHC) has been developed including four TCGA-correlated subtypes: (1) deoxyribonucleic acid (DNA) polymerase epsilon mutant (POLE-mut); (2) mismatch repair protein deficiency (dMMR); (3) protein 53 abnormal expression (p53abn); and (4) no specific molecular profile (NSMP) (León-Castillo et al .2020, Stelloo et al. 2015, Stelloo et al. 2016, Talhouk et al. 2017).

Since 2022, the European Society of Medical Oncology (ESMO) recommends that molecular classification through IHC staining for p53 and MMR proteins (MLH1, PMS2, MSH2, MSH6) in combination with targeted tumour sequencing (POLE hotspot analysis) is carried out for all endometrial cancers regardless of histological type (Oaknin et al. 2022).

Clinical presentation, diagnosis and stage/prognosis

The disease often presents as postmenopausal bleeding with a median age at diagnosis of 61 years (Crosbie et al. 2022). The majority of patients are diagnosed at an early stage (FIGO Stage I or II), and these patients have a better prognosis with 5-year survival rates ranging from 74% to 91%. For patients diagnosed at a later stage or with advanced endometrial cancer, the 5-year survival rates range from 50% to 66% for Stage III and 20% to 26% for Stage IV disease (Creasman et al. 2006). The prognosis for patients with advanced or recurrent EC depends upon site and extent of the recurrence, tumour size, whether the patient had received prior radiotherapy, the relapse-free interval, and histology. Approximately 40% of ECs are diagnosed as locally advanced tumours, and most recurrences occur within 3 years of primary treatment.

For patients with advanced or recurrent endometrial cancer, biomarker testing is routinely performed following diagnosis and staging and is part of the clinical guidelines that informs treatment decisions (NCCN 2023, Oaknin et al. 2022).

Management

Patients with advanced (stage III/IV) or recurrent EC may receive a combination of surgery, radiotherapy, and systemic therapy depending on the extent of disease and local practices. Patients with stage III and IVA disease with no residual tumour after surgery are considered to have high-risk EC and generally receive adjuvant chemotherapy with carboplatin and paclitaxel, which can be given with concurrent or subsequent radiation therapy (NCCN 2023, Oaknin et al. 2022).

The current SoC for first-line treatment for patients with stage III and IVA EC with residual tumour after surgery, stage IVB disease, or as 1L therapy for recurrent disease comprises platinum-based chemotherapy, with the combination of carboplatin and paclitaxel as the preferred regimen (Miller et al. 2020, Oaknin et al. 2022, NCCN 2023).

Recently, studies evaluating the addition of immune checkpoint inhibitors pembrolizumab or dostarlimab, initiated in combination with SoC chemotherapy and continued as maintenance monotherapy, have reported statistically significant PFS vs SoC chemotherapy for the first-line

treatment of patients with advanced or recurrent endometrial cancer (NRG-GY018 [NCT03914612] Eskander et al. 2023; RUBY Part 1 [NCT03981796] Mirza et al. 2023).

The Phase 3 study, NRG-GY018, is investigating pembrolizumab in combination with paclitaxel and carboplatin as first-line treatment for patients with advanced or recurrent endometrial cancer. Recent results have shown a statistically significant improvement in PFS compared with chemotherapy alone regardless of MMR status (dMMR: HR 0.30; 95% CI 0.19, 0.48; pMMR: HR 0.54; 95% CI 0.41, 0.71) (Eskander et al. 2023). The trial randomised 816 patients and secondary endpoints include OS, ORR, DoR, and safety. Patients were randomised to receive pembrolizumab + chemotherapy Q3W for approximately 6 cycles followed by pembrolizumab as a single agent every 6 weeks for up to 14 cycles, or placebo + chemotherapy. This treatment regimen evaluated in NRG-GY018 is not yet approved.

Part 1 of the Phase 3 study, RUBY (NCT03981796) is evaluating the efficacy and safety of dostarlimab + chemotherapy followed by dostarlimab vs placebo + chemotherapy followed by placebo in patients with first-line advanced or recurrent endometrial cancer. Recent results demonstrated a statistically significant benefit in PFS in the pre-specified dMMR/MSI-H subgroup (HR 0.28; 95% CI 0.16, 0.50) and overall ITT population (HR 0.64; 95% CI 0.51, 0.80) (Mirza et al. 2023). The positive results from RUBY Part 1 have resulted in a recent approval in the EU for patients with dMMR/MSI-H primary advanced or recurrent EC.

For patients who progress following prior platinum-based chemotherapy, pembrolizumab (as monotherapy or in combination with lenvatinib) and dostarlimab (as monotherapy) are approved and recommended by both the NCCN and ESMO guidelines as second-line treatment for patients who have progressed following prior treatment and who have no satisfactory alternative treatment options (NCCN 2023, Oaknin et al. 2022). The choice of treatment is mainly guided by a patient's dMMR or pMMR status.

Unmet need

There is a high unmet need for new treatment options in advanced or recurrent endometrial cancer. For patients diagnosed with advanced endometrial cancer the 5-year survival rates range from 50% to 66% for Stage III and 20% to 26% for Stage IV disease (Creasman et al. 2006). Few patients receive a second-line therapy and the poor survival rate for advanced endometrial cancer is due, in part, to the limited treatment options available after first-line chemotherapy (Halla 2022).

Patients with advanced or recurrent endometrial cancer who relapse after the primary treatment have limited options and a poor prognosis. Most patients will progress either during chemotherapy or at some point after chemotherapy has finished, thus more options are needed in the first-line in order to improve outcomes and delay second-line treatment. For those patients with advanced or recurrent endometrial cancer that respond to platinum-based chemotherapy, there are therapeutic gaps from the completion of chemotherapy to disease Patients with advanced (stage III/IV) or recurrent EC may receive a combination of surgery, radiotherapy, and systemic therapy depending on the extent of disease and local practices. Patients with stage III and IVA disease with no residual tumour after surgery are considered to have high-risk EC and generally receive adjuvant chemotherapy with carboplatin and paclitaxel, which can be given with concurrent or subsequent radiation therapy (NCCN 2023, Oaknin et al. 2022).

The current SoC for first-line treatment for patients with stage III and IVA EC with residual tumour after surgery, stage IVB disease, or as 1L therapy for recurrent disease comprises platinum-based chemotherapy, with the combination of carboplatin and paclitaxel as the preferred regimen (Miller et al. 2020, Oaknin et al. 2022, NCCN 2023).

Recently, studies evaluating the addition of immune checkpoint inhibitors pembrolizumab or dostarlimab, initiated in combination with SoC chemotherapy and continued as maintenance monotherapy, have reported statistically significant PFS vs SoC chemotherapy for the first-line treatment of patients with advanced or recurrent endometrial cancer (NRG-GY018 [NCT03914612] Eskander et al. 2023; RUBY Part 1 [NCT03981796] Mirza et al. 2023).

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Part 1 of the Phase 3 study, RUBY (NCT03981796) is evaluating the efficacy and safety of dostarlimab + chemotherapy followed by dostarlimab vs placebo + chemotherapy followed by placebo in patients with first-line advanced or recurrent endometrial cancer. Recent results demonstrated a statistically significant benefit in PFS in the pre-specified dMMR/MSI-H subgroup (HR 0.28; 95% CI 0.16, 0.50) and overall ITT population (HR 0.64; 95% CI 0.51, 0.80) (Mirza et al. 2023). The positive results from RUBY Part 1 have resulted in a recent approval in the EU for patients with dMMR/MSI-H primary advanced or recurrent EC.

For patients who progress following prior platinum-based chemotherapy, pembrolizumab (as monotherapy or in combination with lenvatinib) and dostarlimab (as monotherapy) are approved and recommended by both the NCCN and ESMO guidelines as second-line treatment for patients who have progressed following prior treatment and who have progression or death.

2.1.2. About the products

Durvalumab (IMFINZI) is a human monoclonal antibody targeting PD-L1 administered via the intravenous route. Olaparib (Lynparza) is a small molecule, oral inhibitor of PARP. Both products have approvals in the EU for a range of indications across multiple tumour types and both are being developed as monotherapies and in combination with other anticancer agents across various oncology indications.

IMFINZI is currently approved in the EU for the treatment of non-small and small cell lung cancer, biliary tract cancer and hepatocellular carcinoma. Lynparza is approved for the treatment of ovarian cancer, breast cancer, pancreatic cancer and prostate cancer.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH received scientific advice from the CHMP on the 17th October 2019 (EMEA/H/SA/3310/3/2019/II). Overall, the study design was deemed acceptable. The proposed population was considered relevant and an unmet need was acknowledged. PFS was accepted as primary endpoint and the importance of having available mature enough OS data was highlighted considering the different treatment duration (maintenance phase) between arms. Difficulties in assessing the contributions of components were foreseen and some remarks about these contributions being dependant on mismatch repair deficiencies or PD-L1 expression status were also made.

2.1.4. General comments on compliance with GCP

The MAH stated that their procedures, internal quality control measures and audit programmes provide reassurance that the clinical study programme was carried out in accordance with Good Clinical Practice, as documented by the ICH, EMA, and the US FDA.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Imfinzi (durvalumab) is a protein and is therefore exempt from the Environmental Risk Assessment (ERA) requirements. This is compliant with the current Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00).

The potential environmental impact from use of the drug substance olaparib has already been evaluated at the time of the initial marketing authorisation application and as part of previous extensions of indication. An update to the ERA for Lynparza was submitted to support this extension of indication.

The following table summarises the result of main studies.

Table 1 Summary of main study results

Substance (INN/Invented Name): Olaparib			
CAS-number: 763113-22-0			
PBT screening		Result	**Conclusion**
Bioaccumulation potential-	OECD107 (Ref 11)	Log P_{ow} = 1.55 at pH 7	< 4.5: **not PBT or vPvB**
PBT Assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	$LogP_{ow}$	1.55	**Not B; therefore: not PBT or vPvB**
Persistence	$DT_{50\ total\ system}$	251 – 551 days	
Toxicity	NOEC	0.32 mg/L	
PBT Statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, refined	0.180	µg/L	> 0.01 µg/L
Other concerns (e.g. chemical class)			None
Phase IIA physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Hydrolysis	OECD 111 (Ref 15)	<10 % (120 hours) at pH 5, 7 and 9	Hydrolytically stable.
Ready Biodegradability Test	OECD 301F (Ref 16)	Negligible biodegradation (day 28: <6%)	Not readily biodegradable.
Aerobic Transformation in Aquatic Sediment systems	OECD 308 (Ref 1919)	DT_{50} values at 20°C LOM $DT_{50water}$ = 7.06 days HOM $DT_{50water}$ = 4.22 days LOM $DT_{50total\ system}$ = 251 days HOM $DT_{50total\ system}$ = 260 days	Olaparib satisfies the criteria of a very persistent compound. Olaparib is expected to partition to aquatic sediments with no evidence of degradation. As the total radioactivity associated with the sediment exceeded 10% the toxicity of olaparib to sediment-dwelling organisms is investigated in Tier B.
		DT_{50} values at 12°C LOM $DT_{50water}$ = 15.0 days HOM $DT_{50water}$ = 8.96 days LOM $DT_{50total\ system}$ = 534 days HOM $DT_{50total\ system}$ = 551 days	
		No metabolites >10% were observed.	
Adsorption-Desorption to two sediments	OECD 106 (Ref 1818)	HOC sediment mean K_d = 111; Koc = 1986 L/Kg LOC sediment mean K_d = 3.8; Koc =27487 L/Kg	

Adsorption-Desorption to sludge	OPPTS 835.1110 (Ref 17),	$Kd_{sludge(ads)}$ = 25 L/Kg	Assessment of olaparib in the terrestrial compartment is not necessary in Tier B.

Phase IIA effect studies

Study type	Test protocol	Endpoint	Value	Unit	Remarks
Algae, Growth Inhibition Test	OECD 201 (Ref 22)	NOEC	83	mg/L	72 hour EC_{50} > 83 mg/L growth rate
Daphnia sp. Reproduction Test	OECD 211 (Ref 23)	NOEC	0.32	mg/L	21 day LOEC = 1 mg/L
Fish, Early Life Stage Toxicity Test	OECD 210 (Ref 24)	NOEC	0.32	mg/L	32 day LOEC = 1 mg/L
Activated Sludge, Respiration Inhibition Test	OECD 209 (Ref 21)	NOEC	100	mg/L	3 hour EC_{50} > 100 mg/L

$PNEC_{microorganism}$ = 10 000 µg/L
$PNEC_{surfacewater}$ = 32 µg/L
$PEC_{groundwater}$ = 0.045 µg/L
$PNEC_{groundwater}$ = 32 µg/L

$PEC_{surfacewater}/PNEC_{microorganism}$ = 1.8×10^{-5}: Olaparib is unlikely to present a risk to microorganisms
$PEC_{surfacewater}/PNEC_{surfacewater}$ = 5.6×10^{-3}: Olaparib is unlikely to present a risk to organisms in surface water
$PEC_{groundwater}/PNEC_{groundwater}$ = 1.4×10^{-3}: Olaparib is unlikely to present a risk to the groundwater environment

Phase IIB effect studies

Study type	Test protocol	Results	Remarks
Toxicity to *Chironomus riparius*	OECD 218 (Ref 25)	28 day NOEC = 0.60 mg/kg dry weight	NOEC normalised to 10% o.c. = 2.61 mg/Kg
Toxicity to *Lubriculus variegatus*	OECD 225 (Ref 2727)	28 day NOEC = 86 mg/kg dry weight	-
Toxicity to *Hyalella azteca*	U.S. EPA 600/R-99/064 (Ref 28)	28 day NOEC = 89.6 mg/kg dry weight	-

$PEC_{sediment}$ = 21.9 µg/kg (dry weight)
$PNEC_{sediment}$ = 261 µg/kg (NOEC from the chironomus test (normalised to 10% o.c.) / 10)

$PEC/PNEC_{sediment}$ = 0.084: Olaparib is unlikely to present a risk to sediment dwelling organisms

Conclusion

Olaparib is unlikely to pose a risk to the environment

2.2.2. Discussion on non-clinical aspects

To support this new indication in endometrial cancer and this new combination of durvalumab and olaparib, the proof of concept is based on published non-clinical data and previous clinical experience.

Immune checkpoint inhibitors (anti-PD1) have shown activity as single agents in advanced or recurrent endometrial cancer. Moreover, several clinical trials for PARP inhibitors either alone or in combination with other agents in advanced and recurrent endometrial cancer are ongoing or have been completed.

The potential activity of combining a PD-L1 inhibitor with a PARP inhibitor is based on the hypothesis that endometrial cancer is an immune checkpoint inhibitor sensitive tumour, and that pharmacological inhibition of PARP by olaparib will result in enhanced immunogenicity, thereby enhancing the activity of durvalumab. Moreover, preclinical studies have demonstrated synergistic antitumor activity for combinations of PARPi with PD-1/ PD-L1 inhibitors (Jiao et al 2017, Shen et al 2019, Lee et al. 2020). Thus, the therapeutic rationale and proof of concept provided by the applicant are considered adequate.

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

An updated ERA for Lynparza (olaparib) has been provided including the new indication which is considered acceptable.

2.2.3. Conclusion on the non-clinical aspects

A full non-clinical package was included in the original MAA for Imfinzi and Lynparza. No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

Durvalumab, due to its proteic nature, is not expected to pose a significant risk to the environment.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of olaparib.

Considering the above data, olaparib is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

The current application is based on the results of the pivotal study D9311C00001 (DUO-E), a randomised, multicentre, double-blind, placebo-controlled, phase III study of first-line carboplatin and paclitaxel in combination with durvalumab, followed by maintenance durvalumab with or without olaparib in patients with newly diagnosed advanced or recurrent endometrial cancer.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the WSA. The WSA has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 2 Listing of Supportive Durvalumab Clinical Studies Included in the Summary of Clinical Pharmacology

Study	DCO	Objectives of study	Study Design and Type of Control	Durvalumab Dosage Regimen
Supportive studies – Phase I				
CD-ON-MEDI4736-1108 [a] (Study 1108) A Phase I/II study to evaluate the safety, tolerability, and pharmacokinetics of MEDI4736 in subjects with advanced solid tumours	16 Oct 2017	Safety, tolerability, efficacy, PK, and immunogenicity	Open-label, multiple-arm, non-randomised	Dose-escalation phase: Durvalumab IV at 0.1, 0.3, 1, 3, and 10 mg/kg Q2W and 15 mg/kg Q3W for up to 12 months or until progression of disease
				Dose-exploration phase: Durvalumab IV at 20 mg/kg Q4W for up to 12 months
				Dose-expansion phase: Durvalumab IV at 10 mg/kg Q2W for up to 12 months
D4190C00002 (Japan Study 02) A Phase I, open-label, multi-centre study to evaluate the safety, tolerability, and PK of MEDI4736 in patients with advanced solid tumours	31 Mar 2018	Safety and tolerability of durvalumab monotherapy or in combination with tremelimumab	Open-label, non-randomised	Dose-escalation phase: Durvalumab IV 1, 3, and 10 mg/kg Q2W; 15 mg/kg Q3W; 20 mg/kg Q4W
				Dose-expansion phase: Durvalumab IV 10 mg/kg Q2W
Supportive studies – Phase II				
D4191C00003 (ATLANTIC) [a] A Phase II non-comparative, open-label, multi-centre, international study of MEDI4736, in patients with locally advanced or metastatic NSCLC (Stage IIIB-IV) who have received at least 2 prior systemic treatment regimens including one platinum-based chemotherapy regimen	03 Jun 2016	Efficacy, safety, tolerability, PK, and immunogenicity	Open-label, single-arm, non-randomised	Durvalumab IV at 10 mg/kg Q2W

Table 2 Listing of Supportive Durvalumab Clinical Studies Included in the Summary of Clinical Pharmacology

Study	DCO	Objectives of study	Study Design and Type of Control	Durvalumab Dosage Regimen
D4193C00001 (HAWK) A Phase II, multi-centre, single-arm, global study of durvalumab monotherapy in patients with recurrent or metastatic SCCHN	05 Oct 2018	Efficacy of durvalumab monotherapy and health-related quality of life	Open-label, single-arm	Durvalumab IV 10 mg/kg Q2W
D4193C00003 (CONDOR) A Phase II, randomised, open-label, multi-centre, global study of durvalumab monotherapy, tremelimumab monotherapy, and durvalumab in combination with tremelimumab in patients with recurrent or metastatic SCCHN	31 Mar 2017	Efficacy of durvalumab in combination with tremelimumab and health-related quality of life	Open-label, randomised	Durvalumab IV 10 mg/kg Q2W
Supportive studies – Phase III				
D4191C00001 (PACIFIC) [a] A Phase III, randomised, double-blind, placebo-controlled, multi-centre, international study of durvalumab as sequential therapy in patients with locally advanced, unresectable NSCLC (Stage III) who have not progressed following definitive, platinum-based concurrent chemoradiation therapy	22 Mar 2018	Efficacy, safety, tolerability, PK, immunogenicity, and health-related quality of life versus SoC	Randomised, double-blind, placebo-controlled	Durvalumab IV at 10 mg/kg Q2W
D419AC00001 (MYSTIC) A Phase III, randomised, open-label, multi-centre, global study of durvalumab monotherapy and durvalumab in combination with tremelimumab compared to SoC in patients with advanced or metastatic NSCLC	04 Oct 2018	Efficacy versus SoC	Open-label, randomised, active comparator	Durvalumab IV 20 mg/kg Q4W

Table 2 Listing of Supportive Durvalumab Clinical Studies Included in the Summary of Clinical Pharmacology

Study	DCO	Objectives of study	Study Design and Type of Control	Durvalumab Dosage Regimen
D4191C00004 (ARCTIC) A Phase III, open-label, randomised, multi-centre, international study of durvalumab, given as monotherapy or in combination with tremelimumab, determined by PD-L1 expression, versus SoC in patients with locally advanced or metastatic NSCLC (Stage IIIB-IV) who have received at least 2 prior systemic treatment regimens including one platinum-based chemotherapy regimen and do not have known EGFR TK activating mutations or ALK rearrangements	09 Feb 2018	Efficacy, safety, tolerability, PK, and immunogenicity versus SoC	Open-label, randomised, active comparator	Durvalumab IV 10 mg/kg Q2W
D4193C00002 (EAGLE) A Phase III, randomised, open-label, multi-centre, global study of durvalumab monotherapy and durvalumab in combination with tremelimumab versus SoC in patients with recurrent or metastatic SCCHN	10 Sep 2018	Efficacy of durvalumab monotherapy and durvalumab in combination with tremelimumab versus SoC	Open-label, randomised	Durvalumab IV 10 mg/kg Q2W
D419QC00001 (CASPIAN) [a] A Phase III, randomised, multi-centre, open-label, comparative study to determine the efficacy of durvalumab or durvalumab and tremelimumab in combination with platinum-based chemotherapy for the first-line treatment in patients with extensive disease SCLC	27 Jan 2020	Efficacy, PK, immunogenicity, safety, and tolerability versus SoC	Open-label, randomised, active comparator	Durvalumab IV 1500 mg Q3W for 4 doses then durvalumab IV 1500 mg Q4W until progression of disease

Table 2 Listing of Supportive Durvalumab Clinical Studies Included in the Summary of Clinical Pharmacology

Study	DCO	Objectives of study	Study Design and Type of Control	Durvalumab Dosage Regimen	
D419MC00004 (POSEIDON) [a] A Phase III, randomised, multi-centre, open-label, comparative global study to determine the efficacy of durvalumab or durvalumab and tremelimumab in combination with platinum-based chemotherapy for first-line treatment in patients with metastatic NSCLC	12 Mar 2021	Efficacy, PK, immunogenicity, safety, and tolerability versus SoC	Open-label, randomised, active comparator	Durvalumab IV 1500 mg Q3W for 4 doses then durvalumab IV 1500 mg Q4W until progression of disease	
D419BC00001 (DANUBE) A Phase III, randomised, open-label, controlled, multi-centre, global study of first line MEDI4736 monotherapy and MEDI4736 in combination with tremelimumab versus SoC chemotherapy in patients with unresectable Stage IV urothelial cancer	27 Jan 2020	Efficacy and safety of durvalumab monotherapy and in combination with tremelimumab versus SoC	Randomised, open-label, controlled (SoC), multi-centre	Durvalumab 1500 mg Q4W	
D419LC00001 (KESTREL) A Phase III study of durvalumab alone and in combination with tremelimumab in patients with metastatic SCCHN	06 Jul 2020	Efficacy and safety of durvalumab monotherapy and in combination with tremelimumab versus SoC	Randomised, open-label, multi-centre, global study	Durvalumab 1500 mg Q4W	
D4190C00022 (Study 22) A study of safety, tolerability, and clinical activity of durvalumab and tremelimumab administered as monotherapy, or durvalumab in combination with tremelimumab or bevacizumab in patients with advanced hepatocellular carcinoma	06 Nov 2020	Safety, tolerability, efficacy, PK, and immunogenicity	Open-label, multiple-arm, randomised	Part 1, Part 2A and China Cohort, Part 2B, Part 3	Durvalumab 1500 mg (20 mg/kg) Q4W
				Part 4	Durvalumab 1120 mg (15 mg/kg)

Table 2 Listing of Supportive Durvalumab Clinical Studies Included in the Summary of Clinical Pharmacology

Study	DCO	Objectives of study	Study Design and Type of Control	Durvalumab Dosage Regimen
D419CC00002 (HIMALAYA) A randomised, open-label, multi-centre Phase III study of durvalumab and tremelimumab as first-line treatment in patients with advanced hepatocellular carcinoma	27 Aug 2021	Efficacy and safety of durvalumab and tremelimumab in combination versus durvalumab alone and sorafenib as SoC	Randomised, open-label	Durvalumab 1500 mg Q4W
D933AC00001 (TOPAZ-1) [a] A Phase III, randomized, double-blind, placebo-controlled, multi-regional, international study of durvalumab in combination with gemcitabine plus cisplatin versus placebo in combination with gemcitabine plus cisplatin for patients with first-line advanced biliary tract cancers.	01 Jun 2021	Efficacy (overall survival) and safety of durvalumab in combination with gemcitabine and cisplatin versus placebo in combination with gemcitabine and cisplatin	Randomized, double-blind, multi-centre, global study	Durvalumab 1500 mg via IV infusion Q3W, starting on Cycle 1 in combination with cisplatin 25 mg/m^2 and gemcitabine 1000 mg/m^2 (each administered on Days 1 and 8 Q3W) up to 8 cycles, followed by durvalumab 1500 mg as monotherapy Q4W until disease progression.

[a] Included in the modelling and simulation report.

ALK = anaplastic lymphoma kinase; DCO = data cut-off; EGFR TK = epidermal growth factor receptor tyrosine kinase; IV = intravenous; NSCLC = non-small cell lung cancer; PD-L1 = programmed cell death ligand 1; PK = pharmacokinetics; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; SCCHN = squamous cell carcinoma of the head and neck; SCLC = small-cell lung cancer; SoC = standard of care.

Table 3: Summary of Supportive Olaparib Clinical Studies Included in the Summary of Clinical Pharmacology

Study	DCO	Study Phase and Patient Population	Olaparib Dosage Regimen
Supportive studies – Phase I			
D081BC00001 (Study 1)	31 Jul 2014	Phase I: Japanese patients with advanced solid tumours	200, 300 mg qd or bd (tablet)
D0816C00004 (Study 04)	3 Sep 2015	Phase I: Patients with advanced solid tumours	300 mg qd or bd (tablet)
D0816C00007 (Study 07)	25 Jun 2015	Phase I: Patients with advanced solid tumours	100 mg qd, 300 mg bd (tablet)
D0816C00008 (Study 08)	2 Sep 2015	Phase I: Patients with advanced solid tumours	300 mg qd (tablet)
D0810C00024 (Study 24)	24 Jan 2012	Phase I: Patients with advanced solid tumours	200, 250, 300, 350, 400, 450 mg, qd or bd (tablet/capsule)
Supportive studies – Phase II			
D081DC00008	22 Sept 2017	Phase II: Metastatic castrate-resistant prostate cancer patients who have received prior chemotherapy containing docetaxel	olaparib 300 mg bd (tablet)
Supportive studies – Phase III			
D0816C00002 (SOLO2)	3 Feb 2020	Phase III: Patients with PSR *BRCA* mutated ovarian cancer	300 mg bd (tablet)
D0816C00010 (SOLO3)	16 Apr 2021	Phase III: Maintenance in 3L+ PSR *gBRCA*m ovarian cancer patients (excluding gastric surgery patients)	300 mg bd (tablet)
D0819C00003 (OlympiAD)	25 Sep 2017	Phase III: Treatment of g*BRCA*1/2m metastatic breast cancer	300 mg bd (tablet)
D081DC00007 (PROfound)	20 Mar 2020	Phase III: Metastatic castrate-resistant prostate cancer with homologous recombination repair gene mutations	300 mg bd (tablet)
D081CC00006 (OlympiA)	12 Jul 2021	Phase III: *BRCA*1/2 mutations and high risk HER2 negative primary breast cancer	300 mg bd (tablet)

bd = twice daily; *BRCA* = breast cancer susceptibility gene; *BRCAm* = *BRCA* mutated; DCO = data cut-off; *gBRCA* = germline *BRCA* (mutations detected in the germline); HER2 = human epidermal growth factor receptor-2; PSR = platinum-sensitive relapsed; qd = once daily.

2.3.2. Bioanalytical methods

Durvalumab pharmacokinetics (PK), anti-drug antibodies (ADA), and neutralising antibody (Nab) samples from DUO-E sites in all countries except China were analysed by BioAgilytix Laboratories (Durham, NC, US). PK, ADA, and NAb samples from sites in China were analysed by Labcorp-Shanghai (Shanghai, China). The bioanalytical methods used in DUO-E for durvalumab bioanalysis are listed in the table below.

Table 4 Bioanalytical methods used in DUO-E for durvalumab bioanalysis

Measurement	Laboratory and Methods	Validation reports [a]
Durvalumab	BioAgilytix BAL-17-078-230 (range 50.00 to 3200.00 ng/mL)	BAL-17-078-230-REP
	Labcorp-Shanghai ICSH 16-032 (range 50.00 to 3200.00 ng/mL)	8359-995
ADA	PPD ICDIM 166 (screening assay cut point: 1.59; confirmatory assay cut point [% inhibition]: 29.4)	RAVC2 and RAVC4
	Labcorp-Shanghai ICSH 18-043 (screening assay cut point: 1.21; confirmatory assay cut point [% inhibition]: 26.5)	8387-613
nAb	PPD ICDIM 324 (assay cut point: 1.20)	RJRG2
	Labcorp-Shanghai ICSH 18-044 (assay cut point: 0.863)	8387-615

[a] Refers to the Method Validation Reports located in Module 5.3.1.4.
ADA = anti-drug antibody; nAb = neutralizing antibody.

Note that samples were not taken in the DUO-E study for PK analysis of olaparib. Therefore, no PK data for olaparib is presented.

2.3.3. Pharmacokinetics

Durvalumab

The PK (serum concentrations) of durvalumab has been determined in the DUO-E study and in supportive studies in patients with different types of solid tumour (Durvalumab Pan-tumour pool, which comprises studies in the safety pool: study 1108, Japan Study 02, ATLANTIC, HAWK, CONDOR, PACIFIC, MYSTIC, ARCTIC, EAGLE, DANUBE, KESTREL, STUDY 22, HIMALAYA; see Table 2 for details of these studies). In the majority of studies, only sparse sampling was performed for the assessment of PK, as was the case in DUO-E (C_{trough} concentrations).

DUO-E is an ongoing phase III, randomised, double-bind, placebo-controlled study to assess the efficacy and safety of durvalumab in combination with first-line platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab (SoC+D) or maintenance durvalumab in combination with olaparib (SoC+D+O) in patients with newly diagnosed advanced or recurrent endometrial cancer compared to first-line platinum-based chemotherapy (paclitaxel and carboplatin) alone (SoC).

This study consisted of a Pre-screening Phase and a Screening Phase, an On-treatment Phase consisting of the Chemotherapy Phase and Maintenance Phase, and a Post-discontinuation Follow-up Phase.

PK Objectives and outcomes/endpoints

PK objectives and endpoints for study DUO-E are described in the below table.

Table 5 Objectives and endpoints

Objectives	Endpoint/Variable
Secondary	
To characterise the PK and immunogenicity of durvalumab and durvalumab in combination with olaparib.	Serum concentrations of durvalumab. Anti-drug antibodies to durvalumab.

Sampling times

Samples for PK and ADA analysis were collected during the On-treatment and Post-discontinuation Follow-up phases. Both, PK and ADA analysis were carried out only for durvalumab. Samples were not taken in the DUO-E study for PK nor ADA analysis of olaparib.

On-treatment sampling schedule, durvalumab PK and ADA blood samples were collected within one hour prior to the durvalumab/placebo infusion on day 85 and 183. ADA blood samples were also collected at pre-dose time on day 1 (see below table).

Table 6 On-treatment sampling schedule

Cycle	Chemotherapy treatment [aa] (Cycles 1 to 6)						Maintenance treatment [aa]				Study Treatment Discontinuation visit (when all study treatments had been discontinued)
	C1 D1	C2 D1	C3 D1	C4 D1	C5 D1	C6 D1	C7 D1	C8 D1	C9 D1	≥ C10D1 to PD	
Visit Frequency	Q3W						Q4W				
Study Week	0	3	6	9	12	15	18	22	26	30 to PD	
Day (visit window + 3 days from C2D1 onwards in chemotherapy treatment [aa], and ± 3 days in maintenance treatment [aa])	1	22	43	64	85	106	127	155	183	211 to PD	
Pharmacokinetic assessments											
Durvalumab PK blood sample [s]					X				X		
Durvalumab ADA blood sample [s]	X (pre-dose)				X				X		

[s]Samples for PK and ADA were collected within one hour prior to the durvalumab/placebo infusion.

Regarding Post-discontinuation Follow-up sampling schedule, durvalumab PK and ADA blood samples were collected 3 months after treatment with durvalumab ended. ADA blood samples were also collected 6 months after treatment with durvalumab ended (see table below).

Table 7 Post-discontinuation Follow-up Phase sampling schedule

Visit	Time since last dose of IP					
	30 days (± 3 days)	Month				At PD per RECIST 1.1 (if treatment discontinued for reasons other than PD)
Evaluation		2 (± 1 week)	3 (± 1 week)	4 (± 1 week)	6 (± 1 week) and then every 6 months (± 2 weeks) [g]	
Pharmacokinetic assessments						
Durvalumab PK blood sample [l]			X			
Durvalumab ADA blood sample [l]			X		X (only 6 months)	

Durvalumab PK and immunogenicity samples were collected 90 days (3 months) (± 7 days) after treatment with durvalumab ended. In addition, a final immunogenicity sample was taken 6 months (± 7 days) after treatment with durvalumab ended

Pharmacokinetic parameters

No non-compartmental analysis was conducted due to the sparse PK sampling scheme of durvalumab in this study; therefore, descriptive statistics for durvalumab serum concentrations are presented.

Pharmacokinetic data analyses only comprised summaries of serum concentrations for durvalumab. The following PK parameters were determined after the steady-state doses: peak and trough concentration.

No statistical analysis was conducted.

Population analysed

Of the 718 patients who were randomised, all patients who received at least one dose of durvalumab per the protocol for whom any post-dose data were available and who did not violate or deviate from the protocol in ways that would have significantly affected the PK analyses were included in the PK Analysis Set. The ADA evaluable patients were patients who received at least one dose of durvalumab and had non-missing baseline ADA and at least one post-baseline ADA result.

The number of patients dosed who provided analysable concentrations of durvalumab were 204 patients in the SoC + D treatment arm and 213 patients in the SoC + D + O treatment arm. The PK and ADA analysis sets and the number of patients in each analysis set are summarised the below table.

Table 8 Analysis Sets

	Number (%) of patients			
	SoC	SoC + D	SoC + D + O	Total
Patients included in PK Analysis Set [c]	NA	204	213	417
Patients excluded from PK Analysis Set	NA	34	26	60
No durvalumab dose	NA	3	1	4
No post first dose PK result	NA	31	25	56
Patients included in ADA Evaluable Analysis Set [d]	NA	198	207	405
Patients excluded from ADA Evaluable Analysis Set	NA	40	32	72
No baseline ADA result	NA	14	7	21
No durvalumab dose	NA	3	1	4
No post baseline ADA result	NA	23	24	47

[c] All Safety Analysis Set patients who received at least one dose of durvalumab per the protocol and had any post-baseline PK data and did not violate or deviate from the protocol in ways that would have significantly affected the PK analyses.
[d] All Safety Analysis Set patients who received at least one dose of durvalumab and had non-missing baseline ADA result and at least one post-baseline ADA.
ADA = Anti-drug antibody; NA = Not applicable; PK = Pharmacokinetics; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Pharmacokinetic and ADA results

During the assessment, the MAH was requested to provide a table of the durvalumab serum concentrations excluding those samples analysed at Labcorp Shanghai. A comparison between durvalumab mean concentrations including full PK analysis set and excluding samples analysed at Labcorp Shanghai is presented in the below table.

Note that because olaparib was only administered after chemotherapy infusions had ended (Week 18), all patients in the SoC + D and SoC + D + O arms at the Week 12 pre-dose visit were effectively receiving the same treatment (durvalumab combined with platinum-based chemotherapy). At the Week 26 pre-dose visit all patients in the SoC + D and SoC + D + O arms were receiving durvalumab monotherapy and durvalumab plus olaparib combination, respectively.

Table 9 Summary of Serum Concentration of Durvalumab (µg/mL) for PK Analysis Set in DUO-E and the Durvalumab Pan-tumour Pool

	Geometric Mean, µg/mL (geometric %CV) [n]				
	DUO-E PK Analysis Set (1120 mg Q3W)		**Durvalumab Pan-tumour Pool [a]**		
Visit, timepoint	**SoC + D (N=204)**	**SoC + D + O (N=213)**	**10 mg/kg Q2W Pool (N = 2520)**	**20 mg/kg Q4W Pool (N = 424)**	**1500 mg Q4W Pool (N = 959)**
Week 12, pre-dose	203.1 (32.63) [76]	196.2 (31.65) [90]	129.2 (121.50) [241]	105.7 (124.61) [206]	118.4 (89.08) [590]
Week 24, pre-dose	NS	NS	165.8 (78.75) [398]	132.9 (59.67) [146]	136.6 (106.64) [202]
Week 26, pre-dose	265.6 (39.62) [26]	236.3 (37.97) [35]	195.7 (28.57) [11]	85.8 (- [b]) [1]	NS
3-month follow-up	28.0 (104.39) [21]	14.0 (206.77) [20]	14.5 (409.47) [625]	9.4 (1735.06) [107]	10.4 (979.37) [257]

a. Durvalumab Pan-tumour pool: Study 1108, Japan Study 02, ATLANTIC, HAWK, CONDOR, PACIFIC, MYSTIC, ARCTIC, EAGLE, DANUBE, KESTREL, STUDY 22, HIMALAYA.

b. %CV value not available as data were only available for one patient.

CV = coefficient of variation; NS = no sample; PK = pharmacokinetic; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

In the DUO-E study, a fixed dose of 1120 mg durvalumab was administered Q3W during the chemotherapy phase and 1500 mg Q4W in the maintenance phase. The initial Q3W schedule of durvalumab was chosen to align with the treatment interval for chemotherapy for ease of use and convenience to patients and investigators. The 1500 mg Q4W dose is an approved dose in several indications. According to the MAH, a dose of 1120 mg Q3W provides the equivalent dose of durvalumab per week as the 1500 mg Q4W dose and was chosen for the chemotherapy phase of this study.

The durvalumab PK profiles for the 1120 mg Q3W and 1500 mg Q4W regimens in subjects with endometrial cancer were simulated using the target patient population from the previously-developed PopPK model developed by AstraZeneca across different tumour types from studies MEDI4736-1108, D4191C00003 (ATLANTIC), D4191C00001 (PACIFIC), D419QC00001 (CASPIAN), D419MC00004 (POSEIDON) and D933AC00001 (TOPAZ-1) (data not shown).

For DUO-E, the individual empirical Bayes estimates of durvalumab PK parameters from the PopPK model were adjusted using covariates from 477 subjects with endometrial cancer and used to predict the durvalumab Cavg during dosing interval (computed as AUC divided by the dosing interval, Cmax and Cmin after first dose and at steady-state). Endometrial tumours were assumed to have the same effect on CL as solid tumours (ie, tumtype was set to 0) and combination therapy was set to 1 to account for the concomitant administration of durvalumab and chemotherapy.

The individual empirical Bayes estimates of durvalumab CL and V1 from the final PopPK model were compared with the individual empirical Bayes estimates used to simulate the DUO-E PK profiles using boxplots across different tumour types. Results showed the predicted Cavg at steady state were comparable among 1120 mg Q3W and 1500 mg Q4W (data not shown), thus suggesting that these regimens provide virtually identical exposure coverage following administration of multiple repeated doses.

Olaparib

The dose of olaparib used in the DUO-E study is 300 mg bd. Olaparib's PK was not assessed in DUO-E trial.

Pharmacokinetic interaction studies

No formal drug-drug interaction studies have been conducted with durvalumab. Pharmacokinetic drug-drug interaction of durvalumab with other therapeutics is not anticipated given that durvalumab is not primarily cleared via hepatic or renal pathways; instead, the primary elimination pathways are protein catabolism via reticuloendothelial system or target-mediated disposition. Durvalumab is not expected to induce or inhibit the major drug metabolising cytochrome P450 pathways.

The clearance of olaparib is mediated predominantly by CYP3A. Concomitant use of strong or moderate CYP3A inhibitors is not recommended, and alternative agents should be considered. Dose adjustments for co-administration with CYP3A inhibitors are described in the olaparib product information.

Immunogenicity

Anti-drug antibody data for durvalumab were available for a total of 405 ADA-evaluable patients (defined as the patients in the safety analysis set who have a non-missing baseline ADA and at least one non-missing post-baseline results): 198 patients in the SoC + D arm, and 207 patients in the SoC + D + O arm.

Anti-drug antibody results were also pooled across 13 supportive studies including patients treated with dosing regimens of durvalumab at 10 mg/kg Q2W, 20 mg/kg Q4W, and 1500 mg Q4W (durvalumab pan-tumour pool), and compared with those in the DUO-E SoC + D arm and SoC + D + O arm.

Table 10 Summary of Immunogenicity Results for Durvalumab (ADA-evaluable Population)

	DUO-E Overall **1120 mg Q3W during the chemotherapy phase and 1500 mg Q4W in the maintenance phase**		**Durvalumab Pan-tumour Pool** **Combined 10 mg/kg Q2W, 20 mg/kg Q4W and 1500 mg Q4W**
ADA Category	**SoC + D (N = 198)** **n (%)**	**SoC + D+O (N = 207)** **n (%)**	**Pan-tumour Pool (N = 3069)** **n (%)**
ADA-evaluable patients	198 (100.0)	207 (100.0)	3069 (100.0)
ADA prevalence [a]	8 (4.0)	9 (4.3)	191 (6.2)
Median (range) of maximum titre	1.5 (1 - 64)	1.0 (1 – 8)	4.0 (1 - 1,024)
ADA incidence [b]	2 (1.0)	0	84 (2.7)
Median (range) of maximum titre	32.5 (1 - 64)	-	4.0 (1 - 1,024)
ADA-positive post-baseline and positive at baseline	0	0	17 (0.6)
Median (range) of maximum titre	-	-	8.0 (2, 32)
ADA-positive post-baseline only or treatment-induced ADA	2 (1.0)	0	82 (2.7)
Median (range) of maximum titre	32.5 (1 - 64)	-	4.0 (1 - 1,024)
ADA positive at baseline only	6 (3.0)	9 (4.3)	92 (3.0)
Median (range) of maximum titre	1.5 (1 - 16)	1.0 (1 – 8)	4.0 (1 - 64)
Treatment-boosted ADA [c]	0	0	2 (0.1)
Median (range) of maximum titre	-	-	12.0 (8 – 16)
Persistent positive ADA [d]	2 (1.0)	0	67 (2.2)
Median (range) of maximum titre	32.5 (1 - 64)	-	4.0 (1 - 1,024)
Transient positive ADA [e]	0	0	32 (1.0)
Median (range) of maximum titre	-	-	4.0 (1 - 128)
nAb positive at any visit	1 (0.5)	0	16 (0.5)
Median (range) of maximum titre	64.0 (64 - 64)	-	16.0 (1 - 1,024)

c. ADA prevalence is the proportion of ADA-evaluable patients who were ADA-positive at any time.

ADA incidence is the proportion of ADA-evaluable patients who were treatment-emergent ADA-positive.

Treatment-boosted ADA is defined as baseline positive ADA titre that was boosted to ≥ 4 fold during the study period.

Persistently positive is defined as having at least 2 post-baseline ADA-positive measurements with at least 16 weeks (112 days) between the first and last positive measurements, or an ADA-positive result at the last available assessment.

Transiently positive is defined as having at least one post-baseline ADA-positive measurement and not fulfilling the conditions for persistently positive.

N is the number of patients in the ADA analysis set in the treatment group. The denominator for calculation of percentage for all categories is the number of ADA evaluable patients (defined as the patients in the safety analysis set who have a non-missing baseline ADA and at least one non-missing post-baseline results) in the treatment group. The denominator for ADA evaluable patients category is N.

If a patient had more than one titre result, the maximum titre result was used, regardless of whether it was baseline or post baseline.

ADA = anti-drug antibody; N = number of patients; nAb = neutralizing antibody; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

2.3.4. Discussion on clinical pharmacology

Analytical methods

The bioanalytical methods used for durvalumab quantification and ADA and NAb determination in USA laboratories for DUO-E study were previously used in other studies carried out with IMFINZI, which were found acceptable in previous regulatory procedures. Overall, the quantification of durvalumab was carried out in accordance with the principles of ICH M10 Guideline. Also, the determination of ADA and NAb was conducted in accordance with the Guideline on Immunogenicity assessment of therapeutic proteins and to the state of the art.

The bioanalytical methods used for durvalumab quantification, and ADA and NAb determination in China laboratories for DUO-E study, and its corresponding method validation reports, were submitted. Overall, the quantification of durvalumab was carried out in accordance with the principles of ICH M10 Guideline. Also, the determination of ADA was conducted in accordance with the Guideline on Immunogenicity assessment of therapeutic proteins and to the state of the art.

The MAH could not provide a cross-validation between the laboratories located in Shanghai (China) and in North Carolina (USA) or between the laboratories located in California (USA) and in North Carolina (USA). For future procedures the MAH is encouraged to perform a suitable cross-validation in case that sample analysis is carried out in more than one laboratory for a single study (as it is stated in the ICH M10 Guideline on bioanalytical method validation and study sample analysis EMA/CHMP/ICH/172948/2019). Additionally, the MAH was asked to disregard those samples analysed for durvalumab concentrations at Labcorp Shanghai because the issues with the haemolysis effect could not be addressed during the procedure.

Pharmacokinetics

The pharmacokinetic properties of durvalumab and olaparib combination for the treatment of adult patients with first-line advanced or recurrent endometrial cancer are supported based on the evidence collected in a Phase 3 clinical trial (DUO-E) together with a pooled assessment of monotherapy data integrated from 13 monotherapy studies of durvalumab. Of note, at the time of the assessment of this application, the combination of durvalumab + olaparib was not approved in any region globally and has only been used in clinical studies (MEDIOLA, NCI study ESR-14-10366).

No PK samples of olaparib were collected in the DUO-E study as the MAH justifies that PK and PD of olaparib as monotherapy have been well characterised in patients with advanced solid tumours and in patients with ovarian, prostate, pancreatic, or breast cancer and there were no data suggesting that patients exposed to olaparib in this trial would be different from the previous oncology studies. Besides, the elimination pathways of durvalumab and olaparib are very different.

In the DUO-E study the interaction between the combination of durvalumab plus olaparib was not evaluated which is considered acceptable.

According to the SmPC of Imfinzi, the main elimination pathways of durvalumab are protein catabolism via reticuloendothelial system or target mediated disposition; whereas olaparib is metabolised via CYP3A4/5. Although it is understood that the potential of DDI between biologics and small molecules is negligible, considering divergent metabolic pathways for both compounds, olaparib samples should have been collected and analysed to confirm that when olaparib is administered with durvalumab, olaparib concentrations fall within the expected range and that durvalumab does not interfere with the PK of olaparib.

Due to the limited experimental sampling available, there is no popPK report that allows justifying the PK properties or the dose through a model-based strategy in patients with endometrial cancer.

The PK evaluation of durvalumab has been conducted by comparing geometric mean and coefficient of variation of Ctrough levels at week 12 and week 26 between SoC+D and SoC+D+O arms from the DUO-E study and with the pooled analysis of durvalumab. Similar exposure levels were observed between both arms from the DUO-E study at week 12 and week 26, suggesting no relevant influence of the co-administration of olaparib in the Ctrough levels throughout time. A 70% increase in Ctrough levels of durvalumab is observed at Week 12 with the proposed dosing regimen (1120 mg Q3W) in patients with endometrial cancer in the DUO-E study compared to the Ctrough levels observed in the pooled analysis of the 1500 mg Q4W regimen. Despite higher Ctrough levels could be expected with the Q3W vs Q4W, the high increased observed could suggest that differences in the PK behaviour do exist between patients with endometrial cancer and the pooled analysis. The MAH stated that simulations of the average steady-state concentrations were similar for both dose regimen (Cavgss of 391 and 393 ug/ml for 1120 mg Q3W and 1500 mg Q4W respectively), which was expected since similar dose amount normalised by the dosing interval was administered. Furthermore, those simulations were performed using the target patient population from the DUO-E study and no comparisons were performed using the characteristics of the pool patient population. Therefore, the higher Ctrough levels seems to be related to the different characteristics of the population included in the DUO-E study compared to the pool dataset.

The MAH has provided the exposure comparison stratifying the different indications of durvalumab. The results showed again higher Ctrough levels for the 1 120 mg Q3W dosing regimen compared to the 1 500 mg Q4W, 20 mg/kg Q4W and 10 mg/kg Q2W regimens across all indications studied. These results clearly demonstrate a different trend from that observed in previous studies, indicating that the greater exposure is not a consequence of variations in the amount of dose administered (since the normalised levels per interval are equivalent), but rather due to differences between the populations.

The MAH has provided model-predicted Ctrough levels at Week 26 of durvalumab for the different target population (solid tumours, non-small cell lung cancer (NSCLC), squamous cell carcinoma of head and neck (SCCHN), transitional cell carcinoma of the urothelium (bladder), hepatocellular carcinoma (HCC) and endometrial cancer) using the proposed dosing regimen. The simulation results showed higher Ctrough concentrations in endometrial cancer compared to the other tumour types. The higher Ctrough levels seems to be related to the different characteristics of the population included in the DUO-E study compared to the pool dataset (women with lower body weight). Using model-predicted concentrations with the previously developed population PK model, slightly lower Ctrough concentrations were predicted for the SoC+D arm (12% difference) and very similar Ctrough concentrations were predicted for the SoC+D+O arm (0.8% difference). Therefore, no relevant differences between model-predicted and observed Ctrough concentrations at week 26 are observed for the DUO-E population suggesting that the popPK model is capable to characterise the observed data and no relevant differences in the PK processes were observed across the populations from the DUO-E and the previous studies.

Durvalumab PK concentrations were within the expected exposure range in both the SoC + D and SoC + D + O treatment arms, and appeared to be similar at both Week 12 and Week 26, indicating that durvalumab PK is not affected by co-administration with SoC or olaparib.

Overall, the Ctrough concentrations of durvalumab were in a similar range for DUO-E as those studies in the durvalumab Pan-tumour pool, which used the same or equivalent durvalumab dosing regimen. These data demonstrate that PK data for durvalumab in DUO-E are consistent with previous studies and not influenced by co-administration with olaparib or SoC.

The dose of olaparib used in the DUO-E study is 300 mg bd, which is the currently approved dose for the tablet formulation (in markets where approval has been obtained). AstraZeneca has extensive clinical experience at 300 mg bd tablet dose of olaparib across multiple tumour indications (ovarian cancer with SOLO1, SOLO2, and PAOLA-1, breast cancer with OlympiAD and OlympiA, pancreatic cancer with POLO, and prostate cancer with PROfound and PROpel).

In the DUO-E study, the exposure to durvalumab was similar in both treatment arms which indicates that there were no clinically meaningful PK drug-drug interactions between durvalumab and olaparib, although exposure to olaparib was not measured throughout the study.

Immunogenicity

Anti-durvalumab antibodies have been analysed during treatment and post-treatment to evaluate the existence of ADA during DUO-E study. This is in accordance with the Guideline on Immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1). In both the SoC + D treatment arm and the SoC + D + O treatment arm, the majority of ADA-positive patients were classified as ADA-positive at baseline only. The treatment-emergent ADA-positive patients were classified as persistently ADA positive because the last available assessment was ADA positive rather than duration of the ADA response being ≥ 16 weeks. Less than 1% of patients who were evaluable for ADA tested positive for nAb against durvalumab. Therefore, the ADA prevalence and incidence were low (<5%). Even though the evaluation of immunogenicity does not suggest any relevant impact between SoC+D+O vs SoC+D nor in comparison with previous studies in other indications, the limited number of ADA-positive patients preclude a definitive conclusion of the effect of ADAs on the PK or safety of durvalumab. However, based on the available data, no immunogenicity effect is expected with the combination of durvalumab with olaparib with the SoC treatment at the proposed dosing regimens.

In endometrial cancer, the posology for Imfinzi is 1 120 mg in combination with carboplatin and paclitaxel every 3 weeks (21 days) for a minimum of 4 and up to 6 cycles, followed by Imfinzi 1 500 mg every 4 weeks as monotherapy (dMMR patients) or in combination with olaparib 300 mg twice daily (pMMR patients) until disease progression or unacceptable toxicity. Patients with a body weight of 30 kg or less during maintenance phase must receive weight-based dosing equivalent to Imfinzi at 20 mg/kg, until weight is greater than 30 kg.

2.3.5. Conclusions on clinical pharmacology

The clinical pharmacology properties of the combination of durvalumab plus SoC (carboplatin and paclitaxel) ± olaparib in adult patients with endometrial cancer have been defined based on the limited PK evidence collected in the Phase 3 study DUO-E. No relevant differences between model-predicted and observed Ctrough concentrations for durvalumab at week 26 were observed for the DUO-E population suggesting that the popPK model is capable to characterise the observed data and no relevant differences in the PK processes were observed across the populations from the DUO-E and the previous studies with durvalumab. No significant immunogenicity issues were detected.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

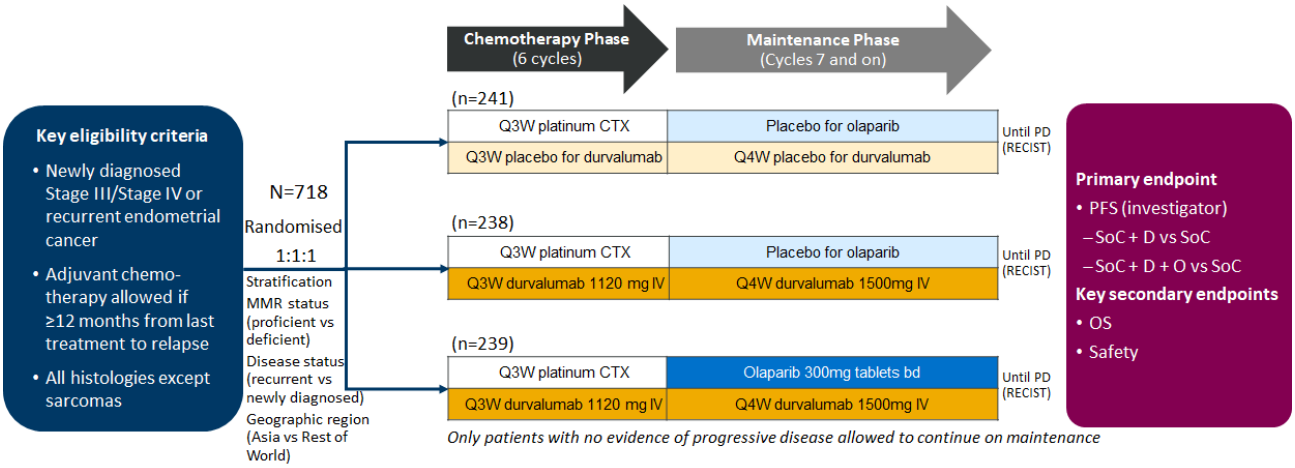
No dose-response studies were submitted as part of this application.

2.4.2. Main study

Study DUO-E: A Randomised, Multicentre, Double-blind, Placebo-controlled, Phase III Study of First-line Carboplatin and Paclitaxel in Combination with Durvalumab, Followed by Maintenance Durvalumab ±Olaparib in Patients with Newly Diagnosed Advanced or Recurrent Endometrial Cancer

Methods

Figure 1 DUO-E Study Design



bd = twice daily; CTX = chemotherapy; D = durvalumab; IV = intravenous; MMR = mismatch repair; O = olaparib; OS = overall survival; PD = progressive disease; PFS = progression free survival; Q3W = every 3 weeks; Q4W = every 4 weeks; RECIST = Response Evaluation Criteria in Solid Tumours; SoC = standard of care; vs = versus.

Study participants

Key inclusion criteria included:

- Aged ≥ 18 years at the time of screening and female.
- Histologically confirmed diagnosis of epithelial endometrial carcinoma. All histologies, including carcinosarcomas, were allowed. Sarcomas were not allowed.
- Must have had endometrial cancer in one of the following categories:
    - Newly diagnosed Stage III disease (measurable disease per RECIST 1.1 following surgery or diagnostic biopsy),
    - Newly diagnosed Stage IV disease (with or without disease following surgery or diagnostic biopsy),
    - Recurrence of disease (measurable or non-measurable disease per RECIST 1.1) where the potential for cure by surgery alone or in combination was poor.
- Naïve to first-line systemic anti-cancer treatment.

    - For patients with recurrent disease only, prior systemic anti-cancer treatment was allowed only if it was administered in the adjuvant setting (as part of the upfront/adjuvant anti-cancer treatment, which may have been concurrent or followed with chemoradiation) and there was at least 12 months from date of last dose of systemic anti-cancer treatment administered to date of subsequent relapse.

- An FFPE tumour sample from the locoregional or a metastatic site must be available and must be suitable for MMR status evaluation using the Ventana MMR IHC panel. In compliance with local regulations, all patients must provide consent for the tumour sample and for MMR testing. The sample must be shipped during the pre-screening period and valid MMR test results (proficient/deficient) MUST be available prior to randomisation at Cycle 1 Day 1.
- Had ECOG performance status of 0 or 1 within 7 days of starting study treatment.
- Body weight >30 kg.
- Adequate organ and bone marrow function, defined as:
    - Haemoglobin ≥ 10.0 g/dL.
    - Absolute neutrophil count ≥ 1.5×10^9/L.
    - Platelet count ≥ 100×10^9/L.
    - Serum bilirubin ≤ 1.5 × the ULN. This did not apply to patients with confirmed Gilbert's syndrome, who would be allowed in consultation with their physician.
    - Alanine aminotransferase and AST ≤ 2.5 × ULN; for patients with hepatic metastases, alanine aminotransferase and AST ≤5 × ULN.
- Measured CrCl > 51 mL/min or calculated CrCl > 51 mL/min as determined by Cockcroft-Gault (using actual body weight), a 24-hour urine test or another validated test as per local practice:

$$\text{Estimated CrCl (mL/min)} = \frac{(140 - \text{age [years]}) \times \text{weight (kg)} \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

Key exclusion criteria included:

- Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g. colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following were exceptions to this criterion:
    - Patients with vitiligo or alopecia,
    - Patients with hypothyroidism (e.g. following Hashimoto syndrome) stable on hormone replacement,
    - Any chronic skin condition that did not require systemic therapy,
    - Patients without active disease in the last 5 years may have been included but only after consultation with the study physician,
    - Patients with coeliac disease controlled by diet alone.
- Major surgical procedure (as defined by the investigator) within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery. Note: Local surgery of isolated lesions for palliative intent is acceptable or diagnostic staging.

- Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension (systolic blood pressure >160 mmHg; diastolic blood pressure >100 mmHg), unstable angina pectoris, cardiac arrhythmia, interstitial lung disease (ILD), serious chronic gastrointestinal conditions associated with diarrhoea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.
- History of leptomeningeal carcinomatosis.
- Brain metastases or spinal cord compression. Patients with suspected brain metastases at screening should have a magnetic resonance imaging (MRI) (preferred) or computed tomography (CT) each preferably with IV contrast of the brain prior to study entry.
- Resting ECG indicating uncontrolled, potentially reversible cardiac conditions, as judged by the investigator (e.g. unstable ischaemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QTcF prolongation ≥500 ms, electrolyte disturbances, etc.), or patients with congenital long QT syndrome.
- MDS/AML or with features suggestive of MDS/AML.
- Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug.
- Prior treatment with PARP inhibitors or exposure to other anti CTLA-4, anti-PD-1, anti-PD-L1, or anti–programmed-cell-death ligand 2 (anti-PD-L2) antibodies.
- Concomitant use of known strong CYP3A inhibitors (e.g. itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (e.g. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting study treatment is 2 weeks. Concomitant use of known strong (e.g. phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (e.g. bosentan, efavirenz, modafinil). The required washout period prior to starting study treatment is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents.

Treatments

Patients were randomised to one of the following treatment arms:

- SoC (**Arm A**; control): Platinum-based chemotherapy (paclitaxel 175 mg/m^2 and carboplatin AUC5 or AUC6) Q3W for a maximum of 6 cycles with durvalumab placebo (IV) Q3W. Following completion of chemotherapy treatment, patients without objective disease progression received durvalumab placebo (IV) Q4W and olaparib placebo (tablets) bd orally as maintenance treatment until disease progression.
- SoC + D (**Arm B**): Platinum-based chemotherapy (paclitaxel and carboplatin) Q3W for a maximum of 6 cycles with 1120 mg durvalumab (IV) Q3W. Following completion of chemotherapy treatment, patients without objective disease progression received 1500 mg durvalumab (IV) Q4W with olaparib placebo (tablets) bd orally as maintenance treatment until disease progression.
- SoC + D + O (**Arm C**): Platinum-based chemotherapy (paclitaxel and carboplatin) Q3W for a maximum of 6 cycles with 1120 mg durvalumab (IV) Q3W. Following completion of

chemotherapy treatment, patients without objective disease progression received 1500 mg durvalumab (IV) Q4W with 300 mg olaparib (tablets) bd orally as maintenance treatment until disease progression.

Patients continued to receive study treatment until radiological disease progression per RECIST 1.1 as assessed by the Investigator unless there was unacceptable toxicity, withdrawal of consent, or another confirmed discontinuation criterion was met. Assessment of tumour status was performed every 9 weeks for the first 18 weeks relative to randomisation and every 12 weeks thereafter.

Patients who discontinued either product (olaparib/placebo or durvalumab/placebo) for reasons other than disease progression could continue treatment with the other product if appropriate based on toxicity considerations and investigator discretion.

Objectives/endpoints

Table 11 Study objectives and endpoints

Primary Objective	Endpoint/Variable
To demonstrate the efficacy of durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab (Arm B) or durvalumab with olaparib (Arm C) when compared to platinum-based chemotherapy (Arm A) by assessment of progression-free survival (PFS), in patients with newly diagnosed advanced or recurrent endometrial cancer	PFS (per RECIST 1.1 as assessed by investigator), defined as the time from randomisation until the date of objective disease progression or death (by any cause in the absence of progression). This will be assessed via determining the efficacy of: • Durvalumab in combination with platinum-based chemotherapy and continued as maintenance in combination with olaparib versus SoC platinum-based chemotherapy. • Durvalumab in combination with platinum-based chemotherapy and continued as maintenance versus SoC platinum-based chemotherapy.

Secondary Objectives	Endpoint/Variable
To determine the efficacy of durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab (Arm B) or durvalumab with olaparib (Arm C) when compared to platinum-based chemotherapy (Arm A) in newly diagnosed advanced or recurrent endometrial cancer patients by assessment of: PFS2, OS, ORR, DoR, TFST, TSST, and TDT	PFS2: Second progression-free survival is defined as the time from randomisation to the earliest of progression event subsequent to first subsequent therapy (assessed by the investigator per local standard clinical practice and may involve any of the following: objective radiological imaging, symptomatic progression), or death due to any cause. OS: Overall survival is defined as the time from the date of randomisation until death due to any cause. ORR: Objective response rate is the proportion of patients with measurable disease at baseline who have complete response (CR) or partial response (PR), as determined by the investigator at local site. DoR: Duration of response is time from the date of first documented response until date of documented progression or death in the absence of disease progression. TFST: Time to first subsequent therapy or death is time from randomisation to the earlier of start date of the first subsequent anti-cancer therapy after discontinuation of randomised treatment or death due to any cause. TSST: Time to second subsequent therapy or death is time from randomisation to the earlier of start date of the second subsequent anti-cancer therapy after discontinuation of first subsequent treatment or death due to any cause. TDT: Time to study treatment discontinuation or death is time from randomisation to the earlier of the date of study treatment discontinuation or death.
To characterise the PK and immunogenicity of durvalumab and durvalumab in combination with olaparib	Serum concentrations of durvalumab Anti-drug antibodies (ADA) to durvalumab
To determine effects on symptoms, functioning and overall health-related quality of life (HRQoL) of durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab (Arm B) or durvalumab with olaparib (Arm C) when compared to platinum-based chemotherapy alone (Arm A) in newly diagnosed advanced or recurrent endometrial cancer patients	Change from baseline in: • Physical functioning score of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30 (EORTC QLQ-C30) • Role functioning score of the EORTC QLQ-C30 • Global health status/quality of life (QoL) score of the EORTC QLQ-C30 • All other functioning and symptom subscale scores of the EORTC QLQ-C30 (excluding the financial subscale) Time to deterioration in: • Physical functioning score of the EORTC QLQ-C30 • Role functioning score of the EORTC QLQ-C30 • Back/pelvic pain of the EORTC QLQ-EN24 • Gastrointestinal (GI) symptoms of the EORTC QLQ-EN24 • Urological symptoms of the EORTC QLQ-EN24

Safety Objective	Endpoint/Variable
To evaluate the safety and tolerability of durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab (Arm B) or durvalumab with olaparib (Arm C) compared to platinum-based chemotherapy (Arm A) in newly diagnosed advanced or recurrent endometrial cancer patients	Safety and tolerability will be evaluated in terms of AEs/serious AEs (SAEs), physical examination, vital signs including blood pressure, pulse, clinical laboratory including clinical chemistry/haematology parameters, and ECG Assessments related to AEs cover: • Occurrence/frequency • Relationship to investigational product (IP) as assessed by investigator • Common Terminology Criteria for Adverse Event (CTCAE) grade • Seriousness • Death • Discontinuation of IP • Dose modifications during the chemotherapy phase and the maintenance phase • AEs of special interest (AESIs) • Other significant AEs • Exposure • Immune-mediated adverse events (imAEs) – given the intended mechanisms of action of durvalumab, particular attention will be given to AEs that may follow enhanced T cell activation, or other imAE

Exploratory Objectives	Endpoint/Variable
To determine the efficacy of durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab in combination with olaparib (Arm C) when compared to durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab (Arm B) in patients with newly diagnosed advanced or recurrent endometrial cancer	Will include, but is not limited to: • PFS (per RECIST 1.1 as assessed by investigator) • OS
To evaluate tumour predictive biomarkers of durvalumab and olaparib in advanced endometrial cancer patients	Will include, but is not limited to the following measurements within the tumour: • Tumour tissue mismatch repair (MMR), microsatellite instability (MSI), tumour mutational burden (TMB) and PD-L1 status. • Mutation status of homologous recombination repair (HRR) genes and homologous recombination deficiency (HRD) score or other genomic scar of homologous recombination deficiency.
To evaluate additional tumour candidate predictive biomarkers of durvalumab and olaparib in advanced endometrial cancer patients	May include, but is not limited to: • CD3+/CD8+ tumour-infiltrating lymphocyte (TIL) densities, Human leukocyte antigen – loss of heterozygosity (HLA-LOH), immune gene expression profiling and other exploratory biomarkers.
To further assess the efficacy of treatment through longitudinal analysis of blood samples collected at regular intervals on study	May include but is not limited to: • Circulating tumour DNA (ctDNA) response to treatment. • Peripheral gene expression profiling, assessment of peripheral chemokines and cytokines, T-cell receptor (TCR) profiling.
To explore whether resistance mechanisms to treatment can be identified through analysis of tumour and blood samples – archival tumour sample and blood samples at baseline and on progression (tumour sample optional on progression)	Analysis and outcome variables yet to be defined but may include molecular analysis of ctDNA.

To explore whether resistance mechanisms to treatment can be identified through analysis of tumour and blood samples – archival tumour sample and blood samples at baseline and on progression (tumour sample optional on progression)	Analysis and outcome variables yet to be defined but may include molecular analysis of ctDNA.
Future exploratory research into factors that may influence development of cancer and/or response to study treatment (where response is defined broadly to include efficacy, tolerability or safety) may be performed on the collected and stored blood or archival tumour samples that were mandatory for entry onto the study or on optional blood or tumour biopsy samples collected during the course of the study.	Analysis and outcome variables yet to be defined.
To collect and store DNA (according to each country's local and ethical procedures) for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to study treatments and or susceptibility to disease (optional) [a]	To identify pharmacogenetic correlates for the response to treatment through the retrospective analysis of DNA extracted from an optional blood sample.
To explore health status of patients with durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab with or without olaparib in patients with advanced or recurrent endometrial cancer	Evaluation of health status by the assessment of • Health state utility derived from the EuroQoL five dimensions, five level health state utility index (EQ-5D-5L) • Quality-adjusted time without symptoms of disease or toxicity (Q-TWiST) • Quality-adjusted PFS (QAPFS)
To explore patient-reported treatment tolerability with durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab with or without olaparib in patients with advanced or recurrent endometrial cancer	Evaluation of selected symptoms from the patient-reported outcomes version of the CTCAE (PRO-CTCAE) and overall treatment tolerability using the patient global impression of treatment tolerability (PGI-TT).
To explore patient-reported severity of cancer symptoms, change in overall health condition, and overall benefit/risk evaluation for durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab with or without olaparib in patients with advanced or recurrent endometrial cancer	Evaluation of patient global impression of severity of cancer symptoms (PGIS), change in health condition (PGIC), and overall perception of benefit/risk (PGI-BR).
To explore healthcare resource associated with durvalumab and olaparib in advanced endometrial cancer patients	Key healthcare resource use will be collected using HOSPAD

Sample size

The study aimed to randomise approximately 699 eligible endometrial cancer patients globally at a 1:1:1 ratio to the study treatments (i.e. approximately 233 patients per treatment arm). The primary PFS analysis was planned to be undertaken when approximately 299 PFS events had occurred (64% maturity) for the SoC + D versus SoC arm comparison, and approximately 281 PFS events had occurred (60% maturity) for the SoC + D + O versus SoC arm comparison. Assuming the average true PFS HR was 0.70 for the SoC + D versus SoC arm comparison and 0.55 for the SoC + D + O versus SoC arm comparison, the study had 80% and > 99% power to demonstrate a statistically significant difference for PFS at the overall 2-sided significance level of 2.5% for each comparison, respectively. The smallest treatment difference that would be statistically significant is an HR of 0.77 for the SoC + D versus SoC arm comparison and 0.76 for the SoC + D + O versus SoC arm comparison.

The assumed median PFS of 12 months for the control arm is in line with data reported for carboplatin/paclitaxel in first-line endometrial cancer from the GOG-209 study (Miller et al. 2012). The

sample size has been derived on the assumption of a 3-month delay in separation of the PFS curves between Arm B versus Arm A and between Arm C versus Arm A. The assumed true average hazard ratio for the durvalumab+placebo arm is 0.70 (corresponding to an improvement in median PFS of 5.5 months over the assumed median PFS of 12 months in the control arm) and for the durvalumab+olaparib arm is 0.55 (corresponding to an improvement in median PFS of 11.2 months).

In addition, the sample size has been derived on the following assumptions:

- 27-month period of recruitment
- Approximately 10% uniform dropout rate over the study period.

The power calculations for OS were based on the following assumptions: 1) Median OS of 22.7 months for the control arm, 2) An HR of 0.75 for OS for the durvalumab+placebo arm versus Control arm and 3) Durvalumab+olaparib arm versus control arm comparisons corresponding to an improvement in median OS of approximately 7.6 months over the assumed median OS of 22.7 months in the control arm.

Randomisation

All patients were centrally assigned to randomised study treatment using an interactive voice/web response system (IVRS/IWRS).

Randomisation was stratified by:

- MMR status (proficient versus deficient)
- Disease status (recurrent versus newly diagnosed)
- Geographic region (Asia versus RoW).

Blinding (masking)

The study was conducted in a double-blind manner: durvalumab and olaparib treatments were both blinded to patients and investigators.

The IVRS/IWRS provided the Investigator(s) or pharmacists the kit identification number to be allocated to the patient at the dispensing visit. Investigators and patients were to remain blinded to each patient's assigned study treatment throughout the course of the study. Patients were not to be unblinded except in medical emergencies when the appropriate management of the patient required knowledge of the treatment randomisation.

Statistical methods

Analysis sets

- All Patients Set: The All Patients Set included all enrolled patients, defined as those who signed the Informed Consent Form (ICF).
- Full Analysis Set (FAS): The FAS included all randomised patients within treatment arms assigned in accordance with the randomisation, regardless of the treatment actually received. Patients who were randomised but did not subsequently receive treatment were included in the FAS. The analysis of data using the FAS therefore follows the principles of intent-to-treat. The FAS was used to analyse efficacy data (including PROs) and baseline characteristics data, as well as biomarker data, and patients were summarised based on the treatment arm they were randomised to regardless of the treatment they actually received.

- Safety Analysis Set (SAS): The SAS consisted of all randomised patients who received any amount of study treatment (durvalumab/placebo or olaparib/placebo). Safety data were not formally analysed but summarised using the Safety Analysis Set. Patients who initially received a dose of durvalumab/placebo were summarised according to the arm to which they were randomised. During the maintenance phase, the SAS included patients who entered the Maintenance Phase (defined as having received at least one dose of olaparib/olaparib placebo).
- Pharmacokinetic Analysis Set: All patients who received at least one dose of durvalumab per the protocol for whom any post-dose data were available and who did not violate or deviate from the protocol in ways that would have significantly affected the PK analyses were included in the PK Analysis Set.
- Anti-drug Antibody Analysis Set: The ADA evaluable patients were patients in the Safety Analysis Set who received at least one dose of durvalumab and had non-missing baseline ADA and at least one post-baseline ADA result.

Assessment of study endpoints

- Primary endpoint: Progression-free Survival (PFS)

The primary objective of the study was to determine the efficacy by PFS (per RECIST 1.1 as assessed by the site investigator) of ArmB (SoC + D) versus Arm A (SoC) and Arm C (SoC + D + O) versus Arm A (SoC). The formal statistical analysis was performed to test the hypotheses of interest:

- H0BA: Arm B = Arm A versus H1BA: Arm B $\neq$ Arm A

and

- H0CA: Arm C = Arm A versus H1CA: Arm C $\neq$ Arm A

Where H0 = the null hypothesis; H1 = the alternate hypothesis.

The study would be considered positive (a success) if either of the above null hypotheses were rejected based on the primary analysis of PFS in the FAS. A pre-specified exploratory analysis comparing SoC + D + O (Arm C) versus SoC + D (Arm B) was also undertaken.

Patients who had not progressed or died at the time of analysis were censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the patient had progressed or died after 2 or more consecutive missed assessments, the patient was censored at the time of the latest evaluable RECIST 1.1 assessment prior to the 2 missed visits.

The primary PFS analysis of SoC + D (Arm B) versus SoC (Arm A) and SoC + D + O (Arm C) versus SoC (Arm A) was performed separately using a log-rank test stratified in accordance with the pre-defined pooling strategy for generation of the p-value. The stratification variables in the statistical modelling were based on the values entered into IVRS at randomisation, even if it was subsequently discovered that these values were incorrect. The HR and its confidence interval were estimated from a stratified Cox Proportional Hazards model (with ties = Efron and the stratification factors as strata) and the CI calculated using a profile likelihood approach (RISKLIMITS=PL).

PFS sensitivity analyses

(a) Evaluation time bias

Sensitivity analyses were performed to assess possible evaluation-time bias that may had been introduced if scans were not performed at the protocol-scheduled time points. The midpoint between the time of progression and the previous evaluable RECIST assessment (using the final date of the assessment) were analysed using a stratified log-rank test, as described for the primary analysis of PFS.

(b) Attrition bias

Attrition bias was assessed by repeating the PFS analysis except that the actual PFS event times, rather than the censored times, of patients who progressed or died in the absence of progression immediately following two, or more, non-evaluable tumour assessments were included. In addition, and within the same sensitivity analysis, patients who took subsequent therapy (note that for this analysis radiotherapy was not considered a subsequent anti-cancer therapy) prior to their last evaluable RECIST assessment or progression or death were censored at their last evaluable assessment prior to taking the subsequent therapy.

(c) *Ascertainment bias*

Ascertainment bias was assessed by analysing the BICR data. The stratified log rank test was repeated on PFS using the BICR data based upon RECIST. The HR and 95% CI was presented using stratified Cox Proportional Hazard model. This sensitivity analysis was also be conducted for the analysis of SoC + D + O (Arm C) vs SoC + D (Arm B).

(d) *Deviation bias (if meaningful to do)*

As a sensitivity analysis to the primary PFS endpoint, an analysis excluding patients with deviations that may affect the efficacy of the trial therapy was performed if > 10% of patients:

- Did not have the intended disease or indication or
- Did not receive any randomised therapy.

A stratified log-rank test was repeated using the investigator RECIST data, using the same ties and stratification factors as described for the primary analysis of PFS. The HR and 95% CI was presented using stratified Cox Proportional Hazard model.

- Overall survival (OS)

Any patient not known to have died at the time of analysis was censored based on the last recorded date on which the patient was known to be alive.

OS of SoC + D (Arm B) versus SoC (Arm A) and SoC + D + O (Arm C) versus SoC (Arm A) was analysed using the same methodology and model as that used for the analysis of PFS. The number and proportion of patients alive at 6 monthly intervals from randomisation (6, 12, 18, 24, etc) was summarised (using the KM analysis) and presented by treatment group. A KM plot of OS was presented by treatment arm.

The HR and its confidence interval was estimated using a stratified Cox Proportional Hazards model (with ties = Efron and the stratification factors as strata) and the CI calculated using a profile likelihood approach.

OS sensitivity analysis

Sensitivity analyses for OS examined the censoring patterns to rule out attrition bias with regard to the treatment comparisons and was achieved by a Kaplan-Meier plot of time to censoring where the censoring indicator of OS was reversed.

The number of patients prematurely censored was summarised by treatment arm. A patient was defined as prematurely censored if their survival status was not defined at the data cut-off (DCO).

In addition, duration of follow-up which was defined as time from randomisation to the date of death (i.e. overall survival) or to the date of censoring (date last known to be alive) for 64 censored patients regardless of treatment arm was summarised using medians in all patients.

Planned analyses

The timing of planned efficacy analyses is summarised in the below table.

Table 12 Planned PFS and OS Analyses

Analysis	Event Driven Assumption (per protocol)	DCO
Primary PFS/First interim OS analysis	~299 PFS events (~64% maturity) for the SoC + D vs SoC comparison and ~281 PFS events (~60% maturity) for the SoC + D + O vs SoC comparison	DCO1: 12 April 2023
Second interim OS analysis	~244 OS events (~52% maturity) for the SoC + D vs SoC comparison and ~244 OS events (~52% maturity) for the SoC + D + O vs SoC comparison	DCO2: ~1H 2025 [a]
Final OS analysis	~280 OS events (~60% maturity) for the SoC + D vs SoC comparison and ~280 OS events (~60% maturity) for the SoC + D + O vs SoC comparison	DCO3: ~1H 2026 [a]

a. DCO2 and DCO 3 timings are based on the latest event projections (as of July 2023) and are subject to change.

DCO = data cut-off; H = half; PFS = progression free survival; OS = overall survival. SoC = standard of care; SoC + D = durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance; vs = versus.

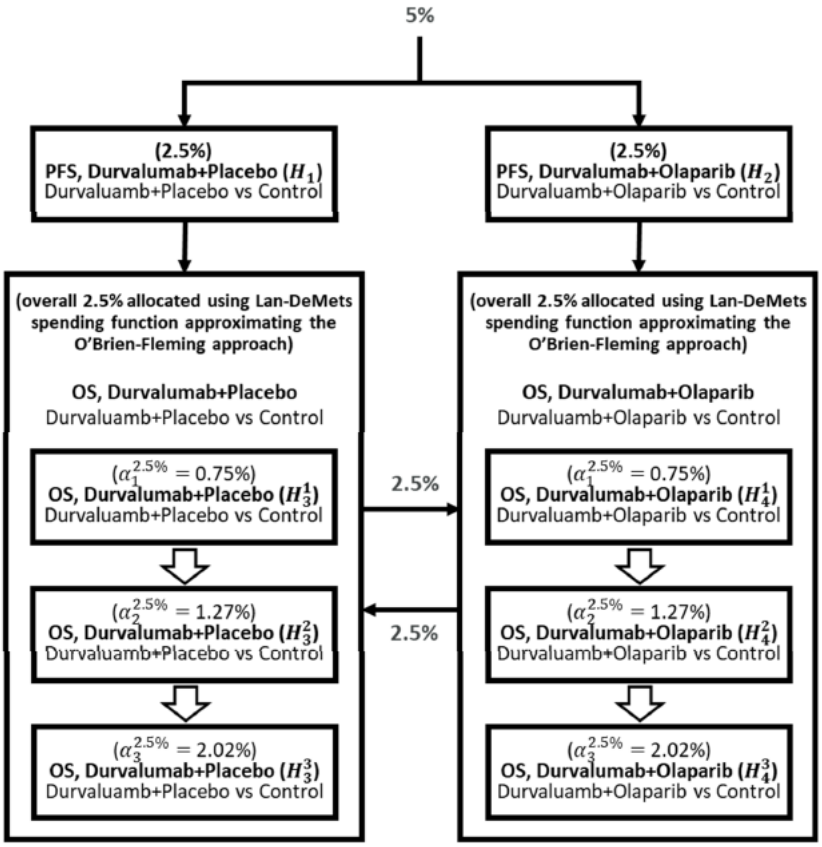
A futility analysis of PFS for the comparison of the SoC + D (Arm B) versus SoC (Arm A) and the SoC + D + O (Arm C) versus SoC (Arm A) was performed approximately 2-months post-last subject randomised (LSR), and when a minimum of 50% of the target number of PFS events for each comparison had occurred (150 of 299 target events across the SoC + D (Arm B) and SoC (Arm A) arms, and 141 of 281 target events across the SoC + D + O (Arm C) and SoC (Arm A) arms) (approximately 25 months after the first patient had been randomised). The boundary for declaring futility and dropping an experimental arm was observing a HR>1.15. At the time of the futility analysis, as the futility boundary was not met for either comparison, the IDMC recommended the study to continue unchanged.

Multiplicity

In order to control the type I error at 5% (2-sided), a multiple testing procedure (MTP) with a gatekeeping strategy was used across the key endpoints (PFS and OS) and treatment comparisons of interest (SoC + D (Arm B) versus SoC (Arm A) and SoC + D + O (Arm C) versus SoC (Arm A)). If the higher level null hypothesis in the MTP was rejected for superiority, the following hypothesis were then to be tested as shown in the figure below.

OS was to be tested at 2 interims and a final time-point. The alpha level allocated to OS was to be controlled at the interim and primary time points by using the Lan DeMets (Lan and DeMets 1983) spending function that approximates an O'Brien Fleming approach, where the alpha level applied at the interim depends upon the proportion of information available. Note: If any interim analysis or primary analysis was statistically significant, the overall alpha (two-sided) was to be allocated to the next level. If the interim results did not meet the criterion of stopping for superiority for a given hypothesis, then follow-up would have continued until the final target number of OS events for that comparison had been observed, following which the hypothesis was retested. If the null hypothesis was then rejected, subsequent testing was to be continued hierarchically.

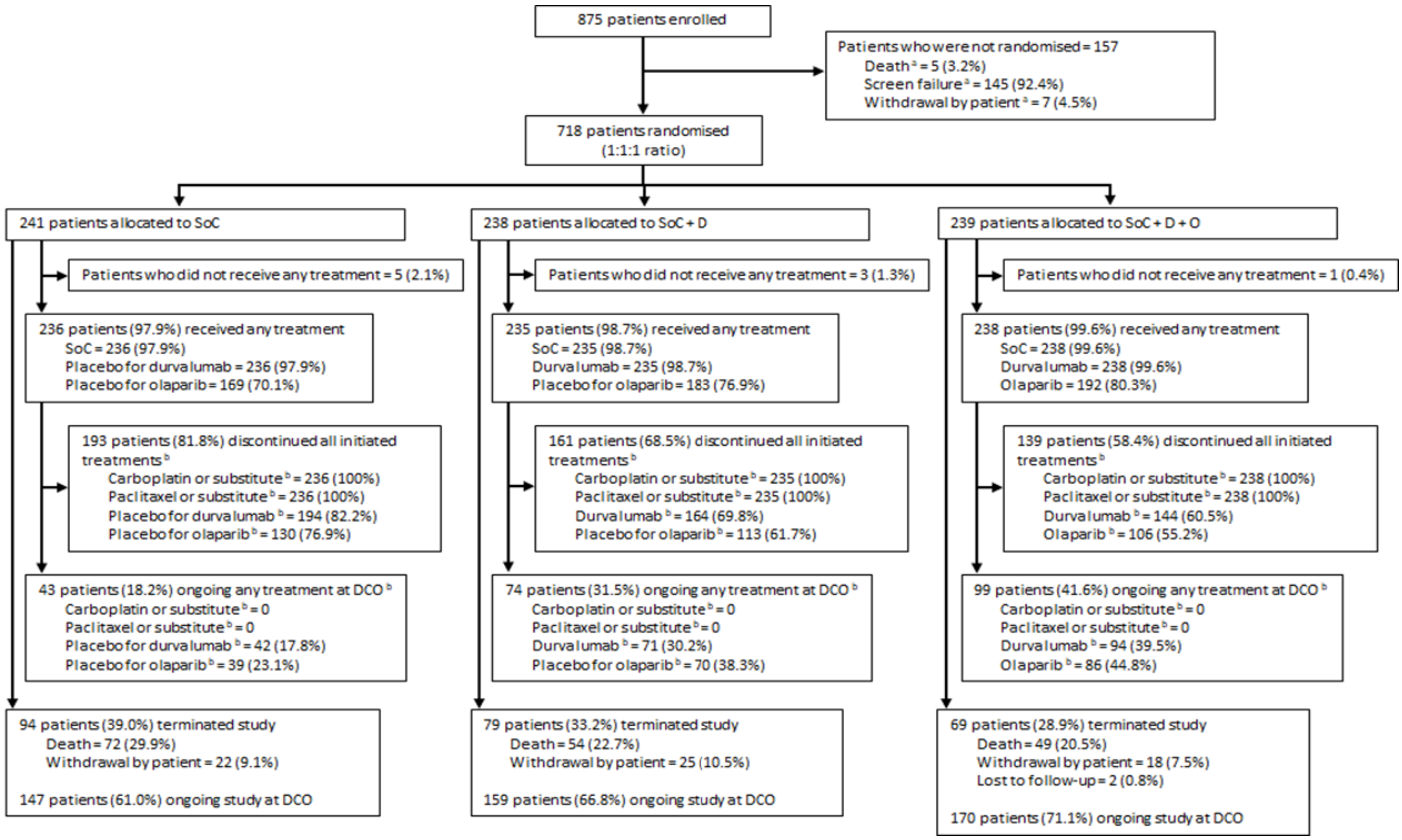
Figure 2 Illustration of multiplicity testing strategy



Results

Participant flow

Figure 3 Patient Disposition (All patients)



Percentages were calculated from number of patients who were not randomised.

B Percentages were calculated from number of patients who received the treatment.

CSR = Clinical Study Report; DCO = Data cut-off; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Recruitment

This is a global study with 718 patients randomised in 179 study centres across 22 countries: Asia (China, Hong Kong, India, Japan, Singapore, and South Korea) and rest of the world (RoW) (Australia, Belgium, Brazil, Canada, Columbia, Estonia, Germany, Greece, Hungary, Israel, Lithuania, Mexico, Poland, Russian Federation, Spain, and the United States).

At the time of the DCO date of 12 April 2023, all patients had discontinued platinum-based chemotherapy as per protocol. The most common reason for discontinuation of durvalumab/placebo and olaparib/placebo was objective disease progression (see below table).

Table 13: Patient Disposition (All Patients)

	Number (%) of patients			
	SoC	SoC + D	SoC + D + O	Total
Patients enrolled [a]	-	-	-	875
Patients randomised	241 (100)	238 (100)	239 (100)	718 (100)
Patients who were not randomised [b]	-	-	-	157
Screen failure	-	-	-	145 (92.4)
Withdrawal by patient	-	-	-	7 (4.5)
Death	-	-	-	5 (3.2)
Due to COVID-19 pandemic	-	-	-	0
Full analysis set	241 (100)	238 (100)	239 (100)	718 (100)
Patients who received any treatment [c]	236 (97.9)	235 (98.7)	238 (99.6)	709 (98.7)
Patients who received SoC	236 (97.9)	235 (98.7)	238 (99.6)	709 (98.7)
Patients who received durvalumab/placebo	236 (97.9)	235 (98.7)	238 (99.6)	709 (98.7)
Patients who received olaparib/placebo	169 (70.1)	183 (76.9)	192 (80.3)	544 (75.8)
Patients who did not receive any treatment [c]	5 (2.1)	3 (1.3)	1 (0.4)	9 (1.3)
Patients ongoing durvalumab/placebo at DCO [d]	42 (17.8)	71 (30.2)	94 (39.5)	207 (29.2)
Patients who discontinued treatment of durvalumab/placebo [d]	194 (82.2)	164 (69.8)	144 (60.5)	502 (70.8)

	Number (%) of patients			
	SoC	SoC + D	SoC + D + O	Total
Objective disease progression	143 (60.6)	113 (48.1)	104 (43.7)	360 (50.8)
Adverse event	17 (7.2)	26 (11.1)	23 (9.7)	66 (9.3)
Patient decision	8 (3.4)	11 (4.7)	9 (3.8)	28 (3.9)
Other	10 (4.2)	12 (5.1)	4 (1.7)	26 (3.7)
Clinical deterioration	15 (6.4)	1 (0.4)	3 (1.3)	19 (2.7)
Development of study-specific discontinuation criteria	1 (0.4)	0	0	1 (0.1)
Patient lost to follow-up	0	0	1 (0.4)	1 (0.1)
Severe non-compliance to protocol	0	1 (0.4)	0	1 (0.1)
Due to COVID-19 pandemic	0	0	0	0
Patients ongoing olaparib/placebo at DCO [d]	39 (23.1)	70 (38.3)	86 (44.8)	195 (35.8)
Patients who discontinued treatment of olaparib/placebo [d, e]	130 (76.9)	113 (61.7)	106 (55.2)	349 (64.2)
Objective disease progression	109 (64.5)	94 (51.4)	73 (38.0)	276 (50.7)
Adverse event	4 (2.4)	10 (5.5)	21 (10.9)	35 (6.4)
Patient decision	4 (2.4)	5 (2.7)	7 (3.6)	16 (2.9)
Clinical deterioration	10 (5.9)	1 (0.5)	2 (1.0)	13 (2.4)
Other	2 (1.2)	3 (1.6)	2 (1.0)	7 (1.3)
Development of study-specific discontinuation criteria	1 (0.6)	0	0	1 (0.2)
Patient lost to follow-up	0	0	1 (0.5)	1 (0.2)
Due to COVID-19 pandemic	0	0	0	0
Patients ongoing carboplatin or substitute at DCO [d]	0	0	0	0
Patients who discontinued treatment of carboplatin or substitute [d]	236 (100)	235 (100)	238 (100)	709 (100)
Maximum cycle of chemotherapy reached	190 (80.5)	189 (80.4)	193 (81.1)	572 (80.7)
Adverse event	20 (8.5)	18 (7.7)	18 (7.6)	56 (7.9)
Objective disease progression	9 (3.8)	13 (5.5)	18 (7.6)	40 (5.6)
Other	11 (4.7)	10 (4.3)	5 (2.1)	26 (3.7)
Patient decision	4 (1.7)	4 (1.7)	2 (0.8)	10 (1.4)
Clinical deterioration	2 (0.8)	0	2 (0.8)	4 (0.6)
Severe non-compliance to protocol	0	1 (0.4)	0	1 (0.1)

	Number (%) of patients			
	SoC	SoC + D	SoC + D + O	Total
Due to COVID-19 pandemic	0	0	0	0
Patients ongoing paclitaxel or substitute at DCO [d]	0	0	0	0
Patients who discontinued treatment of paclitaxel or substitute [d]	236 (100)	235 (100)	238 (100)	709 (100)
Maximum cycle of chemotherapy reached	186 (78.8)	183 (77.9)	188 (79.0)	557 (78.6)
Adverse event	25 (10.6)	23 (9.8)	24 (10.1)	72 (10.2)
Objective disease progression	8 (3.4)	13 (5.5)	18 (7.6)	39 (5.5)
Other	11 (4.7)	11 (4.7)	4 (1.7)	26 (3.7)
Patient decision	4 (1.7)	4 (1.7)	2 (0.8)	10 (1.4)
Clinical deterioration	2 (0.8)	0	2 (0.8)	4 (0.6)
Severe non-compliance to protocol	0	1 (0.4)	0	1 (0.1)
Due to COVID-19 pandemic	0	0	0	0
Patients ongoing any treatment at DCO [d]	43 (18.2)	74 (31.5)	99 (41.6)	216 (30.5)
Patients who discontinued all initiated treatments (carboplatin, paclitaxel, durvalumab/placebo, and olaparib/placebo) [d]	193 (81.8)	161 (68.5)	139 (58.4)	493 (69.5)
Patients ongoing study at DCO	147 (61.0)	159 (66.8)	170 (71.1)	476 (66.3)
Patients who terminated study [f]	94 (39.0)	79 (33.2)	69 (28.9)	242 (33.7)
Death	72 (29.9)	54 (22.7)	49 (20.5)	175 (24.4)
Withdrawal by patient	22 (9.1)	25 (10.5)	18 (7.5)	65 (9.1)
Lost to follow-up	0	0	2 (0.8)	2 (0.3)
Due to COVID-19 pandemic	0	0	0	0
Patients who started Maintenance Phase [g]	169 (70.1)	183 (76.9)	192 (80.3)	544 (75.8)
Patients who received durvalumab/placebo in Maintenance Phase	169 (70.1)	178 (74.8)	190 (79.5)	537 (74.8)
Patients who discontinued durvalumab/placebo in Maintenance Phase	130 (53.9)	110 (46.2)	102 (42.7)	342 (47.6)
Patients who did not start Maintenance phase but started durvalumab/placebo at maintenance dose [h]	16 (6.6)	6 (2.5)	10 (4.2)	32 (4.5)

[a] Informed consent received.

[b] Percentages were calculated from number of patients who were not randomised.

[c] Any of the following treatments: durvalumab/placebo, olaparib/placebo, carboplatin or substitute, or paclitaxel or substitute.

[d] Percentages were calculated from number of patients who received the treatment.

[e] Note: Olaparib was to be administered in the Maintenance Phase only (per the CSP, see Appendix 16.1.1).

[f] Represents patients' disposition status at time of discontinuation from study. Some patients subsequently had vital status information collected from publicly available resources (where it was possible to do so under applicable local laws) for the purpose of the OS analysis, as detailed in the CSP (see Appendix 16.1.1).

[g] Received at least one dose of olaparib/placebo.

[h] Patients who continued durvalumab/placebo after the end of chemotherapy treatment; however, as they did not initiate olaparib/placebo they were not included in the 'Maintenance Phase' (see Section 9.8.2).

COVID-19 = Coronavirus disease 2019; CSP = Clinical Study Protocol; DCO = Data cut-off; OS = Overall survival; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Conduct of the study

Protocol amendments

The original clinical study protocol (CSP) was dated 21 October 2019. The most current version of the CSP is version 6.0 (dated 24 January 2023). All CSP amendments were made prior to the DCO date of the primary analysis of PFS (12 April 2023), and CSP Version 5.0 (dated 07 June 2022) was current at the DCO date. The most relevant changes have been extracted the CSR and are summarised in the adapted table below:

Table 14 Protocol Amendments Related to Changes in Study Conduct

Amendment Number/Date	Key details of amendment	Main reason(s) for amendment
Original CSP, 21 October 2019		
Amendments made *before* the start of patient recruitment		
Version 2.0, 28 October 2019	Exploratory objective added for the comparison between durvalumab + olaparib (Arm C) and durvalumab + placebo (Arm B). (Sections 8, 9.7, and 9.8.1.2)	To highlight that an exploratory analysis of the comparison between the durvalumab + olaparib and durvalumab + placebo arms would be undertaken.
	Updated Exclusion Criterion 6: Uncontrolled hypertension defined as systolic blood pressure > 160 mmHg and/or diastolic blood pressure > 100 mmHg. (Section 9.3.2)	To provide a clear definition.
Amendments made *after* the start of patient recruitment		
Amendment Number/Date	**Key details of amendment**	**Main reason(s) for amendment**
Version 5.0 *, 07 June 2022	Objectives were updated to include the PFS comparison of Arm C (durvalumab in combination with platinum-based chemotherapy followed by maintenance durvalumab in combination with olaparib) versus Arm A (platinum-based chemotherapy) as primary. The formal statistical analysis method, sample size assumptions, and timing of primary analysis of PFS were revised. The multiplicity testing strategy was amended to enable the 2 key PFS comparisons of interest (ie, Arm B versus Arm A, and Arm C versus Arm A) to be tested independently with an equal alpha split of 2.5% assigned to each comparison of interest. In addition, based on external data, an assumed 3 months lag-effect for durvalumab, when administered in combination with chemotherapy, was taken into account. (Sections 8, 9.7, 9.8.1, 9.8.4, and 9.8.5)	To enable the 2 key PFS comparison of interest (ie, Arm B versus Arm A and Arm C versus Arm A) to be tested independently. In addition, the statistical sections were updated to incorporate the impact of the lag effect due to evolving data on durvalumab (and other immunotherapies agents) from external trials in multiple tumour settings, including CASPIAN (NCT03043872; Paz-Ares et al 2019), POSEIDON (NCT03164616; Johnson et al 2021), and TOPAZ-1 (NCT03875235; Oh et al 2022), which had demonstrated the potential for a lag/delay in the treatment effect of immunotherapies when administered in combination with chemotherapy.
	Progression-free survival futility boundary and analysis timepoint were updated. (Sections 6.3, 9.8.6, and 9.8.7)	The futility boundary and timing were updated to ensure sufficient data maturity and follow-up after recruitment completion, to mitigate against the increased risk of incorrectly stopping the study for futility, given the potential for a lag/delay in the treatment effect.
	Text was updated to reflect pneumonitis was reclassified from an important potential risk to a potential risk for olaparib. (Section 9.8.3.2)	To align with the latest information on olaparib in the IB Edition 21 update.

* This CSR provides data from the global population (DCO of 12 April 2023) at which time CSP Version 5.0 was in effect (see Appendix 16.1.1). All patients in the global population were enrolled under CSP Version 5.0 (see Appendix 16.1.1).

Changes to planned analyses

The original SAP was dated 6 March 2020. The most relevant changes are shown in the table below.

Table 15 Changes to Planned Analyses

Key details of change (Section of this report affected)	Reason for change	SAP amendment?
Changes made before unblinding of study data (Date of unblinding: 12 May 2023)		
SAP Version 2.0, 01 February 2022		
Derivation of primary or secondary endpoints		
PD-L1 cut points were defined as a tumour area positivity score ≥ 1%. (No relevant sections affected in the CSR)	To specify PD-L1 cut points for the subgroup analysis.	YES
SAP Version 3.0, 29 June 2022		
Derivation of primary or secondary endpoints		
Objectives were updated to include the PFS comparison of Arm C (durvalumab in combination with platinum-based chemotherapy followed by maintenance durvalumab in combination with olaparib) versus Arm A (platinum-based chemotherapy) as primary. (Sections 8, 9.7, 9.8.1, 9.8.4, 9.8.5, and 11.1.1)	To enable the 2 key PFS comparisons of interest (ie, Arm B versus Arm A and Arm C versus Arm A) to be tested independently.	YES
Statistical analysis method for the primary or secondary endpoints		
The formal statistical analysis method, sample size assumptions, and timing of primary analysis of PFS was revised. The multiplicity testing strategy was amended to enable the 2 key PFS comparisons of interest (ie, Arm B versus Arm A and Arm C versus Arm A) to be tested independently with an equal alpha split of 2.5% assigned to each comparison of interest. In addition, based on external data, an assumed 3-month lag-effect for durvalumab, when administered in combination with chemotherapy, was taken into account. (Sections 9.8.1, 9.8.4, 9.8.5, and 11.1.1)	To incorporate the impact of the lag effect due to evolving data on durvalumab (and other immunotherapies agents) from external trials in multiple tumour settings, including CASPIAN (NCT03043872; Paz-Ares et al 2019), POSEIDON (NCT03164616; Johnson et al 2021) and TOPAZ-1 (NCT03875235; Oh et al 2022), which had demonstrated the potential for a lag/delay in the treatment effect of immunotherapies when administered in combination with chemotherapy.	YES

Key details of change (Section of this report affected)	Reason for change	SAP amendment?
Progression-free survival futility boundary and analysis timepoint were updated. (Sections 9.8.6 and 9.8.7)	The futility boundary and timing were updated to ensure sufficient data maturity and follow-up after recruitment completion, to mitigate against the increased risk of incorrectly stopping the study for futility, given the potential for a lag/delay in the treatment effect.	YES
SAP Version 4.0, 24 November 2022		
Derivation of primary or secondary endpoints		
The planned tumour predictive biomarker subgroup analysis was updated to include HRRm status (HRRm versus non-HRRm versus Unknown), replacing the previously specified HRD status subgroup analysis. (Sections 11.1.1.4 and 11.1.2)	Within the endometrial cancer setting, cut-off(s) for tumour HRD status measure of genomic instability relevant tests were not analytically or clinically defined. Instead, this subgroup analysis was to focus on mutations in genes involved in the HRR pathway (termed HRR genes).	YES

Other		
Correction was made to the estimated timing of the second interim analysis for OS, which was predicted to occur 51 months after first patient randomised (but was incorrectly stated to occur 51 months after last patient randomised). (Section 9.8.6)	Typographical error.	YES

Key details of change (Section of this report affected)	Reason for change	SAP amendment?
A post-hoc subgroup analysis performed by *BRCA*m status. (No relevant sections affected in the CSR)	To support regulatory agency requests to assess efficacy by *BRCA*m status. This analysis will be reported separately outside the CSR.	NO
Post-hoc sensitivity analyses of PFS were performed, accounting for patients who received another anticancer therapy prior to progression or death. (Section 11.1.1.3)	To address FDA requests for additional sensitivity analysis of PFS, accounting for patients who received another anticancer therapy prior to progression or death.	NO
A global interaction test sensitivity analysis to include factors (such as PD-L1) that were excluded due to the unknown category having insufficient events. (Section 11.1.1.4)	To ensure a global interaction test was performed including all factors, where possible.	NO
Post-hoc sensitivity analyses of PFS using a 4-component, unstratified Max-Combo test and an unstratified Restricted Mean Survival Time analysis of an area-under-the-curve approach were undertaken (Fleming and Harrington 1991, Karrison 2016). (Section 11.7.1)	To address FDA requests for additional sensitivity analysis to assess non-proportional hazards for PFS.	NO

ADA = Anti-drug antibody; AE = Adverse event; AEPI = Adverse event of possible interest; AESI = Adverse event of special interest; *BRCA*m = Breast cancer susceptibility gene 1 or 2 mutation; CA-125 = Cancer antigen 125; COVID-19 = Coronavirus disease 2019; CPH = Cox Proportional Hazards; CRF = Case Report Form; CSP = Clinical Study Protocol; CSR = Clinical Study Report; EORTC QLQ-EN24 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Endometrial Cancer Module; FDA = Food and Drug Administration; FIGO = Federation Internationale de Gynecologie et d'Obstetrique; HRD = Homologous recombination deficiency; HRR = Homologous recombination repair; HRRm = Homologous recombination repair mutation; imAE = Immune-mediated adverse event; IP = Investigational product; ITT = Intention-to-treat; MRI = Magnetic resonance imaging; NA = Not applicable; OS = Overall survival; PD-L1 = Programmed cell death ligand 1; PFS = Progression-free survival; PK = Pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumours; SAP = Statistical Analysis Plan; TDT = Time from randomisation to discontinuation of treatment or death; TEAE = Treatment-emergent adverse event.

Protocol deviations

Table 16 Important Protocol Deviations (FAS)

Important protocol deviation [a]	Number (%) of patients			
	SoC (N = 241)	SoC + D (N = 238)	SoC + D + O (N = 239)	Total (N = 718)
Number of patients with at least one important deviation	22 (9.1)	33 (13.9)	24 (10.0)	79 (11.0)
Received prohibited concomitant medications (including other anti-cancer therapy or chronic use of immunosuppressive medications) as outlined in Table 7 Section 6.5.2 of the protocol (see Appendix 16.1.1)	6 (2.5)	10 (4.2)	8 (3.3)	24 (3.3)
Patient randomised and not met IC #5 of being naive to first line systemic anti-cancer treatment	4 (1.7)	4 (1.7)	4 (1.7)	12 (1.7)
Patients randomised and received their randomised study treatment at an incorrect dose or who received an alternative study treatment to that which they were randomised [b]	1 (0.4)	5 (2.1)	5 (2.1)	11 (1.5)
Patients randomised in IVRS but did not receive any study drug treatment	5 (2.1)	3 (1.3)	1 (0.4)	9 (1.3)
Non-compliance with patient withdrawal criteria defined in the protocol (ie, patient continued in study but should have been withdrawn)	0	2 (0.8)	4 (1.7)	6 (0.8)
Patient was randomised and did not meet IC #11 adequate organ and bone marrow function per lab criteria	2 (0.8)	3 (1.3)	0	5 (0.7)
Patient randomised and did not meet IC #4 of having endometrial cancer in newly diagnosed Stage III disease or newly diagnosed Stage IV disease or recurrence of disease	1 (0.4)	1 (0.4)	2 (0.8)	4 (0.6)
Main ICF missing patient or Investigator signatures and/or signature dates (including different signature dates and/or illogical dates)	1 (0.4)	2 (0.8)	0	3 (0.4)
Patient was randomised and did not meet IC #12 measured creatinine clearance > 51 mL/min	1 (0.4)	1 (0.4)	1 (0.4)	3 (0.4)
Main ICF not signed before project specific assessments or procedures commenced	1 (0.4)	1 (0.4)	0	2 (0.3)

Important protocol deviation [a]	Number (%) of patients			
	SoC (N = 241)	SoC + D (N = 238)	SoC + D + O (N = 239)	Total (N = 718)
Patient randomised and did not meet IC #6 of having an available and suitable FFPE tumour sample from the locoregional or a metastatic site for MMR status evaluation	0	1 (0.4)	1 (0.4)	2 (0.3)
Baseline RECIST scan > 42 days before randomisation	0	1 (0.4)	0	1 (0.1)
Patient randomised and did not meet IC #3 of having histologically confirmed diagnosis of epithelial endometrial carcinoma	0	1 (0.4)	0	1 (0.1)
Patient randomised and met EC #5 of having protocol specified active or prior documented autoimmune or inflammatory disorders apart from listed exceptions	0	0	1 (0.4)	1 (0.1)
Patient randomised and met EC # 6 of having uncontrolled intercurrent illness including but not limited to noted illnesses	1 (0.4)	0	0	1 (0.1)
Patient randomised and did not meet IC #7 of having ECOG performance status of 0 or 1 within 7 days of starting study treatment	0	1 (0.4)	0	1 (0.1)
Number of patients with at least one COVID-19 related important deviation	0	0	0	0

[a] Important deviations before the start of any treatment and during any treatment.

[b] All patients correctly received the study treatment to which they were randomised; all 11 occurrences of this important protocol deviation were due to patients receiving their randomised treatment at an incorrect dose for at least one treatment cycle (see Appendix 16.2.2, Appendix 16.2.5.1, Appendix 16.2.5.2, and Appendix 16.2.5.3).

The same patient may have had more than one important protocol deviation.

COVID-19 = Coronavirus disease 2019; EC = Exclusion Criterion; ECOG = Eastern Cooperative Oncology Group; FAS = Full Analysis Set; FFPE = Formalin-fixed paraffin-embedded; IC = Inclusion Criterion; ICF = Informed Consent Form; IVRS = Interactive voice response system; MMR = Mismatch repair; N = Total number of patients; RECIST = Response Evaluation Criteria in Solid Tumours; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

The COVID-19 related protocol deviations are reflected as disruptions (see below table).

Table 17 Summary of COVID-19 Study Disruptions (FAS)

	Number (%) of patients			
	SoC (N = 241)	SoC + D (N = 238)	SoC + D + O (N = 239)	Total (N = 718)
Patients randomised prior to the start of COVID-19 pandemic	0	0	0	0
Patients randomised post start of COVID-19 pandemic	241 (100)	238 (100)	239 (100)	718 (100)
Patients with ≥ 1 disruption due to COVID-19 pandemic	18 (7.5)	25 (10.5)	33 (13.8)	76 (10.6)
Patients with visit impacted	15 (6.2)	23 (9.7)	30 (12.6)	68 (9.5)
Patients with study drug impacted	9 (3.7)	7 (2.9)	11 (4.6)	27 (3.8)

Any date before 11 March 2020 was considered prior to the start of the COVID-19 pandemic. Any date on or following this time was considered post start of the COVID-19 pandemic.

Patients may have had more than one COVID-19 study disruption.

Percentages were calculated using number of patients in each treatment group (N) as the denominator.

COVID-19 = Coronavirus disease 2019; FAS = Full Analysis Set; N = Total number of patients; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Baseline data

Demographics

Table 18 Demographic and Patient Characteristics (FAS; DCO 12 April 2023)

Characteristic	Number (%) of patients			
	SoC (N = 241)	SoC + D (N = 238)	SoC + D + O (N = 239)	Total (N = 718)
Age (years)				
N	241	238	239	718
Mean (SD)	62.1 (10.36)	63.3 (9.82)	62.4 (9.90)	62.6 (10.03)
Median (Min-Max)	64.0 (31-85)	64.0 (22-84)	63.0 (27-86)	64.0 (22-86)
Age group (years), n (%)				
< 65	124 (51.5)	122 (51.3)	135 (56.5)	381 (53.1)
≥ 65	117 (48.5)	116 (48.7)	104 (43.5)	337 (46.9)
Race, n (%)				
White	143 (59.3)	136 (57.1)	133 (55.6)	412 (57.4)
Asian	73 (30.3)	72 (30.3)	70 (29.3)	215 (29.9)
Black or African American	10 (4.1)	11 (4.6)	14 (5.9)	35 (4.9)
Other	10 (4.1)	8 (3.4)	12 (5.0)	30 (4.2)
American Indian or Alaska native	0	6 (2.5)	6 (2.5)	12 (1.7)
Native Hawaiian or Other Pacific Islander	2 (0.8)	0	1 (0.4)	3 (0.4)
Not reported	3 (1.2)	5 (2.1)	3 (1.3)	11 (1.5)

Characteristic	Number (%) of patients			
	SoC (N = 241)	SoC + D (N = 238)	SoC + D + O (N = 239)	Total (N = 718)
Ethnic group, n (%)				
Not Hispanic or Latino	218 (90.5)	208 (87.4)	206 (86.2)	632 (88.0)
Hispanic or Latino	20 (8.3)	28 (11.8)	32 (13.4)	80 (11.1)
Missing	3 (1.2)	2 (0.8)	1 (0.4)	6 (0.8)
Time from initial diagnosis to randomisation (weeks) – Newly diagnosed patients				
N	114	113	112	339
Mean (SD)	8.8 (4.49)	9.8 (6.11)	10.1 (14.02)	9.6 (9.17)
Median (Min-Max)	7.7 (3-29)	8.3 (3-35)	7.6 (3-150)	7.9 (3-150)
Time from initial diagnosis to randomisation (weeks) – Recurrent patients				
N	127	125	127	379
Mean (SD)	178.8 (149.43)	166.8 (112.17)	161.3 (131.60)	169.0 (131.90)
Median (Min-Max)	129.1 (8-804)	132.0 (7-556)	120.9 (24-909)	126.1 (7-909)
Time from recent progression to randomisation (weeks) – Recurrent patients				
N	127	124	127	378
Mean (SD)	8.3 (9.98)	8.4 (8.10)	8.0 (5.86)	8.2 (8.13)
Median (Min-Max)	6.3 (0-87)	6.9 (0-59)	6.9 (1-34)	6.7 (0-87)

Note: Disease status (recurrent versus newly diagnosed) was as collected on the eCRF.

CSR = Clinical Study Report; DCO = Data cut-off; eCRF = Electronic Case Report Form; FAS = Full Analysis Set; Max = Maximum; Min= Minimum; N = Total number of patients; n = Number of patients included in analysis; SD = Standard deviation; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Baseline disease characteristics

Table 19 Disease Characteristics, Extent at Baseline/Primary Diagnosis, and Baseline Biomarker Characteristics (FAS; DCO 12 April 2023)

Characteristic/extent	Number (%) of patients			
	SoC (N = 241)	SoC + D (N = 238)	SoC + D + O (N = 239)	Total (N = 718)
ECOG performance status				
(0) Normal activity	156 (64.7)	156 (65.5)	166 (69.5)	478 (66.6)
(1) Restricted activity	85 (35.3)	81 (34.0)	73 (30.5)	239 (33.3)
(2) In bed ≤ 50% of the time	0	1 (0.4)	0	1 (0.1)
Histology type [a]				
Endometrioid	139 (57.7)	141 (59.2)	152 (63.6)	432 (60.2)
Serous	54 (22.4)	58 (24.4)	42 (17.6)	154 (21.4)
Carcinosarcoma	21 (8.7)	12 (5.0)	18 (7.5)	51 (7.1)
Mixed, Epithelial	11 (4.6)	9 (3.8)	9 (3.8)	29 (4.0)

Characteristic/extent	Number (%) of patients			
	SoC (N = 241)	SoC + D (N = 238)	SoC + D + O (N = 239)	Total (N = 718)
Other	6 (2.5)	9 (3.8)	5 (2.1)	20 (2.8)
Clear Cell	7 (2.9)	4 (1.7)	8 (3.3)	19 (2.6)
Undifferentiated	3 (1.2)	4 (1.7)	5 (2.1)	12 (1.7)
Mucinous	0	1 (0.4)	0	1 (0.1)
Tumour grade [a]				
Well differentiated (G1)	57 (23.7)	51 (21.4)	51 (21.3)	159 (22.1)
Moderately differentiated (G2)	63 (26.1)	66 (27.7)	73 (30.5)	202 (28.1)
Poorly differentiated (G3)	96 (39.8)	97 (40.8)	90 (37.7)	283 (39.4)
Unassessable (GX)	24 (10.0)	24 (10.1)	24 (10.0)	72 (10.0)
Missing	1 (0.4)	0	1 (0.4)	2 (0.3)
FIGO stage [a]				
Stage IA	32 (13.3)	40 (16.8)	33 (13.8)	105 (14.6)
Stage IB	32 (13.3)	26 (10.9)	31 (13.0)	89 (12.4)
Stage II	13 (5.4)	12 (5.0)	9 (3.8)	34 (4.7)
Stage IIIA	10 (4.1)	8 (3.4)	14 (5.9)	32 (4.5)
Stage IIIB	4 (1.7)	7 (2.9)	7 (2.9)	18 (2.5)
Stage IIIC	28 (11.6)	35 (14.7)	24 (10.0)	87 (12.1)
Stage IIIC1	18 (7.5)	13 (5.5)	15 (6.3)	46 (6.4)
Stage IIIC2	10 (4.1)	22 (9.2)	9 (3.8)	41 (5.7)
Stage IVA	0	0	0	0
Stage IVB	120 (49.8)	110 (46.2)	120 (50.2)	350 (48.7)
Missing	2 (0.8)	0	1 (0.4)	3 (0.4)
Recurrence of earlier cancer				
Yes	127 (52.7)	125 (52.5)	127 (53.1)	379 (52.8)
No	114 (47.3)	113 (47.5)	112 (46.9)	339 (47.2)
Baseline overall disease classification				
Metastatic [b]	206 (85.5)	201 (84.5)	193 (80.8)	600 (83.6)
Locally advanced [c]	22 (9.1)	25 (10.5)	29 (12.1)	76 (10.6)
Missing	13 (5.4)	12 (5.0)	17 (7.1)	42 (5.8)
MMR per IVRS [d]				
Proficient	192 (79.7)	192 (80.7)	191 (79.9)	575 (80.1)
Deficient	49 (20.3)	46 (19.3)	48 (20.1)	143 (19.9)
Debulking surgery history				
Yes	202 (83.8)	205 (86.1)	207 (86.6)	614 (85.5)
No	39 (16.2)	33 (13.9)	32 (13.4)	104 (14.5)
Unknown	0	0	0	0

Characteristic/extent	Number (%) of patients			
	SoC (N = 241)	SoC + D (N = 238)	SoC + D + O (N = 239)	Total (N = 718)
Prior chemotherapy				
Yes	51 (21.2)	51 (21.4)	54 (22.6)	156 (21.7)
No	190 (78.8)	187 (78.6)	185 (77.4)	562 (78.3)
PD-L1 [e]				
Positive	163 (67.6)	170 (71.4)	150 (62.8)	483 (67.3)
Negative	75 (31.1)	61 (25.6)	82 (34.3)	218 (30.4)
Unknown	3 (1.2)	7 (2.9)	7 (2.9)	17 (2.4)
HRR mutation				
HRRm	32 (13.3)	26 (10.9)	39 (16.3)	97 (13.5)
Non-HRRm	132 (54.8)	138 (58.0)	141 (59.0)	411 (57.2)
Unknown [f]	77 (32.0)	74 (31.1)	59 (24.7)	210 (29.2)
BRCA mutation [g]				
BRCAm	15 (6.2)	11 (4.6)	15 (6.3)	41 (5.7)
non-*BRCAm*	149 (61.8)	153 (64.3)	165 (69.0)	467 (65.0)
Unknown [f]	77 (32.0)	74 (31.1)	59 (24.7)	210 (29.2)

a. Pathology-related disease characteristics were collected at the time of primary diagnosis of disease under investigation.

b. Metastatic disease - patient had any metastatic site of disease.

c. Locally advanced - patient had only locally advanced sites of disease.

d. Note: 2 patients with "unknown" MMR status per central laboratory were randomised as "deficient" per IVRS based on local testing. Two additional patients were mis-stratified in IVRS (one patient: dMMR per central laboratory was randomised as pMMR per IVRS; one patient: pMMR per central laboratory was randomised as dMMR per IVRS). For MMR status per central laboratory result, see Table 20, DUO-E CSR, Module 5.3.5.1.

e. The Ventana SP263 PD-L1 assay was used: PD-L1 positive samples were samples with PD-L1 expression with a tumour area positivity score ≥ 1%; PD L1 negative samples were samples with PD-L1 expression with a tumour area positivity score < 1%; and PD-L1 unknown samples were samples with PD-L1 expression not available either due to a test fail (unevaluable sample or assay failure) or sample slide out of cut-slide stability.

f. Retrospective testing of HRRm status used the FoundationOneCDx (F1CDx) tumour tissue NGS assay (FoundationOneCDx-P170019/S017). Per data on file, the unknown samples included 26 patients with a failed F1CDx assay test, 43 patients who withdrew consent before their sample was shipped for testing, and 141 patients whose HRRm testing could not be performed due to lack of sample availability (including all 36 patients enrolled from Mainland China where testing was not performed due to China HGR regulations).

g. The percentages are based on the FAS.

BRCA = Breast cancer susceptibility gene 1 or 2; *BRCAm* = Breast cancer susceptibility gene 1 or 2 mutation; CSP = Clinical Study Protocol; CSR = Clinical Study Report; DCO = Data cut-off; dMMR = Mismatch repair deficient; ECOG = Eastern Cooperative Oncology Group; eCRF = Electronic Case Report Form; F1CDx = FoundationOneCDx; FAS = Full Analysis Set; FIGO = Federation Internationale de Gynecologie et d'Obstetrique; G = Grade; HGR = Human genetic resources; HRR = Homologous recombination repair; HRRm = Homologous recombination repair related gene mutation; IVRS = Interactive voice response system; MMR = Mismatch repair; N = Total number of patients; NGS = Next-generation sequencing; PD-L1 = Programmed cell death ligand 1; pMMR = Mismatch repair proficient; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Prior anti-cancer therapy

Table 20 Most Frequently Received Prior Cancer Therapy (Frequency ⩾1% in Any Treatment Arm) (FAS)

Treatment modality/ Anti-cancer therapy [a]	Number (%) of patients			
	SoC (N = 241)	SoC + D (N = 238)	SoC + D + O (N = 239)	Total (N = 718)
Number of patients with prior cancer therapy	52 (21.6)	52 (21.8)	54 (22.6)	158 (22.0)
Cytotoxic chemotherapy	51 (21.2)	51 (21.4)	54 (22.6)	156 (21.7)
Carboplatin	41 (17.0)	43 (18.1)	48 (20.1)	132 (18.4)
Paclitaxel	42 (17.4)	40 (16.8)	43 (18.0)	125 (17.4)
Cisplatin	12 (5.0)	10 (4.2)	9 (3.8)	31 (4.3)
Doxorubicin	5 (2.1)	2 (0.8)	3 (1.3)	10 (1.4)
Docetaxel	2 (0.8)	3 (1.3)	2 (0.8)	7 (1.0)

[a] Therapies before start of study treatment.
Patients with multiple treatment in the same modality were counted only once in that modality.
WHODrug Global B3-format 09-2020.

FAS = Full Analysis Set; N = Total number of patients; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance; WHO = World Health Organization.

Baseline biomarker characteristics

Table 21 Baseline Biomarker Characteristics (FAS)

Biomarker	Number (%) of patients			
	SoC (N = 241)	SoC + D (N = 238)	SoC + D + O (N = 239)	Total (N = 718)
PD-L1 [a]				
Positive	163 (67.6)	170 (71.4)	150 (62.8)	483 (67.3)
Negative	75 (31.1)	61 (25.6)	82 (34.3)	218 (30.4)
Unknown	3 (1.2)	7 (2.9)	7 (2.9)	17 (2.4)
HRR mutation				
HRRm	32 (13.3)	26 (10.9)	39 (16.3)	97 (13.5)
ATM	11 (4.6)	16 (6.7)	16 (6.7)	43 (6.0)
BRCA2	5 (2.1)	8 (3.4)	9 (3.8)	22 (3.1)
BRCA1	10 (4.1)	3 (1.3)	7 (2.9)	20 (2.8)
CHEK1	2 (0.8)	5 (2.1)	4 (1.7)	11 (1.5)
CDK12	1 (0.4)	5 (2.1)	3 (1.3)	9 (1.3)
CHEK2	4 (1.7)	1 (0.4)	4 (1.7)	9 (1.3)
BARD1	2 (0.8)	0	4 (1.7)	6 (0.8)
BRIP1	0	4 (1.7)	2 (0.8)	6 (0.8)
RAD54L	3 (1.2)	0	2 (0.8)	5 (0.7)
PALB2	1 (0.4)	0	2 (0.8)	3 (0.4)
RAD51B	2 (0.8)	0	1 (0.4)	3 (0.4)
RAD51C	1 (0.4)	0	0	1 (0.1)
RAD51D	0	1 (0.4)	0	1 (0.1)
FANCL	0	0	0	0
Non-HRRm	132 (54.8)	138 (58.0)	141 (59.0)	411 (57.2)
Unknown [b]	77 (32.0)	74 (31.1)	59 (24.7)	210 (29.2)

[a] The Ventana SP263 PD-L1 assay was used: PD-L1 positive samples were samples with PD-L1 expression with a tumour area positivity score ≥ 1%; PD-L1 negative samples were samples with PD-L1 expression with a tumour area positivity score < 1%; and PD-L1 unknown samples were samples with PD-L1 expression not available either due to a test fail (unevaluable sample or assay failure) or sample slide out of cut-slide stability.

[b] Retrospective testing of HRRm status was by the FoundationOne® CDx tumour tissue NGS assay (FoundationOne® CDx-P170019/S017). Per data on file, the unknown samples included 26 patients with a failed FoundationOne® CDx assay test, 43 patients who withdrew consent before their sample was shipped for testing, and 141 patients whose HRRm testing could not be performed due to lack of sample availability (including all 36 patients enrolled from Mainland China where testing was not performed due to China HGR regulations).

ATM = Ataxia-telangiectasia mutated; *BRCA1/2* = Breast cancer susceptibility gene 1 or 2; *BARD1* = BRCA1 associated RING domain 1; *BRIP1* = BRCA1 interacting helicase 1; *CDK12* = Cyclin-dependent kinase 12; *CHEK1/2* = Checkpoint kinase 1 or 2; *FANCL* = Fanconi anemia complementation group L; FAS = Full Analysis Set; HGR = Human Genetic Resources; HRR = Homologous recombination repair; HRRm = Homologous recombination repair mutation; N = Number of patients in treatment group; NGS = Next-generation sequencing; *PALB2* = Partner and localizer of BRCA2; PD-L1 = Programmed cell death ligand 1; *RAD51B/C/D* = RAD51 paralog B/C/D; *RAD54L* = RAD54 like; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance;
SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Numbers analysed

The analysis sets and the number of patients in each analysis set are summarised in the below table.

Table 22 Analysis Sets (All Patients)

	Number (%) of patients			
	SoC	SoC + D	SoC + D + O	Total
Patients randomised	241	238	239	718
Patients included in Full Analysis Set [a]	241	238	239	718
Patients excluded from Full Analysis Set	0	0	0	0
Patients included in Safety Analysis Set [b]	236	235	238	709
Patients excluded from Safety Analysis Set	5	3	1	9
Patients included in PK Analysis Set [c]	NA	204	213	417
Patients excluded from PK Analysis Set	NA	34	26	60
No durvalumab dose	NA	3	1	4
No post first dose PK result	NA	31	25	56
Patients included in ADA Evaluable Analysis Set [d]	NA	198	207	405
Patients excluded from ADA Evaluable Analysis Set	NA	40	32	72
No baseline ADA result	NA	14	7	21
No durvalumab dose	NA	3	1	4
No post baseline ADA result	NA	23	24	47

[a] All randomised patients with treatment groups assigned in accordance with the randomisation, regardless of the treatment actually received.

[b] All randomised patients who received any amount of study treatment (durvalumab/placebo or olaparib/placebo).

[c] All Safety Analysis Set patients who received at least one dose of durvalumab per the protocol and had any post-baseline PK data and did not violate or deviate from the protocol in ways that would have significantly affected the PK analyses.

[d] All Safety Analysis Set patients who received at least one dose of durvalumab and had non-missing baseline ADA result and at least one post-baseline ADA.

ADA = Anti-drug antibody; NA = Not applicable; PK = Pharmacokinetics; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Outcomes and estimation

Primary endpoint: PFS by Investigator assessment

Table 23 Progression-free Survival According to RECIST 1.1, Based on Investigator Assessments (FAS; 61% Maturity; DCO 12 April 2023)

	Number (%) of patients		
	SoC (N = 241)	SoC + D (N = 238)	SoC + D + O (N = 239)
Total events, n (%) [a]	**173 (71.8)**	**139 (58.4)**	**126 (52.7)**
RECIST progression	160 (66.4)	129 (54.2)	115 (48.1)
New lesions [b]	87 (36.1)	74 (31.1)	72 (30.1)
Target lesions [b]	82 (34.0)	65 (27.3)	51 (21.3)
Non-target lesions [b]	50 (20.7)	43 (18.1)	32 (13.4)
Death in the absence of progression	13 (5.4)	10 (4.2)	11 (4.6)
Censored patients, n (%)	**68 (28.2)**	**99 (41.6)**	**113 (47.3)**
Progression-free at time of analysis	54 (22.4)	86 (36.1)	107 (44.8)
Censored death [c]	9 (3.7)	6 (2.5)	0
Withdrawn consent	3 (1.2)	4 (1.7)	3 (1.3)
No post-baseline evaluable tumour assessment	1 (0.4)	3 (1.3)	2 (0.8)
Censored RECIST progression [d]	1 (0.4)	0	0
Lost to follow-up	0	0	1 (0.4)
Median PFS (95% CI), months [e]	**9.6 (9.0, 9.9)**	**10.2 (9.7, 14.7)**	**15.1 (12.6, 20.7)**
Hazard ratio versus SoC [f]	-	**0.71**	**0.55**
95% CI for HR [f]	-	0.57, 0.89	0.43, 0.69
2-sided p-value [g]	-	0.003	< 0.0001
Hazard ratio versus SoC + D [f]	-	-	**0.78**
95% CI for HR [f]	-	-	0.61, 0.99
Percentage (95% CI) of patients who were progression-free at			
6 months [e]	82.5 (76.9, 86.8)	83.8 (78.4, 88.0)	83.9 (78.6, 88.0)
12 months [e]	41.1 (34.6, 47.5)	48.5 (41.8, 54.9)	61.5 (54.9, 67.4)
18 months [e]	21.7 (16.0, 27.9)	37.8 (31.0, 44.5)	46.3 (39.2, 53.0)
Median (range) duration of follow-up in censored patients (months)	12.6 (0.0, 31.6)	15.4 (0.0, 29.1)	15.4 (0.0, 31.7)

[a] Patients who had not progressed/died (or who progressed/died after 2 missed assessments) were censored at the latest visit (or the latest visit prior to the 2 missed assessments), or at Day 1.

[b] Target lesions, non-target lesions, and new lesions were not necessarily mutually exclusive categories.

[c] Death which occurred after 2 or more missed RECIST assessments in the absence of progression.

[d] Progression event occurred after 2 or more missed assessments or within 2 assessments of Day 1 where the patient had no evaluable assessments or did not have a baseline assessment.

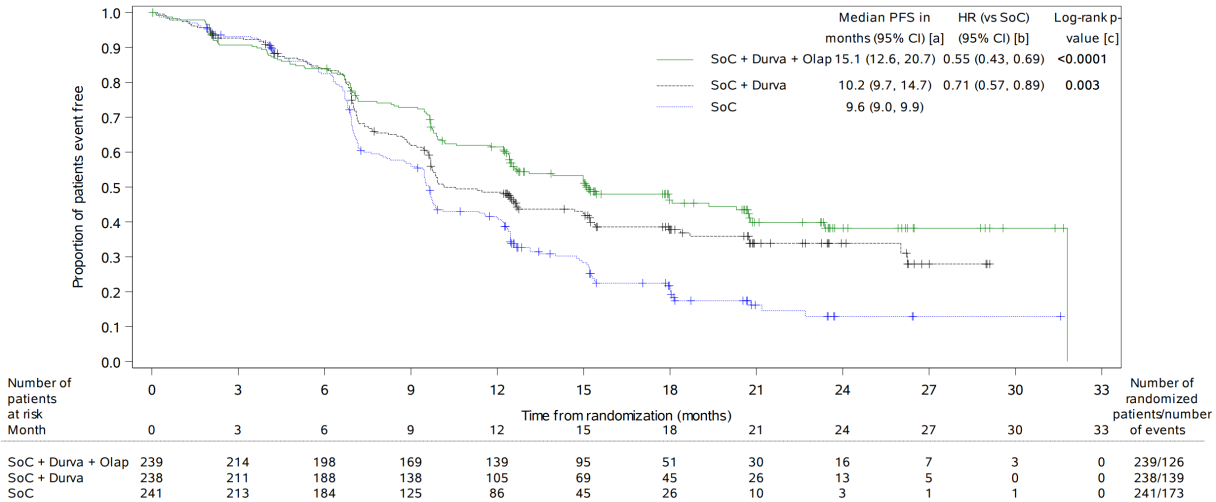
[e] Calculated using the KM technique. Confidence intervals for median PFS were derived based on Brookmeyer-Crowley method.

[f] Note a pooling strategy was applied to the primary comparisons of PFS for SoC + D + O versus SoC and SoC + D versus SoC whereby stratification factors were removed until there were at least 5 events in each stratum of interest across the 3 treatment arms, as defined in the SAP (see Appendix 16.1.9). The HR and CI were estimated from a CPH model stratified by: MMR and disease status. A HR less than 1 favoured the treatment arm of interest over the reference arm.

[g] The p-value was calculated using a log rank test stratified by variables in (f).

CI = Confidence interval; CPH = Cox Proportional Hazards; FAS = Full Analysis Set; HR = Hazard ratio; KM = Kaplan-Meier; MMR = Mismatch repair; N = Total number of patients; n = Number of patients; PFS = Progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours; SAP = Statistical Analysis Plan; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Figure 4 Progression-free Survival Kaplan-Meier Plot, Based on Investigator Assessments (FAS; DCO 12 April 2023)



d. Calculated using the KM technique. Confidence interval for median PFS was derived based on Brookmeyer-Crowley method.

e. Note a pooling strategy was applied to the primary comparisons of PFS for SoC + D + O versus SoC and SoC + D versus SoC whereby stratification factors were removed until there were at least 5 events in each stratum of interest across the 3 treatment arms, as defined in the DUO-E SAP (see Appendix 16.1.9, DUO-E CSR, Module 5.3.5.1). The HR and CI were estimated from a CPH model stratified by: MMR and disease status. The CI was calculated using a profile likelihood approach. A HR less than 1 favoured the treatment arm of interest over the reference arm.

f. The p-value was calculated using a log rank test stratified by variables in (b).

+ indicates a censored observation.

Progression was determined by site Investigator assessment using RECIST 1.1.

CI = Confidence interval; CPH = Cox Proportional Hazards; CSR = Clinical Study Report; Durva = Durvalumab; FAS = Full Analysis Set; HR = Hazard ratio; KM = Kaplan-Meier; MMR = Mismatch repair; Olap = Olaparib; PFS = Progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours; SAP = Statistical Analysis Plan; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

SoC + D Versus SoC comparison

The analysis of PFS showed a statistically significant improvement in PFS for patients treated with SoC + D compared with SoC, with a HR point estimate of 0.71; 95% CI: 0.57, 0.89; 2-sided p-value = 0.003. Median PFS in the SoC + D arm was 10.2 (95% CI: 9.7, 14.7) months compared with 9.6 (95% CI: 9.0, 9.9) months in the SoC arm. The median duration of follow-up in censored patients was 15.4 months in the SoC + D arm and 12.6 months in the SoC arm.

SoC + D + O Versus SoC comparison

The analysis of PFS showed a statistically significant improvement in PFS for patients treated with SoC + D + O compared with SoC alone, with a HR point estimate of 0.55; 95% CI: 0.43, 0.69; 2 sided p-value < 0.0001. Median PFS in the SoC + D + O arm was 15.1 (95% CI: 12.6, 20.7) months (while it was 9.6 months in the SoC arm).

Secondary endpoints

Overall survival (OS)

The first OS interim analysis was performed at the time of the PFS primary analysis. At the time of the primary PFS analysis/first interim OS analysis (DCO 12 April 2023), the OS data were 27.7% mature across the 3 treatment arms (199 events/718 patients). At this first interim analysis of OS, 2-sided significance levels of $p < 0.0011$ and $p < 0.0006$ were allocated for the comparisons of SoC + D versus SoC and SoC + D + O versus SoC, respectively. As the pre-defined statistical thresholds for superiority for SoC + D versus SoC and SoC + D + O versus SoC were not met at the time of the primary PFS analysis/first interim analysis of OS, OS will be analysed and re-tested at future DCOs.

Table 24 Overall Survival Analysis (FAS; DCO 12 April 2023)

	SoC (N = 241)	SoC + D (N = 238)	SoC + D + O (N = 239)
Death, n (%)	**82 (34.0)**	**65 (27.3)**	**52 (21.8)**
Censored patients, n (%)	**159 (66.0)**	**173 (72.7)**	**187 (78.2)**
Still in survival follow-up [a]	147 (61.0)	159 (66.8)	170 (71.1)
Terminated prior to death [b]	12 (5.0)	14 (5.9)	17 (7.1)
Withdrawn consent	12 (5.0)	14 (5.9)	15 (6.3)
Lost to follow-up	0	0	2 (0.8)
Median OS (95% CI), months [c]	**25.9 (23.9, NR)**	**NR (NR, NR)**	**NR (NR, NR)**
Hazard ratio versus SoC [d]	-	**0.77**	**0.59**
95% CI for HR [d]	-	0.56, 1.07	0.42, 0.83
2-sided p-value [e]	-	0.120	0.003
Hazard ratio versus SoC + D [d]	-	-	**0.77**
95% CI for HR [d]	-	-	0.53, 1.10
Percentage (95% CI) of patients who were alive at			
6 months [c]	91.2 (86.8, 94.2)	93.7 (89.7, 96.1)	95.8 (92.3, 97.7)
12 months [c]	79.7 (74.0, 84.3)	84.2 (78.9, 88.3)	87.7 (82.7, 91.3)
18 months [c]	69.0 (62.3, 74.8)	74.6 (68.0, 80.1)	79.4 (73.2, 84.3)
Median (range) duration of follow-up in censored patients (months)	18.6 (0.5, 32.9)	18.4 (2.1, 33.0)	18.7 (1.1, 33.4)

[a] Included patients known to be alive at DCO.

[b] Included patients with unknown survival status or patients who were lost to follow-up.

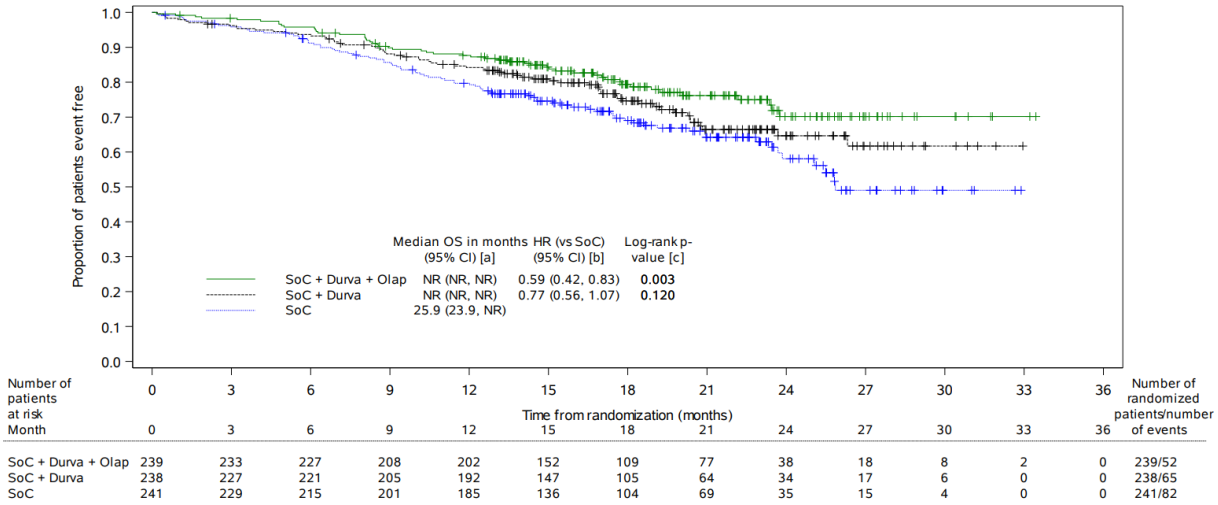
[c] Calculated using KM technique. Confidence interval for median survival was derived based on the Brookmeyer-Crowley method.

[d] Note a pooling strategy was applied to the primary comparisons of PFS for SoC + D + O versus SoC and SoC + D versus SoC whereby stratification factors were removed until there were at least 5 events in each stratum of interest across the 3 treatment arms, as defined in the SAP (see Appendix 16.1.9). This analysis was conducted with the same principles. The HR and CI were estimated from a stratified CPH model with the following variables: Unstratified. The CI was calculated using a profile likelihood approach. A HR less than 1 favoured the treatment arm of interest over the reference arm.

[e] The p-value was calculated using a log rank test stratified by variables in (d).

CI = Confidence interval; CPH = Cox Proportional Hazards; DCO = Data cut-off; FAS = Full Analysis Set; HR = Hazard ratio; KM = Kaplan-Meier; N = Total number of patients; n = Number of patients; NR = Not reached; OS = Overall survival; PFS = Progression-free survival; SAP = Statistical Analysis Plan; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Figure 5 Overall Survival Kaplan-Meier Plot (FAS; DCO 12 April 2023)



[g] Calculated using the KM technique. Confidence interval for median OS was derived based on Brookmeyer-Crowley method.

[h] Note a pooling strategy was applied to the primary comparisons of PFS for SoC + D + O versus SoC and SoC + D versus SoC whereby stratification factors were removed until there were at least 5 events in each stratum of interest across the 3 treatment arms, as defined in the DUO-E SAP (see Appendix 16.1.9, DUO-E CSR, Module 5.3.5.1). This analysis was conducted with the same principles. The HR compared to the SoC group and CI were estimated from a CPH model with following variables: Unstratified. The CI was calculated using a profile likelihood approach. A HR less than 1 favoured the treatment arm of interest over the reference arm.

[i] The p-value was calculated using a log rank test stratified by variables in (b).

+ indicates a censored observation. 2-sided p-value.

CI = Confidence interval; CPH = Cox Proportional Hazards; CSR = Clinical Study Report; DCO = Data cut-off; Durva = Durvalumab; HR = Hazard ratio; FAS = Full Analysis Set; KM = Kaplan-Meier; NR = Not reached; Olap = Olaparib; OS = Overall survival; PFS = Progression-free survival; SAP = Statistical Analysis Plan; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance; vs = Versus.

SoC + D Versus SoC comparison

At the time of the primary PFS analysis/first interim analysis of OS in the FAS, there were 147 patients with an OS event among 479 patients across the SoC and SoC + D arms (30.7% maturity). The OS HR point estimate showed a numerical improvement for the SoC + D arm compared with the SoC arm (HR: 0.77; 95% CI: 0.56, 1.07; p = 0.120), but the results did not reach statistical significance (p value stopping boundary of p < 0.0011). The median OS was not reached in the SoC + D arm compared with 25.9 months in the SoC arm. Overall, the median duration of follow-up for survival in all patients was 17.1 and 16.4 months in the SoC + D arm and the SoC arm, respectively.

SoC + D + O Versus SoC

At the time of the primary PFS analysis/first interim analysis of OS in the FAS, there were 134 patients with an OS event among the 480 patients across the SoC and SoC + D + O arms (27.9% maturity). The OS HR point estimate showed a numerical improvement for the SoC + D + O arm compared with the SoC arm (HR: 0.59; 95% CI: 0.42, 0.83; p = 0.003), but the results did not reach statistical significance (p value stopping boundary of p < 0.0006). The median OS was not reached in the SoC + D + O arm compared with 25.9 months in the SoC arm. Overall, the median duration of follow-up for survival in all patients was 17.5 and 16.4 months in the SoC + D + O arm and the SoC arm, respectively.

Objective response rate (ORR)

Objective response rate was assessed in 584/718 patients (81.3%) with measurable disease at baseline.

Table 25 Objective Response Rate Based on Investigator Assessment, All Patients with Measurable Disease at Baseline (FAS; DCO 12 April 2023)

Group	N	Number (%) of patients with response [a]	Comparison versus SoC	
			Odds ratio	95% CI
SoC + D + O	184	117 (63.6)	1.44	0.95, 2.18
SoC + D	202	125 (61.9)	1.32	0.89, 1.98
SoC	198	109 (55.1)	NA	NA

j. Responses included confirmed responses of CR/PR that were recorded at one visit and confirmed by repeat imaging, not less than 4 weeks after the visit when the response was first observed, with no evidence of progression between the initial and CR/PR confirmation visit.

The analysis was performed using logistic regression model adjusted with the following variables (by comparison): MMR and disease status.

An odds ratio > 1 favoured the comparator arm.

RECIST Version 1.1.

CI = Confidence interval; CR = Complete response; CSR = Clinical Study Report; DCO = Data cut-off; FAS = Full Analysis Set; MMR = Mismatch repair; N = Number of patients in treatment group with measurable disease at baseline; NA = Not applicable; PFS = Progression-free survival; PR = Partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SoC = Standard of Care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Duration of Response (DoR)

Table 26 Duration and Onset of Objective Response in Patients with Objective Response based on Investigator Assessment (FAS; All Patients with Confirmed Response)

	Number (%) of patients		
	SoC N = 109	**SoC + D N = 125**	**SoC + D + O N = 117**
Time to onset of response from randomisation (months)			
Number of patients with objective response, n	109	125	117
Min	1.2	1.2	1.6
25th percentile	2.0	2.0	2.0
Median	2.1	2.1	2.1
75th percentile	2.3	2.3	2.3
Max	17.8	7.2	15.2
Duration of response from onset of response (months) [a,b]			
Number of responders who subsequently progressed or died, n (%)	78 (71.6)	63 (50.4)	50 (42.7)
Min	2.1*	2.4*	2.8*
25th percentile	5.1	6.0	8.1
Median	7.7	13.1	29.9
75th percentile	13.5	NR	29.9
Max	29.7*	26.9*	29.9

Subsequent therapies

In the SoC, SoC + D, and SoC + D + O arms, 127 patients (52.7%), 99 patients (41.6%), and 88 patients (36.8%), respectively, received further anti-cancer therapy post-discontinuation of study treatment.

The most commonly reported subsequent treatments included: cytotoxic chemotherapy (carboplatin, paclitaxel, doxorubicin, doxorubicin hydrochloride, and cisplatin), immunotherapy (pembrolizumab), targeted therapy (lenvatinib), and radiotherapy.

There were 54 patients (22.4%) in the SoC arm, 34 patients (14.3%) in the SoC + D arm, and 28 patients (11.7%) in the SoC + D + O arm who received subsequent immunotherapy. Of these patients, the majority received pembrolizumab (45 patients [18.7%], 31 patients [13.0%], and 27 patients [11.3%], respectively); PARP inhibitors (olaparib) were received as a subsequent therapy by 2 patients in the SoC + D arm and no patients in either the SoC or SoC + D + O arms.

Time from randomisation to second progression or death (PFS2)

At the DCO, there were 245 PFS2 events across the 3 treatment arms (34.1% maturity).

Table 27 Time from Randomisation to Second Progression or Death Based on Local Standard Clinical Practice (FAS)

	SoC (N = 241)	SoC + D (N = 238)	SoC + D + O (N = 239)
Total events [a], n (%)	**96 (39.8)**	**85 (35.7)**	**64 (26.8)**
Second progression	31 (12.9)	38 (16.0)	26 (10.9)
Objective radiological imaging progression	29 (12.0)	34 (14.3)	23 (9.6)
Symptomatic progression	1 (0.4)	4 (1.7)	2 (0.8)
Other	1 (0.4)	0	1 (0.4)
Death in the absence of second progression	65 (27.0)	47 (19.7)	38 (15.9)
Censored patients, n (%)	**145 (60.2)**	**153 (64.3)**	**175 (73.2)**
Second progression-free at time of analysis	141 (58.5)	148 (62.2)	169 (70.7)
PFS1 event	87 (36.1)	60 (25.2)	62 (25.9)
PFS1 censored	54 (22.4)	88 (37.0)	107 (44.8)
Withdrawn consent	4 (1.7)	5 (2.1)	5 (2.1)
Lost to follow-up	0	0	1 (0.4)
Median PFS2 (95% CI), months [b]	**19.1 (16.4, 22.9)**	**22.2 (18.7, NR)**	**NR (NR, NR)**
Hazard ratio versus SoC [c]	-	**0.80**	**0.55**
95% CI for HR [c]	-	0.59, 1.07	0.40, 0.76

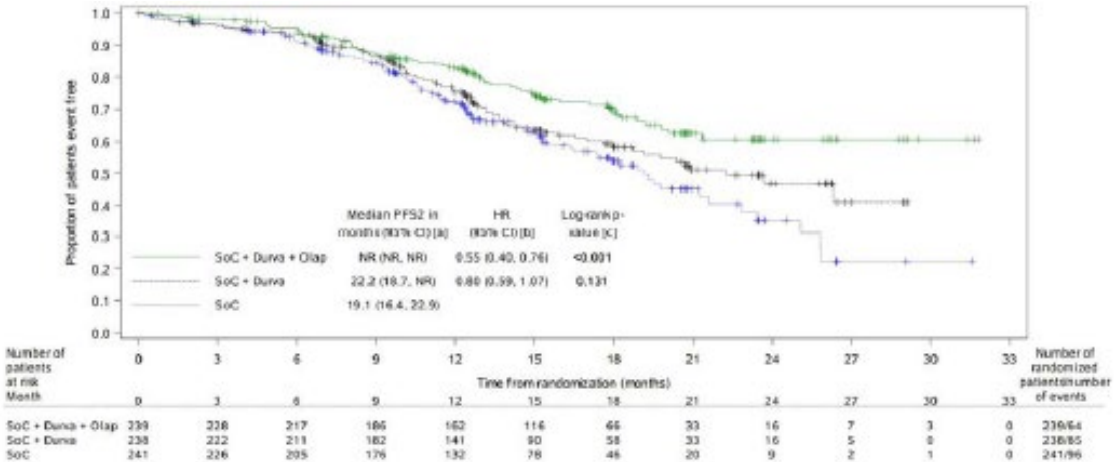
[a] Patients who had not progressed for a second time or died were censored at the time of the latest assessment where they were known to be alive and without a second progression, or at Day 1 if there were no progression assessments.

[b] Calculated using the KM technique. Confidence interval for median PFS2 was derived based on the Brookmeyer-Crowley method.

[c] Note a pooling strategy was applied to the primary comparisons of PFS for SoC + D + O versus SoC and SoC + D versus SoC whereby stratification factors were removed until there were at least 5 events in each stratum of interest across the 3 treatment arms, as defined in the SAP (see Appendix 16.1.9). This analysis was conducted with the same stratification factors. The HR compared to the SoC group and CI were estimated from a CPH model with following variables: unstratified. The CI was calculated using a profile likelihood approach. A HR less than 1 favoured the treatment arm of interest over the reference arm.

CI = Confidence interval; CPH = Cox Proportional Hazards; FAS = Full Analysis Set; HR = Hazard ratio; KM = Kaplan-Meier; N = Total number of patients; n = Number of patients; NR = Not reached; PFS = Progression-free survival; PFS1 = First progression-free survival; PFS2 = Second progression-free survival; SAP = Statistical Analysis Plan; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Figure 6 Kaplan-Meier Plot of Time from Randomisation to Second Progression or Death (FAS)



[a] Calculated using the KM technique. Confidence interval for median PFS2 was derived based on Brookmeyer-Crowley method.

[b] Note a pooling strategy was applied to the primary comparisons of PFS for SoC + D + O versus SoC and SoC + D versus SoC whereby stratification factors were removed until there were at least 5 events in each stratum of interest across the 3 treatment arms, as defined in the SAP (see Appendix 16.1.9). This analysis was conducted with the same stratification factors. The HR compared to the SoC group and CI were estimated from a CPH model with following variables: Unstratified. The CI was calculated using a profile likelihood approach. A HR less than 1 favoured the treatment arm of interest over the reference arm.

[c] The p-value was calculated using a log rank test stratified by variables in (b)

Progression was determined based on local standard clinical practice.

+ indicates a censored observation.

CI = Confidence interval; CPH = Cox Proportional Hazards; Durva = Durvalumab; FAS = Full Analysis Set; HR = Hazard ratio; KM = Kaplan-Meier; NR = Not reached; Olap = Olaparib; PFS = Progression-free survival; PFS2 = Second progression-free survival; SAP = Statistical Analysis Plan; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Time from randomisation to first subsequent therapy or death (TFST)

At the DCO, the TFST data were 54.7% mature across the three treatment arms (393 events/718 patients).

Table 28 Time from Randomisation to First Subsequent Cancer Therapy or Death (FAS)

	SoC (N = 241)	SoC + D (N = 238)	SoC + D + O (N = 239)
Total events [a], n (%)	**160 (66.4)**	**128 (53.8)**	**105 (43.9)**
Subsequent therapy	119 (49.4)	94 (39.5)	82 (34.3)
Death	41 (17.0)	34 (14.3)	23 (9.6)
Censored patients [b], n (%)	**81 (33.6)**	**110 (46.2)**	**134 (56.1)**
Median TFST (95% CI), (months) [c]	**11.1 (10.2, 12.7)**	**14.0 (11.5, 19.8)**	**21.4 (18.1, NR)**
Hazard ratio versus SoC [d]	-	**0.72**	**0.50**
95% CI for HR [d]	-	0.57, 0.91	0.39, 0.64

[a] Time from randomisation to first subsequent cancer therapy or death was the time from randomisation to the earlier of start date of first subsequent disease related cancer therapy after discontinuation of investigational treatment or death.

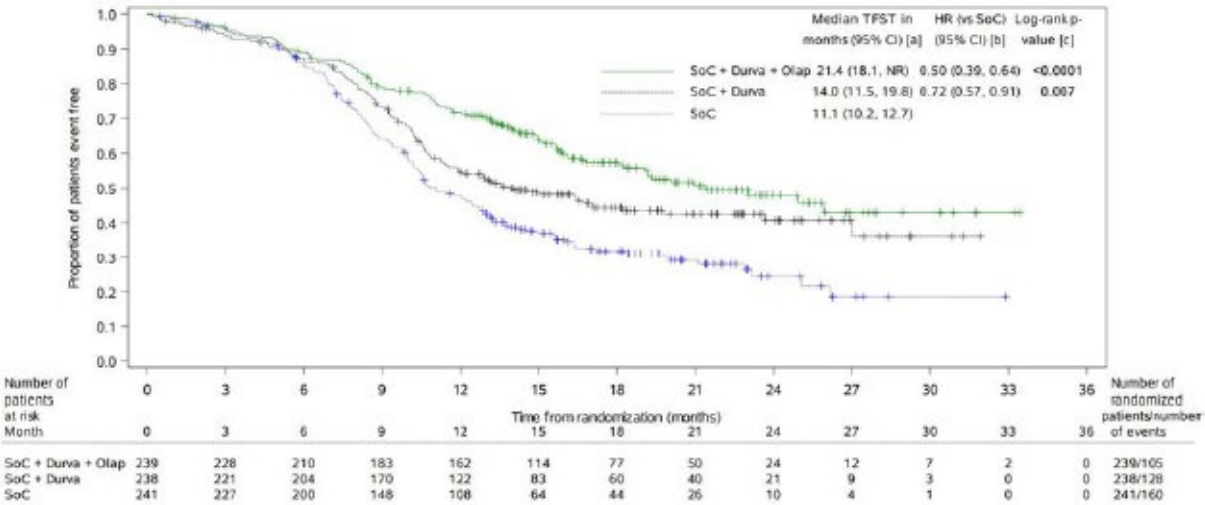
[b] Patients who had not discontinued the study and were not known to have had a first subsequent cancer therapy were censored at the last date that they were known not to have received subsequent cancer therapy. Patients who discontinued the study for reasons other than death before first subsequent therapy were censored at the earliest of the last date known to be alive and discontinuation date.

[c] Calculated using the KM technique. Confidence interval for median event-free survival was derived based on the Brookmeyer-Crowley method.

[d] Note a pooling strategy was applied to the primary comparisons of PFS for SoC + D + O versus SoC and SoC + D versus SoC whereby stratification factors were removed until there were at least 5 events in each stratum of interest across the 3 treatment arms, as defined in the SAP (see Appendix 16.1.9). This analysis was conducted with the same stratification factors. The HR compared to the SoC group and CI were estimated from a CPH model with following variables: MMR and disease status. The CI was calculated using a profile likelihood approach. A HR less than 1 favoured the treatment arm of interest over the reference arm.

CI = Confidence interval; CPH = Cox Proportional Hazards; FAS = Full Analysis Set; HR = Hazard ratio; KM = Kaplan-Meier; MMR = Mismatch repair; N = Total number of patients; n = Number of patients; NR = Not reached; PFS = Progression-free survival; SAP = Statistical Analysis Plan; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance; TFST = Time from randomisation to first subsequent cancer therapy or death.

Figure 7 Time from Randomisation to First Subsequent Cancer Therapy or Death, Kaplan-Meier Plot (FAS)



[a] Calculated using the KM technique. Confidence interval for median PFS was derived based on Brookmeyer-Crowley method.

[b] Note a pooling strategy was applied to the primary comparisons of PFS for SoC + D + O versus SoC and SoC + D versus SoC whereby stratification factors were removed until there were at least 5 events in each stratum of interest across the 3 treatment arms, as defined in the SAP (see Appendix 16.1.9). This analysis was conducted with the same stratification factors. The HR compared to the SoC group and CI were estimated from a CPH model with the following variables: MMR and disease status. The CI was calculated using a profile likelihood approach. A HR less than 1 favoured the treatment arm of interest over the reference arm.

[c] The p-value was calculated using a log rank test stratified by variables in (b).

+ indicates a censored observation.

CI = Confidence interval; CPH = Cox Proportional Hazards; Durva = Durvalumab; FAS = Full Analysis Set; HR = Hazard ratio; KM = Kaplan-Meier; MMR = Mismatch repair; NR = Not reached; Olap = Olaparib; PFS = Progression-free survival; SAP = Statistical Analysis Plan; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance; TFST = Time from randomisation to first subsequent cancer therapy or death.

Time from randomisation to second subsequent therapy or death

At the DCO, the TSST data were 31.3% mature across the 3 treatment arms (225 events/718 patients).

Table 29 Time from Randomisation to Second Subsequent Cancer Therapy or Death (FAS)

	SoC (N = 241)	SoC + D (N = 238)	SoC + D + O (N = 239)
Total events [a], n (%)	**93 (38.6)**	**75 (31.5)**	**57 (23.8)**
Subsequent therapy	20 (8.3)	21 (8.8)	11 (4.6)
Death	73 (30.3)	54 (22.7)	46 (19.2)
Censored patients [b], n (%)	**148 (61.4)**	**163 (68.5)**	**182 (76.2)**
Median TSST (95% CI), months [c]	**23.9 (21.6, NR)**	**NR (NR, NR)**	**NR (NR, NR)**
Hazard ratio versus SoC [d]	-	**0.77**	**0.57**
95% CI for HR [d]	-	0.57, 1.05	0.40, 0.78

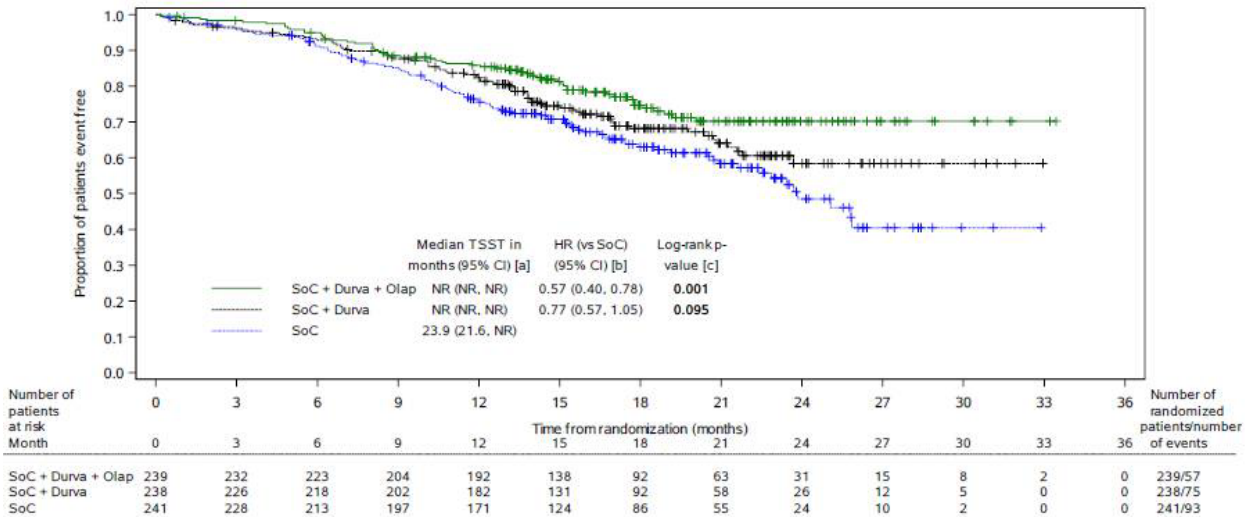
[a] Time from randomisation to second subsequent therapy or death was the time from randomisation to the earlier of start date of second subsequent disease related cancer therapy after discontinuation of first subsequent therapy or death.

[b] Patients who had not discontinued the study and were not known to have had a second subsequent cancer therapy were censored at the last date that they were known not to have received a second subsequent cancer therapy. Patients who discontinued the study for reasons other than death before second subsequent therapy were censored at the earliest of the last date known to be alive and discontinuation date.

[c] Calculated using the KM technique. Confidence interval for median event-free survival was derived based on the Brookmeyer-Crowley method.

[d] Note a pooling strategy was applied to the primary comparisons of PFS for SoC + D + O versus SoC and SoC + D versus SoC whereby stratification factors were removed until there were at least 5 events in each stratum of interest across the 3 treatment arms, as defined in the SAP (see Appendix 16.1.9). This analysis was conducted with the same stratification factors. The HR compared to the SoC group and CI were estimated from a CPH model with following variables: unstratified. The CI was calculated using a profile likelihood approach. A HR less than 1 favoured the treatment arm of interest over the reference arm.

Figure 8 Time from Randomisation to Second Subsequent Cancer Therapy or Death, Kaplan-Meier Plot (FAS)



[a] Calculated using the KM technique. Confidence interval for median PFS was derived based on Brookmeyer-Crowley method.

[b] Note a pooling strategy was applied to the primary comparisons of PFS for SoC + D + O versus SoC and SoC + D versus SoC whereby stratification factors were removed until there were at least 5 events in each stratum of interest across the 3 treatment arms, as defined in the SAP (see Appendix 16.1.9). This analysis was conducted with the same stratification factors. The HR compared to the SoC group and CI were estimated from a CPH model with the following variables: Unstratified. The CI was calculated using a profile likelihood approach. A HR less than 1 favoured the treatment arm of interest over the reference arm.

[c] The p-value was calculated using a log rank test stratified by variables in (b).

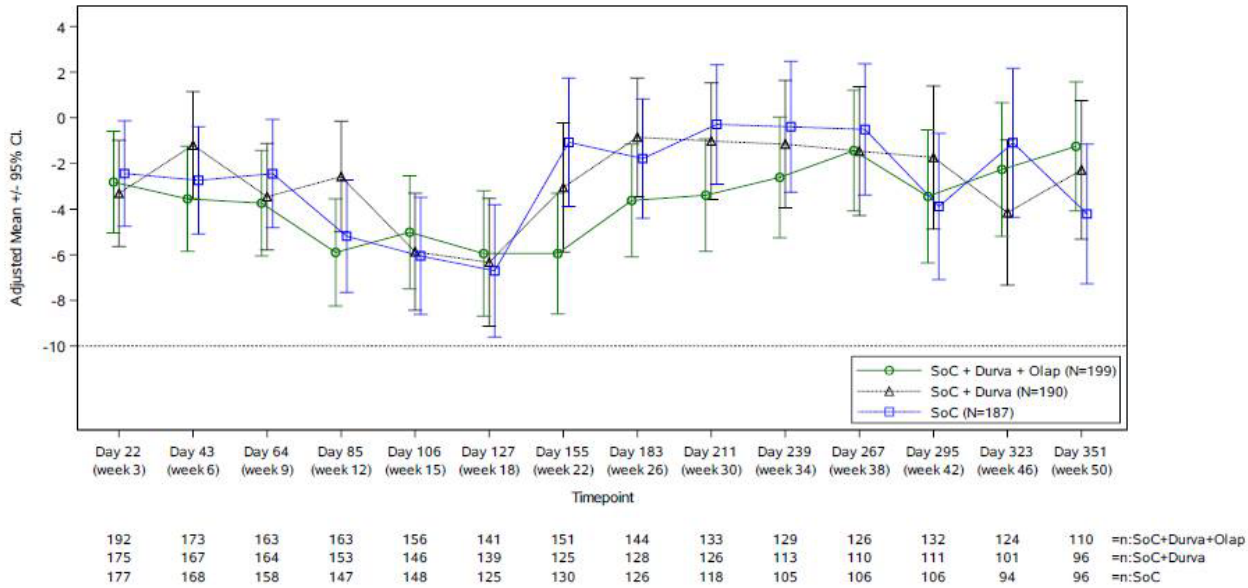
+ indicates a censored observation.

Patient-Reported Outcomes

Patient reported outcomes included as secondary endpoints in the study were assessed using the EORTC QLQ-C30 and EORTC QLQ-EN24. The PRO-CTCAE, PGI-TT, PGIC, PGIS, PGI-BR, and EQ-5D-5L questionnaires were collected as exploratory endpoints.

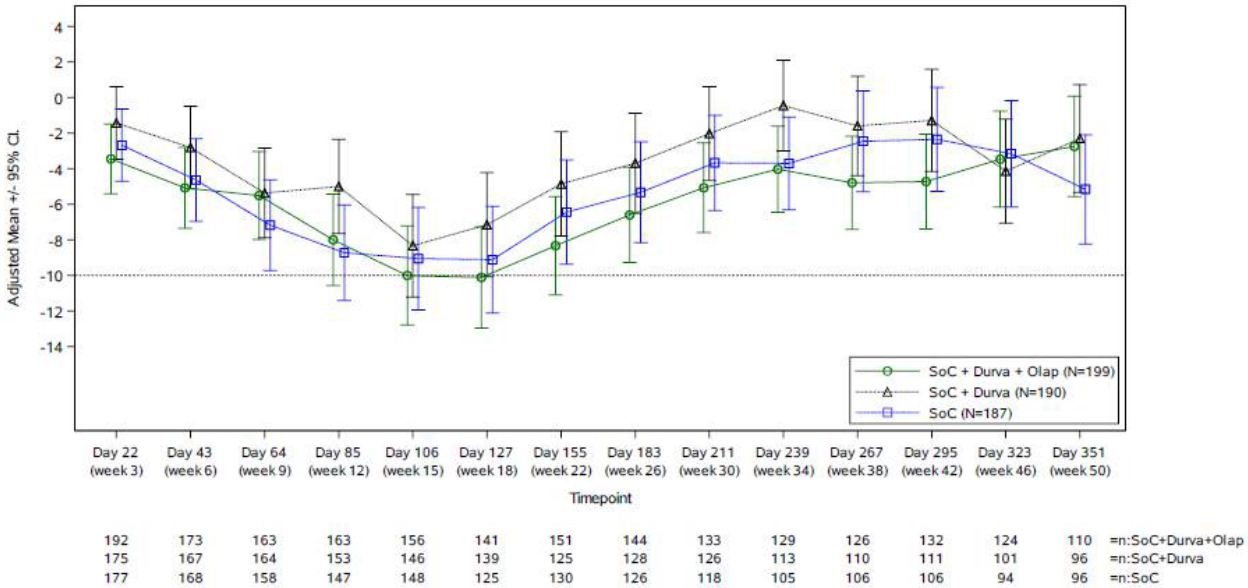
EORTC QLQ-C30

Figure 9 EORTC QLQ-C30 Global Health Status/QoL Change from Baseline, Plot of Adjusted Mean ± 95% CI (FAS)



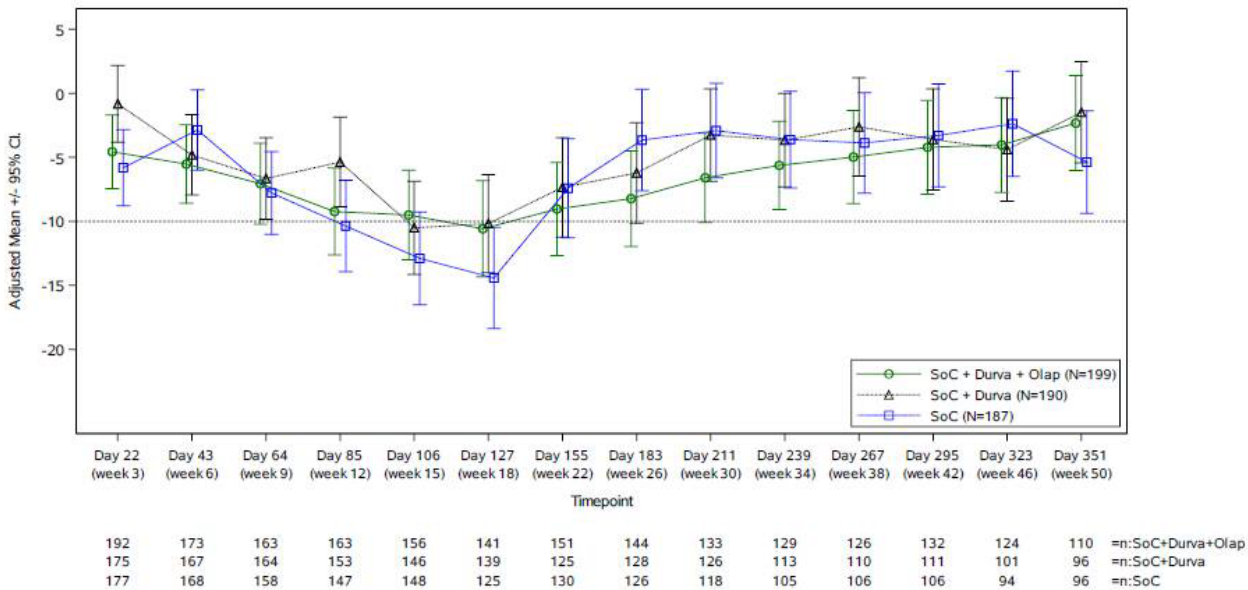
CI = Confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items; FAS = Full Analysis Set; N = Number of patients with a baseline and on-treatment value for scale/item and time point; n = Number of patients; QoL = Quality of life; SoC = Standard of care; SoC + Durva = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + Durva + Olap = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Figure 10 EORTC QLQ-C30 Physical Functioning Change from Baseline, Plot of Adjusted Mean ± 95% CI (FAS)



CI = Confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items; FAS = Full Analysis Set; N = Number of patients with a baseline and on-treatment value for scale/item and time point; n = Number of patients; SoC = Standard of care; SoC + Durva = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + Durva + Olap = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

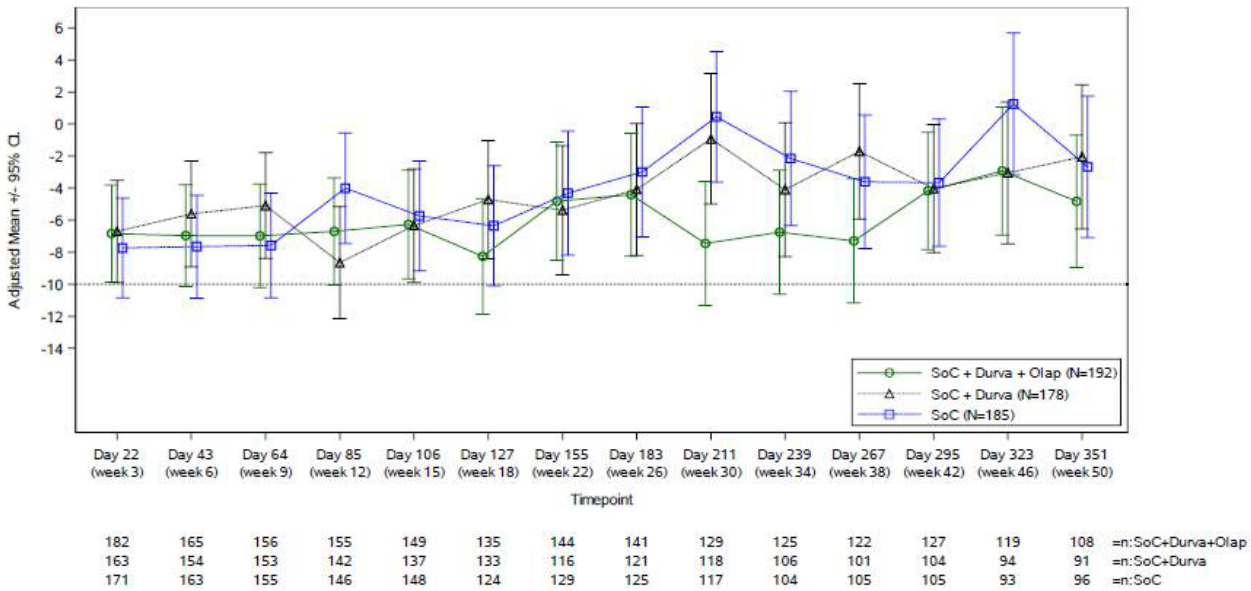
Figure 11 EORTC QLQ-C30 Role Functioning Change from Baseline, Plot of Adjusted Mean ± 95% CI (FAS)



CI = Confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items; FAS = Full Analysis Set; N = Number of patients with a baseline and on-treatment value for scale/item and time point; n = Number of patients; SoC = Standard of care; SoC + Durva = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + Durva + Olap = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

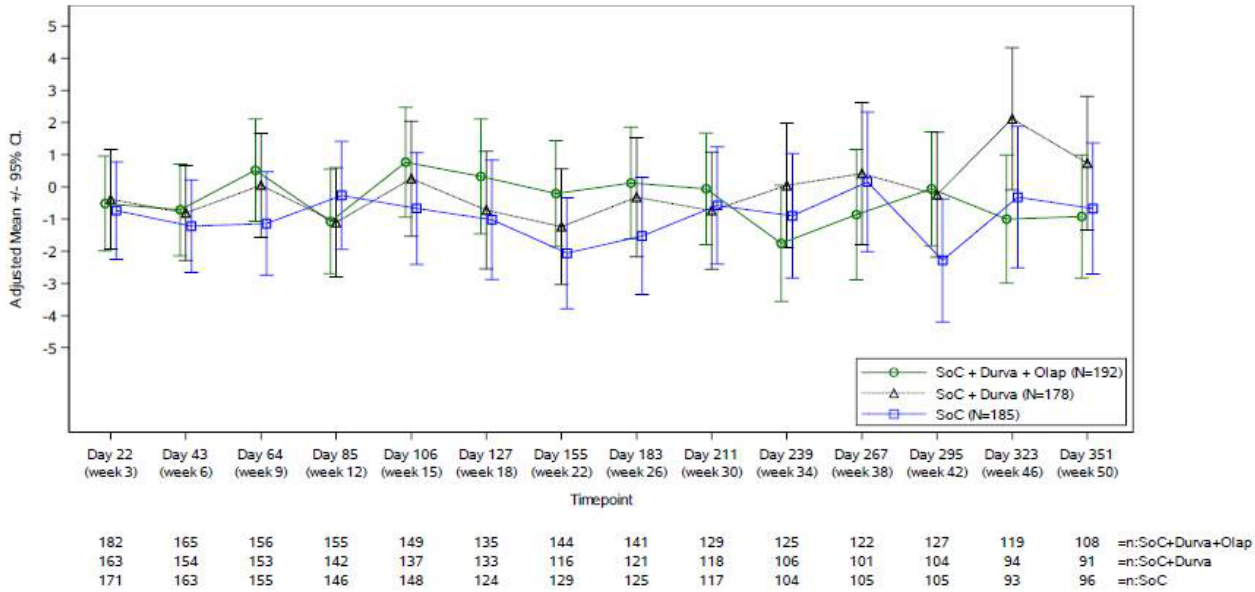
Endometrial Cancer Symptoms and Functioning: EORTC QLQ-EN24

Figure 12 EORTC QLQ-EN24 Pain in Back and Pelvis Symptoms Change from Baseline, Plot of Adjusted Mean ± 95% CI (FAS)



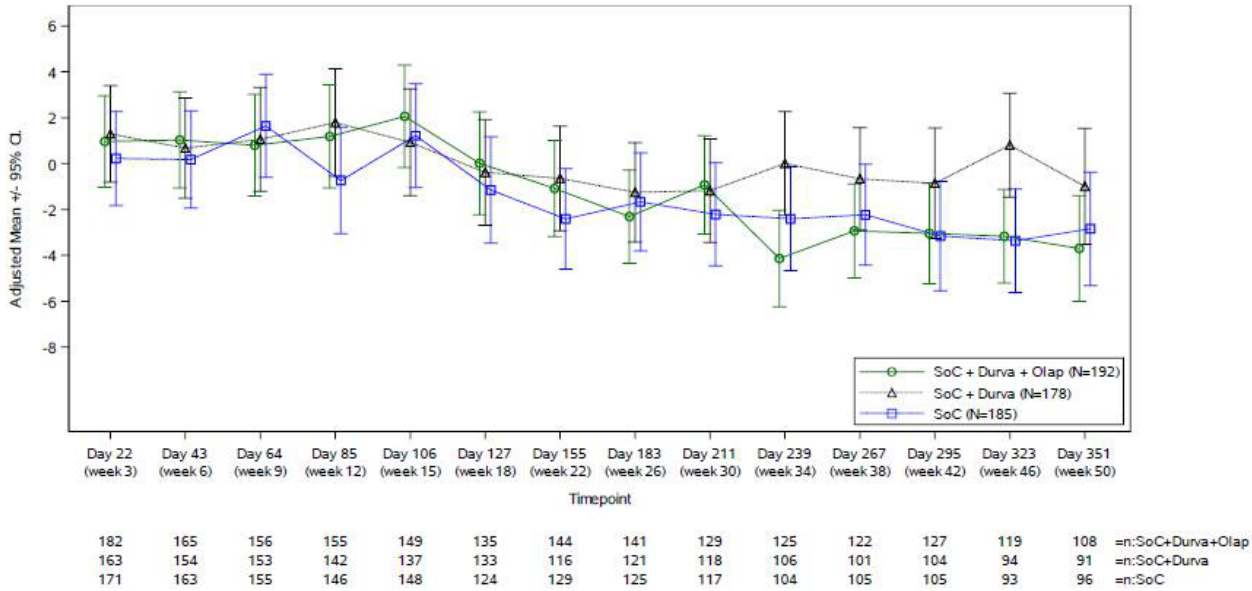
CI = Confidence interval; EORTC QLQ-EN24 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Endometrial Cancer Module; FAS = Full Analysis Set; N = Number of patients with a baseline and on-treatment value for scale/item and time point; n = Number of patients; SoC = Standard of care; SoC + Durva = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + Durva + Olap = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Figure 13 EORTC QLQ-EN24 Gastrointestinal Symptoms Change from Baseline, Plot of Adjusted Mean ± 95% CI (FAS)



CI = Confidence interval; EORTC QLQ-EN24 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Endometrial Cancer Module; FAS = Full Analysis Set; N = Number of patients with a baseline and on-treatment value for scale/item and time point; n = Number of patients; SoC = Standard of care; SoC + Durva = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + Durva + Olap = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Figure 14EORTC QLQ-EN24 Urological Symptoms Change from Baseline, Plot of Adjusted Mean ± 95% CI (FAS)



CI = Confidence interval; EORTC QLQ-EN24 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Endometrial Cancer Module; FAS = Full Analysis Set; N = Number of patients with a baseline and on-treatment value for scale/item and time point; n = Number of patients; SoC = Standard of care; SoC + Durva = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + Durva + Olap = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

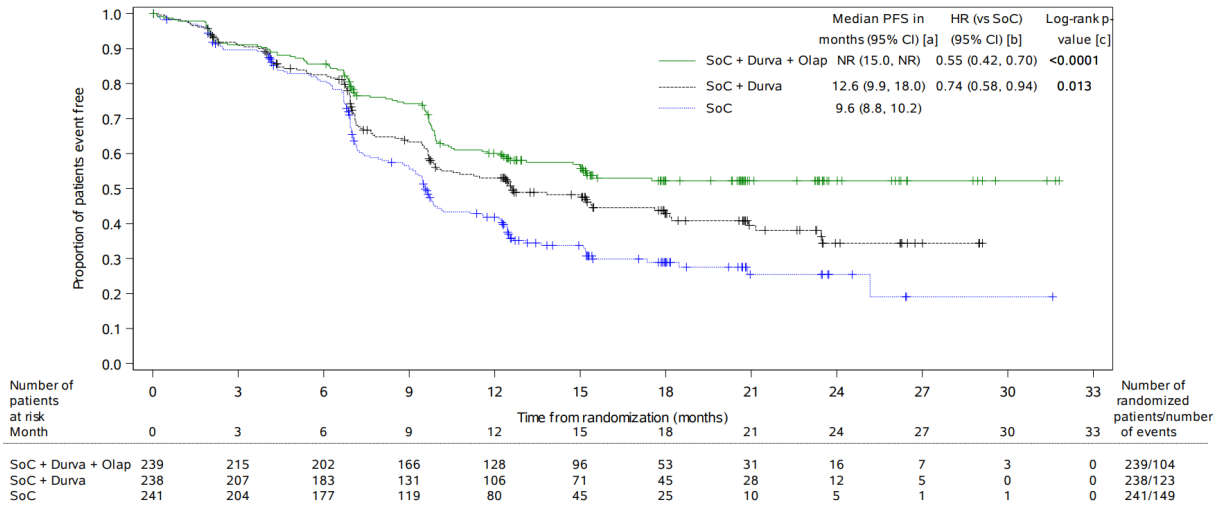
Ancillary analyses

Sensitivity analyses of PFS

Pre-Specified Sensitivity Analysis of PFS by BICR

The KM plot for PFS by BICR is presented in the below figure.

Figure 15 Progression-free Survival Based on BICR Assessments, Kaplan-Meier Plot (FAS; DCO 12 April 2023)



k. Calculated using the KM technique. Confidence interval for median PFS was derived based on Brookmeyer-Crowley method.

l. Note a pooling strategy was applied to the primary comparisons of PFS for SoC + D + O versus SoC and SoC + D versus SoC whereby stratification factors were removed until there were at least 5 events in each stratum of interest across the 3 treatment arms, as defined in the DUO-E SAP (see Appendix 16.1.9, DUO-E CSR, Module 5.3.5.1). This analysis was conducted with the same stratification factors. The HR and CI were estimated from a CPH model stratified by: MMR and disease status. The CI was calculated using a profile likelihood approach. A HR less than 1 favoured the treatment arm of interest over the reference arm.

m. The p-value was calculated using a log rank test stratified by variables in (b).

Progression was determined by BICR assessment using RECIST 1.1.

+ indicates a censored observation.

BICR = Blinded Independent Central Review; CI = Confidence interval; CPH = Cox Proportional Hazards; CSR = Clinical Study Report; Durva = Durvalumab; HR = Hazard ratio; FAS = Full Analysis Set; KM = Kaplan-Meier; MMR = Mismatch repair; Olap = Olaparib; PFS = Progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours; SAP = Statistical Analysis Plan; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

SoC + D Versus SoC

The results of a sensitivity analysis of PFS per BICR assessment for SoC + D versus SoC (ascertainment bias HR: 0.74; 95% CI: 0.58, 0.94) were consistent with those per Investigator assessment of PFS (HR: 0.71; 95% CI: 0.57, 0.89). Comparisons between Investigator and BICR of RECIST 1.1 progression is presented in the below table. For the SoC + D versus SoC comparison, there was a 17.3% (1 - [(124 + 100 + 72 + 100) / 479]) discordance between Investigators and central reviews in declaring progression.

SoC + D + O Versus SoC

The results of a sensitivity analysis of PFS per BICR assessment for SoC + D + O versus SoC (ascertainment bias HR: 0.55; 95% CI: 0.42, 0.70) were consistent with those per Investigator assessment of PFS (HR: 0.55; 95% CI: 0.43, 0.69). For the SoC + D versus SoC comparison, there was a 15.8% (1 – [(124 + 89 + 72 + 119) / 480]) discordance between Investigators and central reviews in declaring progression.

Table 30 Disagreements Between Investigator and Central Reviews of RECIST Progression (FAS)

	Number (%) of patients			Difference	
	SoC (N = 241)	SoC + D (N = 238)	SoC + D + O (N = 239)	SoC + D - SoC	SoC + D + O - SoC
RECIST progression [a] declared by:					
Investigator and central review	124 (51.5)	100 (42.0)	89 (37.2)	NA	NA
Progression date agreement (within 2 weeks)	84 (34.9)	70 (29.4)	52 (21.8)	NA	NA
Progression date ≥ 2 weeks earlier by central review than by Investigator	33 (13.7)	23 (9.7)	28 (11.7)	NA	NA
Progression date ≥ 2 weeks earlier by Investigator than by central review	7 (2.9)	7 (2.9)	9 (3.8)	NA	NA
Investigator but not central review	36 (14.9)	29 (12.2)	26 (10.9)	NA	NA
Central review but not Investigator	9 (3.7)	9 (3.8)	5 (2.1)	NA	NA
No progression by both	72 (29.9)	100 (42.0)	119 (49.8)	NA	NA
Early discrepancy rate [b]	0.32	0.29	0.35	-0.03	0.03
Late discrepancy rate [c]	0.51	0.53	0.51	0.02	0.00

[a] Progression events that did not occur within 2 planned RECIST assessments of the last evaluable assessment (or Day 1) were censored.
[b] Frequency of BICR progressions declared before the Investigator review progressions (≥ 2 weeks earlier and including progressions declared by BICR but not Investigator) as a proportion of all BICR review progressions.
[c] Frequency of BICR review progressions declared after the Investigator review progressions (≥ 2 weeks later and including progressions declared by Investigator review but not BICR) as a proportion of all discrepancies (including early and late discrepancies).

RECIST Version 1.1.

BICR = Blinded Independent Central Review; FAS = Full Analysis Set; N = Total number of patients; NA = Not applicable; RECIST = Response Evaluation Criteria in Solid Tumours; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Other sensitivity analyses of PFS

Other pre-planned and *post-hoc* sensitivity analyses were consistent with the primary PFS analysis.

Table 31 Sensitivity Analysis of Progression-free Survival (FAS)

	Number of events/Total number of patients (%)	Median PFS (months) [a]	Comparison with SoC		
			HR [b]	95% CI [b]	2-sided p-value [c]
Analysis to assess possible evaluation-time bias [d, e, f]	SoC + D + O: 126/239 (52.7)	13.9	0.54	0.43, 0.68	< 0.0001
	SoC + D: 139/238 (58.4)	10.5	0.72	0.57, 0.90	0.004
	SoC: 173/241 (71.8)	8.3	NA	NA	NA
Analysis to assess possible attrition bias [d, g]	SoC + D + O: 125/239 (52.3)	15.2	0.53	0.42, 0.66	< 0.0001
	SoC + D: 141/238 (59.2)	10.1	0.70	0.56, 0.88	0.002
	SoC: 179/241 (74.3)	9.5	NA	NA	NA
Analysis to assess possible ascertainment bias [e, h]	SoC + D + O: 104/239 (43.5)	NR	0.55	0.42, 0.70	< 0.0001
	SoC + D: 123/238 (51.7)	12.6	0.74	0.58, 0.94	0.013
	SoC: 149/241 (61.8)	9.6	NA	NA	NA
Analysis to assess the impact of COVID-19 deaths [d, e, i]	SoC + D + O: 125/239 (52.3)	15.2	0.55	0.43, 0.69	< 0.0001
	SoC + D: 139/238 (58.4)	10.2	0.71	0.57, 0.89	0.004
	SoC: 172/241 (71.4)	9.7	NA	NA	NA
Analysis to assess impact of censoring at the last evaluable RECIST assessment prior to first subsequent therapy [d, j]	SoC + D + O: 125/239 (52.3)	15.2	0.54	0.43, 0.68	< 0.0001
	SoC + D: 137/238 (57.6)	10.1	0.71	0.57, 0.90	0.004
	SoC: 171/241 (71.0)	9.7	NA	NA	NA
Analysis to assess impact of assigning an event at the time of initiation of first subsequent therapy [d, k]	SoC + D + O: 126/239 (52.7)	15.1	0.53	0.42, 0.67	< 0.0001
	SoC + D: 141/238 (59.2)	10.0	0.72	0.57, 0.90	0.004
	SoC: 175/241 (72.6)	9.5	NA	NA	NA

[a] Calculated using the KM technique.

[b] Note a pooling strategy was applied to the primary comparisons of PFS for SoC + D + O versus SoC and SoC + D versus SoC whereby stratification factors were removed until there were at least 5 events in each stratum of interest across the 3 treatment arms, as defined in the SAP (see Appendix 16.1.9). This analysis was conducted with the same stratification factors. The HR and CI were estimated from a stratified CPH model with the following variables: MMR and disease status for evaluation bias; MMR and disease status for attrition bias; MMR and disease status for ascertainment bias; MMR and disease status for COVID-19 bias; MMR and disease status for censoring at the last evaluable RECIST assessment prior to first subsequent therapy; and MMR and disease status for assigning an event at the time of initiation of first subsequent therapy. The CI was calculated using a profile likelihood approach. A HR less than 1 favoured the treatment arm of interest over the reference arm.

[c] The p-values were calculated using a log-rank test stratified by variables in (b).

[d] Progression was determined by site Investigator assessment using RECIST 1.1.

[e] Patients who had not progressed or died (or who progressed or died after 2 missed assessments) were censored at the latest visit (or at the latest visit prior to the 2 missed assessments), or at Day 1.

[f] The midpoint between the time of progression and the previous evaluable RECIST assessment (using the final date of the assessment) was analysed.

[g] Patients who progressed or died after 2 or more missed visits were considered as events. Patients with subsequent anti-cancer therapy were censored at their last visit prior to starting this therapy.

[h] Progression was determined by BICR using RECIST 1.1.

[i] Patients who had a PFS event due to death where primary/secondary cause of death was due to COVID-19 infection, or a COVID-19 infection reported as a fatal AE, were censored at their last evaluable assessment prior to their COVID infection death date.

[j] Patients who initiated first subsequent therapy before progression were censored at the last evaluable RECIST assessment prior to progression.

[k] Patients who initiated first subsequent therapy before progression were treated as progression events at the date of their initiation of first subsequent therapy.

Table 32 Sensitivity Analysis of Progression-free Survival (FAS)

	Number of events/Total number of patients (%)	Median PFS in months [a]	Comparison with SoC	
			HR [b]	95% CI [b]
Primary Analysis	SoC + D + O: 126/239 (52.7)	15.1	0.55	0.43, 0.69
	SoC + D: 139/238 (58.4)	10.2	0.71	0.57, 0.89
	SoC: 173/241 (71.8)	9.6	NA	NA
Analysis to assess impact of censoring at the last evaluable RECIST assessment prior to first subsequent therapy [c, d]	SoC + D + O: 125/239 (52.3)	15.2	0.54	0.43, 0.68
	SoC + D: 137/238 (57.6)	10.1	0.71	0.57, 0.90
	SoC: 171/241 (71.0)	9.7	NA	NA
Analysis to assess impact of assigning an event at the time of initiation of first subsequent therapy [c, e]	SoC + D + O: 126/239 (52.7)	15.1	0.53	0.42, 0.67
	SoC + D: 141/238 (59.2)	10.0	0.72	0.57, 0.90
	SoC: 175/241 (72.6)	9.5	NA	NA

a. Calculated using the KM technique. CI for median PFS was derived based on Brookmeyer-Crowley method.

b. A pooling strategy was applied to the primary comparisons of PFS for SoC + D + O versus SoC and SoC + D versus SoC whereby stratification factors were removed until there were at least 5 events in each stratum of interest across the 3 treatment arms, as defined in the SAP. This analysis was conducted with the same stratification factors. The HR and CI were estimated from a stratified Cox Proportional Hazards model with the following variables: MMR and disease status. The CI was calculated using a profile likelihood approach. A HR less than 1 favoured the treatment arm of interest over the reference arm.

c. Progression was determined by site Investigator assessment using RECIST 1.1.

d. Patients who initiated first subsequent therapy before progression were censored at the last evaluable RECIST assessment prior to taking the first subsequent therapy .

e. Patients who initiated first subsequent therapy before progression were treated as progression events at the date of their initiation of first subsequent therapy.

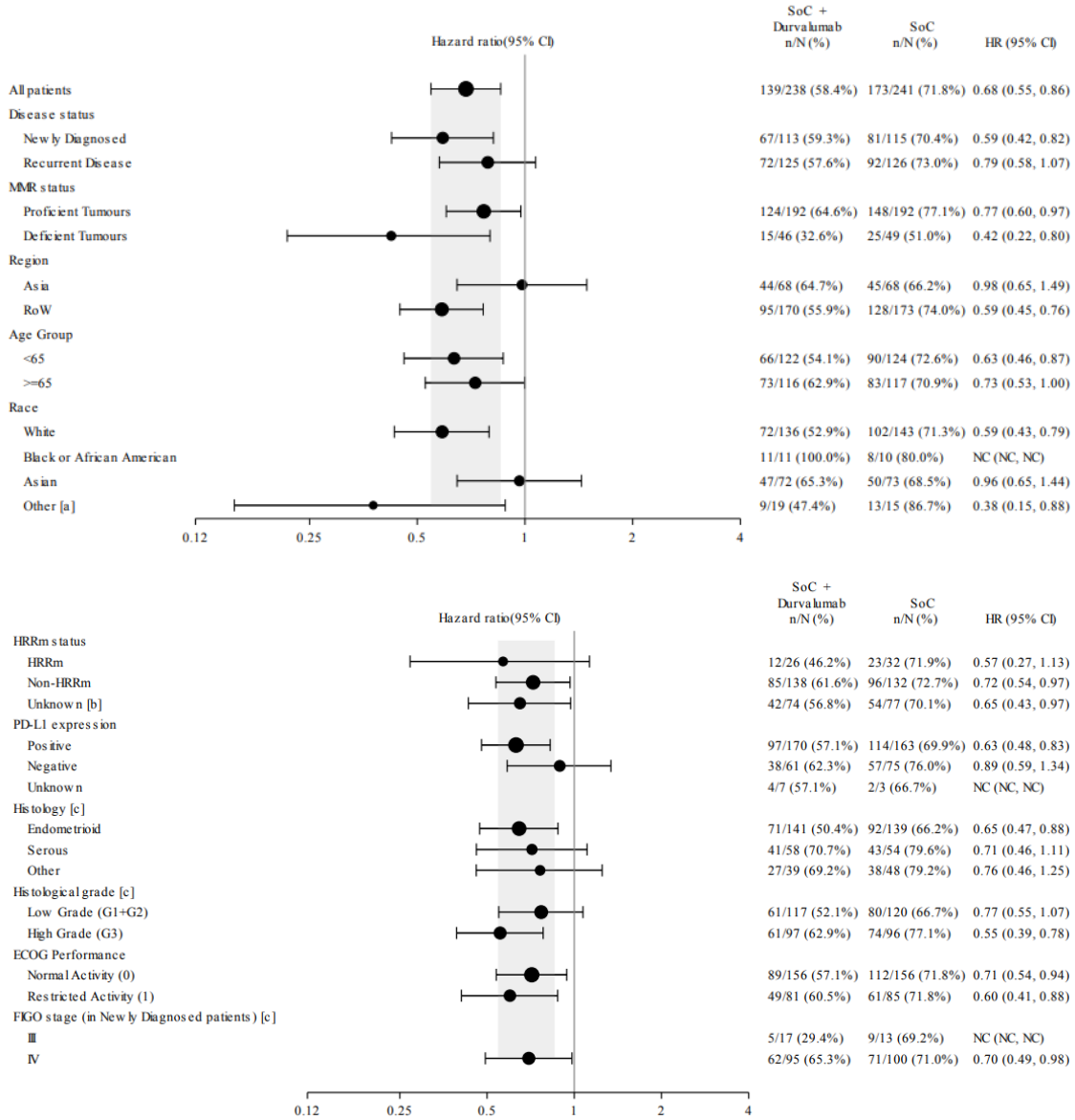
Sensitivity analyses of OS

Post-hoc OS sensitivity analyses were performed, upon request, using methods that do not rely on the proportional *hazards* assumption. An analysis using unstratified piecewise HRs calculated over distinct time periods was performed for OS at DCO1. In addition, further analyses using a 4-component, unstratified Max-Combo test, and an unstratified Restricted Mean Survival Time analysis of an area-under-the curve approach were provided (Fleming and Harrington 1991, Karrison 2016). These *post-hoc* analyses were overall concordant with the main OS analysis.

Subgroup analyses of PFS

Exploratory subgroup analyses of PFS were performed for pre-planned subgroups to assess the consistency of treatment effect across potential or expected prognostic/predictive factors.

Figure 16 Progression-free Survival, SoC + D Versus SoC, Forest Plot, by Subgroup (FAS; DCO 12 April 2023)



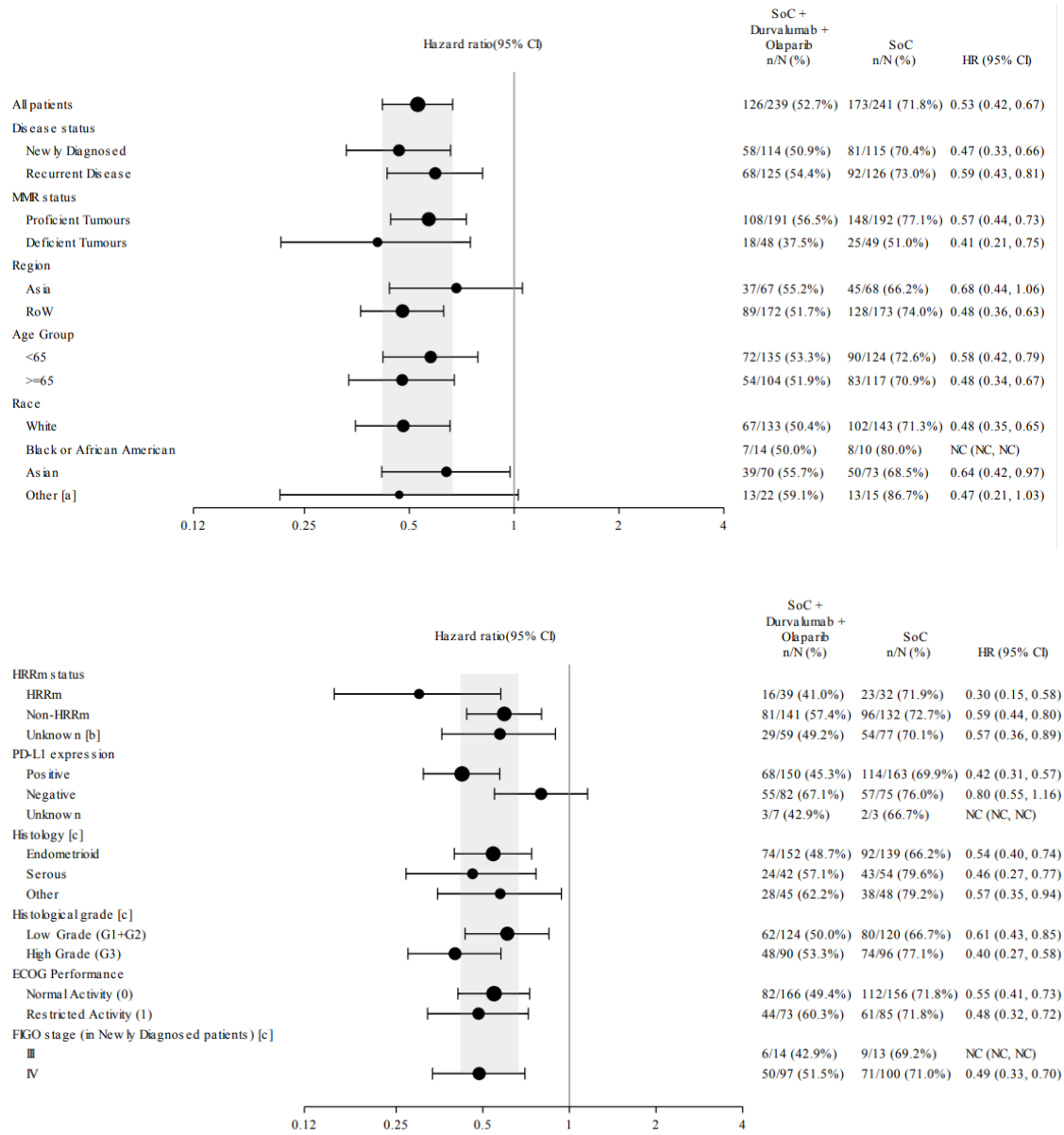
a. Includes patients with race 'Not reported'.

b. Includes patients recruited in China where HRR testing was not performed, patients with samples that were unavailable for testing.

c. As determined at time of initial diagnosis of disease under investigation. All other subgroups are measured at study baseline. RECIST version 1.1.

The hazard ratio and CI are estimated from an unstratified Cox proportional hazards models with treatment as the only covariate and with the Efron method to control for ties. The CI is calculated using a profile likelihood approach. A hazard ratio less than 1 will favour the treatment arm of interest over the reference arm. Size of the circles is proportional to the number of events. The grey band represents the 95% confidence interval for the overall (All patients) hazard ratio.

Figure 17 Progression-free Survival, SoC + D + O Versus SoC Forest Plot, by Subgroup (FAS; DCO 12 April 2023)



a. Includes patients with race 'Not reported'.

b. Includes patients recruited in China where HRR testing was not performed, patients with samples that were unavailable for testing.

c. As determined at time of initial diagnosis of disease under investigation. All other subgroups are measured at study baseline. RECIST version 1.1.

The hazard ratio and CI are estimated from an unstratified Cox proportional hazards models with treatment as the only covariate and with the Efron method to control for ties. The CI is calculated using a profile likelihood approach. A hazard ratio < 1 favours SoC + Durvalumab + Olaparib to be associated with a longer progression-free survival than SoC alone. Size of the circles is proportional to the number of events. The grey band represents the 95% confidence interval for the overall (All patients) hazard ratio.

Subgroup analyses of OS

At the time of DCO1 and the initial submission, OS subgroup analyses were not performed. These were pre-planned to be conducted at the time of the final analysis of OS with greater maturity, hence no OS forest plot was generated at the time of the primary analysis of PFS. *Post hoc* exploratory OS subgroup analyses were performed by PD-L1, HRRm and BRCAm, based on DCO1, and are provided below.

MMR Subgroups (as randomised)

In pre-planned exploratory subgroup analyses, PFS was investigated in the MMR status stratification factor subgroups. Study enrolment was for an ITT population in first-line advanced or recurrent endometrial cancer with randomisation stratified by MMR status (proficient versus deficient) using the FDA-cleared Class II Ventana MMR immunohistochemistry panel assay. In total, 575/718 patients (80.1%) were pMMR and 143/718 patients (19.9%) were dMMR.

A selected summary of patient demographics and disease characteristics by MMR status is presented in the below table.

Table 33 Selected Summary of Patient Demographics and Disease Characteristics by MMR Status (FAS; DCO 12 April 2023)

	FAS			dMMR			pMMR		
	SoC N=241	SoC + D N=238	SoC + D + O N=239	SoC N=49	SoC + D N=46	SoC + D + O N=48	SoC N=192	SoC + D N=192	SoC + D + O N=191
Demographics									
Age (years)									
Median	64.0	64.0	63.0	63.0	63.0	61.0	64.0	64.0	64.0
Min	31	22	27	34	45	40	31	22	27
Max	85	84	86	85	84	80	82	83	86
Age Group (years)									
< 65	124 (51.5)	122 (51.3)	135 (56.5)	25 (51.0)	25 (54.3)	37 (70.8)	99 (51.6)	97 (50.5)	101 (52.9)
≥ 65	117 (48.5)	116 (48.7)	104 (43.5)	24 (49.0)	21 (45.7)	14 (29.2)	93 (48.4)	95 (49.5)	90 (47.1)
Race									
White	143 (59.3)	136 (57.1)	133 (55.6)	30 (61.2)	29 (63.0)	29 (60.4)	113 (58.9)	107 (55.7)	104 (54.5)
Asian	73 (30.3)	72 (30.3)	70 (29.3)	15 (30.6)	14 (30.4)	13 (27.1)	58 (30.2)	58 (30.2)	57 (29.8)
Black or African American	10 (4.1)	11 (4.6)	14 (5.9)	2 (4.1)	0	1 (2.1)	8 (4.2)	11 (5.7)	13 (6.8)
Other	10 (4.1)	8 (3.4)	12 (5.0)	0	1 (2.2)	3 (6.3)	10 (5.2)	7 (3.6)	9 (4.7)
Not reported	3 (1.2)	5 (2.1)	3 (1.3)	2 (4.1)	1 (2.2)	2 (4.2)	1 (0.5)	4 (2.1)	1 (0.5)
Native Hawaiian or Other Pacific Islander	2 (0.8)	0	1 (0.4)	NA	NA	NA	2 (1.0)	0	1 (0.5)
American Indian or Alaska Native	0	6 (2.5)	6 (2.5)	0	1 (2.2)	0	0	5 (2.6)	6 (3.1)
Region by IVRS									
Asia	68 (28.2)	68 (28.6)	67 (28.0)	14 (28.6)	14 (30.4)	13 (27.1)	54 (28.1)	54 (28.1)	54 (28.3)
Rest of World	173 (71.8)	170 (71.4)	172 (72.0)	35 (71.4)	32 (69.6)	35 (72.9)	138 (71.9)	138 (71.9)	137 (71.7)
Disease Characteristics									
ECOG Performance Status									
(0) Normal activity	156 (64.7)	156 (65.5)	166 (69.5)	29 (59.2)	23 (50.0)	31 (64.6)	127 (66.1)	133 (69.3)	135 (70.7)

	FAS			dMMR			pMMR		
	SoC N=241	**SoC + D N=238**	**SoC + D + O N=239**	**SoC N=49**	**SoC + D N=46**	**SoC + D + O N=48**	**SoC N=192**	**SoC + D N=192**	**SoC + D + O N=191**
(1) Restricted activity	85 (35.3)	81 (34.0)	73 (30.5)	20 (40.8)	23 (50.0)	17 (35.4)	65 (33.9)	58 (30.2)	56 (29.3)
(2) In bed ≤ 50% of the time	0	1 (0.4)	0	0	0	0	0	1 (0.5)	0
Histology type									
Endometrioid	139 (57.7)	141 (59.2)	152 (63.6)	41 (83.7)	33 (71.7)	45 (93.8)	98 (51.0)	108 (56.3)	107 (56.0)
Serous	54 (22.4)	58 (24.4)	42 (17.6)	2 (4.1)	2 (4.3)	0	52 (27.1)	56 (29.2)	42 (22.0)
Carcinosarcoma	21 (8.7)	12 (5.0)	18 (7.5)	2 (4.1)	3 (6.5)	0	19 (9.9)	9 (4.7)	18 (9.4)
Mixed, epithelial	11 (4.6)	9 (3.8)	9 (3.8)	3 (6.1)	3 (6.5)	1 (2.1)	8 (4.2)	6 (3.1)	8 (4.2)
Clear cell	7 (2.9)	4 (1.7)	8 (3.3)	0	0	0	7 (3.6)	4 (2.1)	8 (4.2)
Other	6 (2.5)	9 (3.8)	5 (2.1)	1 (2.0)	4 (8.7)	0	5 (2.6)	5 (2.6)	5 (2.6)
Undifferentiated	3 (1.2)	4 (1.7)	5 (2.1)	0	1 (2.2)	2 (4.2)	3 (1.6)	3 (1.6)	3 (1.6)
Transitional cell	0	0	0	0	0	0	0	0	0
Mucinous	0	1 (0.4)	0	0	0	0	0	1 (0.5)	0
Disease Status [a]									
Newly Diagnosed									
Stage III	12 (5.0)	17 (7.1)	12 (5.0)	3 (6.1)	6 (13.0)	2 (4.2)	9 (4.7)	11 (5.7)	10 (5.2)
Stage IV	101 (41.9)	96 (40.3)	99 (41.4)	21 (42.9)	14 (30.4)	19 (39.6)	80 (41.7)	82 (42.7)	80 (41.9)
Recurrent	127 (52.7)	125 (52.5)	127 (53.1)	25 (51.0)	26 (56.5)	26 (54.2)	102 (53.1)	99 (51.6)	101 (52.9)
Prior chemotherapy									
Yes	51 (21.2)	51 (21.4)	54 (22.6)	5 (10.2)	6 (13.0)	4 (8.3)	46 (24.0)	45 (23.4)	50 (26.2)
No	190 (78.8)	187 (78.6)	185 (77.4)	44 (89.8)	40 (87.0)	44 (91.7)	146 (76.0)	147 (76.6)	141 (73.8)
Prior radiotherapy	71 (29.5)	73 (30.7)	85 (35.6)	18 (36.7)	17 (37.0)	18 (37.5)	53 (27.6)	56 (29.2)	67 (35.1)
HRRm Status									
Positive	32 (13.3)	26 (10.9)	39 (16.3)	15 (30.6)	12 (26.1)	18 (37.5)	17 (8.9)	14 (7.3)	21 (11.0)
Negative	132 (54.8)	138 (58.0)	141 (59.0)	21 (42.9)	17 (37.0)	23 (47.9)	111 (57.8)	121 (63.0)	118 (61.8)
Unknown [b]	77 (32.0)	74 (31.1)	59 (24.7)	13 (26.5)	17 (37.0)	7 (14.6)	64 (33.3)	57 (29.7)	52 (27.2)
PD-L1 Expression									
Positive	163 (67.6)	170 (71.4)	150 (62.8)	39 (79.6)	37 (80.4)	38 (79.2)	124 (64.6)	133 (69.3)	112 (58.6)
Negative	75 (31.1)	61 (25.6)	82 (34.3)	8 (16.3)	8 (17.4)	9 (18.8)	67 (34.9)	53 (27.6)	73 (38.2)
Unknown	3 (1.2)	7 (2.9)	7 (2.9)	2 (4.1)	1 (2.2)	1 (2.1)	1 (0.5)	6 (3.1)	6 (3.1)

	FAS			dMMR			pMMR		
	SoC N=241	SoC + D N=238	SoC + D + O N=239	SoC N=49	SoC + D N=46	SoC + D + O N=48	SoC N=192	SoC + D N=192	SoC + D + O N=191
***BRCAm* Status**									
Positive	15 (6.2)	11 (4.6)	15 (6.3)	5 (10.2)	5 (10.9)	8 (16.7)	10 (5.2)	6 (3.1)	7 (3.1)
Negative	149 (61.8)	153 (64.3)	165 (69.0)	31 (63.3)	24 (52.2)	33 (68.8)	118 (61.5)	129 (67.2)	132 (69.1)
Unknown [b]	77 (32.0)	74 (31.1)	59 (24.7)	13 (26.5)	17 (37.0)	7 (14.6)	64 (33.3)	57 (29.7)	52 (27.2)

a. Disease status (recurrent vs newly diagnosed) is as collected on the eCRF.

b. Retrospective testing of HRRm/*BRCAm* status was by the FoundationOneCDx (F1CDx) tumour tissue NGS assay (FoundationOneCDx-P170019/S017). Per data on file, the unknown samples include 26 patients with a failed F1CDx assay test, 43 patients who withdrew consent before their sample was shipped for testing and 141 patients whose HRRm/*BRCAm* testing could not be performed due to lack of sample availability (including all 36 patients enrolled from Mainland China where testing was not performed due to China HGR regulations).

Note: Tumour MMR testing was performed prospectively using the FDA-cleared Class II Ventana MMR IHC panel at the central laboratory. Tumour PD-L1 testing was performed retrospectively post-randomisation at the central laboratory on the same sample as MMR testing using the Ventana PD-L1 SP263 formulation locked assay with a tumour area positivity score and an exploratory cut-off of ≥ 1%.

BRCAm = *BRCA* mutation; CSR = clinical study report; DCO = data cut-off; dMMR = mismatch repair deficient; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; FAS = full analysis set; FDA = Food and Drug Administration; HGR = human genetic resources; HRRm = homologous recombination repair gene mutation; IHC = immunohistochemistry; IVRS = interactive voice response system; NGS = next generation sequencing; Max = maximum; Min = minimum; MMR = mismatch repair; N = number of patients in treatment; PD-L1 = programmed cell death-ligand 1; pMMR = mismatch repair proficient; SoC = standard of care; SoC + D = durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Overall, the median follow-up time for PFS in censored patients with dMMR tumour status was 15.5 months in the platinum-based chemotherapy + durvalumab arm and 10.2 months in the platinum-based chemotherapy arm. At the time of PFS analysis, interim OS data were 26% mature with events in 25 of 95 patients treated with platinum-based chemotherapy + durvalumab and platinum-based chemotherapy.

The median follow-up time in censored patients with pMMR tumour status was 15.2 months in the platinum-based chemotherapy + durvalumab + olaparib arm and 12.8 months in the platinum-based chemotherapy. At the time of PFS analysis, interim OS data were 29% mature with events in 110 of 383 patients.

Overall, there was a lower risk of disease progression (as assessed by the Investigator) or death in the SoC + D arm versus SoC and the SoC + D + O arm versus SoC, irrespective of MMR status.

Table 34 Progression-free Survival According to RECIST 1.1, Based on Investigator Assessments, by MMR Status (FAS; DCO 12 April 2023)

	SoC	SoC + D	SoC + D + O
dMMR			
Number (%) of patients with events / N [a]	25/49 (51.0)	15/46 (32.6)	18/48 (37.5)
Median PFS, months (95% CI) [b]	7.0 (6.7, 14.8)	NR (NR, NR)	31.8 (12.4, NR)
HR vs SoC (95% CI) [c]	NA	0.42 (0.22, 0.80)	0.41 (0.21, 0.75)
HR vs SoC + D (95% CI) [c]	NA	NA	0.97 (0.49, 1.98)
Patients alive & progression free at 12 months, % (95% CI) [b]	43.3 (27.3, 58.3)	67.9 (51.1, 80.0)	70.0 (54.7, 81.0)
Patients alive & progression free at 18 months, % (95% CI) [b]	31.7 (16.7, 47.9)	67.9 (51.1, 80.0)	62.7 (46.9, 75.0)

	SoC	SoC + D	SoC + D + O
pMMR			
Number (%) of patients with events / N [a]	148/192 (77.1)	124/192 (64.6)	108/191 (56.5)
Median PFS, months (95% CI) [b]	9.7 (9.2, 10.1)	9.9 (9.4, 12.5)	15.0 (12.4, 18.0)
HR vs SoC (95% CI) [c]	NA	0.77 (0.60, 0.97)	0.57 (0.44, 0.73)
HR vs SoC + D (95% CI) [c]	NA	NA	0.76 (0.59, 0.99)
Patients alive & progression free at 12 months, % (95% CI) [b]	40.8 (33.6, 47.8)	44.4 (37.1, 51.4)	59.4 (52.0, 66.0)
Patients alive & progression free at 18 months, % (95% CI) [b]	20.0 (14.1, 26.7)	31.3 (24.2, 38.6)	42.0 (34.1, 49.6)

a. Patients who had not progressed/died (or who progressed/died after 2 missed assessments) were censored at the latest visit (or the latest visit prior to the 2 missed assessments), or at Day 1.

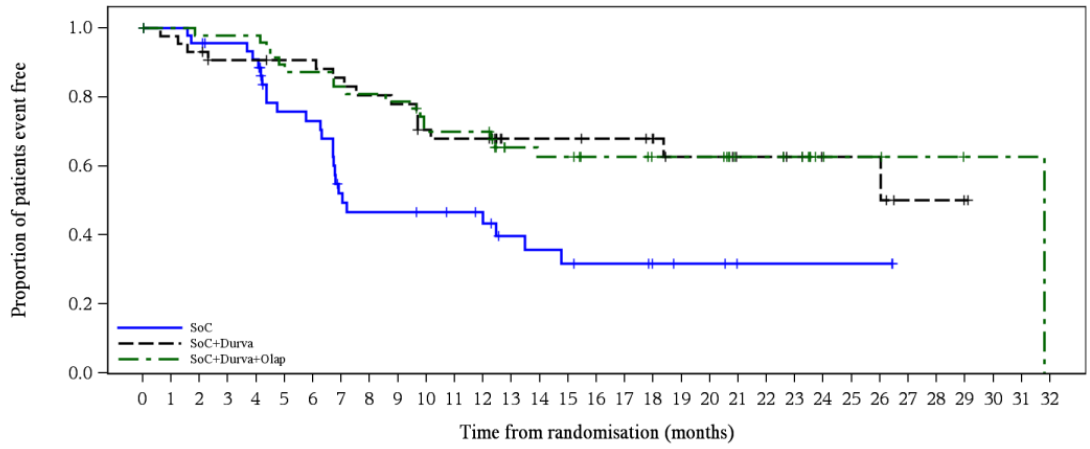
b. Calculated using the KM technique. CI for median PFS is derived based on the Brookmeyer-Crowley method.

c. The HR and CI were estimated from an unstratified CPH model. A HR less than 1 favoured the treatment arm of interest over the reference arm.

CI = Confidence interval; CPH = Cox Proportional Hazards; DCO = Data cut-off; dMMR = Mismatch repair deficient; FAS = Full Analysis Set; HR = Hazard ratio; KM = Kaplan-Meier; MMR = Mismatch repair; N = Total number of patients; NA = Not applicable; NR = Not reached; PFS = Time from randomisation to first progression or death; pMMR = Mismatch repair proficient; RECIST = Response Evaluation Criteria in Solid Tumours; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance; vs = Versus.

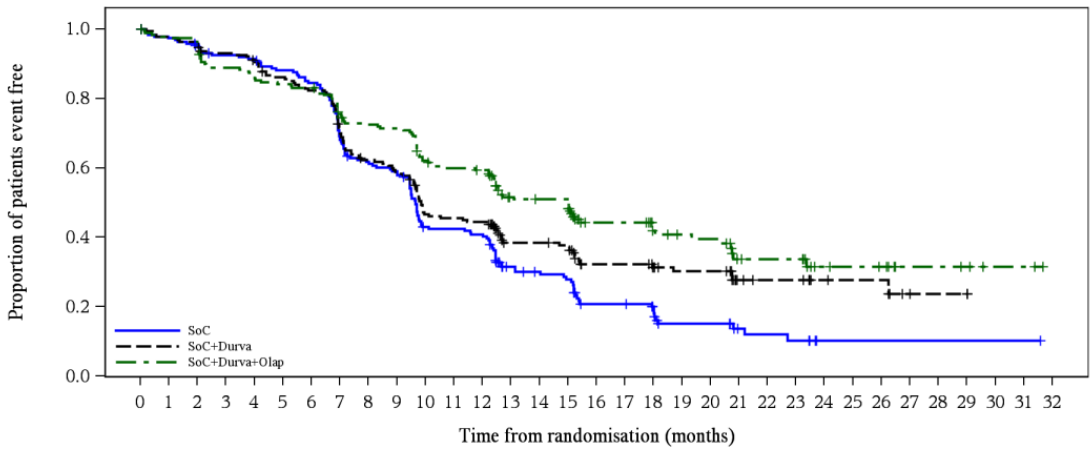
Figure 18 Progression-free Survival Kaplan-Meier Plot by MMR Status, Based on Investigator Assessments (FAS; DCO 12 April 2023)

dMMR Subgroup



Number of patients at risk																														Number of randomized patients/ number of events
SoC	49	45	43	41	39	29	28	19	17	17	16	15	13	10	9	8	7	7	5	4	4	2	2	2	2	2	2	0	0	0	0	0	0	49/25
SoC+Durva	46	42	40	37	37	36	36	34	32	31	27	26	26	19	19	19	17	17	14	11	11	9	9	7	5	5	5	2	2	1	0	0	0	46/15
SoC+Durva+Olap	48	47	46	46	46	41	41	39	38	37	32	32	32	24	23	23	18	18	16	16	16	10	10	9	4	3	3	2	2	1	1	1	0	48/18

pMMR Subgroup



Number of patients at risk																														Number of randomized patients/ number of events
SoC	192	184	178	172	170	163	156	126	113	108	77	76	73	44	40	37	25	25	21	13	13	8	7	6	1	1	1	1	1	1	1	1	0	192/148
SoC+Durva	192	186	182	174	169	159	152	128	113	107	83	81	79	53	53	50	36	36	31	27	27	17	15	15	8	7	7	3	2	2	0	0	0	192/124
SoC+Durva+Olap	191	185	183	168	164	159	157	141	134	132	114	109	107	77	75	72	46	46	35	32	31	20	19	19	12	11	10	5	5	4	2	2	0	191/108

+ indicates a censored observation. Progression was determined by site Investigator assessment using RECIST 1.1.

DCO = Data cut-off; dMMR = Mismatch repair deficient; Durva = Durvalumab; Olap = Olaparib; FAS = Full Analysis Set; pMMR = mismatch repair proficient; RECIST = Response Evaluation Criteria in Solid Tumours; SoC = Standard of care; SoC + Durva = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + Durva + Olap = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Table 35 Summary of Key Efficacy Endpoints by MMR Status (FAS; DCO 12 April 2023)

	FAS			dMMR			pMMR		
	SoC N=241	**SoC + D N=238**	**SoC + D + O N=239**	**SoC N=49**	**SoC + D N=46**	**SoC + D + O N=48**	**SoC N=192**	**SoC + D N=192**	**SoC + D + O N=191**
PFS									
Events (%) [a]	173 (71.8)	139 (58.4)	126 (52.7)	25 (51.0)	15 (32.6)	18 (37.5)	148 (77.1)	124 (64.6)	108 (56.5)
Median PFS (months) (95% CI) [b]	9.6 (9.0, 9.9)	10.2 (9.7, 14.7)	15.1 (12.6, 20.7)	7.0 (6.7, 14.8)	NR (NR, NR)	31.8 (12.4, NR)	9.7 (9.2, 10.1)	9.9 (9.4, 12.5)	15.0 (12.4, 18.0)
HR vs SoC (95% CI) [c, d]	NA	0.71 (0.57, 0.89)	0.55 (0.43, 0.69)	NA	0.42 (0.22, 0.80)	0.41 (0.21, 0.75)	NA	0.77 (0.60, 0.97)	0.57 (0.44, 0.73)
HR vs SoC + D (95% CI) [c, d]	NA	NA	0.78 (0.61, 0.99)	NA	NA	0.97 (0.49, 1.98)	NA	NA	0.76 (0.59, 0.99)
Patients alive & progression free at 12 months (%) (95% CI) [b]	41.1 (34.6, 47.5)	48.5 (41.8, 54.9)	61.5 (54.9, 67.4)	43.3 (27.3, 58.3)	67.9 (51.1, 80.0)	70.0 (54.7, 81.0)	40.8 (33.6, 47.8)	44.4 (37.1, 51.4)	59.4 (52.0, 66.0)
OS									
Events (%)	82 (34.0)	65 (27.3)	52 (21.8)	18 (36.7)	7 (15.2)	6 (12.5)	64 (33.3)	58 (30.2)	46 (24.1)
Median OS (months) (95% CI) [b]	25.9 (23.9, NR)	NR (NR, NR)	NR (NR, NR)	23.7 (16.9, NR)	NR (NR, NR)	NR (NR, NR)	25.9 (25.1, NR)	NR (NR, NR)	NR (NR, NR)
HR vs SoC (95% CI) [e]	NA	0.77 (0.56, 1.07)	0.59 (0.42, 0.83)	NA	0.34 (0.13, 0.79)	0.28 (0.10, 0.68)	NA	0.91 (0.64, 1.30)	0.69 (0.47, 1.00)
HR vs SoC + D (95% CI) [e]	NA	NA	0.77 (0.53, 1.10)	NA	NA	NC (NC, NC)	NA	NA	0.75 (0.51, 1.11)
Survival rate at 12 months (%) (95% CI) [b]	79.7 (74.0, 84.3)	84.2 (78.9, 88.3)	87.7 (82.7, 91.3)	74.4 (59.4, 84.6)	91.2 (78.2, 96.6)	89.2 (76.0, 95.4)	81.0 (74.6, 85.9)	82.5 (76.3, 87.2)	87.3 (81.7, 91.3)
ORR [f]									
Number of patients with response (%) [g] / N	109/198 (55.1)	125/202 (61.9)	117/184 (63.6)	17/42 (40.5)	30/42 (71.4)	27/37 (73.0)	92/156 (59.0)	95/160 (59.4)	90/147 (61.2)
Odds ratio vs SoC (95% CI)	NA	1.32 (0.89, 1.98)	1.44 (0.95, 2.18)	NA	3.68 (1.51, 9.39)	3.97 (1.57, 10.65)	NA	1.02 (0.65, 1.59)	1.10 (0.69, 1.74)
DoR									
Number of responders who subsequently progressed or died / Number of patients who responded (%)	78/109 (71.6)	63/125 (50.4)	50/117 (42.7)	6/17 (35.3)	7/30 (23.3)	8/27 (29.6)	72/92 (78.3)	56/95 (58.9)	42/90 (46.7)
DoR from onset of response (months), median [h]	7.7	13.1	21.3	10.5	NR	29.9	7.6	10.6	18.7

a. Patients who have not progressed/died (or who progress/die after 2 missed assessments) are censored at the latest visit (or the latest visit prior to the 2 missed assessments), or at Day 1.

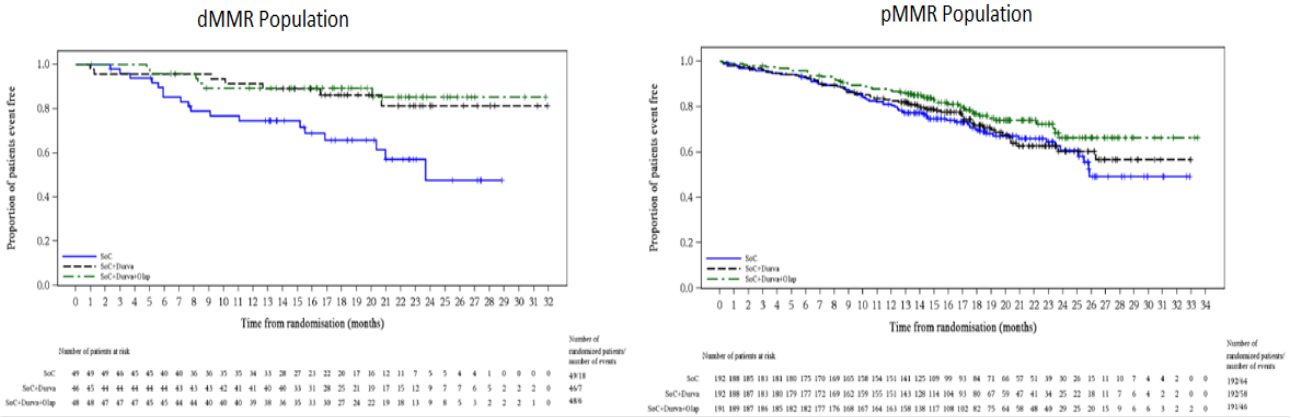
b. Calculated using the KM technique. CI for median PFS is derived based on Brookmeyer-Crowley method.

c. For the FAS, a pooling strategy was applied to the primary comparisons of PFS for SoC + D + O vs SoC and SoC + D vs SoC whereby stratification factors were removed until there were at least 5 events in each stratum of interest across the 3 treatment arms, as defined in the SAP. The HR and CI were estimated from a Cox Proportional Hazards model stratified by: MMR and disease status. An HR less than 1 will favour the treatment arm of interest over the reference arm.

d. For dMMR and pMMR, the HR and CI are estimated from an unstratified Cox Proportional Hazards model. A HR less than 1 will favour the investigational arm over SoC.
e. The HR and CI are estimated from an unstratified Cox Proportional Hazards model. The CI is calculated using a profile likelihood approach. An HR less than 1 will favour the treatment arm of interest over the reference arm.
f. The analysis was performed using logistic regression model adjusted with the following variables (by comparison): MMR and disease status.
g. Responses include confirmed responses of CR/PR that is recorded at 1 visit and confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit.
h. DoR is the time from the first confirmed CR/PR until the date of progression or the date of censoring for PFS. Calculated using the KM technique.

CI = confidence interval; CR = complete response; CSR = clinical study report; DCO = data cut-off; dMMR = mismatch repair deficient; DoR = duration of response; FAS = full analysis set; HR = hazard ratio; KM = Kaplan-Meier; MMR = mismatch repair; NA = not applicable; NC = not calculated; NR = not reached; ORR = objective response rate; OS = overall survival; PFS = progression free survival; pMMR = mismatch repair proficient; PR = partial response; SAP = statistical analysis plan; SoC = standard of care; SoC + D = durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Figure 19 KM Plots of OS Subgroup Analyses for the dMMR and pMMR Populations (FAS)



+ indicates a censored observation.

HRRm Subgroups (including BRCAm)

In pre-planned exploratory subgroup analyses, PFS was investigated in the HRRm subgroups. A subgroup analysis by BRCAm status was not pre-planned, however, a post hoc subgroup analysis by BRCAm status was performed.

Patients were randomised on study irrespective of their HRRm/BRCAm status. Central retrospective FoundationOne CDx next generation sequencing was conducted on the same tissue sample used to determine MMR and PD-L1 status to identify the mutation status in fourteen HRR genes (ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L). Overall, 97 patients (13.5%) were classified as HRRm, 411 patients (57.2%) as non-HRRm, and 210 patients (29.2%) as HRRm unknown (mutation testing was not performed or mutation testing failed.

Of the 97 patients classified as having an HRRm, 41 patients (5.7% of the FAS) had a known BRCA mutation (including one patient with co-occurring BRCA1 and BRCA2 mutations and this patient was only counted once), with a higher prevalence of BRCAm in the dMMR population. Overall, 467 patients (65.0% of the FAS) were non BRCAm, and 210 patients (29.2%) were BRCAm unknown.

Table 36 Progression-free Survival Subgroup Analyses by HRRm and BRCAm Status (FAS; DCO 12 April 2023)

	SoC	SoC + D	SoC + D + O
HRRm			
Number (%) of patients with events / N [a]	23/32 (71.9)	12/26 (46.2)	16/39 (41.0)
Median PFS, months (95% CI) [b]	9.5 (6.9, 12.5)	9.7 (7.0, NR)	NR (NR, NR)
HR vs SoC (95% CI) [c]	NA	0.57 (0.27, 1.13)	0.30 (0.15, 0.58)
HR vs SoC + D (95% CI) [c]	NA	NA	0.59 (0.28, 1.28)
Non-HRRm			
Number (%) of patients with events / N [a]	96/132 (72.7)	85/138 (61.6)	81/141 (57.4)
Median PFS, months (95% CI) [b]	9.7 (8.8, 12.4)	11.3 (9.7, 15.0)	15.0 (12.4, 20.3)
HR vs SoC (95% CI) [c]	NA	0.72 (0.54, 0.97)	0.59 (0.44, 0.80)
HR vs SoC + D (95% CI) [c]	NA	NA	0.83 (0.61, 1.13)
HRRm Unknown [d]			
Number (%) of patients with events / N [a]	54/77 (70.1)	42/74 (56.8)	29/59 (49.2)
Median PFS, months (95% CI) [b]	9.5 (7.0, 11.4)	9.9 (8.8, 18.4)	12.4 (8.4, NR)
HR vs SoC (95% CI) [c]	NA	0.65 (0.43, 0.97)	0.57 (0.36, 0.89)
HR vs SoC + D (95% CI) [c]	NA	NA	0.87 (0.54, 1.39)
BRCAm			
Number (%) of patients with events / N [a]	12/15 (80.0)	5/11 (45.5)	6/15 (40.0)
Median PFS, months (95% CI) [b]	9.8 (6.9, 12.5)	9.7 (0.6, NR)	NR (NR, NR)
HR vs SoC (95% CI) [c]	NA	NC (NC, NC)	NC (NC, NC)
HR vs SoC + D (95% CI) [c]	NA	NA	NC (NC, NC)
Non-*BRCAm*			
Number (%) of patients with events / N [a]	107/149 (71.8)	92/153 (60.1)	91/165 (55.2)
Median PFS, months (95% CI) [b]	9.7 (8.3, 12.2)	11.3 (9.7, 15.0)	15.1 (12.6, 20.7)
HR vs SoC (95% CI) [c]	NA	0.72 (0.54, 0.95)	0.56 (0.42, 0.74)
HR vs SoC + D (95% CI) [c]	NA	NA	0.78 (0.59, 1.05)
***BRCAm* Unknown [d]**			
Number (%) of patients with events / N [a]	54/77 (70.1)	42/74 (56.8)	29/59 (49.2)
Median PFS, months (95% CI) [b]	9.5 (7.0, 11.4)	9.9 (8.8, 18.4)	12.4 (8.4, NR)
HR vs SoC (95% CI) [c]	NA	0.65 (0.43, 0.97)	0.57 (0.36, 0.89)
HR vs SoC + D (95% CI) [c]	NA	NA	0.87 (0.54, 1.39)

a. Patients who had not progressed/died (or who progressed/died after 2 missed assessments) were censored at the latest visit (or the latest visit prior to the 2 missed assessments), or at Day 1.

b. Calculated using the KM technique. Confidence interval for median PFS is derived based on the Brookmeyer-Crowley method.

c. The HR and CI were estimated from an unstratified CPH model with treatment as the only covariate and with the Efron method to control for ties. A HR less than 1 favoured the treatment arm of interest over the reference arm. Analysis was not performed if there were too few events available for a meaningful analysis of a particular subgroup (less than 20 events across both treatment groups in a subgroup).

d. Retrospective testing of HRRm status used the FoundationOneCDx (F1CDx) tumour tissue NGS assay (FoundationOneCDx-P170019/S017). Per data on file, the unknown samples included 26 patients with a failed F1CDx assay test, 43 patients who withdrew consent before their sample was shipped for testing, and 141 patients whose HRRm testing could not be performed due to lack of sample availability (including all 36 patients enrolled from Mainland China where testing was not performed due to China HGR regulations).

RECIST Version 1.1.

BRCAm = Breast cancer susceptibility gene 1 or 2 mutation; *BRCAm* = Breast cancer susceptibility gene mutation; CI = Confidence interval; CPH = Cox Proportional Hazards; CSR = Clinical Study Report; DCO = Data cut-off; F1CDx = FoundationOneCDx; HGR = Human genetic resources; HR = Hazard ratio; HRRm = Homologous recombination repair gene mutation; N = Number for patients included in the subgroup analysis; NA = Not applicable; NC = Not calculated; NGS = Next-generation sequencing; NR = Not reached; PFS = Progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance; vs = Versus.

Table 37 Overall Survival Subgroup Analyses by HRRm Status (FAS; DCO 12 April 2023)

	SoC	SoC + D	SoC + D + O
Global (FAS)			
Events, n/N (%)	82/241 (34.0)	65/238 (27.3)	52/239 (21.8)
Median OS, months (95% CI) [a]	25.9 (23.9, NR)	NR (NR, NR)	NR (NR, NR)
HR vs SoC (95% CI) [b]		0.77 (0.56, 1.07)	0.59 (0.42, 0.83)
HRRm			
Events, n/N (%)	8/32 (25.0)	6/26 (23.1)	5/39 (12.8)
Median OS, months (95% CI) [a]	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)
HR vs SoC (95% CI) [b]		NC (NC, NC)	NC (NC, NC)
Non-HRRm			
Events, n/N (%)	52/132 (39.4)	34/138 (24.6)	33/141 (23.4)
Median OS, months (95% CI) [a]	25.1 (20.9, NR)	NR (NR, NR)	NR (NR, NR)
HR vs SoC (95% CI) [b]		0.56 (0.36, 0.87)	0.53 (0.34, 0.82)
HRR mutation unknown [c]			
Events, n/N (%)	22/77 (28.6)	25/74 (33.8)	14/59 (23.7)
Median OS, months (95% CI) [a]	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)
HR vs SoC (95% CI) [b]		1.17 (0.66, 2.09)	0.84 (0.42, 1.62)

a. Calculated using the KM technique. CI for median is derived based on the Brookmeyer-Crowley method.

b. The HR and CI are estimated from an unstratified Cox Proportional Hazards model. An HR less than 1 will favour the investigational arm over SoC.

c. Retrospective testing of HRRm/*BRCAm* status used the FoundationOneCDx (F1CDx) tumour tissue NGS assay. The unknown samples included patients with a failed F1CDx assay test, patients who withdrew consent before their sample was shipped for testing, and patients whose HRRm/*BRCAm* testing could not be performed due to lack of sample availability (including all patients enrolled from Mainland China where testing was not performed due to China HGR regulations). HRRm unknown and *BRCAm* unknown subgroups constitute the same subgroup of patients.

d. As per the statistical analysis plan, the HR and CI are not presented if there are less than 20 events per treatment comparison.

Table 38 Overall Survival Subgroup Analyses by *BRCAm* Status (FAS; DCO 12 April 2023)

	SoC	SoC + D	SoC + D + O
Global (FAS)			
Events, n/N (%)	82/241 (34.0)	65/238 (27.3)	52/239 (21.8)
Median OS, months (95% CI) [a]	25.9 (23.9, NR)	NR (NR, NR)	NR (NR, NR)
HR vs SoC (95% CI) [b]		0.77 (0.56, 1.07)	0.59 (0.42, 0.83)
BRCAm			
Events, n/N (%)	4/15 (26.7)	3/11 (27.3)	2/15 (13.3)
Median OS, months (95% CI) [a]	25.5 (17.3, NR)	NR (NR, NR)	NR (NR, NR)
HR vs SoC (95% CI) [b]		NC (NC, NC)	NC (NC, NC)
Non-BRCAm			
Events, n/N (%)	56/149 (37.6)	37/153 (24.2)	36/165 (21.8)
Median OS, months (95% CI) [a]	25.9 (22.9, NR)	NR (NR, NR)	NR (NR, NR)
HR vs SoC (95% CI) [b]		0.59 (0.39, 0.89)	0.52 (0.34, 0.79)
***BRCA* mutation unknown [c]**			
Events, n/N (%)	22/77 (28.6)	25/74 (33.8)	14/59 (23.7)
Median OS, months (95% CI) [a]	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)
HR vs SoC (95% CI) [b]		1.17 (0.66, 2.09)	0.84 (0.42, 1.62)

a. Calculated using the KM technique. CI for median is derived based on the Brookmeyer-Crowley method.

b. The HR and CI are estimated from an unstratified Cox Proportional Hazards model. An HR less than 1 favours the investigational arm over SoC.

c. Retrospective testing of HRRm/*BRCAm* status used the FoundationOneCDx (F1CDx) tumour tissue NGS assay. The unknown samples included patients with a failed F1CDx assay test, patients who withdrew consent before their sample was shipped for testing, and patients whose HRRm/*BRCAm* testing could not be performed due to lack of sample availability (including all patients enrolled from Mainland China where testing was not performed due to China HGR regulations). HRRm unknown and *BRCAm* unknown subgroups constitute the same subgroup of patients.

As per the statistical analysis plan, the HR and CI are not presented if there are less than 20 events per treatment comparison.

PD-L1 expression subgroups

In pre-planned exploratory subgroup analyses, PFS was investigated in the PD-L1 subgroups. Patients were randomised on study irrespective of their PD-L1 status. The Ventana SP263 PD L1 assay was used and PD-L1 positive samples were samples with PD L1 expression with a tumour area positivity score ≥ 1%. Negative PD L1 samples were samples with PD-L1 expression with a tumour area positivity score < 1%. Unknown PD-L1 samples were samples with PD-L1 expression not available either due to a test fail (unevaluable sample or assay failure) or sample slide out of cut-slide stability.

Table 39 PFS Subgroup Analyses by PD-L1 Expression (FAS)

	SoC	SoC + D	SoC + D + O
FAS			
Number (%) of patients with events / N [a]	173/241 (71.8)	139/238 (58.4)	126/239 (52.7)
Median PFS (months) (95% CI) b	9.6 (9.0, 9.9)	10.2 (9.7, 14.7)	15.1 (12.6, 20.7)
HR vs SoC (95% CI) c	NA	0.71 (0.57, 0.89)	0.55 (0.43, 0.69)
HR vs SoC + D (95% CI) c	NA	NA	0.78 (0.61, 0.99)
Positive			
Number (%) of patients with events / N [a]	114/163 (69.9)	97/170 (57.1)	68/150 (45.3)
Median PFS (months) [b]	9.5	11.3	20.8
HR vs SoC (95% CI) [d]	NA	0.63 (0.48, 0.83)	0.42 (0.31, 0.57)
HR vs SoC + D (95% CI) [d]	NA	NA	0.67 (0.49, 0.91)

	SoC	SoC + D	SoC + D + O
Negative			
Number (%) of patients with events / N [a]	57/75 (76.0)	38/61 (62.3)	55/82 (67.1)
Median PFS (months) [b]	9.9	9.7	10.1
HR vs SoC (95% CI) [d]	NA	0.89 (0.59, 1.34)	0.80 (0.55, 1.16)
HR vs SoC + D (95% CI) [d]	NA	NA	0.93 (0.61, 1.41)
Unknown			
Number (%) of patients with events / N [a]	2/3 (66.7)	4/7 (57.1)	3/7 (42.9)
Median PFS (months) [b]	6.9	12.7	Not reached
HR vs SoC (95% CI) [d]	NA	NC (NC, NC)	NC (NC, NC)
HR vs SoC + D (95% CI) [d]	NA	NA	NC (NC, NC)

a. Patients who have not progressed/died (or who progress/die after 2 missed assessments) are censored at the latest visit (or the latest visit prior to the 2 missed assessments), or at Day 1.

b. Calculated using the KM technique. CI for median PFS is derived based on Brookmeyer-Crowley method.

c. Note a pooling strategy was applied to the primary comparisons of PFS for SoC + D + O vs SoC and SoC + D vs SoC whereby stratification factors were removed until there were at least 5 events in each stratum of interest across the 3 treatment arms, as defined in the SAP. The HR and CI were estimated from a Cox Proportional Hazards model stratified by: MMR and disease status. An HR less than 1 will favour the treatment arm of interest over the reference arm.

d. The HR and CI are estimated from an unstratified Cox Proportional Hazards model with treatment as the only covariate and with the Efron method to control for ties. A HR less than 1 favours the treatment arm of interest over the reference arm. Analysis is not performed if there are too few events available for a meaningful analysis of a particular subgroup (less than 20 events across both treatment groups in a subgroup).

CI = confidence interval; FAS = full analysis set; HR = hazard ratio; HRR = homologous recombination repair; HRRm = homologous recombination repair gene mutation; KM = Kaplan-Meier; MMR = mismatch repair; NA = not applicable; NC = not calculated; PD-L1 = programmed cell death-ligand 1; PFS = progression free survival; SAP = statistical analysis plan; SoC = standard of care; SoC + D = durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Table 40 Overall Survival by PD-L1 Status (FAS; DCO 12 April 2023)

	SoC	SoC + D	SoC + D + O
Global (FAS)			
Events, n/N (%)	82/241 (34.0)	65/238 (27.3)	52/239 (21.8)
Median OS, months (95% CI) [a]	25.9 (23.9, NR)	NR (NR, NR)	NR (NR, NR)
HR vs SoC (95% CI) [b]		0.77 (0.56, 1.07)	0.59 (0.42, 0.83)
PD-L1 Positive			
Events, n/N (%)	56/163 (34.4)	43/170 (25.3)	25/150 (16.7)
Median OS, months (95% CI) [a]	25.8 (23.7, NR)	NR (NR, NR)	NR (NR, NR)
HR vs SoC (95% CI) [b]		0.65 (0.44, 0.97)	0.42 (0.26, 0.67)
PD-L1 Negative			
Events, n/N (%)	24/75 (32.0)	20/61 (32.8)	25/82 (30.5)
Median OS, months (95% CI) [a]	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)
HR vs SoC (95% CI) [b]		1.19 (0.65, 2.16)	0.99 (0.56, 1.74)

a. Calculated using the KM technique. CI for the median is derived based on the Brookmeyer-Crowley method.

b. The HR and CI are estimated from an unstratified Cox Proportional Hazards model. A HR less than 1 will favour the investigational arm over SoC.

As per the statistical analysis plan, the HR and CI are not presented if there are less than 20 events per treatment comparison. For example, within the PD-L1 unknown subgroup, as only 17 patients (2.4%) were randomised (OS results in PD-L1 unknown patients are available on request [Table 4110.1.3])

Note: Tumour PD-L1 testing was performed retrospectively post-randomization at a central laboratory on the same samples as MMR testing using the Ventana PD-L1 SP263 formulation locked assay with a tumour area positivity score and an exploratory cut-off of ≥1%. PD-L1 negative samples were samples with PD-L1 status with a tumour area positivity score <1%.

Additional exploratory subgroup analyses by MRR status

Within the dMMR and pMMR sub-populations, post-hoc subgroup-by-subgroup analyses of PFS by PD-L1 status, HRRm status, and BRCAm status were performed, upon request, using data from the primary PFS analysis DCO (DCO1).

dMMR sub-population

dMMR sub-population by PD-L1 subgroups

Of the 143 patients randomised in the dMMR sub-population, the majority of patients (80%; 114/143) were PD-L1 positive, as anticipated based on published literature indicating increased PD-L1 expression and immune cell infiltration in dMMR endometrial cancer (Asaka et al 2019).

Table 41 PFS Subgroup Analyses for the ITT Population and dMMR Subgroup (per IVRS) by PD-L1 Status (FAS; DCO 12 April 2023)

		All patients			dMMR		
		SoC	**SoC + D**	**SoC + D + O**	**SoC**	**SoC + D**	**SoC + D + O**
All patients	**Events, n/N (%)**	173/241 (71.8)	139/238 (58.4)	126/239 (52.7)	25/49 (51.0)	15/46 (32.6)	18/48 (37.5)
	Median PFS, months (95% CI) [a]	9.6 (9.0, 9.9)	10.2 (9.7, 14.7)	15.1 (12.6, 20.7)	7.0 (6.7, 14.8)	NR (NR, NR)	31.8 (12.4, NR)
	HR vs SoC (95% CI) [b]		0.68 (0.55, 0.86)	0.53 (0.42, 0.67)		0.42 (0.22, 0.80)	0.41 (0.21, 0.75)
PD-L1 positive	**Events, n/N (%)**	114/163 (69.9)	97/170 (57.1)	68/150 (45.3)	20/39 (51.3)	12/37 (32.4)	14/38 (36.8)
	Median PFS, months (95% CI) [a]	9.5 (7.9, 9.9)	11.3 (9.7, 15.4)	20.8 (15.1, NR)	7.0 (6.7, NR)	NR (NR, NR)	31.8 (12.4, NR)
	HR vs SoC (95% CI) [b]		0.63 (0.48, 0.83)	0.42 (0.31, 0.57)		0.41 (0.19, 0.84)	0.41 (0.20, 0.82)
PD-L1 negative	**Events, n/N (%)**	57/75 (76.0)	38/61 (62.3)	55/82 (67.1)	4/8 (50.0)	3/8 (37.5)	3/9 (33.3)
	Median PFS, months (95% CI) [a]	9.9 (7.6, 12.5)	9.7 (7.0, 14.7)	10.1 (9.5, 15.0)	12.5 (5.7, NR)	NR (NR, NR)	NR (NR, NR)
	HR vs SoC (95% CI) [b]		0.89 (0.59, 1.34)	0.80 (0.55, 1.16)		NC (NC, NC)	NC (NC, NC)

a. Calculated using the Kaplan-Meier technique. CI for median is derived based on the Brookmeyer-Crowley method.

b. The HR and CI are estimated from an unstratified CPH model. A HR less than 1 will favour the investigational arm over SoC. As per the statistical analysis plan, the HR and CI are not presented if there are less than 20 events per treatment comparison.

PFS according to RECIST 1.1, based on site investigator assessments.

Table 42 OS Subgroup Analyses for ITT Population and dMMR Subgroup (per IVRS) by PD-L1 Status (FAS; DCO 12 April 2023)

		All patients			dMMR		
		SoC	**SoC + D**	**SoC + D + O**	**SoC**	**SoC + D**	**SoC + D + O**
All patients	**Events, n/N (%)**	82/241 (34.0)	65/238 (27.3)	52/239 (21.8)	18/49 (36.7)	7/46 (15.2)	6/48 (12.5)
	Median OS, months (95% CI) [a]	25.9 (23.9, NR)	NR (NR, NR)	NR (NR, NR)	23.7 (16.9, NR)	NR (NR, NR)	NR (NR, NR)

		All patients			dMMR		
		SoC	SoC + D	SoC + D + O	SoC	SoC + D	SoC + D + O
	HR vs SoC (95% CI) [b]		0.77 (0.56, 1.07)	0.59 (0.42, 0.83)		0.34 (0.13, 0.79)	0.28 (0.10, 0.68)
PD-L1 positive	Events, n/N (%)	56/163 (34.4)	43/170 (25.3)	25/150 (16.7)	16/39 (41.0)	5/37 (13.5)	5/38 (13.2)
	Median OS, months (95% CI) [a]	25.8 (23.7, NR)	NR (NR, NR)	NR (NR, NR)	23.7 (15.5, NR)	NR (NR, NR)	NR (NR, NR)
	HR vs SoC (95% CI) [b]		0.65 (0.44, 0.97)	0.42 (0.26, 0.67)		0.26 (0.08-0.66)	0.25 (0.08-0.65)
PD-L1 negative	Events, n/N (%)	24/75 (32.0)	20/61 (32.8)	25/82 (30.5)	1/8 (12.5)	2/8 (25.0)	0/9 (0.0)
	Median OS, months (95% CI) [a]	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)
	HR vs SoC (95% CI) [b]		1.19 (0.65, 2.16)	0.99 (0.56, 1.74)		NC (NC, NC)	NC (NC, NC)

a. Calculated using the Kaplan-Meier technique. CI for median is derived based on the Brookmeyer-Crowley method.

b. The HR and CI are estimated from an unstratified CPH model. A HR less than 1 will favour the investigational arm over SoC. As per the statistical analysis plan, the HR and CI are not presented if there are less than 20 events per treatment comparison.

dMMR sub-population by HRRm subgroups

Of the 143 patients randomised in the dMMR sub-population, more patients (31.5%; 45/143) compared to the pMMR sub-population (9%; 52/575) were HRRm, as anticipated based on published literature linking MMR deficiency and hypermutation (Campbell et al 2017).

Table 43 PFS Subgroup Analyses for the ITT Population and dMMR Subgroup (per IVRS) by HRRm Status (FAS; DCO 12 April 2023)

		All patients			dMMR		
		SoC	**SoC + D**	**SoC + D + O**	**SoC**	**SoC + D**	**SoC + D + O**
All patients	**Events, n/N (%)**	173/241 (71.8)	139/238 (58.4)	126/239 (52.7)	25/49 (51.0)	15/46 (32.6)	18/48 (37.5)
	Median PFS, months (95% CI) [a]	9.6 (9.0, 9.9)	10.2 (9.7, 14.7)	15.1 (12.6, 20.7)	7.0 (6.7, 14.8)	NR (NR, NR)	31.8 (12.4, NR)
	HR vs SoC (95% CI) [b]		0.68 (0.55, 0.86)	0.53 (0.42, 0.67)		0.42 (0.22, 0.80)	0.41 (0.21, 0.75)
HRRm	**Events, n/N (%)**	23/32 (71.9)	12/26 (46.2)	16/39 (41.0)	8/15 (53.3)	4/12 (33.3)	5/18 (27.8)
	Median PFS, months (95% CI) [a]	9.5 (6.9,12.5)	9.7 (7.0,NR)	NR (NR,NR)	13.5 (6.3, NR)	NR (NR, NR)	NR (NR, NR)
	HR vs SoC (95% CI) [b]		0.57 (0.27, 1.13)	0.30 (0.15, 0.58)		NC (NC, NC)	NC (NC, NC)
Non-HRRm	**Events, n/N (%)**	96/132 (72.7)	85/138 (61.6)	81/141 (57.4)	11/21 (52.4)	7/17 (41.2)	11/23 (47.8)
	Median PFS, months (95% CI) [a]	9.7 (8.8,12.4)	11.3 (9.7,15.0)	15.0 (12.4,20.3)	6.8 (4.4, NR)	26.0 (7.5, NR)	31.8 (9.9, NR)
	HR vs SoC (95% CI) [b]		0.72 (0.54, 0.97)	0.59 (0.44, 0.80)		NC (NC, NC)	0.46 (0.19, 1.11)
HRRm unknown	**Events, n/N (%)**	54/77 (70.1)	42/74 (56.8)	29/59 (49.2)	6/13 (46.2)	4/17 (23.5)	2/7 28.6)
	Median PFS, months (95% CI) [a]	9.5 (7.0,11.4)	9.9 (8.8,18.4)	12.4 (8.4, NR)	6.8 (4.2, NR)	NR (NR, NR)	NR (NR, NR)
	HR vs SoC (95% CI) [b]		0.65 (0.43,0.97)	0.57 (0.36,0.89)		NC (NC, NC)	NC (NC, NC)

a. Calculated using the Kaplan-Meier technique. CI for median is derived based on the Brookmeyer-Crowley method.

b. The HR and CI are estimated from an unstratified CPH model. A HR less than 1 will favour the investigational arm over SoC.

As per the statistical analysis plan, the HR and CI are not presented if there are less than 20 events per treatment comparison.

PFS according to RECIST 1.1, based on site investigator assessments.

Table 44 OS Subgroup Analyses by ITT Population and dMMR Subgroup (per IVRS) by HRRm Status (FAS; DCO 12 April 2023)

		All patients			dMMR		
		SoC	**SoC + D**	**SoC + D + O**	**SoC**	**SoC + D**	**SoC + D + O**
All patients	**Events, n/N (%)**	82/241 (34.0)	65/238 (27.3)	52/239 (21.8)	18/49 (36.7)	7/46 (15.2)	6/48 (12.5)
	Median OS, months (95% CI) [a]	25.9 (23.9, NR)	NR (NR, NR)	NR (NR, NR)	23.7 (16.9, NR)	NR (NR, NR)	NR (NR, NR)
	HR vs SoC (95% CI) [b]		0.77 (0.56, 1.07)	0.59 (0.42, 0.83)		0.34 (0.13, 0.79)	0.28 (0.10, 0.68)
HRRm	**Events, n/N (%)**	8/32 (25.0)	6/26 (23.1)	5/39 (12.8)	3/15 (20.0)	3/12 (25.0)	2/18 (11.1)
	Median OS, months (95% CI) [a]	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)
	HR vs SoC (95% CI) [b]		NC (NC, NC)	NC (NC, NC)		NC (NC, NC)	NC (NC, NC)
Non-HRRm	**Events, n/N (%)**	52/132 (39.4)	34/138 (24.6)	33/141 (23.4)	10/21 (47.6)	1/17 (5.9)	3/23 (13.0)
	Median OS, months (95% CI) [a]	25.1 (20.9, NR)	NR (NR, NR)	NR (NR, NR)	20.3 (7.6, NR)	NR (NR, NR)	NR (NR, NR)
	HR vs SoC (95% CI) [b]		0.56 (0.36,0.87)	0.53 (0.34,0.82)		NC (NC, NC)	NC (NC, NC)
HRRm unknown	**Events, n/N (%)**	22/77 (28.6)	25/74 (33.8)	14/59 (23.7)	5/13 (38.5)	3/17 (17.6)	1/7 (14.3)
	Median OS, months (95% CI) [a]	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)
	HR vs SoC (95% CI) [b]		1.17 (0.66, 2.09)	0.84 (0.42, 1.62)		NC (NC, NC)	NC (NC, NC)

a. Calculated using the Kaplan-Meier technique. CI for median is derived based on the Brookmeyer-Crowley method.

b. The HR and CI are estimated from an unstratified CPH model. A HR less than 1 will favour the investigational arm over SoC.

As per the statistical analysis plan, the HR and CI are not presented if there are less than 20 events per treatment comparison.

dMMR sub-population by BRCAm subgroups

Of the 143 patients randomised in the dMMR sub-population, relatively more patients (12.6%; 18/143) compared to the pMMR sub-population (4%; 23/575) were BRCAm.

Table 45 PFS Subgroup Analyses for the ITT Population and dMMR Subgroup (per IVRS) by BRCAm **Status (FAS; DCO 12 April 2023)**

		All patients			dMMR		
		SoC	**SoC + D**	**SoC + D + O**	**SoC**	**SoC + D**	**SoC + D + O**
All patients	**Events, n/N (%)**	173/241 (71.8)	139/238 (58.4)	126/239 (52.7)	25/49 (51.0)	15/46 (32.6)	18/48 (37.5)
	Median PFS, months (95% CI) [a]	9.6 (9.0,9.9)	10.2 (9.7, 14.7)	15.1 (12.6, 20.7)	7.0 (6.7, 14.8)	NR (NR, NR)	31.8 (12.4, NR)
	HR vs SoC (95% CI) [b]		0.68 (0.55, 0.86)	0.53 (0.42, 0.67)		0.42 (0.22, 0.80)	0.41 (0.21, 0.75)
BRCAm	**Events, n/N (%)**	12/15 (80.0)	5/11 (45.5)	6/15 (40.0)	4/5 (80.0)	3/5 (60.0)	2/8 (25.0)
	Median PFS, months (95% CI) [a]	9.8 (6.9,12.5)	9.7 (0.6, NR)	NR (NR, NR)	7.0 (4.2, NR)	8.4 (0.6, NR)	NR (NR, NR)
	HR vs SoC (95% CI) [b]		NC (NC, NC)	NC (NC, NC)		NC (NC, NC)	NC (NC, NC)
Non-*BRCAm*	**Events, n/N (%)**	107/149 (71.8)	92/153 (60.1)	91/165 (55.2)	15/31 (48.4)	8/24 (33.3)	14/33 (42.4)
	Median PFS, months (95% CI) [a]	9.7 (8.3,12.2)	11.3 (9.7,15.0)	15.1 (12.6, 20.7)	12.0 (6.3, NR)	26.0 (9.7, NR)	31.8 (12.3, NR)
	HR vs SoC (95% CI) [b]		0.72 (0.54, 0.95)	0.56 (0.42, 0.74)		0.52 (0.21,1.21)	0.51 (0.24,1.09)
***BRCAm* unknown**	**Events, n/N (%)**	54/77 (70.1)	42/74 (56.8)	29/59 (49.2)	6/13 (46.2)	4/17 (23.5)	2/7 (28.6)
	Median PFS, months (95% CI) [a]	9.5 (7.0, 11.4)	9.9 (8.8,18.4)	12.4 (8.4, NR)	6.8 (4.2, NR)	NR (NR, NR)	NR (NR, NR)
	HR vs SoC (95% CI) [b]		0.65 (0.43,0.97)	0.57 (0.36,0.89)		NC (NC, NC)	NC (NC, NC)

a. Calculated using the Kaplan-Meier technique. CI for median is derived based on the Brookmeyer-Crowley method.

b. The HR and CI are estimated from an unstratified CPH model. A HR less than 1 will favour the investigational arm over SoC.

As per the statistical analysis plan, the HR and CI are not presented if there are less than 20 events per treatment comparison.

PFS according to RECIST 1.1, based on site investigator assessments.

Table 46 OS Subgroup Analyses for the ITT Population and dMMR Subgroup (per IVRS) by *BRCAm* Status (FAS; DCO 12 April 2023)

		All patients			dMMR		
		SoC	**SoC + D**	**SoC + D + O**	**SoC**	**SoC + D**	**SoC + D + O**
All patients	**Events, n/N (%)**	82/241 (34.0)	65/238 (27.3)	52/239 (21.8)	18/49 (36.7)	7/46 (15.2)	6/48 (12.5)
	Median PFS, months (95% CI) [a]	25.9 (23.9, NR)	NR (NR, NR)	NR (NR, NR)	23.7 (16.9, NR)	NR (NR, NR)	NR (NR, NR)
	HR vs SoC (95% CI) [b]		0.77 (0.56, 1.07)	0.59 (0.42, 0.83)		0.34 (0.13, 0.79)	0.28 (0.10, 0.68)
BRCAm	**Events, n/N (%)**	4/15 (26.7)	3/11 (27.3)	2/15 (13.3)	2/5 (40.0)	2/5 (40.0)	1/8 (12.5)
	Median PFS, months (95% CI) [a]	25.5 (17.3, NR)	NR (NR, NR)	NR (NR, NR)	23.7 (5.9, NR)	NR (NR, NR)	NR (NR, NR)
	HR vs SoC (95% CI) [b]		NC (NC, NC)	NC (NC, NC)		NC (NC, NC)	NC (NC, NC)
Non-*BRCAm*	**Events, n/N (%)**	56/149 (37.6)	37/153 (24.2)	36/165 (21.8)	11/31 (35.5)	2/24 (8.3)	4/33 (12.1)
	Median PFS, months (95% CI) [a]	25.9 (22.9, NR)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)
	HR vs SoC (95% CI) [b]		0.59 (0.39, 0.89)	0.52 (0.34, 0.79)		NC (NC, NC)	NC (NC, NC)
***BRCAm* unknown**	**Events, n/N (%)**	22/77 (28.6)	25/74 (33.8)	14/59 (23.7)	5/13 (38.5)	3/17 (17.6)	1/7 (14.3)
	Median PFS, months (95% CI) [a]	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)
	HR vs SoC (95% CI) [b]		1.17 (0.66, 2.09)	0.84 (0.42, 1.62)		NC (NC, NC)	NC (NC, NC)

a. Calculated using the Kaplan-Meier technique. CI for median is derived based on the Brookmeyer-Crowley method.

b. The HR and CI are estimated from an unstratified CPH model. A HR less than 1 will favour the investigational arm over SoC.

As per the statistical analysis plan, the HR and CI are not presented if there are less than 20 events per treatment comparison.

pMMR sub-population

pMMR sub-population by PD-L1 subgroups

Of the 575 patients randomized in the pMMR sub-population, most patients (64%; 369/575) were PD-L1 positive.

In the pMMR/PD-L1 positive subgroup, the PFS results for each experimental arm versus SoC are consistent with the overall pMMR subgroup analysis results (SoC + D vs SoC: HR: 0.71; 95% CI: 0.53, 0.95; SoC + D + O vs SoC: HR: 0.44; 95% CI: 0.31, 0.61, see Table 37). Similarly, OS in the pMMR/PD-L1 positive subgroup for each experimental arm versus SoC are consistent (SoC + D vs SoC HR: 0.83; 95% CI: 0.53, 1.29; SoC + D + O vs SoC HR: 0.50; 95% CI: 0.29, 0.85).

In the pMMR/PD-L1 negative subgroup, a numerical improvement in PFS for the SoC + D arm vs SoC and SoC + D + O arm vs SoC were observed (SoC + D vs SoC HR: 0.95; 95% CI: 0.61, 1.45; SoC + D + O vs SoC HR: 0.87; 95% CI: 0.59, 1.28, see Table 37). An OS HR of 1.16 (95% CI 0.62, 2.15) was observed for the SoC + D arm vs SoC and an OS HR of 1.01 (95% CI 0.57, 1.80) was observed for the SoC + D + O arm vs SoC.

Table 47 PFS Subgroup Analyses for the ITT Population and pMMR Subgroup (per IVRS) by PD-L1 Status (FAS; DCO 12 April 2023)

		All patients			pMMR		
		SoC	**SoC + D**	**SoC + D + O**	**SoC**	**SoC + D**	**SoC + D + O**
All patients	**Events, n/N (%)**	173/241 (71.8)	139/238 (58.4)	126/239 (52.7)	148/192 (77.1)	124/192 (64.6)	108/191 (56.5)
	Median PFS, months (95% CI) [a]	9.6 (9.0, 9.9)	10.2 (9.7, 14.7)	15.1 (12.6, 20.7)	9.7 (9.2, 10.1)	9.9 (9.4, 12.5)	15.0 (12.4, 18.0)
	HR vs SoC (95% CI) [b]		0.68 (0.55, 0.86)	0.53 (0.42, 0.67)		0.77 (0.60, 0.97)	0.57 (0.44, 0.73)
PD-L1 positive	**Events, n/N (%)**	114/163 (69.9)	97/170 (57.1)	68/150 (45.3)	94/124 (75.8)	85/133 (63.9)	54/112 (48.2)
	Median PFS, months (95% CI) [a]	9.5 (7.9, 9.9)	11.3 (9.7, 15.4)	20.8 (15.1, NR)	9.5 (8.3, 9.9)	9.9 (9.5, 12.5)	18.1 (12.7, NR)
	HR vs SoC (95% CI) [b]		0.63 (0.48, 0.83)	0.42 (0.31, 0.57)		0.71 (0.53, 0.95)	0.44 (0.31, 0.61)
PD-L1 negative	**Events, n/N (%)**	57/75 (76.0)	38/61 (62.3)	55/82 (67.1)	53/67 (79.1)	35/53 (66.0)	52/73 (71.2)
	Median PFS, months (95% CI) [a]	9.9 (7.6, 12.5)	9.7 (7.0, 14.7)	10.1 (9.5, 15.0)	9.8 (7.6, 12.4)	8.9 (6.9, 12.7)	9.7 (8.4, 12.6)
	HR vs SoC (95% CI) [b]		0.89 (0.59, 1.34)	0.80 (0.55, 1.16)		0.95 (0.61, 1.45)	0.87 (0.59, 1.28)

a. Calculated using the Kaplan-Meier technique. CI for median is derived based on the Brookmeyer-Crowley method.

b. The HR and CI are estimated from an unstratified CPH model. A HR less than 1 will favour the investigational arm over SoC.

As per the statistical analysis plan, the HR and CI are not presented if there are less than 20 events per treatment comparison.

Progression-free survival (PFS) according to RECIST 1.1, based on site investigator assessments.

Table 48 OS Subgroup Analyses for the ITT Population and pMMR Subgroup (per IVRS) by PD-L1 Status (FAS; DCO 12 April 2023)

		All patients			pMMR		
		SoC	**SoC + D**	**SoC + D + O**	**SoC**	**SoC + D**	**SoC + D + O**
All patients	**Events, n/N (%)**	82/241 (34.0)	65/238 (27.3)	52/239 (21.8)	64/192 (33.3)	58/192 (30.2)	46/191 (24.1)
	Median OS, months (95% CI) [a]	25.9 (23.9, NR)	NR (NR, NR)	NR (NR, NR)	25.9 (25.1, NR)	NR (NR, NR)	NR (NR, NR)
	HR vs SoC (95% CI) [b]		0.77 (0.56, 1.07)	0.59 (0.42, 0.83)		0.91 (0.64, 1.30)	0.69 (0.47, 1.00)
PD-L1 positive	**Events, n/N (%)**	56/163 (34.4)	43/170 (25.3)	25/150 (16.7)	40/124 (32.3)	38/133 (28.6)	20/112 (17.9)
	Median OS, months (95% CI) [a]	25.8 (23.7, NR)	NR (NR, NR)	NR (NR, NR)	25.9 (25.1, NR)	NR (NR, NR)	NR (NR, NR)
	HR vs SoC (95% CI) [b]		0.65 (0.44, 0.97)	0.42 (0.26, 0.67)		0.83 (0.53-1.29)	0.50 (0.29-0.85)
PD-L1 negative	**Events, n/N (%)**	24/75 (32.0)	20/61 (32.8)	25/82 (30.5)	23/67 (34.3)	18/53 (34.0)	25/73 (34.2)
	Median OS, months (95% CI) [a]	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)
	HR vs SoC (95% CI) [b]		1.19 (0.65, 2.16)	0.99 (0.56, 1.74)		1.16 (0.62-2.15)	1.01 (0.57 -1.80)

a. Calculated using the Kaplan-Meier technique. CI for median is derived based on the Brookmeyer-Crowley method.

b. The HR and CI are estimated from an unstratified CPH model. A HR less than 1 will favour the investigational arm over SoC.

As per the statistical analysis plan, the HR and CI are not presented if there are less than 20 events per treatment comparison.

pMMR sub-population by HRRm subgroups

Of the 575 patients randomized in the pMMR sub-population, only 9% (52/575) of patients were HRRm.

Table 49 PFS Subgroup Analyses for the ITT Population and pMMR Subgroup (per IVRS) by HRRm Status (FAS; DCO 12 April 2023)

		All patients			pMMR		
		SoC	**SoC + D**	**SoC + D + O**	**SoC**	**SoC + D**	**SoC + D + O**
All patients	**Events, n/N (%)**	173/241 (71.8)	139/238 (58.4)	126/239 (52.7)	148/192 (77.1)	124/192 (64.6)	108/191 (56.5)
	Median PFS, months (95% CI) [a]	9.6 (9.0, 9.9)	10.2 (9.7, 14.7)	15.1 (12.6, 20.7)	9.7 (9.2, 10.1)	9.9 (9.4, 12.5)	15.0 (12.4, 18.0)
	HR vs SoC (95% CI) [b]		0.68 (0.55, 0.86)	0.53 (0.42, 0.67)		0.77 (0.60, 0.97)	0.57 (0.44, 0.73)
HRRm	**Events, n/N (%)**	23/32 (71.9)	12/26 (46.2)	16/39 (41.0)	15/17 (88.2)	8/14 (57.1)	11/21 (52.4)
	Median PFS, months (95% CI) [a]	9.5 (6.9,12.5)	9.7 (7.0,NR)	NR (NR,NR)	9.5 (6.8, 12.3)	13.8 (6.9, NR)	15.2 (10.1, NR)
	HR vs SoC (95% CI) [b]		0.57 (0.27, 1.13)	0.30 (0.15, 0.58)		0.44 (0.17, 1.07)	0.25 (0.10, 0.58)
Non-HRRm	**Events, n/N (%)**	96/132 (72.7)	85/138 (61.6)	81/141 (57.4)	85/111 (76.6)	78/121 (64.5)	70/118 (59.3)
	Median PFS, months (95% CI) [a]	9.7 (8.8,12.4)	11.3 (9.7,15.0)	15.0 (12.4,20.3)	9.7 (9.0, 12.5)	10.0 (9.5, 12.7)	15.0 (12.2, 19.4)
	HR vs SoC (95% CI) [b]		0.72 (0.54, 0.97)	0.59 (0.44, 0.80)		0.79 (0.58, 1.08)	0.62 (0.45, 0.86)
HRRm unknown	**Events, n/N (%)**	54/77 (70.1)	42/74 (56.8)	29/59 (49.2)	48/64 (75.0)	38/57 (66.7)	27/52 (51.9)
	Median PFS, months (95% CI) [a]	9.5 (7.0,11.4)	9.9 (8.8,18.4)	12.4 (8.4, NR)	9.5 (7.1, 11.4)	9.7 (7.4, 12.4)	12.3 (7.1, NR)
	HR vs SoC (95% CI) [b]		0.65 (0.43,0.97)	0.57 (0.36,0.89)		0.83 (0.54, 1.26)	0.58 (0.36, 0.93)

a. Calculated using the Kaplan-Meier technique. CI for median is derived based on the Brookmeyer-Crowley method.

b. The HR and CI are estimated from an unstratified CPH model. A HR less than 1 will favour the investigational arm over SoC.

As per the statistical analysis plan, the HR and CI are not presented if there are less than 20 events per treatment comparison.

Progression-free survival (PFS) according to RECIST 1.1, based on site investigator assessments.

Table 50 OS Subgroup Analyses for the ITT Population and pMMR Subgroup (per IVRS) by HRRm Status (FAS; DCO 12 April 2023)

		All patients			pMMR		
		SoC	**SoC + D**	**SoC + D + O**	**SoC**	**SoC + D**	**SoC + D + O**
All patients	**Events, n/N (%)**	82/241 (34.0)	65/238 (27.3)	52/239 (21.8)	64/192 (33.3)	58/192 (30.2)	46/191 (24.1)
	Median OS, months (95% CI) [a]	25.9 (23.9, NR)	NR (NR, NR)	NR (NR, NR)	25.9 (25.1, NR)	NR (NR, NR)	NR (NR, NR)
	HR vs SoC (95% CI) [b]		0.77 (0.56, 1.07)	0.59 (0.42, 0.83)		0.91 (0.64, 1.30)	0.69 (0.47, 1.00)
HRRm	**Events, n/N (%)**	8/32 (25.0)	6/26 (23.1)	5/39 (12.8)	5/17 (29.4)	3/14 (21.4)	3/21 (14.3)
	Median OS, months (95% CI) [a]	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	25.5 (17.3, NR)	NR (NR, NR)	NR (NR, NR)
	HR vs SoC (95% CI) [b]		NC (NC, NC)	NC (NC, NC)		NC (NC, NC)	NC (NC, NC)
Non-HRRm	**Events, n/N (%)**	52/132 (39.4)	34/138 (24.6)	33/141 (23.4)	42/111 (37.8)	33/121 (27.3)	30/118 (25.4)
	Median OS, months (95% CI) [a]	25.1 (20.9, NR)	NR (NR, NR)	NR (NR, NR)	25.1 (23.5, NR)	NR (NR, NR)	NR (NR, NR)
	HR vs SoC (95% CI) [b]		0.56 (0.36,0.87)	0.53 (0.34,0.82)		0.69 (0.43,1.08)	0.63 (0.39,1.00)
HRRm unknown	**Events, n/N (%)**	22/77 (28.6)	25/74 (33.8)	14/59 (23.7)	17/64 (26.6)	22/57 (38.6)	13/52 (25.0)
	Median OS, months (95% CI) [a]	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	19.2 (15.5, NR)	NR (NR, NR)
	HR vs SoC (95% CI) [b]		1.17 (0.66, 2.09)	0.84 (0.42, 1.62)		1.58 (0.84, 3.01)	0.95 (0.45, 1.96)

a. Calculated using the Kaplan-Meier technique. CI for median is derived based on the Brookmeyer-Crowley method.

b. The HR and CI are estimated from an unstratified CPH model. A HR less than 1 will favour the investigational arm over SoC.

As per the statistical analysis plan, the HR and CI are not presented if there are less than 20 events per treatment comparison.

pMMR sub-population by BRCAm subgroups

Of the 575 patients randomized in the pMMR sub-population, only 4.0% (23/575) of patients were BRCAm.

Table 51 PFS Subgroup Analyses for the ITT Population and pMMR Subgroup (per IVRS) by *BRCAm* Status (FAS; DCO 12 April 2023)

		All patients			pMMR		
		SoC	**SoC + D**	**SoC + D + O**	**SoC**	**SoC + D**	**SoC + D + O**
All patients	**Events, n/N (%)**	173/241 (71.8)	139/238 (58.4)	126/239 (52.7)	148/192 (77.1)	124/192 (64.6)	108/191 (56.5)
	Median PFS, months (95% CI) [a]	9.6 (9.0,9.9)	10.2 (9.7, 14.7)	15.1 (12.6, 20.7)	9.7 (9.2, 10.1)	9.9 (9.4, 12.5)	15.0 (12.4, 18.0)
	HR vs SoC (95% CI) [b]		0.68 (0.55, 0.86)	0.53 (0.42, 0.67)		0.77 (0.60, 0.97)	0.57 (0.44, 0.73)
BRCAm	**Events, n/N (%)**	12/15 (80.0)	5/11 (45.5)	6/15 (40.0)	8/10 (80.0)	2/6 (33.3)	4/7 (57.1)
	Median PFS, months (95% CI) [a]	9.8 (6.9,12.5)	9.7 (0.6, NR)	NR (NR, NR)	9.9 (4.2, 12.5)	NR (NR, NR)	15.2 (2.0, NR)
	HR vs SoC (95% CI) [b]		NC (NC, NC)	NC (NC, NC)		NC (NC, NC)	NC (NC, NC)
Non-*BRCAm*	**Events, n/N (%)**	107/149 (71.8)	92/153 (60.1)	91/165 (55.2)	92/118 (78.0)	84/129 (65.1)	77/132 (58.3)
	Median PFS, months (95% CI) [a]	9.7 (8.3,12.2)	11.3 (9.7,15.0)	15.1 (12.6, 20.7)	9.7 (8.8,12.2)	9.9 (9.2,12.7)	15.0 (12.5,19.4)
	HR vs SoC (95% CI) [b]		0.72 (0.54, 0.95)	0.56 (0.42, 0.74)		0.77 (0.57,1.04)	0.57 (0.42, 0.78)
***BRCAm* unknown**	**Events, n/N (%)**	54/77 (70.1)	42/74 (56.8)	29/59 (49.2)	48/64 (75.0)	38/57 (66.7)	27/52 (51.9)
	Median PFS, months (95% CI) [a]	9.5 (7.0, 11.4)	9.9 (8.8,18.4)	12.4 (8.4, NR)	9.5 (7.1, 11.4)	9.7 (7.4,12.4)	12.3 (7.1, NR)
	HR vs SoC (95% CI) [b]		0.65 (0.43,0.97)	0.57 (0.36,0.89)		0.83 (0.54,1.26)	0.58 (0.36,0.93)

a. Calculated using the Kaplan-Meier technique. CI for median is derived based on the Brookmeyer-Crowley method.

b. The HR and CI are estimated from an unstratified CPH model. A HR less than 1 will favour the investigational arm over SoC.

As per the statistical analysis plan, the HR and CI are not presented if there are less than 20 events per treatment comparison.

Progression-free survival (PFS) according to RECIST 1.1, based on site investigator assessments.

Table 52 OS Subgroup Analyses for the ITT Population and pMMR Subgroup (per IVRS) by *BRCAm* Status (FAS; DCO 12 April 2023)

		All patients			pMMR		
		SoC	**SoC + D**	**SoC + D + O**	**SoC**	**SoC + D**	**SoC + D + O**
All patients	**Events, n/N (%)**	82/241 (34.0)	65/238 (27.3)	52/239 (21.8)	64/192 (33.3)	58/192 (30.2)	46/191 (24.1)
	Median PFS, months (95% CI) [a]	25.9 (23.9, NR)	NR (NR, NR)	NR (NR, NR)	25.9 (25.1, NR)	NR (NR, NR)	NR (NR, NR)
	HR vs SoC (95% CI) [b]		0.77 (0.56, 1.07)	0.59 (0.42, 0.83)		0.91 (0.64, 1.30)	0.69 (0.47, 1.00)
BRCAm	**Events, n/N (%)**	4/15 (26.7)	3/11 (27.3)	2/15 (13.3)	2/10 (20.0)	1/6 (16.7)	1/7 (14.3)
	Median PFS, months (95% CI) [a]	25.5 (17.3, NR)	NR (NR, NR)	NR (NR, NR)	25.5 (17.3, NR)	NR (NR, NR)	NR (NR, NR)
	HR vs SoC (95% CI) [b]		NC (NC, NC)	NC (NC, NC)		NC (NC, NC)	NC (NC, NC)
Non-*BRCAm*	**Events, n/N (%)**	56/149 (37.6)	37/153 (24.2)	36/165 (21.8)	45/118 (38.1)	35/129 (27.1)	32/132 (24.2)
	Median PFS, months (95% CI) [a]	25.9 (22.9, NR)	NR (NR, NR)	NR (NR, NR)	25.1 (22.9, NR)	NR (NR, NR)	NR (NR, NR)
	HR vs SoC (95% CI) [b]		0.59 (0.39, 0.89)	0.52 (0.34, 0.79)		0.68 (0.44,1.06)	0.58 (0.37,0.91)
***BRCAm* unknown**	**Events, n/N (%)**	22/77 (28.6)	25/74 (33.8)	14/59 (23.7)	17/64 (26.6)	22/57 (38.6)	13/52 (25.0)
	Median PFS, months (95% CI) [a]	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	19.2 (15.5, NR)	NR (NR, NR)
	HR vs SoC (95% CI) [b]		1.17 (0.66, 2.09)	0.84 (0.42, 1.62)		1.58 (0.84,3.01)	0.95 (0.45,1.96)

a. Calculated using the Kaplan-Meier technique. CI for median is derived based on the Brookmeyer-Crowley method.

b. The HR and CI are estimated from an unstratified CPH model. A HR less than 1 will favour the investigational arm over SoC.

As per the statistical analysis plan, the HR and CI are not presented if there are less than 20 events per treatment comparison.

Clinical studies in special populations

Table 53 Clinical studies in special populations

	Controlled Trials	Non-controlled trials
Renal impairment* patients (Subjects number /total number)	0/709	0
Hepatic impairment** patients (Subjects number /total number)	0/709	0
Paediatric patients <18 years (Subjects number /total number)	0/709	0
Age 65-74 (Subjects number /total number)	266/709	0
Age 75-84 (Subjects number /total number)	65/709	0
Age 85+ (Subjects number /total number)	2/709	0

* Renal impairment is defined as having CKD Stage 3b, 4 or 5 (KDIGO definition)
** Hepatic impairment is defined as having Child-Pugh score B or C

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 54 Summary of Efficacy for trial DUO-E (D9311C00001)

Title: A Randomised, Multicentre, Double-blind, Placebo-controlled, Phase III Study of First-line Carboplatin and Paclitaxel in Combination with Durvalumab, Followed by Maintenance Durvalumab with or without Olaparib in Patients with Newly Diagnosed Advanced or Recurrent Endometrial Cancer (DUO-E)			
Study identifier	D9311C00001; GOG-3041; ENGOT-EN10, EudraCT number: 2019-004112-60; EU CT number: 2022-502746-27-00		
Design	Randomised, multicentre, double-blind, placebo-controlled, phase III study		
	Duration of main phase: Duration of run-in phase: Duration of extension phase:		Ongoing (first patient randomised 02 June 2020) Not applicable Not applicable
Hypothesis	Superiority The hypothesis of the DUO-E study is that SoC + durvalumab + olaparib and SoC + durvalumab combination therapies will improve PFS when compared with SoC for the treatment of patients with newly diagnosed advanced or recurrent endometrial cancer.		
Treatment groups	Arm A (standard of care [SoC]; control)		Platinum-based chemotherapy (paclitaxel and carboplatin) every 3 weeks (Q3W) for a maximum of 6 cycles with durvalumab placebo (intravenous [IV]) Q3W. Following completion of chemotherapy treatment, patients without objective disease progression received durvalumab placebo (IV) every 4 weeks (Q4W) and olaparib placebo (tablets) twice daily (bd) orally as maintenance treatment until disease progression. 241 patients randomised.
	Arm B (SoC + durvalumab)		Platinum-based chemotherapy (paclitaxel and carboplatin) Q3W for a maximum of 6 cycles with 1120 mg durvalumab (IV) Q3W. Following completion of chemotherapy treatment, patients without objective disease progression received 1500 mg durvalumab (IV) Q4W with olaparib placebo (tablets) bd orally as maintenance treatment until disease progression. 238 patients randomised.
	Arm C (SoC + durvalumab + olaparib)		Platinum-based chemotherapy (paclitaxel and carboplatin) Q3W for a maximum of 6 cycles with 1120 mg durvalumab (IV) Q3W. Following completion of chemotherapy treatment, patients without objective disease progression received 1500 mg durvalumab (IV) Q4W with 300 mg olaparib (tablets) bd orally as maintenance treatment until disease progression. 239 patients randomised.
Endpoints and definitions	Dual primary endpoint	Progression-free survival (PFS)	Time from randomisation until the date of objective disease progression (per RECIST 1.1 as assessed by the investigator) or death (by any cause in the absence of progression). This was assessed via determining the efficacy of: • Durvalumab in combination with platinum-based chemotherapy and continued as maintenance in combination with olaparib versus SoC platinum-based chemotherapy

			• Durvalumab in combination with platinum-based chemotherapy and continued as maintenance versus SoC platinum-based chemotherapy
	Key secondary endpoint	Overall survival (OS)	Time from the date of randomisation until death due to any cause
Database lock	Data cutoff (DCO1): 12 April 2023; Database lock: 12 May 2023. The data presented below are for the final analysis of PFS and first interim analysis of OS.		
Results and analysis			
Analysis description	**Progression-free survival (dMMR sub-group)**		
Analysis population and time point description	Adult female patients with histologically confirmed diagnosis of epithelial endometrial carcinoma (excluding sarcomas): newly diagnosed Stage III, newly diagnosed Stage IV, or recurrent endometrial cancer and that is mismatch repair deficient (dMMR) DCO1: 12 April 2023		
Descriptive statistics and estimate variability	Treatment group	Arm A (SoC)	Arm B (SoC + durvalumab)	Arm C (SoC + durvalumab + olaparib)
	Number of subjects	49	46	48
	Median PFS[a] (95% CI)	7.0 (6.7, 14.8)	NR (NR, NR)	31.8 (12.4, NR)
Effect estimate per comparison	Dual primary endpoint: PFS (Arm B vs Arm A)	Comparison groups	Arm B (SoC + durvalumab) vs Arm A (SoC)	
		Hazard ratio[b]	0.42	
		95% CI[b]	0.22, 0.80	
	Dual primary endpoint: PFS (Arm C vs Arm A)	Comparison groups	Arm C (SoC + durvalumab + olaparib) vs Arm A (SoC)	
		Hazard ratio[b]	0.41	
		95% CI[b]	0.21, 0.75	
Notes	[a] Calculated using KM technique. Confidence intervals for median PFS were derived based on Brookmeyer-Crowley method. [b] The HR and CI were estimated from an unstratified CPH model. A HR less than 1 favours the treatment arm of interest over the reference arm. NR = not reached At randomisation, patients were stratified according to tumour tissue MMR status (MMR proficient tumours versus MMR deficient tumours), disease status (recurrent endometrial cancer versus newly diagnosed endometrial cancer), and geographic region (Asia versus rest of world)		
Analysis description	**Progression-free survival (pMMR sub-group)**		
Analysis population and time point description	Adult female patients with histologically confirmed diagnosis of epithelial endometrial carcinoma (excluding sarcomas): newly diagnosed Stage III, newly diagnosed Stage IV, or recurrent endometrial cancer and that is mismatch repair proficient (pMMR)		

	DCO1: 12 April 2023			
Descriptive statistics and estimate variability	Treatment group	Arm A (SoC)	Arm B (SoC + durvalumab)	Arm C (SoC + durvalumab + olaparib)
	Number of subjects	192	192	191
	Median PFS[a] (95% CI)	9.7 (9.2, 10.1)	9.9 (9.4, 12.5)	15.0 (12.4, 18.0)
Effect estimate per comparison	Dual primary endpoint: PFS (Arm B vs Arm A)	Comparison groups	Arm B (SoC + durvalumab) vs Arm A (SoC)	
		Hazard ratio[b]	0.77	
		95% CI[b]	0.60, 0.97	
	Dual primary endpoint: PFS (Arm C vs Arm A)	Comparison groups	Arm C (SoC + durvalumab + olaparib) vs Arm A (SoC)	
		Hazard ratio[b]	0.57	
		95% CI[b]	0.44, 0.73	
Notes	[a] Calculated using KM technique. Confidence intervals for median PFS were derived based on Brookmeyer-Crowley method. [b] The HR and CI were estimated from an unstratified CPH model. A HR less than 1 favours the treatment arm of interest over the reference arm. NR = not reached At randomisation, patients were stratified according to tumour tissue MMR status (MMR proficient tumours versus MMR deficient tumours), disease status (recurrent endometrial cancer versus newly diagnosed endometrial cancer), and geographic region (Asia versus rest of world)			
Analysis description	**Overall survival (dMMR sub-group)**			
Analysis population and time point description	Adult female patients with histologically confirmed diagnosis of epithelial endometrial carcinoma (excluding sarcomas): newly diagnosed Stage III, newly diagnosed Stage IV, or recurrent endometrial cancer and that is mismatch repair deficient (dMMR) DCO1: 12 April 2023			
Descriptive statistics and estimate variability	Treatment group	Arm A (SoC)	Arm B (SoC + durvalumab)	Arm C (SoC + durvalumab + olaparib)
	Number of subjects	49	46	48
	Median OS[a] (95% CI)	23.7 (16.9, NR)	NR (NR, NR)	NR (NR, NR)
Effect estimate per comparison	Key secondary endpoint: OS (Arm B vs Arm A)	Comparison groups	Arm B (SoC + durvalumab) vs Arm A (SoC)	
		Hazard ratio[b]	0.34	
		95% CI[b]	0.13, 0.79	
	Key secondary endpoint: OS (Arm C vs Arm A)	Comparison groups	Arm C (SoC + durvalumab + olaparib) vs Arm A (SoC)	
		Hazard ratio[b]	0.28	

		95% CI[b]	0.10, 0.68	
Notes	[a] Calculated using KM technique. Confidence interval for median survival was derived based on the Brookmeyer-Crowley method. [b] The HR and CI were estimated from an unstratified CPH model. The CI was calculated using a profile likelihood approach. A HR less than 1 favours the treatment arm of interest over the reference arm. NR = not reached At randomisation, patients were stratified according to tumour tissue MMR status (MMR proficient tumours versus MMR deficient tumours), disease status (recurrent endometrial cancer versus newly diagnosed endometrial cancer), and geographic region (Asia versus rest of world)			
Analysis description	**Overall survival (pMMR sub-group)**			
Analysis population and time point description	Adult female patients with histologically confirmed diagnosis of epithelial endometrial carcinoma (excluding sarcomas): newly diagnosed Stage III, newly diagnosed Stage IV, or recurrent endometrial cancer and that is mismatch repair proficient (pMMR) DCO1: 12 April 2023			
Descriptive statistics and estimate variability	Treatment group	Arm A (SoC)	Arm B (SoC + durvalumab)	Arm C (SoC + durvalumab + olaparib)
	Number of subjects	192	192	191
	Median OS[a] (95% CI)	25.9 (25.1, NR)	NR (NR, NR)	NR (NR, NR)
Effect estimate per comparison	Key secondary endpoint: OS (Arm B vs Arm A)	Comparison groups	Arm B (SoC + durvalumab) vs Arm A (SoC)	
		Hazard ratio[b]	0.91	
		95% CI[b]	0.64, 1.30	
	Key secondary endpoint: OS (Arm C vs Arm A)	Comparison groups	Arm C (SoC + durvalumab + olaparib) vs Arm A (SoC)	
		Hazard ratio[b]	0.69	
		95% CI[b]	0.47, 1.00	
Notes	[a] Calculated using KM technique. Confidence interval for median survival was derived based on the Brookmeyer-Crowley method. [b] The HR and CI were estimated from an unstratified CPH model. The CI was calculated using a profile likelihood approach. A HR less than 1 favours the treatment arm of interest over the reference arm. NR = not reached At randomisation, patients were stratified according to tumour tissue MMR status (MMR proficient tumours versus MMR deficient tumours), disease status (recurrent endometrial cancer versus newly diagnosed endometrial cancer), and geographic region (Asia versus rest of world)			

2.4.3. Discussion on clinical efficacy

In the context of this application, the MAH is seeking authorisation for the use of durvalumab in combination with chemotherapy, followed by maintenance treatment with durvalumab as monotherapy or in combination with olaparib for the first-line treatment of adults with advanced or recurrent endometrial cancer based on the results from the DUO-E pivotal study.

Design and conduct of clinical studies

DUO-E is a phase III, randomised, multicentre, double-blind, placebo-controlled, study of first-line platinum-based chemotherapy in combination with durvalumab, followed by maintenance durvalumab with or without olaparib in patients with newly diagnosed advanced or recurrent endometrial cancer.

This is a three-arm study where enrolled patients were randomized 1:1:1 to receive paclitaxel and carboplatin (Arm A, SoC chemotherapy) followed by durvalumab and olaparib placebo or SoC chemotherapy in combination with durvalumab followed by durvalumab and olaparib placebo maintenance (Arm B) or SoC chemotherapy in combination with durvalumab followed by maintenance treatment with durvalumab and olaparib (Arm C). Patients could receive up to 6 cycles of paclitaxel 175 mg/m^2 and carboplatin AUC5-6 Q3W that is, indeed, considered the standard of care in this disease setting. Durvalumab was administered at a 1120 mg dose Q3W for 6 cycles, in combination with chemotherapy, and then, 1500 mg Q4W during the maintenance phase until disease progression. Olaparib was administered at the approved dose of 300 mg BD until disease progression during the maintenance phase. According to the MAH, the study was conducted in a double-blind manner as for durvalumab and olaparib.

Randomization was stratified by MMR status (proficient versus deficient), disease status (newly diagnosed versus recurrent) and region (Asia versus RoW).

The main objective of this trial included two comparisons of interest: demonstration of the efficacy of Arm B versus Arm A and the efficacy of Arm C versus Arm A.

The primary endpoint is PFS assessed by investigator. The use of this endpoint was endorsed in the scientific advice the MAH received (EMEA/H/SA/3310/3/2019/II), which is acceptable considering the study was double-blind, although assessment by BICR would have been preferred. Moreover, PFS by BICR is included as sensitivity analysis, which is reassuring. As secondary endpoints, PFS2, OS, ORR, DoR, TFST, TSST and TDT were assessed. With regard to PROs, evaluation of HRQoL based on EORTC QLQ-C30 and EORTC QLQ-EN24 was included as secondary objective and other measurements, such as EQ-5D-5L, as exploratory objective. Determining the efficacy of Arm B versus Arm C, in terms of PFS and OS, was also an exploratory objective of the study.

For both comparisons, the stratified log-rank test to generate p-values and the stratified Cox PH model to obtain the HR and its confidence interval was used. This approach is considered acceptable. Additionally, several sensitivity analyses were planned to address potential biases, namely: 1) evaluation-time bias, 2) attrition bias, 3) ascertainment bias, 4) deviation bias and 5) if PH assumption does not hold, a piecewise HR calculated over distinct time periods was planned. Different scenarios concerning censoring rules, model assumptions, and assessment strategies have been considered by the MAH to address these biases. These sensitivity analyses are welcome, and they are useful to contextualise the result of the primary endpoint.

The definition of OS and the analysis methodology are acceptable. However, to ensure the robustness of the results obtained from this endpoint, additional sensitivity and supplementary analyses were required. An unstratified piecewise hazard ratio over different time points analysis and further sensitivity analyses based on Max-Combo test and the unstratified Restricted Mean Survival Time

(RMST) methodology were provided, overall consistent with the primary OS analysis. Furthermore, in the same way as for PFS, the MAH provided data using the composite strategy for the requested types of ICEs, not only for OS but also for a number of additional secondary endpoints. Overall, these analyses ensure that there are no potential biases concerning this type of intercurrent events.

For OS, two interim analyses and one final analysis were planned per protocol. The first interim analysis was planned to be performed at the same time as the primary PFS analysis, estimated to occur when approximately 74% of the target number of OS events would have occurred (i.e. 208 of 280 OS events per comparison). The second OS IA is planned when approximately 244 OS events (87% of the target number of OS events) have occurred for each comparison. According to the latest projections, this analysis will take place in the first half of 2025. The final OS analysis will take place when 280 events (60% maturity) are reported for each comparison and it is projected to occur one year later than the IA2. Both the second IA and the final OS analyses have been requested as an annex II condition (PAES).

A multiple testing procedure was established to control the type I error rate at 0.05 (two-sided) for the overall study. The alpha is allocated to both comparisons of the dual primary endpoint (i.e. Arm B vs. Arm A, and Arm C vs. Arm A). If these comparisons are statistically significant, the alpha will then be hierarchically passed to the OS endpoint for each respective comparison. This scheme also accounts for Type I error control across various IAs for OS. The strategy allows the recycling of the alpha value for each comparison at this endpoint, provided they are statistically significant at the pre-specified boundary for each IA or final OS analysis. This approach is acceptable from a methodological perspective and no issues have been raised.

Up to the data cut-off (12 April 2023), several protocol amendments were issued resulting in six different versions of the study protocol (version 6.0 dated on 24 January 2023). All amendments were issued prior to the DCO date and Protocol Version 5.0 (07 June 2022) was current at the DCO date because Version 6.0 (dated 24 January 2023) had not yet been approved in all countries at that time. The most relevant change to the protocol made during the conduct of the study was the upgrade of the Arm C versus Arm A comparison from secondary to primary objective of the study and the related changes to the planned analyses. This change was performed within Version 5.0 (June 2022), therefore, a high number of patients had already been randomized. This update was made, a priori, in a blinded manner and it is understood as a sponsor’s decision. In addition, statistical assumptions were updated to account for a delay in the durvalumab treatment effect of 3 months as compared to chemotherapy. This change is understood, as a delay in the initiation of the activity of immunotherapy products has been widely documented, because of its mechanism of action. In the first amendment issued, the exploratory objective to compare Arm B versus Arm C was added, but this change was made before the start of patient recruitment. The changes implemented in the SAP have also been summarised and provided by the MAH. Some changes related to the planned subgroup analyses were implemented, including HRRm status analyses and the addition of a post-hoc subgroup analysis by BRCAm status.

Efficacy data and additional analyses

A total of 875 subjects were screened and 718 patients were randomized. The most common reason for patients not being randomized was screen failure (145 patients, 92.4%) due to (not) meeting inclusion/exclusion criteria.

From these 718 patients randomized to the SoC + D + O arm (n=239), SoC + D arm (n=238) or SoC treatment arm (n=241), 709 patients (98.7%) received any study treatment and 544 patients (75.8%) started the Maintenance phase. A slight imbalance among treatment arms is observed with regard to the proportion of patients who started maintenance treatment (i.e. patients who received

olaparib/placebo). In the SoC arm, 70.1% of randomized patients received olaparib placebo, in the SoC + D arm this number was of 76.9% and in the SoC + D + O the percentage of patients who received olaparib was of 80.3%. While the difference between both experimental arms and SoC (76.9% and 80.3% vs 70.1%) might be a result of the increased activity expected from the addition of durvalumab to SoC chemotherapy, the difference between both experimental arms (76.9% vs 80.3%) is not easily understood. From the 165 patients who did not start the maintenance phase, in 67 (41%) of them this was due to a PFS event during the neoadjuvant phase (SoC: 8.9%, SoC + D: 8.9%, SoC + D + O: 10.5%). By analysing patient disposition relative to study maintenance phase and the summary of subjects who did not receive durvalumab/placebo after discontinuing chemotherapy, no specific trend or additional reason of concern has been identified but it is hard to elucidate if observed imbalances were due to toxicity, suspecting treatment assignment or other different motives. At the DCO of 12 April 2023, 18.2% patients in the SoC arm, 31.5% in the SoC + D arm and 41.6% in the SoC + D + O arm were ongoing any treatment.

Regarding demographics, the three treatment arms were well balanced, with only a slightly higher proportion of patients <65 years of age in the SoC + D + O arm. In the ITT population, there were 69 (9.6%) patients ≥75 years of age. Most patients were White (57.4% overall) and approximately one third were Asian. At study entry, 66.6% of patients had an ECOG PS 0 and 33.3% of patients had an ECOG 1. The most common histology types were endometrioid (60.2%), serous (21.4%), and carcinosarcoma (7.1%), but there were also some patients with mixed epithelial (4%), other (2.8%), clear cell (2.6%), undifferentiated (1.7%) or mucinous (0.1%) histology. Overall, the 52.8% of the randomized patients presented recurrent disease and 47.2% were newly diagnosed. For MMR status (by IVRS), 80.1% of patients had pMMR tumours and 19.9% had dMMR tumours. As MMR status was a stratification factor, it was well balanced between treatment arms. Overall, PD-L1 expression status was positive (≥1%) for 67.3% of patients and negative (<1%) for 30.4%. Some imbalances were observed among the three treatment arms, as a slightly higher percentage of PD-L1 positive patients was included in the SoC + D arm (71.4%) compared to the SoC arm (67.6%) and the SoC + D + O arm (62.8%). The Ventana SP263 PD-L1 assay was used. For HRR mutation status, again some imbalances were found between arms. Overall, 13.5% of randomized patients were HRRm and 57.2% were not, but it must be noted that 29.2% had HRR status unknown. The highest percentage of HRRm patients was in the SoC + D + O arm but also the highest percentage of Non-HRRm, as this was the treatment arm with a lowest number of patients with unknown status (24.7%). Retrospective testing of HRRm status used the FoundationOne CDx (F1CDx) tumour tissue NGS assay. There were 42 (5.9%) patients with BRCA1/BRCA2 mutation.

Among patients with dMMR tumour status, demographic and baseline characteristics were generally well balanced between the treatment arms. Baseline demographics across all three arms were as follows: median age of 62 years (range: 34 to 85), 41% age 65 or older, 1.5% age 75 or older, 62% White, 29% Asian, and 2% Black or African American. Disease characteristics were as follows: ECOG PS of 0 (58%) or 1 (42%), 46% newly diagnosed and 54% recurrent disease. The histologic subtypes were endometrioid (83%), mixed epithelial (5%), serous (3%), carcinosarcoma (3%), undifferentiated (2%), and other (3%).

Among patients with pMMR tumour status, demographic and baseline characteristics were generally well balanced between the treatment arms. Baseline demographics across all three arms were as follows: median age of 64 years (range: 22 to 86); 48% age 65 or older; 8% age 75 or older; 56% White, 30% Asian, and 6% Black or African American. Disease characteristics were as follows: ECOG PS of 0 (69%) or 1 (31%); 47% newly diagnosed and 53% recurrent disease. The histologic subtypes were endometrioid (54%), serous (26%), carcinosarcoma (8%), mixed epithelial (4%), clear cell (3%), undifferentiated (2%), mucinous (<1%), and other (3%).

The primary analysis of the **primary endpoint** (PFS by INV) was performed when a total of 312 events had been reported for the SoC + D vs SoC comparison and 299 events for the SoC + D + O vs SoC comparison. Censored patients were 68 (28.2%) in the SoC arm, 99 (41.6%) in the SoC + D and 113 (47.3%) in the SoC + D + O treatment arm. No concerns have been identified regarding imbalances in censoring. The study met both primary objectives, showing a statistically significant result in PFS for both comparisons. A HR point estimate of 0.71 (95% CI: 0.57, 0.89), 2-sided p-value = 0.003 was obtained for the SoC + D vs SoC comparison. Median PFS in the SoC + D arm was 10.2 months (95% CI: 9.7, 14.7) compared with 9.6 months (95% CI: 9.0, 9.9) in the SoC arm. For the SoC + D + O vs SoC comparison, the HR point estimate was 0.55 (95% CI: 0.43, 0.69), 2 sided p-value < 0.0001. Median PFS in the SoC + D + O arm was 15.1 months (95% CI: 12.6, 20.7) (while it was 9.6 months in the SoC arm). For the exploratory comparison of SoC + D + O vs SoC + D, the HR point estimate was 0.78 (95% CI: 0.61, 0.99), showing a smaller difference in efficacy between both experimental arms. KM curves started to separate at approximately 6 months.

For the **secondary endpoint** of OS, an interim analysis was performed at the time of the primary PFS analysis. Up to the DCO (12 April 2023), 199 events (overall 27.7% maturity) had been reported among the three treatment arms. Within this analysis, the pre-defined statistical thresholds for superiority for SoC + D versus SoC and SoC + D + O versus SoC were not met so OS will be tested at a second IA. For the SoC + D vs SoC comparison, the OS HR point estimate was 0.77 (95% CI: 0.56, 1.07), while HR was 0.59 (95% CI: 0.42, 0.83) for the SoC + D + O vs SoC comparison. For the exploratory comparison of SoC + D + O vs SoC + D, a HR of 0.77 (95% CI: 0.53, 1.10) was estimated. KM curves show mild separation but with a high number of censored observations due to immaturity of the data. A second IA and the FA are planned to take place in the future. According to the MAH's predictions, the IA2 will occur in 1H 2025 and the FA in 1H 2026. Due to the immaturity of the OS data at the time of the primary analysis, concerns related to the long-term efficacy of the medicinal product have been identified. The MAH will submit further OS results (IA2 and FA) end of 2025 and end of 2026 respectively as an Annex II condition (PAES) to further characterise the long-term efficacy of durvalumab and olaparib in the first line treatment of endometrial cancer.

Other secondary endpoints show the same trend in favour of the experimental arm. ORR was 55.1% in the SoC arm, 61.9% in the SoC + D arm and 63.6% in the SoC + D + O treatment arm. DoR shows relevant differences between arms. Median DoR was 7.7 months in the SoC arm, 13.1 months in the SoC + D arm and 29.9 months in the SoC + D + O treatment arm. PFS2 was also assessed as secondary endpoint, with 245 reported events across all treatment arms (34.1% maturity). There was a numerical improvement in PFS2 for the SoC + D arm compared with the SoC arm (HR: 0.80; 95% CI: 0.59, 1.07) but the benefit was higher for the SoC + D + O vs SoC comparison (0.55; 95% CI: 0.40, 0.76). TFST and TSST, other secondary endpoints showed also the same trend with a higher benefit for the SoC + D + O arm.

PROs were measured, as secondary endpoints, using the EORTC QLQ-C30 and EORTC QLQ-EN24. The PRO-CTCAE, PGI-TT, PGIC, PGIS, PGI-BR, and EQ-5D-5L questionnaires were collected as exploratory endpoints. Focusing on the EORTC QLQ-C30 questionnaire, compliance rates at baseline were 82.1% for the SoC arm, 84.7% for the SoC + D arm, and 87.3% for the SoC + D + O arm but decreased over time. A clinically meaningful change from baseline in EORTC QLQ-C30 subscales/scores was defined as an absolute change in score of ≥ 10 points. There were no relevant differences for global health status/QoL in either comparison, with a slight worsening in the SoC + D + O arm compared to the other two treatment arms. As expected, for the symptom of nausea/vomiting, there was an initial deterioration that further worsened during maintenance for the SoC + D + O arm. Regarding the EORTC QLQ-EN24 key symptoms, most of their differences were not considered clinically meaningful except for taste change.

Several **sensitivity analyses for PFS** were planned. PFS was assessed by BICR and it showed consistent results with the investigator's assessment. For the SoC + D versus SoC comparison, PFS by BICR HR point estimate was 0.74 (95% CI: 0.58, 0.94) while it was 0.71 (95% CI: 0.57, 0.89) by investigator's assessment. For the SoC + D + O versus SoC comparison, PFS by BICR point estimate was 0.55 (95% CI: 0.42, 0.70), almost identical to investigator's assessment (HR: 0.55; 95% CI: 0.43, 0.69).

For **PFS subgroup analyses**, the pre-defined subgroups showed overall consistent results. Benefit seemed to be slightly superior in both comparisons for newly diagnosed patients opposite to patients with recurrent disease, although this result is somehow expected. The most relevant differences with regard to subgroup analyses have been observed for MMR and HRRm (including BRCAm) subgroups.

According to **MMR status**, an improvement in PFS was observed with SoC + D and SoC + D + O over SoC for both dMMR (HR 0.42 [95%CI: 95% CI: 0.22, 0.80); 0.41 [95% CI: 0.21, 0.75]) and pMMR (HR 0.77 [95% CI: 0.60, 0.97]; 0.57 [95% CI: 0.44, 0.73]) populations. These results exhibit the predictive value of dMMR status for response to immune-checkpoint inhibitors, suggesting that, for the specific subgroup of dMMR, the addition of D to SoC chemotherapy might be sufficient for a PFS benefit. Based on the exploratory comparison of SoC + D + O vs SoC + D, no difference was observed in the dMMR subgroup (HR 0.97; 95% CI: 0.49, 1.98). In view of these results and acknowledging the limitations of this (subgroup) analysis, the benefit of SoC + D appears clear in patients with dMMR, questioning the added contribution of olaparib in these patients. This should be seen in the context of a deficient study design where it is not possible to disentangle the real effect of the initial treatment phase and the maintenance treatment and where there are others biomarkers, such as PD-L1 expression or HRR mutation that are known effect modifiers for the components of this combination treatment. For the pMMR subgroup, an improvement in PFS is observed with SoC + D vs SoC (HR: 0.77; 95%CI: 0.60, 0.97), although there is almost no difference in median PFS (9.9 vs 9.7 months) and the KM curves show a delayed separation. This benefit is lower than the observed for SoC + D + O vs SoC (HR: 0.57; 95% CI: 0.44, 0.73; median PFS 15.0 months). Regarding OS, a trend in favour of SoC + D + O is observed over SoC + D (HR 0.69; 95% CI: 0.47, 1.00). However, no benefit can be observed with SoC + D vs SoC (HR 0.91; 95% CI. 0.64, 1.30), although it is acknowledged that data are still immature. As a consequence, the MAH was requested to justify the B/R of SoC+D and SoC+D+O in the subgroups of pMMR and dMMR, respectively. The MAH proposed to restrict the claimed therapeutic indication for SoC + D to the dMMR sub-population and the indication for SoC + D + O to patients with pMMR tumours.

For the subgroup analyses by **HRRm status**, results for both HRRm and non-HRRm subgroups are overall consistent with the primary PFS analysis, with the highest benefit observed for the comparison of SoC + D + O vs SoC in HRRm patients. An exploratory subgroup analysis by BRCAm status was also performed although the small sample size in the BRCAm subgroup (41 [5.7%]) and the very low number of events prevent any comparison. HRRm and, specifically, BRCAm are known predictive factors of response to PARPi as olaparib. However, the presence of these biomarkers was not a stratification factor and there is a non-negligible number of patients whose HRRm status was unknown and some imbalances have already been identified among treatment arms, which makes interpretation of these analyses quite difficult.

Regarding the results by **PD-L1 expression**, it must be noted that the comparisons are hampered by the smaller representation of the PD-L1 negative (PD-L1 expression <1%) population. . Focusing on the pMMR population, most patients in this subgroup were PD-L1 positive (64%). The efficacy of SoC + D + O (the only regimen intended to be used in pMMR patients according to the new claimed indication) in terms of PFS was higher in PD-L1 positive (HR 0.44; 95% CI: 0.31, 0.61) than in PD-L1

negative, in which the effect is less clear (HR 0.87; 95% CI: 0.59, 1.28). However, it is important to note that the number of patients was relatively low. OS results were in line with the PFS results.

For OS subgroup analyses by MMR status, for the indication in patients with **dMMR** tumours, the benefit is considered established for **SoC + D** based on the already available PFS results (HR 0.42; 95% CI: 0.22, 0.80). In addition, a positive trend in OS has been identified (HR 0.34; 95% CI: 0.13, 0.79), although this IA is based on 7 (15.2%) events in the SoC + D arm and 18 (36.7%) events in the SoC arm. Updated OS results are needed to further characterise the efficacy. These results are supported by the biological rationale of dMMR status being a predictive factor for the efficacy of anti-PD1 compounds, already highlighted by published results with other anti-PD1 medicinal products (Eskander et al, 2023, Mirza et al. 2023).

For the indication in the **pMMR** subpopulation, a clear benefit in terms of PFS has been shown for **SoC + D + O** over SoC (HR 0.57; 95% CI: 0.44, 0.73; median PFS of 15.0 months vs 9.7 months, respectively). Additionally, a positive trend for OS has been identified (HR 0.69; 95% CI: 0.47, 1.00) although with a low number of reported events (46 [24.1%] in the SoC + D + O and 64 [33.3%] in the SoC arm). The biological rationale to support this combination was however not so clear. It was hypothesized by the MAH that inhibition of PARP by olaparib has the potential to enhance the anti-tumour immune response via STING pathway activation and downstream type I interferon production, which can boost T-cell activity. Such increased T-cell activity is expected to enhance the activity of an immune checkpoint inhibitor, such as durvalumab, although this has not been proven yet. In patients with pMMR, anti-PD1 monotherapy or in combination with chemotherapy has shown little added value to standard chemotherapy, as it has been reported in previous studies and even in the DUO-E study. The study design doesn't allow to disentangle the contribution of individual components or phases of the proposed combination treatment, however the addition of olaparib as maintenance treatment, has resulted in an improved efficacy, based on the reported results.

OS data shows a trend in favour of the SoC + D+ O over SoC alone in pMMR patients and in favour of S0C + D over SoC alone in dMMR patients, although more mature data will be required to further confirm these results and rule out a (potential) detrimental effect in the long-term. Due to the immaturity of the OS data and the identified concerns related to the long-term efficacy of the medicinal products, the MAH will submit further OS results (IA2 and FA) when available as an Annex II condition (PAES) to further characterise the long-term efficacy of durvalumab and olaparib in the first line treatment of endometrial cancer.

At the time of DCO1 (12 April 2023), OS subgroup analyses were not performed since OS subgroup analyses for pre-defined subgroups, as per the statistical analysis plan, were pre-planned to be conducted at the time of the final analysis of OS with greater maturity However, during the procedure the MAH provided post hoc exploratory subgroup analyses by PD-L1, HRRm and BRCAm based on DCO1. As expected, the higher benefit was observed for the PD-L1 positive (1% cut-off) subgroup being the HR point estimate for the PD-L1 positive group 0.65 (95% CI: 0.44, 0.97) for the SoC + D vs SoC comparison and 0.42 (95% CI: 0.26, 0.67) for the SoC + D + O vs SoC comparison while for the PD-L1 negative subgroup, HR point estimate was 1.19 (95% CI: 0.65, 2.16) and 0.99 (95% CI: 0.56, 1.74) for the SoC + D and the SoC + D + O vs SoC comparisons, respectively. This analysis was performed with a 34% of events in the SoC arms, 27.3% in the SoC + D arm and 21.8% in the SoC + D + O arm. Although immature, these results show no apparent benefit for the PD-L1 negative subgroup. For the HRRm subgroup, HR and CI could not be calculated due to the low number of events but they were estimated for the non-HRRm and the HRRm unknown, which were bigger subgroups. For the non-HRR subgroup, similar results as observed in the ITT population were observed for both SoC + D and SoC + D + O vs SoC comparisons. KM curves are consistent with this observation. Similarly, for the BRCAm subgroup, analyses could not be performed due to the low number of events but HR and

CIs were obtained for the non-BRCAm and BRCAm unknown subgroups. Again, similar results as observed in the ITT population were reported for SoC + D and SoC + D +O treatment arms.

To conclude, the study design and the inclusion of a heterogeneous population in terms of the presence of different biomarkers that may be key for the effect of the treatment constitute limitations of the study to establish the benefit-risk of these combinations in the overall population.

Wording of the indication

A restricted indication for both Imfinzi and Lynparza based on MMR status was discussed during the procedure:

Durvalumab:

Endometrial Cancer

*IMFINZI in combination with **carboplatin and paclitaxel** ~~platinum-based chemotherapy, followed by maintenance with IMFINZI as monotherapy or in combination with olaparib,~~ is indicated for the first-line treatment of adults with **primary** advanced or recurrent endometrial cancer who are candidates for systemic therapy, followed by **maintenance** treatment with:*

- *IMFINZI as monotherapy in endometrial cancer **that is mismatch repair deficient (dMMR)***
- *IMFINZI in combination with olaparib in endometrial cancer **that is mismatch repair proficient (pMMR)***

Olaparib:

Endometrial cancer

*Lynparza in combination with durvalumab is indicated for the maintenance treatment of adult patients with **primary** advanced or recurrent endometrial cancer **that is mismatch repair proficient (pMMR)** whose disease has not progressed on first-line treatment with durvalumab in combination with **carboplatin and paclitaxel**~~platinum-based chemotherapy~~.*

2.4.4. Conclusions on the clinical efficacy

Based on the efficacy results of the DUO-E study, carboplatin and paclitaxel in combination with durvalumab followed by maintenance treatment with durvalumab with/without olaparib have shown a clinically relevant benefit in PFS over carboplatin and paclitaxel in 1L treatment of patients with primary advanced or recurrent endometrial cancer. Results of several sensitivity analyses and secondary endpoints were consistent. However, the benefit of SoC + D was limited in the subgroup of pMMR and no additional benefit was observed with the addition of olaparib to SoC + D in dMMR patients. Thus, a restricted indication was agreed during the evaluation.

Furthermore, at the time of the primary analysis (DCO 12 April 2023), OS data were not sufficiently mature and while a detrimental effect seems unlikely, results of IA2 and of the final analysis should be provided by the MAH, once available, to better characterise the efficacy of the proposed regimens (Annex II condition).

The following measures are considered necessary to address issues related to efficacy:

Imfinzi

Post-authorisation efficacy study (PAES): In order to further characterise the long-term efficacy of durvalumab in combination with carboplatin and paclitaxel for the first line treatment of adults with primary advanced or recurrent endometrial cancer who are candidates for systemic therapy, followed

by maintenance treatment with durvalumab as monotherapy in endometrial cancer that is mismatch repair deficient (dMMR) or in combination with olaparib in endometrial cancer that is mismatch repair proficient (pMMR), the MAH should submit the results of the second interim OS analysis and the final OS analysis from study D9311C00001 (DUO-E), a phase III randomised double-blind placebo-controlled multicentre study.

Lynparza

Post-authorisation efficacy study (PAES): In order to further characterise the long-term efficacy of olaparib in combination with durvalumab for the maintenance treatment of adult patients with primary advanced or recurrent endometrial cancer that is mismatch proficient (pMMR) whose disease has not progressed on first-line treatment with durvalumab in combination with carboplatin and paclitaxel, the MAH should submit the results of the second interim OS analysis and the final OS analysis from study D9311C00001 (DUO-E), a phase III randomised double-blind placebo-controlled multicentre study.

2.5. Clinical safety

Introduction

The safety assessment of durvalumab in combination with platinum-based chemotherapy followed by maintenance with durvalumab as monotherapy or in combination with olaparib is based primarily on data from the pivotal study DUO-E (DCO date of 12 April 2023 unless otherwise specified). In DUO-E study, a total of 718 patients were randomised in a 1:1:1 ratio to receive either SoC (241 patients), SoC + D (238 patients), or SoC + D + O (239 patients); of these, 709 patients (98.7%) received study treatment; 5 patients in the SoC arm, 3 patients in the SoC + D arm, and one patient in the SoC + D + O arm did not receive study treatment.

The assessment of safety is also supported by data from the following pools (safety pooling):

- **Durvalumab pan-tumour pool** (N=4045). This pool consists of data from 13 studies. All patients received at least one dose of durvalumab monotherapy given at a dose of either 10 mg/kg Q2W IV (or equivalent) or 20 mg/kg Q4W IV (or equivalent) for any line of therapy (across tumour types) plus patients receiving durvalumab monotherapy at a dose of 1500 mg Q4W. The DUO-E data were not included in the durvalumab Pan tumour Pool. The safety data are based on the DCOs for the individual studies within the pool.

  The clinical studies included in the durvalumab Pan tumour Pool and the numbers of patients contributing to the pooled datasets are: HIMALAYA (D419CC00002) (n=388), Study 22 (D4190C00022) (n=104), Study 1108 (D4190C00001) (n=1001), Japan Study 02 (D4190C00002) (n=124), ARCTIC (D4191C00004) (n=179), MYSTIC (D419AC00001) (n=369), CONDOR (D4193C00003) (n=65), EAGLE (D4193C00002) (n=237), HAWK (D4193C00001) (n=112), PACIFIC (D4191C00001) (n=475), ATLANTIC (D4191C00003 (n=444), DANUBE (D419BC00001 (n=345), KESTREL (D419LC00001) (n=202).

- **Olaparib 300 mg bd tablet pool** (N=3556). This pool consists of data from 21 studies across multiple solid tumour types. All patients received olaparib 300 mg bd tablets as monotherapy. The safety data are based on the DCOs for the individual studies within the pool.

  The clinical studies included in the olaparib 300 mg bd Tablet Pool (N = 3556 with solid tumours) and the numbers of patients contributing to the pooled datasets are: POLO D081FC00001 (n=90), PROfound D081DC00007 (n=256), OlympiA D081CC00006 (n=911), OlympiAD D0819C00003 (n=205), SOLO1 D0818C00001 (n=260), SOLO1 (China cohort) D0818C00001 (n=44 (note that 4 of the patients were counted as part of the SOLO1 safety

analysis set and are not counted again in the pool)), OPINION D0816C00020 (n=279), SOLO3 D0816C00010 (n=178), SOLO2 D0816C00002 (n=195), SOLO2 (China cohort) D0816C00002 (n=22), OReO D0816C00014 (n=146), LUCY D0816C00018 (n=255), VIOLETTE D5336C00001 (n=110), LIGHT D0816L00003 (n=271), D081CC00001 (n=69), China PK Study D081BC00002 (n=20), D081BC00001 (n=19), Study 08 D0816C00008 (n=19), Study 07 D0816C00007 (n=56), Study 06 D0816C00006 (n=43), D0816C00005 (n=31), Study 04 D0816C00004 (n=57), Study 24 D0810C00024 (n=24).

- **Olaparib monotherapy combined therapeutic dose pool** (N=4499). This pool consists of all patients in the olaparib 300 mg bd pool plus all patients who have received olaparib as monotherapy at the therapeutic dose of 400 mg bd for the capsule formulation (as a continuous dose). This pool is used to characterise the adverse event of special interest (AESIs) for olaparib, myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML) new primary malignancies (NPMs), and pneumonitis.

  A total of 943 patients who received olaparib capsules at a dose of 400 mg bd in the following 13 studies: study D9010C00008 (N = 33), study D081AC00001 (N = 31), study D0816C00012 (ORZORA; N = 181 [N = 177 in capsule pool), study D0810C00042 (Study 42; N = 298), study D0810C00024 (Study 24; N = 197 [N = 37 in capsule pool]), study D0810C00020 (Study 20; N = 90 [N = 90 in capsule pool]), study D0810C00019 (Study 19; N = 136 [N = 136 in capsule pool]), study D0810C00012 (Study 12; N = 64 [N = 55 in capsule pool]), study D0810C00009 (Study 09; N = 57 [N = 33 in capsule pool]), study D0810C00008 (N = 54 [N = 27 in capsule pool]), study D0810C00007 (N = 60 [N = 12 in capsule pool]), study D0810C00002 (Study 02; N = 98 [N = 8 in capsule pool]), study D0810C00001 (Study 01; N = 12 [N = 6 in capsule pool]).

- The **Olaparib Entire Clinical Programme** (N = 21793 as of 15 June 2023; includes patients receiving olaparib monotherapy capsule doses, olaparib in combination with other anti-cancer agents or olaparib monotherapy tablet doses) is also summarised to provide a more complete picture of the events of MDS/AML and NPMs only.

  Pooled safety data represents a heterogeneous group of participants with different indications and regimens compared with participants in DUO-E.

Patient exposure

The duration of exposure in DUO-E study, and the durvalumab and olaparib pools are summarised in in the below table.

Table 55 Duration of Exposure in DUO-E Overall, and the Durvalumab and Olaparib Pools (Safety Analysis Set, DCO 12 April 2023)

		DUO-E Overall			Durvalumab Pan-tumour Pool (N = 4045)	Olaparib 300 mg bd Tablet Pool (N = 3556)
		SoC (N = 236)	SoC + D (N = 235)	SoC + D + O (N = 238)		
Carboplatin or substitute SoC	Intended exposure (weeks) [a]					
	N	236	235	238	NA	NA
	Mean (SD)	17.4 (4.25)	17.7 (4.49)	17.9 (4.03)	NA	NA
	Median (Min – Max)	18.1 (0.7-32.7)	18.1 (0.9-29.3)	18.1 (0.7-30.1)	NA	NA

		DUO-E Overall			Durvalumab Pan-tumour Pool (N = 4045)	Olaparib 300 mg bd Tablet Pool (N = 3556)
		SoC (N = 236)	SoC + D (N = 235)	SoC + D + O (N = 238)		
	Total treatment years [b]	78.834	79.934	81.487	NA	NA
Paclitaxel or substitute SoC	Intended exposure (weeks) [a]					
	N	236	235	238	NA	NA
	Mean (SD)	17.3 (4.30)	17.5 (4.60)	17.8 (4.02)	NA	NA
	Median (Min – Max)	18.1 (0.7-32.7)	18.1 (0.9-29.3)	18.1 (0.7-30.1)	NA	NA
	Total treatment years [b]	78.398	78.924	81.248	NA	NA
Durvalumab/ placebo	Total treatment exposure (weeks) [c]					
	N	236	235	238	4045	NA
	Mean (SD)	43.9 (27.12)	49.9 (32.12)	58.1 (32.79)	28.9 (32.18)	NA
	Median (Min – Max)	39.2 (1-143)	43.0 (1-138)	57.1 (1-144)	16.1 (0-220)	NA
	Total treatment years [b]	198.6	224.7	265.2	2240.4	NA
Olaparib/ placebo	Total treatment exposure (weeks) [d, e]					
	N	169	183	192	NA	3556
	Mean (SD)	32.7 (24.44)	37.9 (28.03)	45.5 (28.63)	NA	52.39 (53.58)
	Median (Min – Max)	24.6 (0.9-124.3)	33.0 (1.6-118.1)	40.2 (1.3-125.0)	NA	44.14 (0.14-423.86)
	Total treatment years	105.927	133.013	167.425	NA	3570.3

a. Intended exposure (weeks) = (minimum of [last dose date where dose > 0 mg + 20 days, date of death, date of DCO] – first dose date + one day)/7.

b. Total treatment years = sum of exposure duration for all patients per treatment arm/365.25.

c. Total treatment duration = (last dose date + X days or death date or DCO whichever occurred earlier - first dose date +1) / 7. X was defined as the planned frequency in dosing (in days) - 1. For Q2W, X = 13. For Q3W, X = 20. For Q4W, X = 27.

d. Intended exposure (weeks) = [(minimum of (last dose date where dose > 0 mg + C days, date of death, date of DCO) – first dose date + 1 day)]/7 where C is equal to the scheduled number of days between doses minus one. C is equal to '20' if the last dose date falls into the chemotherapy phase and '27' if the last dose date falls into the maintenance phase. (DUO-E pool).

e. Total treatment duration = (last dose date of continuous treatment - first dose date of continuous treatment +1) / 7. (Olaparib tablet pool).

Note that the terms 'intended exposure' and 'total treatment exposure' are interchangeable.
bd = twice daily; DCO = data cut-off; N = number of patients; n = number of patients included in analysis; Max = maximum; Min = minimum; NA = not applicable; QXW = every X weeks; SD = standard deviation; SoC = standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

The duration of durvalumab exposure in DUO-E maintenance, and the durvalumab Pan-tumour pool are summarised in the table below.

Table 56 Duration of Durvalumab Exposure in DUO-E Maintenance, and the Durvalumab Pan-tumour Pool (Safety Analysis Set)

		DUO-E Maintenance			Durvalumab Pan-tumour Pool (N = 4045)
		SoC (N = 169)	SoC + D (N = 183)	SoC + D + O (N = 192)	
Durvalumab/ placebo	Total treatment duration (weeks) [a]				
	N	169	183	192	4045
	Mean (SD)	33.1 (24.18)	38.3 (28.33)	46.0 (28.35)	28.9 (32.18)
	Median (Min – Max)	24.4 (4-124)	32.3 (0-118)	42.8 (0-125)	16.1 (0-220)
	Total treatment years [b]	107.2	134.2	169.3	2240.4

a. Total treatment duration = (last dose date + X days or death date or DCO whichever occurs earlier - first dose date +1)/7. X is defined as the planned frequency in dosing (in days) - 1. For Q2W, X = 13. For Q3W, X = 20. For Q4W, X = 27

b. Total treatment years = sum of exposure duration for all patients per treatment arm/365.25.

DCO = data cut-off; N = number of patients; n = number of patients included in analysis; Max = maximum; Min = minimum; SD = standard deviation; SoC = standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance; Q3W = every 3 weeks; Q4W = every 4 weeks.

Adverse events

An overview of adverse events (AEs) in any category in DUO-E is presented in the below for the overall phase and for the maintenance phase.

Table 57 Overview of adverse events in any category in DUO-E overall and the durvalumab and olaparib pools (Safety Analysis Set, DCO 12 April 2023)

	Number (%) of patients [a]				
	DUO-E Overall			Durvalumab Pan-tumour Pool (N = 4045)	Olaparib 300 mg bd Tablet Pool (N = 3556)
	SoC (N = 236)	SoC + D (N = 235)	SoC + D + O [b] (N = 238)		
Any AE	236 (100.0)	232 (98.7)	237 (99.6)	3826 (94.6)	3403 (95.7)
Any AE with maximum CTCAE Grade 3 or higher	133 (56.4)	129 (54.9)	160 (67.2)	NA	1258 (35.4)
Any AE with maximum CTCAE Grade 3 or 4	126 (53. 4)	125 (53. 2)	156 (65. 5)	1601 (39.6)	NA
Any AE with outcome = death	8 (3.4)	4 (1.7)	5 (2.1)	231 (5.7)	32 (0.9)
Any SAE (including events with outcome = death)	73 (30.9)	73 (31.1)	85 (35.7)	1448 (35.8)	670 (18.8)
Any AE leading to discontinuation of durvalumab/placebo [c]	19 (8.1)	26 (11.1)	22 (9.2)	397 (9.8)	NA
Any AE leading to discontinuation of olaparib/placebo [c]	5 (2.1)	11 (4.7)	21 (8.8)	NA	331 (9.3)
Any AE leading to discontinuation of SoC [c]	32 (13.6)	31 (13.2)	31 (13.0)	NA	NA

	Number (%) of patients [a]				
	DUO-E Overall			Durvalumab Pan-tumour Pool (N = 4045)	Olaparib 300 mg bd Tablet Pool (N = 3556)
	SoC (N = 236)	SoC + D (N = 235)	SoC + D + O [b] (N = 238)		
Any AE leading to dose delay or interruption of durvalumab/placebo [d]	90 (38.1)	112 (47.7)	131 (55.0)	1121 (27.7)	NA
Any AE leading to dose reduction of olaparib/placebo [e]	5 (2.1)	14 (6.0)	65 (27.3)	NA	778 (21.9)
Any AE leading to dose interruption of olaparib/placebo [f]	31 (13.1)	36 (15.3)	110 (46.2)	NA	1350 (38.0)
Any AE leading to dose interruption of SoC [f]	83 (35.2)	85 (36.2)	85 (35.7)	NA	NA
Any immune mediated AEs	16 (6.8)	66 (28.1)	56 (23.5)	718 (17.8)	NA
Any infusion reaction AEs	24 (10.2)	15 (6.4)	14 (5.9)	65 (1.6)	NA

a. Patients with multiple AEs in the same category were counted only once in that category. Patients with AEs in more than one category were counted once in each of those categories.

b. Olaparib was only administered during the Maintenance phase of DUO-E.

c. AEs on the AE CRF form with Action taken = 'Drug permanently discontinued'. For SoC, AEs were counted as leading to discontinuation of treatment if action taken was equal to 'Drug permanently discontinued' for at least one agent.

d. Includes AEs on the AE CRF form with action taken indicating dose delay or dose interruption, and AEs meeting study level dose delay definitions, where applicable.

e. AEs on the AE CRF form with Action taken = 'Dose reduced'.

f. AEs on the AE CRF form with Action taken = 'Drug interrupted'. For durvalumab/placebo, this includes dose interruption during infusion as indicated in the exposure CRF form as well as dose that skipped or delayed. For SoC, AEs were counted as leading to dose interruption if action taken was equal to 'Drug interrupted' for at least one agent.

For DUO-E, table includes AEs with an onset date on or after the date of first dose of study treatment up until the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurred first.
Durvalumab Pan-Tumour Pool includes adverse events with an onset date on or after the date of first dose or pre-treatment AEs that increased in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication (or surgery) or up to and including the date of initiation of the first subsequent therapy (whichever occurred first).
Disease progression AEs reported in Study 1108 were not included in this summary.
Olaparib Tablet Pool included adverse events with an onset date between the date of first dose of continuous treatment and 30 days following the last dose.
MedDRA version 25.1.
All studies use CTCAE version 4.03 except for DUO-E which uses version 5.0.
AE = adverse event; CRF = case report form; CTCAE = Common Terminology Criteria for Adverse Events version 5.0; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients; NA = not available; SAE = serious adverse event; SoC = standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Table 58 Overview of adverse events in any category in DUO-E maintenance phase and the durvalumab and olaparib pools (Safety Analysis Set, DCO 12 April 2023)

	Number (%) of patients [a]				
	DUO-E Maintenance Phase			Durvalumab Pan-tumour Pool (N = 4045)	Olaparib 300 mg bd Tablet Pool (N = 3556)
	SoC (N = 169)	SoC + D (N = 183)	SoC + D + O (N = 192)		
Any AE	143 (84.6)	158 (86.3)	184 (95.8)	3826 (94.6)	3403 (95.7)

	Number (%) of patients [a]				
	DUO-E Maintenance Phase			Durvalumab Pan-tumour Pool (N = 4045)	Olaparib 300 mg bd Tablet Pool (N = 3556)
	SoC (N = 169)	SoC + D (N = 183)	SoC + D + O (N = 192)		
Any AE with maximum CTCAE Grade 3 or higher	28 (16.6)	30 (16.4)	79 (41.1)	NA	1258 (35.4)
Any AE with maximum CTCAE Grade 3 or 4	26 (15.4)	31 (16.9)	78 (40.6)	1601 (39.6)	NA
Any AE with outcome = death	2 (1.2)	0	3 (1.6)	231 (5.7)	32 (0.9)
Any SAE (including events with outcome = death)	19 (11.2)	22 (12.0)	42 (21.9)	1448 (35.8)	670 (18.8)
Any AE leading to discontinuation of durvalumab/placebo [b]	4 (2.4)	9 (4.9)	16 (8.3)	397 (9.8)	NA
Any AE leading to discontinuation of olaparib/placebo [b]	5 (3.0)	10 (5.5)	21 (10.9)	NA	331 (9.3)
Any AE leading to discontinuation of SoC [b]	1 (0.6)	2 (1.1)	1 (0.5)	NA	NA
Any AE leading to dose delay or interruption of durvalumab/placebo [c]	18 (10.7)	38 (20.8)	68 (35.4)	1121 (27.7)	NA
Any AE leading to dose reduction of olaparib/placebo [d]	4 (2.4)	13 (7.1)	63 (32.8)	NA	778 (21.9)
Any AE leading to dose interruption of olaparib/placebo [e]	30 (17.8)	33 (18.0)	106 (55.2)	NA	1350 (38.0)
Any AE leading to dose reduction of SoC	NA	NA	NA	NA	NA
Any AE leading to dose interruption of SoC [e]	1 (0.6)	1 (0.5)	2 (1.0)	NA	NA
Any AE leading to dose modification of study treatment [f]	39 (23.1)	57 (31.1)	120 (62.5)	1130 (27.9)	1484 (41.7)
Any immune-mediated AEs	6 (3.6)	27 (14.8)	27 (14.1)	718 (17.8)	NA
Any infusion reaction AEs	1 (0.6)	1 (0.5)	1 (0.5)	65 (1.6)	NA

a. Patients with multiple AEs in the same category are counted only once in that category. Patients with AEs in more than one category are counted once in each of those categories.

b. AEs on the AE CRF form with Action taken = 'Drug permanently discontinued'. For SoC, AEs were counted as leading to discontinuation of treatment if action taken was equal to 'Drug permanently discontinued' for at least one agent.

c. Includes AEs on the AE CRF form with action taken indicating dose delay or dose interruption, and AEs meeting study level dose delay definitions, where applicable

d. AEs on the AE CRF form with Action taken = 'Dose reduced'

e. AEs on the AE CRF form with Action taken = 'Drug interrupted'. For durvalumab/placebo, this includes dose interruption during infusion as indicated in the exposure CRF form as well as dose that skipped or delayed. For SoC, AEs are counted as leading to dose interruption if action taken was equal to 'Drug interrupted' for at least one agent. Includes AEs on the AE CRF form with action taken indicating dose reduction, dose delay or dose interruption, and AEs meeting study level dose delay definitions, where applicable.

For DUO-E, table includes AEs with an onset date on or after the date of first dose of study treatment up until the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurred first.
Durvalumab Pan-Tumour Pool includes adverse events with an onset date on or after the date of first dose or pre-treatment AEs that increased in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication (or surgery) or up to and including the date of initiation of the first subsequent therapy (whichever occurred first). Disease progression AEs reported in Study 1108 are not included in this summary.
Olaparib Tablet Pool included adverse events with an onset date between the date of first dose of continuous treatment and 30 days following the last dose.
MedDRA version 25.1.
All studies use CTCAE version 4.03 except for DUO-E which uses version 5.0.
AE = adverse event; CRF = case report form; CTCAE = Common Terminology Criteria for Adverse Events version 5.0; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients; NA = not available; SAE = serious adverse event; SoC = standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Common adverse events

The below tables (overall phase and maintenance phase) summarise the most common AEs, regardless of causality, that occurred in at least 10% of patients in any treatment arm.

Table 59 Most common adverse events (Frequency ≥ 10% in any treatment arm in DUO-E overall; adjusted by patient years' exposure) and the durvalumab and olaparib pools (Safety Analysis Set, DCO 12 April 2023)

	DUO-E Overall						Durvalumab Pan-tumour Pool (N = 4045)	Olaparib 300 mg bd Tablet Pool (N = 3556)
	SoC (N = 236)		SoC + D (N = 235)		SoC + D + O [a] (N = 238)			
PT	n (%) [b]	n/100 PY [c]	n (%) [b]	n/100 PY [c]	n (%) [b]	n/100 PY [c]	n (%) [d]	n (%) [d]
Patients with any AE	**236 (100.0)**	**118.31**	**232 (98.7)**	**100.6**	**237 (99.6)**	**87**	**3826 (94.6)**	**3403 (95.7)**
Anaemia	128 (54.2)	64.17	111 (47.2)	48.13	147 (61.8)	53.96	523 (12.9)	1221 (34.3)
Nausea	105 (44.5)	52.64	96 (40.9)	41.63	130 (54.6)	47.72	678 (16.8)	2046 (57.5)
Alopecia	118 (50.0)	59.16	118 (50.2)	51.17	121 (50.8)	44.42	36 (0.9)	119 (3.3)
Fatigue	87 (36.9)	43.62	82 (34.9)	35.56	93 (39.1)	34.14	998 (24.7)	1328 (37.3)
Constipation	81 (34.3)	40.61	64 (27.2)	27.75	78 (32.8)	28.63	653 (16.1)	539 (15.2)
Diarrhoea	66 (28.0)	33.09	74 (31.5)	32.09	67 (28.2)	24.6	649 (16.0)	778 (21.9)
Vomiting	43 (18.2)	21.56	49 (20.9)	21.25	61 (25.6)	22.39	422 (10.4)	989 (27.8)
Neuropathy peripheral	66 (28.0)	33.09	61 (26.0)	26.45	60 (25.2)	22.03	78 (1.9)	68 (1.9)
Peripheral sensory neuropathy	66 (28.0)	33.09	60 (25.5)	26.02	60 (25.2)	22.03	38 (0.9)	82 (2.3)
Arthralgia	58 (24.6)	29.08	71 (30.2)	30.79	58 (24.4)	21.29	536 (13.3)	437 (12.3)
Decreased appetite	46 (19.5)	23.06	42 (17.9)	18.21	55 (23.1)	20.19	769 (19.0)	649 (18.3)
Neutrophil count decreased	63 (26.7)	31.58	44 (18.7)	19.08	50 (21.0)	18.36	24 (0.6)	299 (8.4)
Neutropenia	31 (13.1)	15.54	36 (15.3)	15.61	49 (20.6)	17.99	32 (0.8)	316 (8.9)
COVID-19	32 (13.6)	16.04	36 (15.3)	15.61	48 (20.2)	17.62	1 (<0.1)	11 (0.3)
Urinary tract infection	50 (21.2)	25.07	33 (14.0)	14.31	48 (20.2)	17.62	272 (6.7)	263 (7.4)
Asthenia	24 (10.2)	12.03	23 (9.8)	9.97	46 (19.3)	16.89	466 (11.5)	470 (13.2)
Abdominal pain	39 (16.5)	19.55	38 (16.2)	16.48	40 (16.8)	14.68	313 (7.7)	482 (13.6)
Platelet count decreased	37 (15.7)	18.55	36 (15.3)	15.61	40 (16.8)	14.68	41 (1.0)	158 (4.4)
Dizziness	31 (13.1)	15.54	32 (13.6)	13.88	40 (16.8)	14.68	236 (5.8)	398 (11.2)
Headache	35 (14.8)	17.55	30 (12.8)	13.01	39 (16.4)	14.32	323 (8.0)	578 (16.3)
Hypomagnesaemia	38 (16.1)	19.05	38 (16.2)	16.48	38 (16.0)	13.95	119 (2.9)	88 (2.5)
White blood cell count decreased	40 (16.9)	20.05	29 (12.3)	12.57	38 (16.0)	13.95	23 (0.6)	294 (8.3)
Pruritus	29 (12.3)	14.54	36 (15.3)	15.61	37 (15.5)	13.58	462 (11.4)	112 (3.1)
Thrombocytopenia	18 (7.6)	9.02	30 (12.8)	13.01	35 (14.7)	12.85	69 (1.7)	183 (5.1)
Back pain	22 (9.3)	11.03	19 (8.1)	8.24	35 (14.7)	12.85	442 (10.9)	370 (10.4)
Cough	25 (10.6)	12.53	35 (14.9)	15.18	33 (13.9)	12.11	643 (15.9)	430 (12.1)
Hypothyroidism	8 (3.4)	4.01	37 (15.7)	16.04	33 (13.9)	12.11	379 (9.4)	13 (0.4)
Myalgia	44 (18.6)	22.06	32 (13.6)	13.88	30 (12.6)	11.01	196 (4.8)	184 (5.2)
Alanine aminotransferase increased	18 (7.6)	9.02	30 (12.8)	13.01	30 (12.6)	11.01	256 (6.3)	152 (4.3)
Oedema peripheral	21 (8.9)	10.53	29 (12.3)	12.57	30 (12.6)	11.01	347 (8.6)	225 (6.3)
Pain in extremity	35 (14.8)	17.55	31 (13.2)	13.44	29 (12.2)	10.65	194 (4.8)	224 (6.3)
Dyspnoea	26 (11.0)	13.03	29 (12.3)	12.57	29 (12.2)	10.65	596 (14.7)	344 (9.7)
Insomnia	33 (14.0)	16.54	24 (10.2)	10.41	29 (12.2)	10.65	300 (7.4)	234 (6.6)
Rash	27 (11.4)	13.54	41 (17.4)	17.78	28 (11.8)	10.28	395 (9.8)	142 (4.0)
Hypokalaemia	20 (8.5)	10.03	27 (11.5)	11.71	28 (11.8)	10.28	174 (4.3)	103 (2.9)

	DUO-E Overall						Durvalumab Pan-tumour Pool (N = 4045)	Olaparib 300 mg bd Tablet Pool (N = 3556)
	SoC (N = 236)		SoC + D (N = 235)		SoC + D + O [a] (N = 238)			
PT	n (%) [b]	n/100 PY [c]	n (%) [b]	n/100 PY [c]	n (%) [b]	n/100 PY [c]	n (%) [d]	n (%) [d]
Dysgeusia	26 (11.0)	13.03	24 (10.2)	10.41	27 (11.3)	9.91	71 (1.8)	387 (10.9)
Stomatitis	18 (7.6)	9.02	19 (8.1)	8.24	25 (10.5)	9.18	122 (3.0)	220 (6.2)
Pyrexia	19 (8.1)	9.53	21 (8.9)	9.11	24 (10.1)	8.81	522 (12.9)	305 (8.6)
Blood creatinine increased	13 (5.5)	6.52	10 (4.3)	4.34	24 (10.1)	8.81	145 (3.6)	201 (5.7)
Infusion related reaction	24 (10.2)	12.03	14 (6.0)	6.07	13 (5.5)	4.77	55 (1.4)	2 (0.1)

[a] Olaparib was only administered during the Maintenance phase of DUO-E.

[b] Number (%) of patients with AEs, sorted in decreasing frequency of PT in DUO-E (SoC + D + O then SoC + D then SoC). Patients with multiple AEs are counted once for each system organ class and PT. Patients with adverse events in more than one preferred term are counted once in each of those preferred terms.

[c] Event rate per 100 patient years (the number of patients with any given AE divided by the total treatment duration in days across all patients in given group, multiplied by 365.25 multiplied by 100. Treatment duration lasted until the later of either) the date of the last dose of olaparib or ii) the date of the last dose of durvalumab +20 days during chemotherapy phase, or the date of the last dose of durvalumab +27 days during the maintenance phase (to account for the infusion exposure period).

[d] Number (%) of patients with AEs, sorted in decreasing frequency of PT in DUO-E (SoC + D + O then SoC + D then SoC). Patients with multiple AEs are counted once for each system organ class and PT.

The total treatment duration across all patients in SoC arm = 199.47 years (Overall); in SoC + D arm = 230.63 years (Overall); in SoC + D + O = 272.41 years (Overall).

For DUO-E, includes AEs with an onset date or that worsened on or after the date of first dose of study treatment up until the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurs first.

Durvalumab Pan-Tumour Pool includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication (or surgery) or up to and including the date of initiation of the first subsequent therapy (whichever occurs first). Disease progression adverse events reported in Study 1108 are not included in this summary.
Percentages are based on the total number of patients in the treatment group (N).

Olaparib Tablet Pool includes AEs with an onset date between the date of first dose of continuous treatment and 30 days following the last dose of continuous treatment.
MedDRA version 25.1
AE = adverse event; bd = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in treatment group; n = number of patients included in analysis; PT = preferred term; PY = patient years; SoC = standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Table 60 Most common adverse events (Frequency ≥ 10% in any treatment group) in DUO-E maintenance phase (adjusted by patient years' exposure) and the durvalumab and olaparib pools (Safety Analysis Set, DCO 12 April 2023)

	DUO-E Maintenance Phase						Durvalumab Pan-tumour Pool (N = 4045)	Olaparib 300 mg bd Tablet Pool (N = 3556)
	SoC (N = 169)		SoC + D (N = 183)		SoC + D + O (N = 192)			
PT	n (%) [a]	n/100 PY [b]	n (%) [a]	n/100 PY [b]	n (%) [a]	n/100 PY [b]	n (%) [c]	n (%) [c]
Patients with any AE	**143 (84.6)**	**132.24**	**158 (86.3)**	**113.77**	**184 (95.8)**	**104.63**	**3826 (94.6)**	**3403 (95.7)**
Nausea	25 (14.8)	23.12	22 (12.0)	15.84	79 (41.1)	44.92	678 (16.8)	2046 (57.5)
Anaemia	17 (10.1)	15.72	16 (8.7)	11.52	70 (36.5)	39.81	523 (12.9)	1221 (34.3)
Fatigue	19 (11.2)	17.57	13 (7.1)	9.36	43 (22.4)	24.45	998 (24.7)	1328 (37.3)
Vomiting	16 (9.5)	14.8	13 (7.1)	9.36	39 (20.3)	22.18	422 (10.4)	989 (27.8)
Diarrhoea	20 (11.8)	18.5	28 (15.3)	20.16	34 (17.7)	19.33	649 (16.0)	778 (21.9)
COVID-19	20 (11.8)	18.5	21 (11.5)	15.12	34 (17.7)	19.33	1 (<0.1)	11 (0.3)
Decreased appetite	6 (3.6)	5.55	9 (4.9)	6.48	28 (14.6)	15.92	769 (19.0)	649 (18.3)
Urinary tract infection	23 (13.6)	21.27	14 (7.7)	10.08	25 (13.0)	14.22	272 (6.7)	263 (7.4)
Abdominal pain	18 (10.7)	16.65	20 (10.9)	14.4	23 (12.0)	13.08	313 (7.7)	482 (13.6)
Back pain	11 (6.5)	10.17	11 (6.0)	7.92	23 (12.0)	13.08	442 (10.9)	370 (10.4)
Arthralgia	16 (9.5)	14.8	34 (18.6)	24.48	22 (11.5)	12.51	536 (13.3)	437 (12.3)
Cough	14 (8.3)	12.95	22 (12.0)	15.84	21 (10.9)	11.94	643 (15.9)	430 (12.1)
Neutropenia	1 (0.6)	0.92	6 (3.3)	4.32	21 (10.9)	11.94	32 (0.8)	316 (8.9)

[a] Number (%) of patients with AEs, sorted in decreasing frequency of PT in DUO-E (SoC + D + O then SoC + D then SoC). Patients with multiple AEs are counted once for each system organ class and PT. Patients with adverse events in more than one preferred term are counted once in each of those preferred terms.

[b] Event rate per 100 patient years (the number of patients with any given AE divided by the total treatment duration in days across all patients in given group, multiplied by 365.25 multiplied by 100. Treatment duration lasted until the later of either i) the date of the last dose of olaparib or ii) the date of the last dose of durvalumab +20 days during chemotherapy phase, or the date of the last dose of durvalumab +27 days during the maintenance phase (to account for the infusion exposure period).

[c] Number (%) of patients with AEs, sorted in decreasing frequency of PT in DUO-E (SoC + D + O then SoC + D then SoC). Patients with multiple AEs are counted once for each system organ class and PT.

The total treatment duration across all patients in SoC arm = 108.13 years (Maintenance); in SoC + D arm = 138.87 years (Maintenance); in SoC + D + O = 175.85 years (Maintenance).

For DUO-E, includes AEs with an onset date or that worsened on or after the date of first dose of study treatment up until the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurs first.

Durvalumab Pan-Tumour Pool includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication (or surgery) or up to and including the date of initiation of the first subsequent therapy (whichever occurs first). Disease progression adverse events reported in Study 1108 are not included in this summary.

Percentages are based on the total number of patients in the treatment group (N).

Olaparib Tablet Pool includes AEs with an onset date between the date of first dose of continuous treatment and 30 days following the last dose of continuous treatment.

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AE = adverse event; bd = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in treatment group; n = number of patients included in analysis; PT = preferred term; PY = patient years; SoC = standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

The below tables summarise the AEs with a difference of at least 5% between the DUO E SoC + D or SoC + D + O and SoC treatment arms.

Table 61 Adverse events with a difference of ≥ 5% between DUO-E SoC + D or SoC + D + O and SoC treatment arms in DUO-E overall (adjusted by patient years' exposure) and the durvalumab and olaparib pools (Safety Analysis Set, DCO 12 April 2023)

	DUO-E Overall						Durvalumab Pan-tumour Pool (N = 4045)	Olaparib 300 mg bd Tablet Pool (N = 3556)
	SoC (N = 236)		SoC + D (N = 235)		SoC + D + O [a] (N = 238)			
PT	n (%) [b]	n/100 PY [c]	n (%) [b]	n/100 PY [c]	n (%) [b]	n/100 PY [c]	n (%) [d]	n (%) [d]
Patients with any AE	**236 (100.0)**	**118.31**	**232 (98.7)**	**100.6**	**237 (99.6)**	**87**	**3826 (94.6)**	**3403 (95.7)**
Anaemia	128 (54.2)	64.17	111 (47.2)	48.13	147 (61.8)	53.96	523 (12.9)	1221 (34.3)
Nausea	105 (44.5)	52.64	96 (40.9)	41.63	130 (54.6)	47.72	678 (16.8)	2046 (57.5)
Vomiting	43 (18.2)	21.56	49 (20.9)	21.25	61 (25.6)	22.39	422 (10.4)	989 (27.8)
Arthralgia	58 (24.6)	29.08	71 (30.2)	30.79	58 (24.4)	21.29	536 (13.3)	437 (12.3)
Neutropenia	31 (13.1)	15.54	36 (15.3)	15.61	49 (20.6)	17.99	32 (0.8)	316 (8.9)
COVID-19	32 (13.6)	16.04	36 (15.3)	15.61	48 (20.2)	17.62	1 (<0.1)	11 (0.3)
Asthenia	24 (10.2)	12.03	23 (9.8)	9.97	46 (19.3)	16.89	466 (11.5)	470 (13.2)
Thrombocytopenia	18 (7.6)	9.02	30 (12.8)	13.01	35 (14.7)	12.85	69 (1.7)	183 (5.1)
Back pain	22 (9.3)	11.03	19 (8.1)	8.24	35 (14.7)	12.85	442 (10.9)	370 (10.4)
Hypothyroidism	8 (3.4)	4.01	37 (15.7)	16.04	33 (13.9)	12.11	379 (9.4)	13 (0.4)
Myalgia	44 (18.6)	22.06	32 (13.6)	13.88	30 (12.6)	11.01	196 (4.8)	184 (5.2)
Alanine aminotransferase increased	18 (7.6)	9.02	30 (12.8)	13.01	30 (12.6)	11.01	256 (6.3)	152 (4.3)
Rash	27 (11.4)	13.54	41 (17.4)	17.78	28 (11.8)	10.28	395 (9.8)	142 (4.0)

[a] Olaparib was only administered during the Maintenance phase of DUO-E.

[b] Number (%) of patients with a ≥ 5% between DUO-E treatment arms in DUO-E overall, sorted by decreasing frequency of PT in DUO-E (SoC + D + O then SoC + D then SoC). Patients with multiple AEs are counted once for each system organ class and PT. Patients with adverse events in more than one preferred term are counted once in each of those preferred terms.

[c] Event rate per 100 patient years (the number of patients with any given AE divided by the total treatment duration in days across all patients in given group, multiplied by 365.25 multiplied by 100. Treatment duration lasted until the later of either i) the date of the last dose of olaparib or ii) the date of the last dose of durvalumab +20 days during chemotherapy phase, or the date of the last dose of durvalumab +27 days during the maintenance phase (to account for the infusion exposure period).

[d] Number (%) of patients with AEs, sorted in decreasing frequency of PT in DUO-E (SoC + D + O then SoC + D then SoC). Patients with multiple AEs are counted once for each system organ class and PT.

The total treatment duration across all patients in SoC arm = 199.47 years (Overall); in SoC + D arm = 230.63 years (Overall); in SoC + D + O = 272.41 years (Overall).

For DUO-E, includes AEs with an onset date or that worsened on or after the date of first dose of study treatment up until the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurs first.

Durvalumab Pan-Tumour Pool includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication (or surgery) or up to and including the date of initiation of the first subsequent therapy (whichever occurs first). Disease progression adverse events reported in Study 1108 are not included in this summary.

Percentages are based on the total number of patients in the treatment group (N).

Olaparib Tablet Pool includes AEs with an onset date between the date of first dose of continuous treatment and 30 days following the last dose of continuous treatment.

MedDRA version 25.1

AE = adverse event; bd = twice daily; COVID-19 = Coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in treatment group; n = number of patients included in analysis; PT = preferred term; PY = patient years; SoC = standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Table 62 Adverse events with a difference of ≥ 5% between DUO-E SoC + D or SoC + D + O and SoC treatment arms in DUO-E maintenance phase (adjusted by patient years' exposure) and the durvalumab and olaparib pools (Safety Analysis Set, DCO 12 April 2023)

	DUO-E Maintenance Phase						Durvalumab Pan-tumour Pool (N = 4045)	Olaparib 300 mg bd Tablet Pool (N = 3556)
	SoC (N = 169)		SoC + D (N = 183)		SoC + D + O (N = 192)			
PT	n (%) [a]	n/100 PY [b]	n (%) [a]	n/100 PY [b]	n (%) [a]	n/100 PY [b]	n (%) [c]	n (%) [c]
Patients with any AE	**143 (84.6)**	**132.24**	**158 (86.3)**	**113.77**	**184 (95.8)**	**104.63**	**3826 (94.6)**	**3403 (95.7)**
Nausea	25 (14.8)	23.12	22 (12.0)	15.84	79 (41.1)	44.92	678 (16.8)	2046 (57.5)
Anaemia	17 (10.1)	15.72	16 (8.7)	11.52	70 (36.5)	39.81	523 (12.9)	1221 (34.3)
Fatigue	19 (11.2)	17.57	13 (7.1)	9.36	43 (22.4)	24.45	998 (24.7)	1328 (37.3)
Vomiting	16 (9.5)	14.8	13 (7.1)	9.36	39 (20.3)	22.18	422 (10.4)	989 (27.8)
Diarrhoea	20 (11.8)	18.5	28 (15.3)	20.16	34 (17.7)	19.33	649 (16.0)	778 (21.9)
COVID-19	20 (11.8)	18.5	21 (11.5)	15.12	34 (17.7)	19.33	1 (<0.1)	11 (0.3)
Decreased appetite	6 (3.6)	5.55	9 (4.9)	6.48	28 (14.6)	15.92	769 (19.0)	649 (18.3)
Arthralgia	16 (9.5)	14.8	34 (18.6)	24.48	22 (11.5)	12.51	536 (13.3)	437 (12.3)
Neutropenia	1 (0.6)	0.92	6 (3.3)	4.32	21 (10.9)	11.94	32 (0.8)	316 (8.9)
Back pain	11 (6.5)	10.17	11 (6.0)	7.92	23 (12.0)	13.08	442 (10.9)	370 (10.4)
Asthenia	2 (1.2)	1.85	6 (3.3)	4.32	19 (9.9)	10.8	466 (11.5)	470 (13.2)
Blood creatinine increased	2 (1.2)	1.85	4 (2.2)	2.88	19 (9.9)	10.8	145 (3.6)	201 (5.7)
Platelet count decreased	5 (3.0)	4.62	5 (2.7)	3.6	17 (8.9)	9.67	41 (1.0)	158 (4.4)
Hypothyroidism	5 (3.0)	4.62	18 (9.8)	12.96	15 (7.8)	8.53	379 (9.4)	13 (0.4)
Dysgeusia	2 (1.2)	1.85	2 (1.1)	1.44	14 (7.3)	7.96	71 (1.8)	387 (10.9)
Oedema peripheral	3 (1.8)	2.77	14 (7.7)	10.08	13 (6.8)	7.39	347 (8.6)	225 (6.3)

[a] Number (%) of patients with a ≥ 5% between DUO-E treatment arms in DUO-E maintenance phase, sorted by decreasing frequency of PT in DUO-E (SoC + D + O then SoC + D then SoC). Patients with multiple AEs are counted once for each system organ class and PT. Patients with adverse events in more than one preferred term are counted once in each of those preferred terms.

[b] Event rate per 100 patient years the number of patients with any given AE divided by the total treatment duration in days across all patients in given group, multiplied by 365.25 multiplied by 100. Treatment duration lasted until the later of either i) the date of the last dose of olaparib or ii) the date of the last dose of durvalumab +20 days during chemotherapy phase, or the date of the last dose of durvalumab +27 days during the maintenance phase (to account for the infusion exposure period).

[c] Number (%) of patients with AEs, sorted in decreasing frequency of PT in DUO-E (SoC + D + O then SoC + D then SoC). Patients with multiple AEs are counted once for each system organ class and PT.

The total treatment duration across all patients in SoC arm = 108.13 years (Maintenance); in SoC + D arm = 138.87 years (Maintenance); in SoC + D + O = 175.85 years (Maintenance).

DUO-E, includes AEs with an onset date or that worsened on or after the date of first dose of olaparib/placebo up until the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurs first.

Durvalumab Pan-Tumour Pool includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication (or surgery) or up to and including the date of initiation of the first subsequent therapy (whichever occurs first). Disease progression adverse events reported in Study 1108 are not included in this summary.

Percentages are based on the total number of patients in the treatment group (N).

Olaparib Tablet Pool includes AEs with an onset date between the date of first dose of continuous treatment and 30 days following the last dose of continuous treatment.

MedDRA version 25.1

AE = adverse event; bd = twice daily; COVID-19 = Coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in treatment group; n = number of patients included in analysis; PT = preferred term; PY = patient years; SoC = standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Adverse events Grade ≥ 3

Different safety analysis standards are used between durvalumab and olaparib (i.e. Grade 5 AEs [deaths] with durvalumab are summarised separately from the Grade 3 to 4 AEs, whereas for olaparib Grade 3 to 5 AEs are combined). Because of this, maximum Grade 3 or 4 AEs will be reported for comparison with the durvalumab Pan Tumour Pool and Grade ≥ 3 AEs will be reported for comparison with the olaparib 300 mg bd Tablet Pool.

Table 63 Most common (Frequency ≥ 2% in SoC, SoC + D or SoC + D + O arm in DUO-E overall or maintenance phase) AEs of maximum CTCAE grade 3 or 4 in DUO-E compared with the durvalumab pool (Safety Analysis Set)

PT	Number (%) of patients [a]						
	DUO-E Overall			DUO-E Maintenance Phase			Durvalumab Pan-tumour Pool (N = 4045)
	SoC (N = 236)	SoC + D (N = 235)	SoC + D + O [b] (N = 238)	SoC (N = 169)	SoC + D (N = 183)	SoC + D + O (N = 192)	
Patients with any AE of maximum CTCAE Grade 3 or 4	**128 (54.2)**	**126 (53.6)**	**160 (67.2)**	**27 (16.0)**	**31 (16.9)**	**80 (41.7)**	**1755 (43.4)**
Anaemia	35 (14.8)	38 (16.2)	56 (23.5)	3 (1.8)	1 (0.5)	36 (18.8)	182 (4.5)
Neutropenia	14 (5.9)	20 (8.5)	28 (11.8)	0	0	10 (5.2)	9 (0.2)
Neutrophil count decreased	36 (15.3)	27 (11.5)	32 (13.4)	1 (0.6)	1 (0.5)	4 (2.1)	6 (0.1)
White blood cell count decreased	11 (4.7)	9 (3.8)	11 (4.6)	0	1 (0.5)	1 (0.5)	2 (<0.1)
Thrombocytopenia	3 (1.3)	7 (3.0)	8 (3.4)	0	0	1 (0.5)	17 (0.4)
Febrile neutropenia	9 (3.8)	6 (2.6)	8 (3.4)	0	0	2 (1.0)	1 (<0.1)
Hypokalaemia	2 (0.8)	6 (2.6)	7 (2.9)	0	1 (0.5)	1 (0.5)	45 (1.1)
Asthenia	4 (1.7)	3 (1.3)	8 (3.4)	0	0	2 (1.0)	53 (1.3)
Urinary tract infection	8 (3.4)	2 (0.9)	7 (2.9)	6 (3.6)	1 (0.5)	4 (2.1)	41 (1.0)
Syncope	1 (0.4)	2 (0.9)	7 (2.9)	0	0	2 (1.0)	24 (0.6)
Nausea	3 (1.3)	1 (0.4)	7 (2.9)	1 (0.6)	0	3 (1.6)	24 (0.6)
Platelet count decreased	9 (3.8)	9 (3.8)	6 (2.5)	0	1 (0.5)	0	8 (0.2)
Hypertension	7 (3.0)	5 (2.1)	6 (2.5)	1 (0.6)	2 (1.1)	1 (0.5)	54 (1.3)
Fatigue	4 (1.7)	5 (2.1)	5 (2.1)	0	1 (0.5)	3 (1.6)	91 (2.2)
Pulmonary embolism	3 (1.3)	4 (1.7)	5 (2.1)	0	1 (0.5)	2 (1.0)	32 (0.8)
Leukopenia	2 (0.8)	2 (0.9)	5 (2.1)	0	0	1 (0.5)	4 (0.1)
Lymphocyte count decreased	5 (2.1)	5 (2.1)	3 (1.3)	0	2 (1.1)	2 (1.0)	15 (0.4)
Diarrhoea	6 (2.5)	4 (1.7)	3 (1.3)	1 (0.6)	1 (0.5)	1 (0.5)	33 (0.8)
Hyponatraemia	4 (1.7)	5 (2.1)	3 (1.3)	0	1 (0.5)	1 (0.5)	119 (2.9)
Peripheral sensory neuropathy	6 (2.5)	0	2 (0.8)	1 (0.6)	0	0	2 (<0.1)
Gamma-glutamyltransferase increased	3 (1.3)	5 (2.1)	2 (0.8)	0	1 (0.5)	1 (0.5)	84 (2.1)
Constipation	5 (2.1)	2 (0.9)	0	0	0	0	18 (0.4)

[a] Number (%) of patients, sorted by decreasing frequency of PT in DUO-E SoC + D + O then the SoC + D arm for the Overall study period.

[b] Olaparib was only administered during the Maintenance phase of DUO-E.

Percentages are based on the total number of patients in the treatment group (N).

For DUO-E, includes AEs with an onset date or that worsen on or after the date of first dose of study treatment (overall) or first dose of olaparib/placebo (maintenance phase) up until the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurs first.

For DUO-E, the worst CTCAE grade is taken from the AE onset date until the first subsequent anti-cancer therapy following discontinuation of treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurs first.

Durvalumab Pan-Tumour Pool includes adverse events with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication (or surgery) or up to and including the date of initiation of the first subsequent therapy (whichever occurs first). Disease progression AEs reported in Study 1108 are not included in this summary.

For the Durvalumab Pan-Tumour pool the worst CTCAE grade is taken across the full duration of the AE regardless of the timing of treatment.

All studies use CTCAE version 4.03 except for DUO-E which uses version 5.0.

MedDRA version 25.1

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in treatment group; PT = preferred term; SoC = standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Table 64 Most common (Frequency ≥ 2% in SoC, SoC + D or SoC + D + O arm in DUO-E in DUO-E maintenance phase) AEs of CTCAE Grade ≥ 3 compared with the olaparib pool (Safety Analysis Set)

PT	Number (%) of patients [a]			
	DUO-E Maintenance Phase			Olaparib 300 mg bd Tablet Pool (N = 3556)
	SoC (N = 169)	SoC + D (N = 183)	SoC + D + O (N = 192)	
Patients with AE of CTCAE Grade ≥ 3	**28 (16.6)**	**30 (16.4)**	**79 (41.1)**	**1258 (35.4)**
Anaemia	1 (0.6)	0	36 (18.8)	499 (14.0)
Neutropenia	0	0	9 (4.7)	105 (3.0)
Urinary tract infection	6 (3.6)	1 (0.5)	4 (2.1)	25 (0.7)

[a] Number (%) of patients with AEs of CTCAE Grade ≥ 3, sorted by decreasing frequency of PT in DUO-E SoC + D + O then SoC + D. Patients with multiple AEs are counted only once by the maximum CTCAE grade for each PT.

For DUO-E, includes AEs with an onset date or that worsened on or after the date of first dose of study treatment (overall) or first dose of olaparib/placebo (maintenance phase) up until the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurs first.

For the Olaparib Tablet Pool, includes AEs with an onset date between the date of first dose of continuous treatment and 30 days following the last dose of continuous treatment.

All studies use CTCAE version 5.0.

MedDRA version 25.1

AE = adverse event; bd = twice daily; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in treatment group; PT = preferred term; SoC = standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Adverse Drug Reactions (ADRs)

Analyses were conducted by the MAH to identify any new ADRs for durvalumab and for olaparib in the DUO-E study, and for durvalumab also taking into account the Durvalumab Pan-tumour Pool and the Olaparib 300 mg bd Tablet Pool. This included analysis of AEs by frequency, severity, AEs by causal relationship, AEs leading to discontinuation, SAEs, individual case/case series review including time to onset, temporal relationship, outcome, and mechanism of action. As a result, no new ADRs were identified specific for durvalumab or specific for olaparib based on the DUO-E study data.

The frequency and severity of durvalumab ADRs in SoC + D and SoC + D + O in DUO-E are consistent with the durvalumab Pan-tumour Pool.

Following expert medical review of the DUO-E study data, in conjunction with data from the overall clinical development programme and post-marketing use, the event of PRCA has been identified as an ADR for the combination of olaparib plus durvalumab.

Table 65 Adverse Drug Reactions by ADR Term and CIOMS Category in the DUO-E Study (Overall and Maintenance Phases) and Durvalumab Pan-tumour Pool, (Safety Analysis Set, DCO 12 April 2023)

	DUO-E study													
	Overall						Maintenance Phase						Durvalumab Pan-tumour pool (N = 4045)	
	SoC (N = 236)		SoC + D (N = 235)		SoC + D + O [a] (N = 238)		SoC (N = 169)		SoC + D (N = 183)		SoC + D + O [a] (N = 192)			
ADR system organ class/ ADR term	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number of patients [b]	CIOMS III category [c]
Patients with any ADR	232 (98.3)	-	224 (95.3)	-	235 (98.7)	-	120 (71.0)	-	138 (75.4)	-	175 (91.1)	-	2958 (73.1)	-
Blood and lymphatic system disorders														
Immune thrombocytopenia	0	NR	1 (0.4)	Un-common	0	NR	0	NR	0	NR	0	NR	3 (< 0.1)	Rare
Anaemia	128 (54.2)	Very common	111 (47.2)	Very common	147 (61.8)	Very common	17 (10.1)		16 (8.7)	Common	70 (36.5)	Very common	NA	-
Neutropenia	91 (38.6)	Very common	76 (32.3)	Very common	94 (39.5)	Very common	7 (4.1)	Common	13 (7.1)	Common	34 (17.7)	Very common	NA	-
Thrombocytopenia	52 (22.0)	Very common	66 (28.1)	Very common	71 (29.8)	Very common	9 (5.3)	Common	6 (3.3)	Common	27 (14.1)	Very common	NA	-
Leukopenia	45 (19.1)	Very common	40 (17.0)	Very common	48 (20.2)	Very common	9 (5.3)	Common	7 (3.8)	Common	19 (9.9)	Common	NA	-
Febrile neutropenia	10 (4.2)	Common	7 (3.0)	Common	8 (3.4)	Common	0	NR	0	NR	2 (1.0)	Common	NA	-
Pancytopenia	1 (0.4)	Un-common	0	NR	2 (0.8)	Un-common	0	NR	0	NR	1 (0.5)	Uncommo n	NA	-
Aplasia pure red cell	NA	-	NA	-	3 (1.3)	Common	NA	-	NA	-	3 (1.6)	Common	NA	-
Cardiac disorders														
Myocarditis	0	NR	0	NR	0	NR	0	NR	0	NR	0	NR	5 (0.1)	Un-common
Endocrine disorders														

	DUO-E study													
	Overall						Maintenance Phase						Durvalumab Pan-tumour pool (N = 4045)	
	SoC (N = 236)		SoC + D (N = 235)		SoC + D + O [a] (N = 238)		SoC (N = 169)		SoC + D (N = 183)		SoC + D + O [a] (N = 192)			
ADR system organ class/ ADR term	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number of patients [b]	CIOMS III category [c]
Hypothyroidism	11 (4.7)	Common	39 (16.6)	Very common	37 (15.5)	Very common	8 (4.7)	Common	19 (10.4)	Very common	19 (9.9)	Common	439 (10.9)	Very common
Hyperthyroidism	4 (1.7)	Common	18 (7.7)	Common	16 (6.7)	Common	1 (0.6)	Un-common	5 (2.7)	Common	4 (2.1)	Common	199 (4.9)	Common
Thyroiditis	0	NR	4 (1.7)	Common	6 (2.5)	Common	0	NR	0	NR	1 (0.5)	Un-common	30 (0.7)	Un-common
Adrenal insufficiency	0	NR	1 (0.4)	Un-common	0	NR	0	NR	1 (0.5)	Un-common	0	NR	24 (0.6)	Un-common
Hypopituitarism/ Hypophysitis	0	NR	0	NR	0	NR	0	NR	0	NR	0	NR	3 (< 0.1)	Rare
Type 1 diabetes mellitus	0	NR	1 (0.4)	Un-common	0	NR	0	NR	0	NR	0	NR	3 (< 0.1)	Rare
Diabetes insipidus	0	NR	0	NR	0	NR	0	NR	0	NR	0	NR	1 (< 0.1)	Rare
Eye disorders														
Uveitis	0	NR	2 (0.9)	Un-common	1 (0.4)	Un-common	0	NR	0	NR	0	NR	1 (< 0.1)	Rare
Gastrointestinal disorders														
Diarrhoea	66 (28.0)	Very common	74 (31.5)	Very common	67 (28.2)	Very common	20 (11.8)	Very common	28 (15.3)	Very common	34 (17.7)	Very common	649 (16.0)	Very common
Abdominal pain	59 (25.0)	Very common	59 (25.1)	Very common	56 (23.5)	Very common	28 (16.6)	Very common	34 (18.6)	Very common	26 (13.5)	Very common	524 (13.0)	Very common

	DUO-E study												Durvalumab Pan-tumour pool (N = 4045)	
	Overall						Maintenance Phase							
	SoC (N = 236)		SoC + D (N = 235)		SoC + D + O [a] (N = 238)		SoC (N = 169)		SoC + D (N = 183)		SoC + D + O [a] (N = 192)			
ADR system organ class/ ADR term	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number of patients [b]	CIOMS III category [c]
Colitis	1 (0.4)	Un-common	5 (2.1)	Common	4 (1.7)	Common	0	NR	3 (1.6)	Common	0	NR	37 (0.9)	Un-common
Pancreatitis	0	NR	0	NR	0	NR	0	NR	0	NR	0	NR	8 (0.2)	Un-common
Nausea	105 (44.5)	Very common	96 (40.9)	Very common	130 (54.6)	Very common	25 (14.8)	Very common	22 (12.0)	Very common	79 (41.1)	Very common	NA	-
Constipation	81 (34.3)	Very common	64 (27.2)	Very common	78 (32.8)	Very common	9 (5.3)	Common	13 (7.1)	Common	13 (6.8)	Common	NA	-
Stomatitis	23 (9.7)	Common	21 (8.9)	Common	27 (11.3)	Very common	6 (3.6)	Common	5 (2.7)	Common	11 (5.7)	Common	NA	-
Vomiting	43 (18.2)	Very common	49 (20.9)	Very common	61 (25.6)	Very common	16 (9.5)	Common	13 (7.1)	Common	39 (20.3)	Very common	NA	-
General disorders and administration site conditions														
Pyrexia	18 (7.6)	Common	21 (8.9)	Common	24 (10.1)	Very common	5 (3.0)	Common	11 (6.0)	Common	15 (7.8)	Common	522 (12.9)	Very common
Oedema peripheral	27 (11.4)	Very common	36 (15.3)	Very common	39 (16.4)	Very common	4 (2.4)	Common	18 (9.8)	Common	19 (9.9)	Common	380 (9.4)	Common
Fatigue	105 (44.5)	Very common	101 (43.0)	Very common	129 (54.2)	Very common	21 (12.4)	Very common	19 (10.4)	Very common	62 (32.3)	Very common	NA	-
Hepatobiliary disorders														

	DUO-E study												Durvalumab Pan-tumour pool (N = 4045)	
	Overall						Maintenance Phase							
	SoC (N = 236)		SoC + D (N = 235)		SoC + D + O [a] (N = 238)		SoC (N = 169)		SoC + D (N = 183)		SoC + D + O [a] (N = 192)			
ADR system organ class/ ADR term	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number of patients [b]	CIOMS III category [c]
AST or ALT increased	26 (11.0)	Very common	31 (13.2)	Very common	35 (14.7)	Very common	10 (5.9)	Common	11 (6.0)	Common	18 (9.4)	Common	369 (9.1)	Common
Hepatitis	1 (0.4)	Un-common	2 (0.9)	Uncommon	2 (0.8)	Uncommon	0	NR	2 (1.1)	Common	1 (0.5)	Un-common	45 (1.1)	Common
Infections and infestations														
Upper respiratory tract infections	24 (10.2)	Very common	21 (8.9)	Common	24 (10.1)	Very common	9 (5.3)	Common	9 (4.9)	Common	15 (7.8)	Common	489 (12.1)	Very common
Pneumonia	1 (0.4)	Un-common	2 (0.9)	Un-common	7 (2.9)	Common	1 (0.6)	Un-common	0	NR	3 (1.6)	Common	319 (7.9)	Common
Oral candidiasis	0	NR	1 (0.4)	Un-common	4 (1.7)	Common	0	NR	0	NR	2 (1.0)	Common	76 (1.9)	Common
Influenza	1 (0.4)	Un-common	3 (1.3)	Common	1 (0.4)	Un-common	1 (0.6)	Un-common	1 (0.5)	Un-common	1 (0.5)	Un-common	57 (1.4)	Common
Dental and oral soft tissue infections	4 (1.7)	Common	9 (3.8)	Common	6 (2.5)	Common	2 (1.2)	Common	6 (3.3)	Common	2 (1.0)	Common	56 (1.4)	Common
Injury, poisoning and procedural complications														
Infusion related reaction	24 (10.2)	Very common	15 (6.4)	Common	14 (5.9)	Common	1 (0.6)	Un-common	1 (0.5)	Uncommon	1 (0.5)	Un-common	65 (1.6)	Common
Metabolism and nutrition disorders														
Decreased appetite	46 (19.5)	Very common	42 (17.9)	Very common	55 (23.1)	Very common	6 (3.6)	Common	9 (4.9)	Common	28 (14.6)	Very common	NA	-

	DUO-E study												Durvalumab Pan-tumour pool (N = 4045)	
	Overall						Maintenance Phase							
	SoC (N = 236)		SoC + D (N = 235)		SoC + D + O [a] (N = 238)		SoC (N = 169)		SoC + D (N = 183)		SoC + D + O [a] (N = 192)			
ADR system organ class/ ADR term	**Number (%) of patients [b]**	**CIOMS III category [c]**	**Number (%) of patients [b]**	**CIOMS III category [c]**	**Number (%) of patients [b]**	**CIOMS III category [c]**	**Number (%) of patients [b]**	**CIOMS III category [c]**	**Number (%) of patients [b]**	**CIOMS III category [c]**	**Number (%) of patients [b]**	**CIOMS III category [c]**	**Number of patients [b]**	**CIOMS III category [c]**
Musculoskeletal and connective tissue disorders														
Arthralgia	58 (24.6)		71 (30.2)	Very common	58 (24.4)	Very common	16 (9.5)	Common	34 (18.6)	Very common	22 (11.5)	Very common	536 (13.3)	Very common
Myalgia	44 (18.6)	Very common	32 (13.6)	Very common	30 (12.6)	Very common	8 (4.7)	Common	7 (3.8)	Common	4 (2.1)	Common	196 (4.8)	Common
Myositis	0	NR	6 (2.6)	Common	1 (0.4)	Un-common	0	NR	0	NR	0	NR	9 (0.2)	Un-common
Immune-mediated arthritis	0	NR	1 (0.4)	Un-common	0	NR	0	NR	1 (0.5)	Un-common	0	NR	3 (< 0.1)	Rare
Nervous system disorders														
Myasthenia Gravis	0	NR	2 (0.9)	Un-common	0	NR	0	NR	1 (0.5)	Un-common	0	NR	3 (< 0.1)	Rare
Meningitis	0	NR	0	NR	0	NR	0	NR	0	NR	0	NR	1 (< 0.1)	Rare
Neuropathy peripheral	138 (58.5)	Very common	126 (53.6)	Very common	123 (51.7)	Very common	8 (4.7)	Common	11 (6.0)	Common	15 (7.8)	Common	NA	-
Renal and urinary disorders														
Blood creatinine increased	13 (5.5)	Common	10 (4.3)	Common	24 (10.1)	Very common	2 (1.2)	Common	4 (2.2)	Common	19 (9.9)	Common	145 (3.6)	Common
Dysuria	12 (5.1)	Common	10 (4.3)	Common	10 (4.2)	Common	6 (3.6)	Common	3 (1.6)	Common	3 (1.6)	Common	60 (1.5)	Common
Nephritis	1 (0.4)	Un-common	0	NR	0	NR	1 (0.6)	Un-common	0	NR	0	NR	12 (0.3)	Un-common

	DUO-E study												Durvalumab Pan-tumour pool (N = 4045)	
	Overall						Maintenance Phase							
	SoC (N = 236)		SoC + D (N = 235)		SoC + D + O [a] (N = 238)		SoC (N = 169)		SoC + D (N = 183)		SoC + D + O [a] (N = 192)			
ADR system organ class/ ADR term	**Number (%) of patients [b]**	**CIOMS III category [c]**	**Number (%) of patients [b]**	**CIOMS III category [c]**	**Number (%) of patients [b]**	**CIOMS III category [c]**	**Number (%) of patients [b]**	**CIOMS III category [c]**	**Number (%) of patients [b]**	**CIOMS III category [c]**	**Number (%) of patients [b]**	**CIOMS III category [c]**	**Number of patients [b]**	**CIOMS III category [c]**
Cystitis noninfective	2 (0.8)	Un-common	2 (0.9)	Uncommon	2 (0.8)	Uncommon	2 (1.2)	Common	1 (0.5)	Un-common	1 (0.5)	Un-common	4 (< 0.1)	Rare
Respiratory, thoracic and mediastinal disorders														
Cough/Productive cough	29 (12.3)	Very common	37 (15.7)	Very common	33 (13.9)	Very common	16 (9.5)	Common	23 (12.6)	Very common	21 (10.9)	Very common	754 (18.6)	Very common
Pneumonitis	1 (0.4)	Un-common	3 (1.3)	Common	10 (4.2)	Common	0	NR	2 (1.1)	Common	6 (3.1)	Common	138 (3.4)	Common
Dysphonia	3 (1.3)	Common	2 (0.9)	Un-common	4 (1.7)	Common	0	NR	1 (0.5)	Un-common	2 (1.0)	Common	103 (2.5)	Common
Interstitial lung disease	0	NR	1 (0.4)	Un-common	2 (0.8)	Uncommon	0	NR	1 (0.5)	Un-common	2 (1.0)	Common	21 (0.5)	Un-common
Skin and subcutaneous tissue disorders														
Rash	48 (20.3)	Very common	62 (26.4)	Very common	56 (23.5)	Very common	12 (7.1)	Common	19 (10.4)	Very common	24 (12.5)	Very common	620 (15.3)	Very common
Pruritus	29 (12.3)	Very common	36 (15.3)	Very common	37 (15.5)	Very common	13 (7.7)	Common	17 (9.3)	Common	12 (6.3)	Common	462 (11.4)	Very common
Dermatitis	1 (0.4)	Un-common	8 (3.4)	Common	4 (1.7)	Common	1 (0.6)	Un-common	4 (2.2)	Common	1 (0.5)	Un-common	28 (0.7)	Un-common
Night sweats	2 (0.8)	Un-common	1 (0.4)	Un-common	2 (0.8)	Un-common	0	NR	0	NR	1 (0.5)	Un-common	60 (1.5)	Common

	DUO-E study												Durvalumab Pan-tumour pool (N = 4045)	
	Overall						Maintenance Phase							
	SoC (N = 236)		SoC + D (N = 235)		SoC + D + O [a] (N = 238)		SoC (N = 169)		SoC + D (N = 183)		SoC + D + O [a] (N = 192)			
ADR system organ class/ ADR term	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number of patients [b]	CIOMS III category [c]
Psoriasis	2 (0.8)	Un-common	1 (0.4)	Un-common	0	NR	1 (0.6)	Un-common	1 (0.5)	Uncommon	0	NR	31 (0.8)	Un-common
Pemphigoid	1 (0.4)	Un-common	1 (0.4)	Un-common	0	NR	0	NR	0	NR	0	NR	5 (0.1)	Un-common
Alopecia	118 (50.0)	Very common	118 (50.2)	Very common	121 (50.8)	Very common	1 (0.6)	Un-common	2 (1.1)	Common	5 (2.6)	Common	NA	-

[a] Olaparib was only administered during the Maintenance phase of DUO-E.

[b] Number (%) of patients with AEs, sorted in alphabetical order by ADR SOC and ADR PT. Within each ADR SOC, ADR PTs are ordered in descending frequency of 'Any CTCAE Grade' in the Durvalumab Pan-tumour pool.

[c] CIOMS III convention and is defined as: (1) very common (≥ 1/10); (2) common (≥ 1/100 to < 1/10); (3) uncommon (≥ 1/1,000 to < 1/100); (4) rare (≥ 1/10,000 to < 1/1,000); (5) very rare (< 1/10,000); and (6) NR (not reported - cannot be estimated from available data)

A patient can have one or more PTs reported under a given SOC.

Patients in DUO-E study who initially received dose of durvalumab/placebo are summarised according to arm to which they were randomised.

Overall SoC (Standard of care) = Carboplatin + paclitaxel. Study treatment = SoC (Carboplatin, paclitaxel), durvalumab/placebo and olaparib/placebo.

Includes AEs with an onset date or that worsen on or after the date of first dose of study treatment (overall) or first dose of olaparib/placebo (maintenance phase) up until the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurred first.

ADR terms are grouped PTs.

Percentages are based on the total number of patients in the treatment group (N).

Disease progression AEs reported in Study 1108 are not included in this summary.

Urticaria events in the infusion related reaction ADR term includes Urticaria starting on same day or one day after latest dose.

MedDRA version 25.1

Some ADRs are specific to chemotherapy, and thus not applicable to the Durvalumab Pan-tumour pool.

ADR = adverse drug reaction; AE = adverse events; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CIOMS = Council for International Organizations of Medical Sciences; MedDRA = Medical Dictionary for Regulatory Activities; NA = not applicable; NR = not reported (cannot be estimated from available data); PT = preferred term; SoC = standard of care; SoC + D = durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance; SOC = system organ class

Table 66 Adverse Drug Reactions Associated with Olaparib Treatment by Treatment Group in DUO-E (Maintenance Phase) for All CTCAE Grades and CTCAE Grades 3 and 4

	Number (%) of patients [a, b]							
	DUO-E Maintenance Phase						Olaparib 300 mg bd Tablet Pool (N = 3556)	
	SoC (N = 169)		SoC + D (N = 183)		SoC + D + O (N = 192)			
ADR system organ class/ ADR term	All Grades	CTCAE Grade ≥ 3 [b]	All Grades	CTCAE Grade ≥ 3 [b]	All Grades	CTCAE Grade ≥ 3 [b]	All Grades	CTCAE Grade ≥ 3 [b]
Blood and lymphatic system disorders								
Anaemia [c]	17 (10.1)	1 (0.6)	16 (8.7)	0	70 (36.5)	36 (18.8)	1249 (35.1)	504 (14.2)
Neutropenia [c]	7 (4.1)	1 (0.6)	13 (7.1)	1 (0.5)	34 (17.7)	12 (6.3)	610 (17.2)	207 (5.8)
Thrombocytopenia [c]	9 (5.3)	0	6 (3.3)	1 (0.5)	27 (14.1)	1 (0.5)	329 (9.3)	70 (2.0)
Lymphopenia [c]	7 (4.1)	0	6 (3.3)	2 (1.1)	9 (4.7)	4 (2.1)	204 (5.7)	51 (1.4)
Leukopenia [c]	9 (5.3)	0	7 (3.8)	1 (0.5)	19 (9.9)	2 (1.0)	472 (13.3)	89 (2.5)
Respiratory, thoracic, and mediastinal disorders								
Cough [c]	16 (9.5)	0	23 (12.6)	0	21 (10.9)	0	459 (12.9)	4 (0.1)
Dyspnoea [c]	10 (5.9)	1 (0.6)	11 (6.0)	1 (0.5)	17 (8.9)	1 (0.5)	376 (10.6)	27 (0.8)
Gastrointestinal disorders								
Nausea	25 (14.8)	1 (0.6)	22 (12.0)	0	79 (41.1)	3 (1.6)	2046 (57.5)	35 (1.0)
Vomiting	16 (9.5)	1 (0.6)	13 (7.1)	1 (0.5)	39 (20.3)	0	989 (27.8)	38 (1.1)
Diarrhoea	20 (11.8)	1 (0.6)	28 (15.3)	1 (0.5)	34 (17.7)	1 (0.5)	778 (21.9)	26 (0.7)
Dyspepsia	5 (3.0)	0	2 (1.1)	0	15 (7.8)	0	315 (8.9)	1 (0.0)
Abdominal pain upper	5 (3.0)	0	8 (4.4)	0	4 (2.1)	0	263 (7.4)	2 (0.1)
Stomatitis [c]	5 (3.0)	0	6 (3.3)	0	10 (5.2)	0	278 (7.8)	9 (0.3)
General disorders and administration site conditions								
Fatigue and asthenia [c]	21 (12.4)	0	19 (10.4)	1 (0.5)	62 (32.3)	4 (2.1)	1752 (49.3)	117 (3.3)

	Number (%) of patients [a, b]							
	DUO-E Maintenance Phase						Olaparib 300 mg bd Tablet Pool (N = 3556)	
	SoC (N = 169)		SoC + D (N = 183)		SoC + D + O (N = 192)			
ADR system organ class/ ADR term	All Grades	CTCAE Grade ≥ 3 [b]	All Grades	CTCAE Grade ≥ 3 [b]	All Grades	CTCAE Grade ≥ 3 [b]	All Grades	CTCAE Grade ≥ 3 [b]
Investigations								
Blood creatinine increased	2 (1.2)	1 (0.6)	4 (2.2)	0	19 (9.9)	0	201 (5.7)	1 (0.0)
Mean cell volume increased	0	0	0	0	0	0	9 (0.3)	0
Metabolism and nutrition disorders								
Decreased appetite	6 (3.6)	0	9 (4.9)	0	28 (14.6)	0	649 (18.3)	18 (0.5)
Nervous system disorders								
Headache	11 (6.5)	0	10 (5.5)	0	18 (9.4)	0	578 (16.3)	9 (0.3)
Dysgeusia [c]	2 (1.2)	0	2 (1.1)	0	15 (7.8)	0	476 (13.4)	0
Dizziness	11 (6.5)	0	14 (7.7)	0	17 (8.9)	0	398 (11.2)	4 (0.1)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)								
MDS/AML [c]	0	0	0	0	0	0	13 (0.4)	13 (0.4)
Skin and subcutaneous tissue disorders								
Rash [c]	10 (5.9)	0	17 (9.3)	0	23 (12.0)	0	262 (7.4)	5 (0.1)
Dermatitis [c]	1 (0.6)	0	4 (2.2)	1 (0.5)	1 (0.5)	0	14 (0.4)	1 (0.0)
Erythema nodosum	0	0	0	0	0	0	2 (0.1)	0
Immune Systems Disorders								
Hypersensitivity [c]	0	0	1 (0.5)	0	3 (1.6)	0	28 (0.8)	1 (0.0)
Angioedema	0	0	0	0	0	0	1 (0.0)	0

	Number (%) of patients [a, b]							
	DUO-E Maintenance Phase						Olaparib 300 mg bd Tablet Pool (N = 3556)	
	SoC (N = 169)		SoC + D (N = 183)		SoC + D + O (N = 192)			
ADR system organ class/ ADR term	All Grades	CTCAE Grade ≥ 3 [b]	All Grades	CTCAE Grade ≥ 3 [b]	All Grades	CTCAE Grade ≥ 3 [b]	All Grades	CTCAE Grade ≥ 3 [b]
Vascular Disorders								
Venous thromboembolic events [c]	0	0	5 (2.7)	1 (0.5)	6 (3.1)	2 (1.0)	117 (3.3)	53 (1.5)

[a] The DUO-E study data includes adverse events with an onset date or that worsen on or after the date of first dose of olaparib/placebo (maintenance phase) up until the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurs first..

[b] For Olaparib 300 mg bd Tablet Pool: patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories

[c] Each patient has only been represented with the maximum reported CTCAE grade within each ADR group.

[d] Adverse drug reaction includes multiple PTs as outlined in Table 2.7.4.1.5.1, Module 5.3.5.3.

Includes AEs with an onset date between the date of first dose of continuous treatment and 30 days following the date of last dose of continuous treatment.

ADR = adverse drug reaction; AE = adverse event; AML = acute myeloid leukaemia; bd = Twice daily; CTCAE = Common Terminology Criteria for Adverse Events; MDS = myelodysplastic syndrome; N = total number of patients; PT = preferred term; SoC = standard of care.

Table 67 Frequency of AEs Identified as ADRs Associated with Olaparib Treatment (Tablet Pool and Combined Therapeutic Dose Pool)

	Olaparib 300 mg bd Tablet Pool N = 3556		Combined Therapeutic Dose Pool (tablet and capsule) N = 4499			
ADR system organ class/ ADR term	All CTCAE Grades [a] n (%)	CTCAE Grades ≥ 3 [b] n (%)	All CTCAE Grades [a] n (%)	CIOMS III Category	CTCAE Grades ≥ 3 [b] n (%)	CIOMS III Category
Blood and lymphatic system disorders						
Anaemia [c]	1249 (35.1)	504 (14.2)	1545 (34.3)	Very common	637 (14.2)	Very common
Neutropenia [c]	610 (17.2)	207 (5.8)	688 (15.3)	Very common	236 (5.2)	Common
Thrombocytopenia [c]	329 (9.3)	70 (2.0)	401 (8.9)	Common	92 (2.0)	Common
Lymphopenia [c]	204 (5.7)	51 (1.4)	217 (4.8)	Common	53 (1.2)	Common
Leukopenia [c]	472 (13.3)	89 (2.5)	532 (11.8)	Very common	110 (2.4)	Common
Gastrointestinal disorders						
Nausea	2046 (57.5)	35 (1.0)	2620 (58.2)	Very common	58 (1.3)	Common
Vomiting	989 (27.8)	38 (1.1)	1319 (29.3)	Very common	65 (1.4)	Common
Diarrhoea	778 (21.9)	26 (0.7)	995 (22.1)	Very common	41 (0.9)	Uncommon
Dyspepsia	315 (8.9)	1 (0.0)	471 (10.5)	Very common	1 (0.0)	Rare
Abdominal pain upper	263 (7.4)	2 (0.1)	351 (7.8)	Common	4 (0.1)	Rare
Stomatitis [c]	278 (7.8)	9 (0.3)	339 (7.5)	Common	12 (0.3)	Uncommon
General disorders and administration site conditions						
Fatigue and asthenia [c]	1752 (49.3)	117 (3.3)	2318 (51.5)	Very common	178 (4.0)	Common
Investigations						
Blood creatinine increased	201 (5.7)	1 (0.0)	259 (5.8)	Common	3 (0.1)	Rare
Mean cell volume increased	9 (0.3)	0	9 (0.2)	Uncommon	0	-
Metabolism and nutrition disorders						
Decreased appetite	649 (18.3)	18 (0.5)	842 (18.7)	Very common	24 (0.5)	Uncommon

	Olaparib 300 mg bd Tablet Pool N = 3556		Combined Therapeutic Dose Pool (tablet and capsule) N = 4499			
ADR system organ class/ ADR term	All CTCAE Grades [a] n (%)	CTCAE Grades ≥ 3 [b] n (%)	All CTCAE Grades [a] n (%)	CIOMS III Category	CTCAE Grades ≥ 3 [b] n (%)	CIOMS III Category
Neoplasms benign, malignant, and unspecified (including cysts and polyps)						
MDS/AML [c]	13 (0.4)	13 (0.4)	19 (0.4)	Uncommon	18 (0.4)	Uncommon
Nervous system disorders						
Headache	578 (16.3)	9 (0.3)	732 (16.3)	Very common	11 (0.2)	Uncommon
Dysgeusia [c]	476 (13.4)	0	599 (13.3)	Very common	0	-
Dizziness	398 (11.2)	4 (0.1)	521 (11.6)	Very common	7 (0.2)	Uncommon
Immune system disorders						
Hypersensitivity [c]	28 (0.8)	1 (0.0)	37 (0.8)	Uncommon	2 (0.0)	Rare
Angioedema	1 (0.0)	0	1 (0.0)	Rare	0	-
Respiratory, thoracic, and mediastinal disorders						
Cough [c]	459 (12.9)	4 (0.1)	605 (13.4)	Very common	5 (0.1)	Uncommon
Dyspnoea [c]	376 (10.6)	27 (0.8)	519 (11.5)	Very common	45 (1.0)	Common
Skin and subcutaneous tissue disorders						
Rash [c]	262 (7.4)	5 (0.1)	369 (8.2)	Common	6 (0.1)	Uncommon
Dermatitis [c]	14 (0.4)	1 (0.0)	18 (0.4)	Uncommon	1 (0.0)	Rare
Erythema nodosum	2 (0.1)	0	2 (0.0)	Rare	0	-
Vascular Disorders						
Venous thromboembolic events [c]	117 (3.3)	53 (1.5)	160 (3.6)	Common	76 (1.7)	Common

[a] Patients with multiple ADRs are counted once for each grouped term.

[b] Each patient has only been represented with the maximum reported CTCAE grade within each ADR group.

[c] Adverse drug reaction includes multiple PTs as outlined in Table 2.7.4.4.6, Pooled Safety Outputs, Module 5.3.5.3.

Includes AEs with an onset date between the date of first dose of continuous treatment and 30 days following the last dose of continuous treatment.

Frequencies of occurrence of adverse reactions are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10000 to < 1/1000), very rare (< 1/10000) including isolated reports.

ADR = adverse drug reaction; AE = adverse event; AML = acute myeloid leukaemia; bd = twice daily; CIOMS = Council for International Organizations of Medical Sciences; CTCAE = Common Terminology Criteria for Adverse Events; MDS = myelodysplastic syndrome; N = Total number of patients; n = number of patients with an event; PT = preferred term; SOC = system organ class.

Table 68 Side-by-side Comparison of Pooled Data Within the Former and Updated Imfinzi SmPC

	IMFINZI as monotherapy N = 4045	IMFINZI in combination with chemotherapy [excluding DUO-E SoC+D arm] N = 603	IMFINZI in combination with chemotherapy [including DUO-E SoC + D arm] N = 838	Platinum-based chemotherapy + IMFINZI + LYNPARZA* N = 238
Infections and infestations				
Very common	Upper respiratory tract infections[a]			Upper respiratory tract infection[a]
Common	Pneumonia[b,c], Influenza, Oral candidiasis, Dental and oral soft tissue infections[d]	Pneumonia[b,c], Upper respiratory tract infections[a]	Pneumonia[b,c], Upper respiratory tract infections[a], **Dental and oral soft tissue infections[d]**	Pneumonia, Oral candidiasis, Dental and oral soft tissue infections[d]
Uncommon		Oral candidiasis, Influenza, Dental and oral soft tissue infections[d]	Oral candidiasis, Influenza	Influenza
Blood and lymphatic system disorders				
Very Common		Anaemia, Leukopenia[e], Neutropenia[f], Thrombocytopenia[g]	Anaemia, Leukopenia[e], Neutropenia[f], Thrombocytopenia[g]	Anaemia[h], Neutropenia[h], Thrombocytopenia[h], Leukopenia[h]

	IMFINZI as monotherapy N = 4045	**IMFINZI in combination with chemotherapy [excluding DUO-E SoC+D arm] N = 603**	**IMFINZI in combination with chemotherapy [including DUO-E SoC + D arm] N = 838**	**Platinum-based chemotherapy + IMFINZI + LYNPARZA* N = 238**
Common		Febrile neutropenia, Pancytopenia[c]	Febrile neutropenia, Pancytopenia[c]	Lymphopenia[i], Febrile neutropenia[h] Aplasia pure red cell
Uncommon			Immune thrombocytopenia	Pancytopenia[h]
Rare	Immune thrombocytopenia[c]			
Immune system disorders				
Common				Hypersensitivity[i,j]
Endocrine disorders				
Very common	Hypothyroidism[k]		**Hypothyroidism[k]**	Hypothyroidism
Common	Hyperthyroidism[l]	Adrenal insufficiency, Hyperthyroidism[l], Hypothyroidism[k]	Hyperthyroidism[l], **Thyroiditis[m]**	Hyperthyroidism, Thyroiditis
Uncommon	Thyroiditis[m], Adrenal insufficiency	Thyroiditis[m], Type 1 diabetes mellitus	**Adrenal insufficiency,** Type 1 diabetes mellitus	
Rare	Type 1 diabetes mellitus, Hypophysitis/Hypopituitarism, Diabetes insipidus			
Eye disorders				
Uncommon			**Uveitis**	Uveitis
Rare	Uveitis	Uveitis		
Metabolism and nutrition disorders				
Very common		Decreased appetite	Decreased appetite	Decreased appetite[h]
Nervous System Disorders				
Very common			**Neuropathy peripheral[n]**	Neuropathy peripheral[n], Dizziness[i], Headache[i], Dysgeusia[i,o]
Common		Neuropathy peripheral[n]		
Uncommon		Myasthenia gravis	Myasthenia gravis	
Rare	Myasthenia gravis, Meningitis[p]			
Not known	Noninfective encephalitis[q], Guillain-Barré syndrome, Myelitis transverse[r]			
Vascular disorders				
Common				Venous thromboembolic events[i,s]
Cardiac disorders				
Uncommon	Myocarditis			
Respiratory, thoracic and mediastinal disorders				
Very common	Cough/Productive cough	Cough/Productive cough	Cough/Productive cough	Cough/Productive cough, Dyspnoea[i,t]
Common	Pneumonitis[c], Dysphonia	Pneumonitis	Pneumonitis	Pneumonitis, Dysphonia
Uncommon	Interstitial lung disease	Interstitial lung disease, Dysphonia	Interstitial lung disease, Dysphonia	Interstitial lung disease
Gastrointestinal disorders				
Very common	Diarrhoea, Abdominal pain[u]	Diarrhoea, Abdominal pain[u], Constipation, Nausea, Vomiting	Diarrhoea, Abdominal pain[u], Constipation, Nausea, Vomiting	Nausea[h], Constipation[h], Diarrhoea, Vomiting[h], Abdominal pain[u], Stomatitis[h]

	IMFINZI as monotherapy N = 4045	**IMFINZI in combination with chemotherapy [excluding DUO-E SoC+D arm] N = 603**	**IMFINZI in combination with chemotherapy [including DUO-E SoC + D arm] N = 838**	**Platinum-based chemotherapy + IMFINZI + LYNPARZA* N = 238**
Common		Stomatitis[v]	Stomatitis[v]	Dyspepsia[i], Colitis[w]
Uncommon	Colitis[w], Pancreatitis[x]	Colitis[w], Pancreatitis[x]	Colitis[w], Pancreatitis[x]	
Hepatobiliary disorders				
Very common		Aspartate aminotransferase increased/Alanine aminotransferase increased[y]	Aspartate aminotransferase increased/Alanine aminotransferase increased[y]	Aspartate aminotransferase increased/Alanine aminotransferase increased
Common	Aspartate aminotransferase increased/Alanine aminotransferase increased[c,y], Hepatitis[c,z]	Hepatitis[c,z]	Hepatitis[c,z]	
Uncommon				Hepatitis[z]
Skin and subcutaneous tissue disorders				
Very common	Rash[aa], Pruritus	Rash[aa], Alopecia, Pruritus	Rash[aa], Alopecia, Pruritus	Alopecia[h], Rash[aa], Pruritus
Common	Night sweats	Dermatitis	Dermatitis	Dermatitis[bb]
Uncommon	Dermatitis, Psoriasis, Pemphigoid[cc]	Pemphigoid[cc], Night sweats, Psoriasis	Pemphigoid[cc], Night sweats, Psoriasis	Night sweats
Musculoskeletal and connective tissue disorders				
Very common	Arthralgia		**Arthralgia**	Arthralgia[h], Myalgia
Common	Myalgia	Myalgia, Arthralgia	Myalgia,	
Uncommon	Myositis	Immune-mediated arthritis	Immune-mediated arthritis, Myositis	Myositis
Rare	Immune-mediated arthritis, Polymyositis[dd]			
Renal and urinary disorders				
Very common				Blood creatinine increased
Common	Blood creatinine increased, Dysuria	Blood creatinine increased, Dysuria	Blood creatinine increased, Dysuria	Dysuria
Uncommon	Nephritis[ee]		Cystitis noninfective	Cystitis noninfective[h]
Rare	Cystitis noninfective			
General disorders and administration site conditions				
Very common	Pyrexia	Pyrexia, Fatigue[h]	Pyrexia, Fatigue[ff], **Oedema peripheral [gg]**	Fatigue[h], Oedema peripheral[gg], Pyrexia
Common	Oedema peripheral[gg]	Oedema peripheral[gg]		
Injury, poisoning and procedural complications				
Common	Infusion-related reaction[hh]	Infusion-related reaction[hh]	Infusion-related reaction[hh]	Infusion related reaction

***** Overall study of induction treatment with up to six 21-day cycles with platinum-based chemotherapy in combination with IMFINZI, followed by maintenance treatment with IMFINZI in combination with olaparib

Adverse reaction frequencies may not be fully attributed to durvalumab alone but may contain contributions from the underlying disease or from other medicinal products used in a combination.

a. includes laryngitis, nasopharyngitis, peritonsillar abscess, pharyngitis, rhinitis, sinusitis, tonsillitis, tracheobronchitis and upper respiratory tract infection.

b. includes pneumocystis jirovecii pneumonia, pneumonia, pneumonia adenoviral, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia haemophilus, pneumonia pneumococcal, pneumonia streptococcal, candida pneumonia and pneumonia legionella.

c. including fatal outcome.

d. includes gingivitis, oral infection, periodontitis, pulpitis dental, tooth abscess and tooth infection.

e. includes leukopenia and white blood cell count decreased.

f. includes neutropenia and neutrophil count decreased.

g. includes thrombocytopenia and platelet count decreased

h. adverse reaction only applies to chemotherapy ADRs in the DUO-E study.

i. adverse reaction only applies to olaparib ADRs in the DUO-E study.
j. includes drug hypersensitivity and hypersensitivity.
k. includes autoimmune hypothyroidism, hypothyroidism, immune-mediated hypothyroidism, blood thyroid stimulating hormone increased.
l. includes hyperthyroidism, Basedow's disease, immune-mediated hyperthyroidism and blood thyroid stimulating hormone decreased.
m. includes autoimmune thyroiditis, thyroiditis, and thyroiditis subacute.
n. includes neuropathy peripheral, paraesthesia and peripheral sensory neuropathy.
o. includes dysgeusia and taste disorder.
p. includes meningitis and noninfective meningitis.
q. reported frequency from ongoing AstraZeneca-sponsored clinical studies outside of the pooled dataset is rare and includes fatal outcome.
r. events were reported from post-marketing data.
s. includes deep vein thrombosis, embolism, embolism venous, pelvic venous thrombosis, superficial venous thrombosis and thrombosis.
t. includes dyspnoea and dyspnoea exertional.
u. includes abdominal pain, abdominal pain lower, abdominal pain upper and flank pain.
v. includes stomatitis and mucosal inflammation
w. includes colitis, enteritis, enterocolitis, and proctitis.
x. includes pancreatitis and pancreatitis acute.
y. includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased and transaminases increased.
z. includes hepatitis, autoimmune hepatitis, hepatitis toxic, hepatic cytolysis, hepatocellular injury, hepatitis acute, hepatotoxicity and immune-mediated hepatitis
aa. includes rash erythematous, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, eczema and rash.
bb. Includes dermatitis and immune-mediated dermatitis.
cc. includes pemphigoid, dermatitis bullous and pemphigus. Reported frequency from completed and ongoing studies is uncommon.
dd. polymyositis (fatal) was observed in a patient treated with IMFINZI from an ongoing sponsored clinical study outside of the pooled dataset: rare in any grade, rare in Grade 3 or 4 or 5.
ee. includes autoimmune nephritis, tubulointerstitial nephritis, nephritis, glomerulonephritis and glomerulonephritis membranous.
ff. includes fatigue and asthenia
gg. includes oedema peripheral and peripheral swelling.
hh. includes infusion-related reaction and urticaria with onset on the day of dosing or 1 day after dosing

CIOMS III convention and was defined as: (1) very common (≥ 1/10); (2) common (≥ 1/100 to < 1/10); (3) uncommon (≥ 1/1,000 to < 1/100); (4) rare (≥ 1/10,000 to < 1/1,000); (5) very rare (< 1/10,000); and (6) NR not reported (cannot be estimated from available data).

Percentages were based on the total number of patients in the treatment group (N).

MedDRA version 25.1.

ADRs leading to dose interruption/reduction/discontinuation of durvalumab and olaparib

Durvalumab in combination with chemotherapy was discontinued due to adverse reactions in 3.6% of patients. The most common adverse reactions leading to treatment discontinuation were anaemia (0.5%), rash (0.5%) and fatigue (0.5%). Durvalumab was delayed or interrupted due to adverse reactions in 31.0% of patients. The most common adverse reactions leading to dose delay or interruption were neutropenia (15.0%), thrombocytopenia (6.8%), anaemia (5.1%) and leukopenia (2.9%).

When used in combination with olaparib following treatment with durvalumab in combination with platinum-based chemotherapy, durvalumab was discontinued in 4.6% of patients. The most common adverse reaction leading to treatment discontinuation was pneumonitis (1.7%). Durvalumab was interrupted in 38.2% of patients. The most common adverse reactions leading to dose interruption were anaemia (13.4%), thrombocytopenia (11.8%), neutropenia (10.1%), leukopenia (2.9%), hypothyroidism (2.1%) and upper respiratory tract infection (2.1%).

When used in combination with durvalumab following treatment with durvalumab in combination with platinum-based chemotherapy, adverse events led to dose interruption and/or reduction of olaparib in 59.9% of patients and led to permanent discontinuation of treatment with olaparib in 10.9% of patients. Adverse events led to permanent discontinuation of placebo in 5.5% of patients treated with platinum-based chemotherapy followed by durvalumab and 3% of patients treated with platinum-based chemotherapy alone. The adverse reactions that most commonly led to dose interruption and/or reduction of olaparib were anaemia (20.8%), nausea (8.3%), neutropenia (7.3%), fatigue/asthenia (5.7%), thrombocytopenia (4.2%), vomiting (4.2%), blood creatinine increased (3.1%), leukopenia (3.1%), and decreased appetitive (2.6%), diarrhoea (2.1%). The adverse reactions that most commonly led to permanent discontinuation of olaparib were anaemia (3.6%) and neutropenia (1%).

Pure red cell aplasia (PRCA)

The event of pure red cell aplasia (PRCA) has been identified as an ADR for the combination of olaparib plus durvalumab from the DUO-E study. This event has not been observed previously in either the durvalumab Pan tumour Pool or the olaparib 300 mg bd Tablet Pool.

Three individual reports of PRCA were observed in the SoC + D + O arm of DUO-E study (DCO 12 April 2023). One event occurred on treatment (the patient was only receiving durvalumab at the time of the event as olaparib had been interrupted due to an AE of neutropenia, and in response to PRCA, durvalumab dose was not changed). Two events occurred in the follow-up period (one patient was only receiving durvalumab at the time of the event as olaparib was discontinued due to an AE of anaemia, and durvalumab was permanently discontinued following the diagnosis of PRCA and the other patient was no longer receiving any study treatments at the time of the event and was experiencing objective disease progression at the time PRCA was diagnosed). At time of reporting, one of the three events of PRCA had resolved, and the patient went on to receive subsequent chemotherapy. Two events were not resolved. All 3 events were CTCAE Grade 3 SAEs and all were considered related to study treatment. In the updated safety data (DCO 18 October 2023) for the DUO-E study with additional 120 days respect to the DCO1 12 April 2023, there have been no additional events of PRCA.

The event has been added with a frequency of "Common"; this has been derived from DUO-E data and reflects 3 patients from 238 (1.3%) treated with durvalumab and olaparib in combination.

Adverse events of special interest (AESIs), adverse events of potential interest (AEPIs), and immune-mediated adverse events (imAEs)

An overview of AESIs, AEPIs, and imAEs in patients receiving SoC, SoC + D, and SoC + D + O for the study overall and for the maintenance phase are presented in the below tables.

Table 69 Summary of AESIs, AEPIs, and ImAEs in Any Category – Overall (Safety Analysis Set)

Adverse event category	Number (%) of patients [a]								
	SoC (N = 236)			SoC + D (N = 235)			SoC + D + O (N = 238)		
	AESI	AEPI	imAE	AESI	AEPI	imAE	AESI	AEPI	imAE
Any AE	106 (44.9)	120 (50.8)	16 (6.8)	136 (57.9)	127 (54.0)	66 (28.1)	136 (57.1)	133 (55.9)	56 (23.5)
Any AE causally related to study treatment [b]	76 (32.2)	80 (33.9)	12 (5.1)	113 (48.1)	88 (37.4)	63 (26.8)	114 (47.9)	96 (40.3)	54 (22.7)
Any AE causally related to durvalumab/placebo [b]	50 (21.2)	51 (21.6)	10 (4.2)	100 (42.6)	55 (23.4)	59 (25.1)	87 (36.6)	62 (26.1)	51 (21.4)
Any AE causally related to olaparib/placebo [b]	9 (3.8)	9 (3.8)	2 (0.8)	18 (7.7)	10 (4.3)	5 (2.1)	31 (13.0)	22 (9.2)	4 (1.7)
Any AE causally related to SoC [b]	51 (21.6)	60 (25.4)	5 (2.1)	58 (24.7)	64 (27.2)	10 (4.3)	56 (23.5)	64 (26.9)	10 (4.2)
Any AE with CTCAE Grade 3 or 4	9 (3.8)	4 (1.7)	3 (1.3)	21 (8.9)	10 (4.3)	19 (8.1)	15 (6.3)	18 (7.6)	18 (7.6)
Any AE with CTCAE Grade 3 or 4, causally related to study treatment [b]	4 (1.7)	2 (0.8)	2 (0.8)	19 (8.1)	7 (3.0)	19 (8.1)	14 (5.9)	15 (6.3)	18 (7.6)
Any AE with CTCAE Grade 3 or 4, causally related to durvalumab/placebo [b]	2 (0.8)	1 (0.4)	2 (0.8)	17 (7.2)	5 (2.1)	18 (7.7)	11 (4.6)	13 (5.5)	18 (7.6)
Any AE with CTCAE Grade 3 or 4, causally related to olaparib/placebo [b]	0	0	0	3 (1.3)	0	3 (1.3)	4 (1.7)	1 (0.4)	1 (0.4)
Any AE with CTCAE Grade 3 or 4, causally related to SoC [b]	4 (1.7)	2 (0.8)	2 (0.8)	5 (2.1)	3 (1.3)	4 (1.7)	3 (1.3)	7 (2.9)	5 (2.1)
Any SAE (including events with outcome = death)	5 (2.1)	0	1 (0.4)	16 (6.8)	6 (2.6)	15 (6.4)	11 (4.6)	5 (2.1)	10 (4.2)
Any SAE (including events with outcome = death), causally related to study treatment [b]	4 (1.7)	0	1 (0.4)	15 (6.4)	3 (1.3)	15 (6.4)	11 (4.6)	5 (2.1)	10 (4.2)
Any SAE (including events with outcome = death), causally related to durvalumab/placebo [b]	2 (0.8)	0	1 (0.4)	14 (6.0)	3 (1.3)	14 (6.0)	7 (2.9)	5 (2.1)	10 (4.2)
Any SAE (including events with outcome = death), causally related to olaparib/placebo [b]	0	0	0	3 (1.3)	0	2 (0.9)	4 (1.7)	0	1 (0.4)
Any SAE (including events with outcome = death), causally related to SoC [b]	4 (1.7)	0	1 (0.4)	5 (2.1)	1 (0.4)	5 (2.1)	3 (1.3)	2 (0.8)	2 (0.8)
Any AE with outcome = death	0	0	0	0	0	0	0	0	0
Received systemic corticosteroids	7 (3.0)	6 (2.5)	9 (3.8)	32 (13.6)	7 (3.0)	36 (15.3)	21 (8.8)	16 (6.7)	33 (13.9)
Received high dose steroids	4 (1.7)	1 (0.4)	4 (1.7)	22 (9.4)	4 (1.7)	26 (11.1)	15 (6.3)	12 (5.0)	24 (10.1)
Received endocrine therapy	7 (3.0)	0	7 (3.0)	36 (15.3)	0	36 (15.3)	32 (13.4)	1 (0.4)	32 (13.4)
Received other immunosuppressants	0	0	0	0	0	0	1 (0.4)	1 (0.4)	2 (0.8)
Any AE leading to discontinuation of study treatment	2 (0.8)	3 (1.3)	2 (0.8)	17 (7.2)	5 (2.1)	16 (6.8)	10 (4.2)	3 (1.3)	6 (2.5)
Any AE leading to discontinuation of durvalumab/placebo	1 (0.4)	3 (1.3)	1 (0.4)	13 (5.5)	4 (1.7)	14 (6.0)	8 (3.4)	2 (0.8)	5 (2.1)
Any AE leading to discontinuation of olaparib/placebo	0	1 (0.4)	1 (0.4)	5 (2.1)	1 (0.4)	5 (2.1)	4 (1.7)	2 (0.8)	1 (0.4)
Any AE leading to discontinuation of SoC	1 (0.4)	0	1 (0.4)	3 (1.3)	2 (0.9)	3 (1.3)	0	0	0
Event outcome resolved	87 (36.9)	71 (30.1)	11 (4.7)	91 (38.7)	69 (29.4)	35 (14.9)	88 (37.0)	86 (36.1)	29 (12.2)
Event outcome not resolved	19 (8.1)	49 (20.8)	5 (2.1)	45 (19.1)	58 (24.7)	31 (13.2)	48 (20.2)	47 (19.7)	27 (11.3)

[a] Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.

[b] As assessed by the Investigator, and programmatically derived from individual causality assessments for combination studies.

Included AEs if they started, or worsened, on or after the date of first dose of any of the investigational study treatments, including durvalumab/placebo or olaparib/placebo, throughout the treatment period and including the safety follow-up periods until the later date of 30 days after the last dose of olaparib/placebo and 90 days after last dose of durvalumab/placebo.

Adverse event of special interest category of Infusion/Hypersensitivity reactions is not included in this table.

Reasons of not recovered/not resolved, recovering/resolving map to an outcome of Not Resolved.

Reasons of recovered/resolved, recovered/resolved with sequelae map to an outcome of Resolved.

AESI List 17.1. CTCAE Version 5.0. MedDRA Version 25.1.

AE = Adverse event; AEPI = Adverse event of possible interest; AESI = Adverse event of special interest; CTCAE = Common Terminology Criteria for Adverse Events; ImAE = Immune-mediated adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = Total number of patients; SAE = Serious adverse event; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Table 70 Summary of AESIs, AEPIs, and ImAEs in Any Category – Maintenance Phase (Safety Analysis Set)

Adverse event category	Number (%) of patients [a]								
	SoC (N = 169)			SoC + D (N = 183)			SoC + D + O (N = 192)		
	AESI	AEPI	imAE	AESI	AEPI	imAE	AESI	AEPI	imAE
Any AE	37 (21.9)	47 (27.8)	6 (3.6)	69 (37.7)	63 (34.4)	27 (14.8)	72 (37.5)	72 (37.5)	27 (14.1)
Any AE causally related to study treatment [b]	18 (10.7)	22 (13.0)	4 (2.4)	47 (25.7)	25 (13.7)	24 (13.1)	55 (28.6)	41 (21.4)	25 (13.0)
Any AE causally related to durvalumab/placebo [b]	14 (8.3)	19 (11.2)	4 (2.4)	43 (23.5)	19 (10.4)	24 (13.1)	42 (21.9)	32 (16.7)	24 (12.5)
Any AE causally related to olaparib/placebo [b]	9 (5.3)	9 (5.3)	2 (1.2)	18 (9.8)	10 (5.5)	5 (2.7)	31 (16.1)	22 (11.5)	4 (2.1)
Any AE causally related to SoC [b]	0	1 (0.6)	0	0	7 (3.8)	0	1 (0.5)	0	0
Any AE with CTCAE Grade 3 or 4	1 (0.6)	1 (0.6)	0	6 (3.3)	1 (0.5)	6 (3.3)	8 (4.2)	7 (3.6)	9 (4.7)
Any AE with CTCAE Grade 3 or 4, causally related to study treatment [b]	0	0	0	6 (3.3)	1 (0.5)	6 (3.3)	8 (4.2)	6 (3.1)	9 (4.7)
Any AE with CTCAE Grade 3 or 4, causally related to durvalumab/placebo [b]	0	0	0	6 (3.3)	1 (0.5)	6 (3.3)	6 (3.1)	6 (3.1)	9 (4.7)
Any AE with CTCAE Grade 3 or 4, causally related to olaparib/placebo [b]	0	0	0	3 (1.6)	0	3 (1.6)	4 (2.1)	1 (0.5)	1 (0.5)
Any AE with CTCAE Grade 3 or 4, causally related to SoC [b]	0	0	0	0	0	0	0	0	0
Any SAE (including events with outcome = death)	0	0	0	5 (2.7)	0	4 (2.2)	7 (3.6)	3 (1.6)	7 (3.6)
Any SAE (including events with outcome = death), causally related to study treatment [b]	0	0	0	5 (2.7)	0	4 (2.2)	7 (3.6)	3 (1.6)	7 (3.6)
Any SAE (including events with outcome = death), causally related to durvalumab/placebo [b]	0	0	0	5 (2.7)	0	4 (2.2)	5 (2.6)	3 (1.6)	7 (3.6)
Any SAE (including events with outcome = death), causally related to olaparib/placebo [b]	0	0	0	3 (1.6)	0	2 (1.1)	4 (2.1)	0	1 (0.5)
Any SAE (including events with outcome = death), causally related to SoC [b]	0	0	0	0	0	0	0	0	0
Any AE with outcome = death	0	0	0	0	0	0	0	0	0
Received systemic corticosteroids	1 (0.6)	5 (3.0)	2 (1.2)	11 (6.0)	3 (1.6)	13 (7.1)	9 (4.7)	6 (3.1)	13 (6.8)
Received high dose steroids	0	1 (0.6)	0	8 (4.4)	1 (0.5)	9 (4.9)	4 (2.1)	6 (3.1)	9 (4.7)
Received endocrine therapy	4 (2.4)	0	4 (2.4)	15 (8.2)	0	15 (8.2)	15 (7.8)	1 (0.5)	16 (8.3)
Received other immunosuppressants	0	0	0	0	0	0	1 (0.5)	1 (0.5)	2 (1.0)
Any AE leading to discontinuation of study treatment	0	1 (0.6)	1 (0.6)	6 (3.3)	2 (1.1)	5 (2.7)	8 (4.2)	3 (1.6)	5 (2.6)
Any AE leading to discontinuation of durvalumab/placebo	0	1 (0.6)	1 (0.6)	4 (2.2)	2 (1.1)	4 (2.2)	6 (3.1)	2 (1.0)	4 (2.1)
Any AE leading to discontinuation of olaparib/placebo	0	1 (0.6)	1 (0.6)	4 (2.2)	1 (0.5)	4 (2.2)	4 (2.1)	2 (1.0)	1 (0.5)
Any AE leading to discontinuation of SoC	0	0	0	0	1 (0.5)	1 (0.5)	0	0	0
Event outcome resolved	27 (16.0)	26 (15.4)	3 (1.8)	41 (22.4)	23 (12.6)	12 (6.6)	46 (24.0)	46 (24.0)	14 (7.3)
Event outcome not resolved	10 (5.9)	21 (12.4)	3 (1.8)	28 (15.3)	40 (21.9)	15 (8.2)	26 (13.5)	26 (13.5)	13 (6.8)

[a] Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.

[b] As assessed by the Investigator, and programmatically derived from individual causality assessments for combination studies.

Included AEs if they started, or worsened, on or after the date of first dose of any of the investigational study treatments, including durvalumab/placebo or olaparib/placebo, throughout the treatment period and including the safety follow-up periods until the later date of 30 days after the last dose of olaparib/placebo and 90 days after last dose of durvalumab/placebo.

Adverse event of special interest category of Infusion/Hypersensitivity reactions is not included in this table.

Reasons of not recovered/not resolved, recovering/resolving map to an outcome of Not Resolved.

Reasons of recovered/resolved, recovered/resolved with sequelae map to an outcome of Resolved.

AESI List 17.1. CTCAE Version 5.0. MedDRA Version 25.1.

AE = Adverse event; AEPI = Adverse event of possible interest; AESI = Adverse event of special interest; CTCAE = Common Terminology Criteria for Adverse Events; ImAE = Immune-mediated adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = Total number of patients; SAE = Serious adverse event; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Myelodysplastic syndrome (MDS)/Acute myeloid leukaemia (AML)

The AE of MDS/AML is categorised as an important identified risk in the Risk Management Plan of olaparib. No events of MDS/AML were reported within any of the 3 treatment arms of DUO-E at either the DCO1 or 120-day safety update DCO date. There was < 1.5% of patients with reported events of MDS/AML across the olaparib program.

For the majority of studies with olaparib, including DUO-E, reports for events of MDS/AML continue to be collected beyond 30 days after the last dose of olaparib through the survival follow up. There have also been reports of MDS/AML from post marketing surveillance, consistent with the characterisation of the events reported from monotherapy clinical studies.

The table below shows the AEs and incidence rates of MDS/AML in DUO-E and the combined therapeutic dose pool.

Table 71 Summary of AEs of MDS/AML

	Olaparib combination/monotherapy arm		Comparator arm	
	Number of AEs	Incidence	Number of AEs	Incidence
DUO-E Maintenance [a] N = 192 SoC + D + O	0	0	0	0
Olaparib Monotherapy Combined Therapeutic Dose Pool N = 4499 olaparib	40	0.9%	NA	NA

a. As of 12 April 2023 (DUO-E primary PFS DCO). Comparator arm for DUO-E is standard of care (N = 169).
Adverse drug reactions may either be grouped preferred terms or individual preferred terms.
Includes all reported AEs (ie, not just treatment emergent).
MedDRA version 25.1.
AE = adverse event; AML = acute myeloid leukaemia; DCO = data cut-off; MDS = myelodysplastic syndrome; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of patients; NA = not applicable; PBRER = periodic benefit-risk evaluation report; PFS = progression-free survival; SoC + D + O = durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

The ADR frequencies for all reported AEs of MDS/AML (i.e. treatment emergent AEs as well as events after the 30 day follow up period throughout the survival follow up) in the olaparib 300 mg bd Tablet Pool and Olaparib Monotherapy Combined Therapeutic Dose Pool are presented in the below table.

Table 72 Frequency of ADR of MDS/AML in the Tablet Pool and Overall for All Reported Events

	Olaparib 300 mg bd Tablet Pool N=3556		Overall (tablet and capsule) N=4499			
System Organ Class/ Preferred Term	All CTCAE Grades [a] n (%)	CTCAE Grades ≥3 [b] n (%)	All CTCAE Grades [a] n (%)	Frequency Descriptor	CTCAE Grades ≥3 [b] n (%)	Frequency Descriptor
Neoplasms benign, malignant, and unspecified (including cysts and polyps)						
MDS/AML [c]	30 (0.8)	28 (0.8)	40 (0.9)	Uncommon	37 (0.8)	Uncommon

[a.] Patients with multiple ADRs are counted once for each grouped term.

[b.] Each patient has only been represented with the maximum reported CTCAE grade within each ADR group.

[c.] MDS/AML includes PTs of AML, MDS, and myeloid leukaemia (tablet pool only).

Frequencies of occurrence of adverse reactions are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10000 to < 1/1000), very rare (< 1/10000) including isolated reports.

Includes all reported AEs (ie, not just treatment emergent).

MedDRA version 25.1.

ADR = adverse drug reaction; AE = adverse event; AML = acute myeloid leukaemia; bd = twice daily; CTCAE = Common Terminology Criteria for Adverse Events; MDS = myelodysplastic syndrome; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of patients; n = number of patients with an event; PT = preferred term.

Potential Risks for the Combination of Durvalumab and Olaparib

Auto-immune haemolytic anaemia (AIHA)

AIHA is not considered a potential risk for either durvalumab or olaparib monotherapy, however, haemolytic anaemia is considered a potential risk for durvalumab. While there have not been any reports of AIHA in the olaparib monotherapy pool, there has been a single report of AIHA in the durvalumab Pan tumour pool.

There were 2 reports of AIHA and a single report of haemolytic anaemia for the combination of durvalumab and olaparib (SoC + D + O arm), and a single report of AIHA in the SoC + D arm. All 4 events were CTCAE Grade 3 and 3 events were also SAEs; all were considered related to study treatment. There have been no additional events of AIHA or haemolytic anaemia reported between the DCO1 (12 April 2023) and the 120-day safety update DCO dates (18 October 2023) for the DUO-E study. By safety update DCO date (18 October 2023), all AIHA/haemolytic anaemia events are 'recovered/resolved' or 'resolved with sequelae'. To date, no reports of AIHA have been observed in the olaparib 300 mg bd Tablet Pool (N = 3556), and a single case has been reported in the durvalumab Pan-tumour Pool (N = 4045).

Following review of all available data, the event AIHA is considered to be a potential risk associated with the combination of durvalumab and olaparib and as such has been reflected in section 4.4 Warnings and Precautions of the SmPC for both Imfinzi and Lynparza. If AIHA is confirmed, treatment with durvalumab and olaparib should be discontinued.

Important Potential Risks for Olaparib

New Primary Malignancies (NPMs)

In DUO-E, based on the long-term collection of data from first dose of study drug (durvalumab/olaparib/placebo) until the last long-term follow-up contact, NPMs were reported for a similar number of patients in the SoC + D arm (1 patient [0.4%]), SoC + D + O arm (2 patients [0.8%]) and the SoC arm (3 patients [1.3%]) of DUO-E. There was only one event occurring in the maintenance phase in the SoC + D + O arm and the overall incidence was less than 1.5% and balanced across all treatment arms. A DCO of 15 June 2023 for the entire clinical program of olaparib is used for the important potential risk of NPMs presented.

Events of MDS/AML, leukaemia (cases classified under AML following adjudication), non melanoma skin cancers, and histologically confirmed benign events were excluded.

The below table shows the AEs of NPMs in DUO-E and the combined therapeutic dose pool and provides incidence rates. The incidence of NPMs was similar for the SoC arm and the SoC + D + O arm of DUO E and the Olaparib Combined Therapeutic Dose Pool. There have been no additional events of NPMs reported between the DCO1 and 120-day safety update DCO dates for the DUO-E study.

Table 73 Summary of AEs of New Primary Malignancies occurring across the olaparib programme

	Olaparib combination/monotherapy arm		Comparator arm	
	Number of patients with AEs	**Incidence [a]**	**Number of AEs**	**Incidence [a]**
DUO-E Maintenance [b] N = 192 SoC + D + O	1	0.5	2	1.2
Olaparib Monotherapy Combined Therapeutic Dose Pool N = 4499 olaparib [c]	65	1.4%	NA	NA

a. The percentage of patients experiencing any event of new primary malignancy.
b. As of 12 April 2023 (DUO-E Primary PFS DCO). Comparator arm for DUO-E is standard of care (N = 169). Note that events of tumour pain and benign malignancies were excluded from this analysis.
AE = adverse event; DCO = data cut-off; N = total number of patients; NA = not applicable; PBRER = periodic benefit-risk evaluation report; PFS = progression-free survival; SoC + D + O = durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Olaparib monotherapy combined therapeutic dose pool

Of the 67 AEs (reported in 65 patients) in the olaparib monotherapy combined therapeutic dose pool, the reported malignancies were: breast cancers (n = 30), gastrointestinal cancers (n = 13), thyroid cancer (n = 4), lung cancer (n = 3), malignant melanoma (n = 2), bladder cancer (n = 2), leukaemia (n = 2), Burkitt lymphoma, endometrial adenocarcinoma, fallopian tube cancer, glioma, lip and/or oral cavity cancer, lymphoma, non-Hodgkin's lymphoma, oesophageal squamous cell carcinoma, plasma cell myeloma, squamous cell carcinoma of the oral cavity, and squamous cell carcinoma of the tongue (n = 1 of each).

As of 15 June 2023, a total of 21,793 patients have been exposed to olaparib during clinical development (including data from ongoing studies, blinded studies, combination studies, Externally Sponsored Research Study, and the managed access programme). In this population, there have been 282 reports of NPMs, giving an estimated cumulative incidence of 1.3%. There have also been reports of NPMs from post marketing surveillance, consistent with the characterisation of the events reported from monotherapy clinical studies.

The incidence of NPMs in patients treated in the SoC + D + O arm from DUO-E was low and consistent with the incidence of NPMs in the SoC arm from DUO-E and consistent with the incidence in the larger pooled populations for the olaparib clinical programme. Taken together, this provides important reassurance that the incidence of NPMs in olaparib-treated patients is low and similar to that with SoC during long term treatment and follow up in this disease setting.

AE in the SOCs of 'Neoplasms benign, malignant and unspecified (including cysts and polyps)' were reported for 7 patients in the SoC arm, 11 patients in the SoC + D arm, and 4 patients in the SoC + D + O arm. New primary malignancies were identified by review of this SOCs, to exclude PTs relating to the underlying cancer or tumor pain, benign events, and events of basal cell carcinoma.

Table 74 Summary of new primary malignancies – Overall and Maintenance Phase (Safety Analysis Set)

	Number (%) of patients [a]					
	Overall			Maintenance		
MedDRA PT	SoC (N = 236)	SoC + D (N = 235)	SoC + D + O (N = 238)	SoC (N = 169)	SoC + D (N = 183)	SoC + D + O (N = 192)
Number of patients with NPM	3 (1.3)	1 (0.4)	2 (0.8)	2 (1.2)	1 (0.5)	1 (0.5)
Adenocarcinoma of colon	0	0	1 (0.4)	0	0	0
Neuroendocrine tumour	0	0	1 (0.4)	0	0	1 (0.5)
Invasive breast carcinoma	0	1 (0.4)	0	0	1 (0.5)	0
Malignant melanoma	1 (0.4)	0	0	1 (0.6)	0	0
Papillary thyroid cancer	1 (0.4)	0	0	0	0	0
Renal neoplasm	1 (0.4)	0	0	1 (0.6)	0	0

[a] Each patient has been represented once for each specific AE of interest.

Specific AEs of interest may either be grouped MedDRA PTs or individual MedDRA PTs.

Included AEs from the first dose of investigational product (durvalumab/olaparib/placebo) until the end of study (ie, not restricted to treatment-emergent events).

CTCAE Version 5.0. MedDRA Version 25.1.

AE = Adverse event; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; N = Total number of patients; NPM = New primary malignancy; PT = Preferred term; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

The imAEs by category for the DUO-E study for the study overall and the maintenance phase are presented in the below tables.

Table 75 Immune-mediated Adverse Events by Category – Overall (Safety Analysis Set)

Category/ Treatment arm	Number (%) of patients												
	Any AE			Treatment related [a]		Received intervention					Event outcome		
	Any AE	Any SAE	CTCAE Grade 3 or 4	Any CTCAE Grade	CTCAE Grade 3 or 4	Systemic cortico-steroids	High dose steroids	Other immuno-suppressants	Requires endocrine therapy	Leading to discontin-uation of study drug	Resulted in death	Not resolved	Resolved
Pneumonitis (grouped term)													
SoC (N = 236)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D (N = 235)	2 (0.9)	2 (0.9)	2 (0.9)	2 (0.9)	2 (0.9)	2 (0.9)	2 (0.9)	0	0	2 (0.9)	0	1 (0.4)	1 (0.4)
SoC + D + O (N = 238)	5 (2.1)	3 (1.3)	3 (1.3)	5 (2.1)	3 (1.3)	5 (2.1)	4 (1.7)	0	0	2 (0.8)	0	0	5 (2.1)
Hepatic events (grouped term)													
SoC (N = 236)	1 (0.4)	0	0	1 (0.4)	0	1 (0.4)	0	0	0	1 (0.4)	0	0	1 (0.4)
SoC + D (N = 235)	6 (2.6)	3 (1.3)	4 (1.7)	6 (2.6)	4 (1.7)	6 (2.6)	4 (1.7)	0	0	4 (1.7)	0	2 (0.9)	4 (1.7)
SoC + D + O (N = 238)	5 (2.1)	1 (0.4)	4 (1.7)	5 (2.1)	4 (1.7)	5 (2.1)	5 (2.1)	1 (0.4)	0	1 (0.4)	0	0	5 (2.1)
Intestinal perforations (grouped term)													
SoC (N = 236)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D (N = 235)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D + O (N = 238)	0	0	0	0	0	0	0	0	0	0	0	0	0
Diarrhoea/colitis (grouped term)													
SoC (N = 236)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D (N = 235)	4 (1.7)	0	2 (0.9)	4 (1.7)	2 (0.9)	4 (1.7)	3 (1.3)	0	0	1 (0.4)	0	1 (0.4)	3 (1.3)
SoC + D + O (N = 238)	4 (1.7)	1 (0.4)	2 (0.8)	4 (1.7)	2 (0.8)	4 (1.7)	4 (1.7)	0	0	0	0	2 (0.8)	2 (0.8)
Hypothyroid events (grouped term)													
SoC (N = 236)	6 (2.5)	0	0	3 (1.3)	0	0	0	0	6 (2.5)	0	0	4 (1.7)	2 (0.8)
SoC + D (N = 235)	34 (14.5)	0	0	31 (13.2)	0	0	0	0	34 (14.5)	0	0	26 (11.1)	8 (3.4)
SoC + D + O (N = 238)	28 (11.8)	1 (0.4)	1 (0.4)	27 (11.3)	1 (0.4)	1 (0.4)	1 (0.4)	0	28 (11.8)	0	0	21 (8.8)	7 (2.9)
Hyperthyroid events (grouped term)													
SoC (N = 236)	2 (0.8)	0	0	2 (0.8)	0	0	0	0	2 (0.8)	0	0	1 (0.4)	1 (0.4)
SoC + D (N = 235)	5 (2.1)	0	0	5 (2.1)	0	1 (0.4)	1 (0.4)	0	4 (1.7)	1 (0.4)	0	0	5 (2.1)
SoC + D + O (N = 238)	4 (1.7)	0	0	4 (1.7)	0	1 (0.4)	1 (0.4)	0	4 (1.7)	0	0	0	4 (1.7)

Category/ Treatment arm	Number (%) of patients												
	Any AE			Treatment related [a]		Received intervention					Event outcome		
	Any AE	Any SAE	CTCAE Grade 3 or 4	Any CTCAE Grade	CTCAE Grade 3 or 4	Systemic cortico-steroids	High dose steroids	Other immuno-suppressants	Requires endocrine therapy	Leading to discontin-uation of study drug	Resulted in death	Not resolved	Resolved
Thyroiditis (grouped term)													
SoC (N = 236)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D (N = 235)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D + O (N = 238)	3 (1.3)	0	0	3 (1.3)	0	0	0	0	3 (1.3)	0	0	3 (1.3)	0
Adrenal insufficiency (grouped term)													
SoC (N = 236)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D (N = 235)	1 (0.4)	0	0	0	0	1 (0.4)	0	0	0	0	0	1 (0.4)	0
SoC + D + O (N = 238)	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	0	0	0	0	1 (0.4)	0
Hypophysitis (grouped term)													
SoC (N = 236)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D (N = 235)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D + O (N = 238)	0	0	0	0	0	0	0	0	0	0	0	0	0
Type I diabetes mellitus (grouped term)													
SoC (N = 236)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D (N = 235)	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	0	0	0	1 (0.4)	0	0	0	1 (0.4)
SoC + D + O (N = 238)	0	0	0	0	0	0	0	0	0	0	0	0	0
Renal events (grouped term)													
SoC (N = 236)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D (N = 235)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D + O (N = 238)	0	0	0	0	0	0	0	0	0	0	0	0	0
Dermatitis/rash events (grouped term)													
SoC (N = 236)	8 (3.4)	1 (0.4)	3 (1.3)	7 (3.0)	2 (0.8)	8 (3.4)	4 (1.7)	0	0	1 (0.4)	0	0	8 (3.4)
SoC + D (N = 235)	15 (6.4)	5 (2.1)	6 (2.6)	15 (6.4)	6 (2.6)	15 (6.4)	10 (4.3)	0	0	4 (1.7)	0	2 (0.9)	13 (5.5)
SoC + D + O (N = 238)	15 (6.3)	0	4 (1.7)	13 (5.5)	4 (1.7)	15 (6.3)	6 (2.5)	0	0	2 (0.8)	0	0	15 (6.3)

Category/ Treatment arm	Number (%) of patients												
	Any AE			Treatment related [a]		Received intervention					Event outcome		
	Any AE	Any SAE	CTCAE Grade 3 or 4	Any CTCAE Grade	CTCAE Grade 3 or 4	Systemic cortico-steroids	High dose steroids	Other immuno-suppressants	Requires endocrine therapy	Leading to discontin-uation of study drug	Resulted in death	Not resolved	Resolved
Myocarditis events (grouped term)													
SoC (N = 236)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D (N = 235)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D + O (N = 238)	0	0	0	0	0	0	0	0	0	0	0	0	0
Myositis events (grouped term)													
SoC (N = 236)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D (N = 235)	2 (0.9)	1 (0.4)	1 (0.4)	2 (0.9)	1 (0.4)	2 (0.9)	1 (0.4)	0	0	2 (0.9)	0	0	2 (0.9)
SoC + D + O (N = 238)	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	0	1 (0.4)	0	1 (0.4)	0
Pancreatic events (grouped term)													
SoC (N = 236)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D (N = 235)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D + O (N = 238)	0	0	0	0	0	0	0	0	0	0	0	0	0
Myasthenia gravis (grouped term)													
SoC (N = 236)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D (N = 235)	1 (0.4)	0	0	1 (0.4)	0	1 (0.4)	1 (0.4)	0	0	0	0	0	1 (0.4)
SoC + D + O (N = 238)	0	0	0	0	0	0	0	0	0	0	0	0	0
Guillain-Barre syndrome													
SoC (N = 236)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D (N = 235)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D + O (N = 238)	0	0	0	0	0	0	0	0	0	0	0	0	0
Other rare/miscellaneous													
SoC (N = 236)	1 (0.4)	0	0	1 (0.4)	0	1 (0.4)	0	0	0	0	0	0	1 (0.4)
SoC + D (N = 235)	5 (2.1)	3 (1.3)	3 (1.3)	5 (2.1)	3 (1.3)	5 (2.1)	4 (1.7)	0	0	3 (1.3)	0	0	5 (2.1)
SoC + D + O (N = 238)	4 (1.7)	2 (0.8)	3 (1.3)	4 (1.7)	3 (1.3)	4 (1.7)	3 (1.3)	0	0	0	0	1 (0.4)	3 (1.3)

[a] As assessed by the Investigator.

Included AEs if they started, or worsened, on or after the date of first dose of any of the investigational study treatments, including durvalumab/placebo or olaparib/placebo, throughout the treatment period and including the safety follow-up periods until the later date of 30 days after the last dose of olaparib/placebo and 90 days after last dose of durvalumab/placebo.

Adverse event of special interest terms of Infusion/Hypersensitivity reactions were not included in this table.

Patients with multiple AEs were counted for each grade they reported an AE for each category.

Reasons of not recovered/not resolved, recovering/resolving were mapped to an outcome of Not Resolved.

Reasons of recovered/resolved, recovered/resolved with sequelae were mapped to an outcome of Resolved.

CTCAE Version 5.0. MedDRA Version 25.1.

AE = Adverse event; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; N = Total number of patients; SAE = Serious adverse event; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Table 76 Immune-mediated Adverse Events by Category – Maintenance Phase (Safety Analysis Set)

Category/ Treatment arm	Number (%) of patients												
	Any AE			Treatment related [a]		Received intervention					Event outcome		
	Any AE	Any SAE	CTCAE Grade 3 or 4	Any CTCAE Grade	CTCAE Grade 3 or 4	Systemic cortico-steroids	High dose steroids	Other immuno-suppressants	Requires endocrine therapy	Leading to discontin-uation of study drug	Resulted in death	Not resolved	Resolved
Pneumonitis (grouped term)													
SoC (N = 169)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D (N = 183)	2 (1.1)	2 (1.1)	2 (1.1)	2 (1.1)	2 (1.1)	2 (1.1)	2 (1.1)	0	0	2 (1.1)	0	1 (0.5)	1 (0.5)
SoC + D + O (N = 192)	2 (1.0)	2 (1.0)	2 (1.0)	2 (1.0)	2 (1.0)	2 (1.0)	1 (0.5)	0	0	1 (0.5)	0	0	2 (1.0)
Hepatic events (grouped term)													
SoC (N = 169)	1 (0.6)	0	0	1 (0.6)	0	1 (0.6)	0	0	0	1 (0.6)	0	0	1 (0.6)
SoC + D (N = 183)	3 (1.6)	1 (0.5)	1 (0.5)	3 (1.6)	1 (0.5)	3 (1.6)	1 (0.5)	0	0	2 (1.1)	0	1 (0.5)	2 (1.1)
SoC + D + O (N = 192)	4 (2.1)	1 (0.5)	3 (1.6)	4 (2.1)	3 (1.6)	4 (2.1)	4 (2.1)	1 (0.5)	0	1 (0.5)	0	0	4 (2.1)
Intestinal perforations (grouped term)													
SoC (N = 169)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D (N = 183)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D + O (N = 192)	0	0	0	0	0	0	0	0	0	0	0	0	0
Diarrhoea/colitis (grouped term)													
SoC (N = 169)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D (N = 183)	4 (2.2)	0	2 (1.1)	4 (2.2)	2 (1.1)	4 (2.2)	3 (1.6)	0	0	1 (0.5)	0	1 (0.5)	3 (1.6)
SoC + D + O (N = 192)	0	0	0	0	0	0	0	0	0	0	0	0	0
Hypothyroid events (grouped term)													
SoC (N = 169)	4 (2.4)	0	0	2 (1.2)	0	0	0	0	4 (2.4)	0	0	3 (1.8)	1 (0.6)
SoC + D (N = 183)	15 (8.2)	0	0	13 (7.1)	0	0	0	0	15 (8.2)	0	0	12 (6.6)	3 (1.6)
SoC + D + O (N = 192)	15 (7.8)	1 (0.5)	1 (0.5)	14 (7.3)	1 (0.5)	1 (0.5)	1 (0.5)	0	15 (7.8)	0	0	11 (5.7)	4 (2.1)
Hyperthyroid events (grouped term)													
SoC (N = 169)	1 (0.6)	0	0	1 (0.6)	0	0	0	0	1 (0.6)	0	0	0	1 (0.6)
SoC + D (N = 183)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D + O (N = 192)	1 (0.5)	0	0	1 (0.5)	0	0	0	0	1 (0.5)	0	0	0	1 (0.5)
Thyroiditis (grouped term)													
SoC (N = 169)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D (N = 183)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D + O (N = 192)	1 (0.5)	0	0	1 (0.5)	0	0	0	0	1 (0.5)	0	0	1 (0.5)	0
Adrenal insufficiency (grouped term)													
SoC (N = 169)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D (N = 183)	1 (0.5)	0	0	0	0	1 (0.5)	0	0	0	0	0	1 (0.5)	0
SoC + D + O (N = 192)	0	0	0	0	0	0	0	0	0	0	0	0	0

Category/ Treatment arm	Number (%) of patients												
	Any AE			Treatment related [a]		Received intervention					Event outcome		
	Any AE	Any SAE	CTCAE Grade 3 or 4	Any CTCAE Grade	CTCAE Grade 3 or 4	Systemic cortico-steroids	High dose steroids	Other immuno-suppressants	Requires endocrine therapy	Leading to discontin-uation of study drug	Resulted in death	Not resolved	Resolved
Hypophysitis (grouped term)													
SoC (N = 169)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D (N = 183)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D + O (N = 192)	0	0	0	0	0	0	0	0	0	0	0	0	0
Type I diabetes mellitus (grouped term)													
SoC (N = 169)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D (N = 183)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D + O (N = 192)	0	0	0	0	0	0	0	0	0	0	0	0	0
Renal events (grouped term)													
SoC (N = 169)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D (N = 183)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D + O (N = 192)	0	0	0	0	0	0	0	0	0	0	0	0	0
Dermatitis/rash events (grouped term)													
SoC (N = 169)	1 (0.6)	0	0	1 (0.6)	0	1 (0.6)	0	0	0	0	0	0	1 (0.6)
SoC + D (N = 183)	2 (1.1)	1 (0.5)	1 (0.5)	2 (1.1)	1 (0.5)	2 (1.1)	2 (1.1)	0	0	0	0	0	2 (1.1)
SoC + D + O (N = 192)	5 (2.6)	0	0	3 (1.6)	0	5 (2.6)	1 (0.5)	0	0	2 (1.0)	0	0	5 (2.6)
Myocarditis events (grouped term)													
SoC (N = 169)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D (N = 183)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D + O (N = 192)	0	0	0	0	0	0	0	0	0	0	0	0	0
Myositis events (grouped term)													
SoC (N = 169)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D (N = 183)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D + O (N = 192)	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)	0	1 (0.5)	0	1 (0.5)	0
Pancreatic events (grouped term)													
SoC (N = 169)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D (N = 183)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D + O (N = 192)	0	0	0	0	0	0	0	0	0	0	0	0	0
Myasthenia gravis (grouped term)													
SoC (N = 169)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D (N = 183)	1 (0.5)	0	0	1 (0.5)	0	1 (0.5)	1 (0.5)	0	0	0	0	0	1 (0.5)
SoC + D + O (N = 192)	0	0	0	0	0	0	0	0	0	0	0	0	0
Guillain-Barre syndrome													
SoC (N = 169)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D (N = 183)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D + O (N = 192)	0	0	0	0	0	0	0	0	0	0	0	0	0

Category/ Treatment arm	Number (%) of patients												
	Any AE			Treatment related [a]		Received intervention					Event outcome		
	Any AE	Any SAE	CTCAE Grade 3 or 4	Any CTCAE Grade	CTCAE Grade 3 or 4	Systemic cortico-steroids	High dose steroids	Other immuno-suppressants	Requires endocrine therapy	Leading to discontin-uation of study drug	Resulted in death	Not resolved	Resolved
Other rare/miscellaneous													
SoC (N = 169)	1 (0.6)	0	0	1 (0.6)	0	1 (0.6)	0	0	0	0	0	0	1 (0.6)
SoC + D (N = 183)	0	0	0	0	0	0	0	0	0	0	0	0	0
SoC + D + O (N = 192)	3 (1.6)	2 (1.0)	3 (1.6)	3 (1.6)	3 (1.6)	3 (1.6)	3 (1.6)	0	0	0	0	1 (0.5)	2 (1.0)

[a] As assessed by the Investigator.

Included AEs if they started, or worsened, on or after the date of first dose of any of the investigational study treatments, including durvalumab/placebo or olaparib/placebo, throughout the treatment period and including the safety follow-up periods until the later date of 30 days after the last dose of olaparib/placebo and 90 days after last dose of durvalumab/placebo.

Adverse event of special interest terms of Infusion/Hypersensitivity reactions were not included in this table.

Patients with multiple AEs were counted for each grade they reported an AE for each category.

Reasons of not recovered/not resolved, recovering/resolving were mapped to an outcome of Not Resolved.

Reasons of recovered/resolved, recovered/resolved with sequelae were mapped to an outcome of Resolved.

CTCAE Version 5.0. MedDRA Version 25.1.

AE = Adverse event; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; N = Total number of patients; SAE = Serious adverse event; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

In the overall phase of the DUO-E study, consistent with the durvalumab mechanism of action, the imAEs were similar in the SoC + D (28.1%) and SoC + D + O (23.5%) arms and were higher than in the SoC arm (6.8%).

Table 77 Immune mediated adverse events in DUO-E overall and maintenance phase (SoC, SoC + D and SoC + D + O) and the durvalumab Pan-tumour Pool Overall (Safety Analysis Set)

	Number (%) of patients [a]						
	DUO-E Overall			DUO-E Maintenance Phase			Durvalumab Pan-tumour Pool (N = 4045)
	SoC (N = 236)	SoC + D (N = 235)	SoC + D + O (N = 238)	SoC (N = 169)	SoC + D (N = 183)	SoC + D + O (N = 192)	
AE Category	**imAE**	**imAE**	**imAE**	**imAE**	**imAE**	**imAE**	**imAE**
Any imAE	16 (6.8)	66 (28.1)	56 (23.5)	6 (3.6)	27 (14.8)	27 (14.1)	718 (17.8)
Any imAE of CTCAE Grade 3 or 4	3 (1.3)	19 (8.1)	18 (7.6)	0	6 (3.3)	9 (4.7)	179 (4.4)
Any serious imAE (including events with outcome of death) [b]	1 (0.4)	15 (6.4)	10 (4.2)	0	4 (2.2)	7 (3.6)	159 (3.9)
Any imAE with outcome of death	0	0	0	0	0	0	15 (0.4)
Any imAE possibly related to study treatment [c]	12 (5.1)	63 (26.8)	54 (22.7)	4 (2.4)	24 (13.1)	25 (13.0)	592 (14.6)
Any imAE possibly related to study treatment of CTCAE Grade 3 or 4 [c]	2 (0.8)	19 (8.1)	18 (7.6)	0	6 (3.3)	9 (4.7)	150 (3.7)
Any serious imAE possibly related to study treatment [b,c]	1 (0.4)	15 (6.4)	10 (4.2)	0	4 (2.2)	7 (3.6)	141 (3.5)
Any imAE possibly related to study treatment with outcome of death [c]	0	0	0	0	0	0	13 (0.3)
Received systemic corticosteroids	9 (3.8)	36 (15.3)	33 (13.9)	2 (1.2)	13 (7.1)	13 (6.8)	434 (10.7)
Received high dose steroids [d]	4 (1.7)	26 (11.1)	24 (10.1)	0	9 (4.9)	9 (4.7)	285 (7.0)
Received endocrine therapy	7 (3.0)	36 (15.3)	32 (13.4)	4 (2.4)	15 (8.2)	16 (8.3)	359 (8.9)
Received other immunosuppressants	0	0	2 (0.8)	0	0	2 (1.0)	15 (0.4)
Any imAE leading to discontinuation of study treatment	1 (0.4)	15 (6.4)	6 (2.5)	1 (0.6)	5 (2.7)	5 (2.6)	114 (2.8)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
[b] Seriousness, as assessed by the investigator. An AE with missing seriousness is considered serious.
[c] As assessed by the investigator, and programmatically derived from individual causality assessments for combination studies. Missing responses are counted as related.
[d] In DUO-E, high dose corticosteroid was defined as systemic corticosteroids at physiologic doses exceeding 10 mg/day of prednisone or its equivalent. For the Durvalumab Pan-tumour pool, a dose of ≥ 40 mg prednisone or equivalent per day (oral) was considered to be a high dose.

For DUO-E, imAEs were included if they started, or worsened, on or after the date of first dose of study treatment (overall) or first dose of olaparib/placebo (maintenance phase) up until the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment or until the end of the safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), which ever occurred first.
All studies use CTCAE version 4.03 except for DUO-E which uses version 5.0.
MedDRA version 25.1.
AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; imAE = immune-mediated AE; PT = preferred term; SAE = serious adverse event.

The median time to onset for imAEs by event type is presented in the below table.

Table 78 Immune-mediated Adverse Events Time to Event – Overall (Safety Analysis Set)

Descriptive statistics	Overall		
	SoC (N = 236)	SoC + D (N = 235)	SoC + D + O (N = 238)
Pneumonitis (grouped term)			
n [a]	0	2	5
Time to onset, median (Min-Max), (days)	NC (NC-NC)	246.5 (198-295)	85.0 (65-321)
Hepatic events (grouped term)			
n [a]	1	6	5
Time to onset, median (Min-Max), (days)	462.0 (462-462)	62.5 (23-656)	253.0 (21-331)
Intestinal perforations (grouped term)			
n [a]	0	0	0
Time to onset, median (Min-Max), (days)	NC (NC-NC)	NC (NC-NC)	NC (NC-NC)
Diarrhoea/colitis (grouped term)			
n [a]	0	4	4
Time to onset, median (Min-Max), (days)	NC (NC-NC)	234.5 (194-296)	49.5 (7-99)
Hypothyroid events (grouped term)			
n [a]	6	34	28
Time to onset, median (Min-Max), (days)	227.5 (64-498)	118.0 (15-307)	137.0 (44-570)
Hyperthyroid events (grouped term)			
n [a]	2	5	4
Time to onset, median (Min-Max), (days)	204.0 (22-386)	44.0 (42-125)	44.0 (22-151)
Thyroiditis (grouped term)			
n [a]	0	0	3
Time to onset, median (Min-Max), (days)	NC (NC-NC)	NC (NC-NC)	170.0 (44-291)

Descriptive statistics	Overall		
	SoC (N = 236)	SoC + D (N = 235)	SoC + D + O (N = 238)
Adrenal insufficiency (grouped term)			
n [a]	0	1	1
Time to onset, median (Min-Max), (days)	NC (NC-NC)	286.0 (286-286)	35.0 (35-35)
Hypophysitis (grouped term)			
n [a]	0	0	0
Time to onset, median (Min-Max), (days)	NC (NC-NC)	NC (NC-NC)	NC (NC-NC)
Type I diabetes mellitus (grouped term)			
n [a]	0	1	0
Time to onset, median (Min-Max), (days)	NC (NC-NC)	387.0 (387-387)	NC (NC-NC)
Renal events (grouped term)			
n [a]	0	0	0
Time to onset, median (Min-Max), (days)	NC (NC-NC)	NC (NC-NC)	NC (NC-NC)
Dermatitis/rash events (grouped term)			
n [a]	8	15	15
Time to onset, median (Min-Max), (days)	33.5 (9-371)	11.0 (5-274)	87.0 (2-308)
Myocarditis events (grouped term)			
n [a]	0	0	0
Time to onset, median (Min-Max), (days)	NC (NC-NC)	NC (NC-NC)	NC (NC-NC)
Myositis events (grouped term)			
n [a]	0	2	1
Time to onset, median (Min-Max), (days)	NC (NC-NC)	82.5 (24-141)	261.0 (261-261)
Pancreatic events (grouped term)			
n [a]	0	0	0
Time to onset, median (Min-Max), (days)	NC (NC-NC)	NC (NC-NC)	NC (NC-NC)
Myasthenia gravis (grouped term)			
n [a]	0	1	0
Time to onset, median (Min-Max), (days)	NC (NC-NC)	419.0 (419-419)	NC (NC-NC)
Guillain-Barre syndrome			
n [a]	0	0	0
Time to onset, median (Min-Max), (days)	NC (NC-NC)	NC (NC-NC)	NC (NC-NC)
Other rare/miscellaneous			
n [a]	1	5	4
Time to onset, median (Min-Max), (days)	155.0 (155-155)	53.0 (11-174)	381.0 (374-476)

[a] Number of events observed.

Included AEs if they started, or worsened, on or after the date of first dose of any of the investigational study treatments, including durvalumab/placebo or olaparib/placebo, throughout the treatment period and including the safety follow-up periods until the later date of 30 days after the last dose of olaparib/placebo and 90 days after last dose of durvalumab/placebo.

Adverse event of special interest terms of Infusion/Hypersensitivity reactions are not included in this table.

CTCAE Version 5.0. MedDRA Version 25.1.

AE = Adverse event; CTCAE = Common Terminology Criteria for Adverse Events; Max = Maximum; MedDRA = Medical Dictionary for Regulatory Activities; Min = Minimum; N = Total number of patients; NC = Not calculable; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Pneumonitis events

In the DUO-E study overall, at the 120-day safety update DCO (18 October 2023), a higher frequency of pneumonitis events (olaparib grouped term) was observed in the SoC + D + O arm (5.5%) vs the SoC + D and SoC arms (2.1% and 0.4%, and respectively). The observed frequency is also higher than has been observed with olaparib monotherapy (1.1% [40 events in 3556 patients in the olaparib 300 mg bd tablet pool]). In the DUO-E study, olaparib was only administered during the maintenance phase. During the maintenance phase and follow-up, 10 patients (5.2%) in the SoC + D + O arm experienced a pneumonitis (olaparib grouped term) event versus 4 patients (2.2%) in the SoC + D arm and no patients in the SoC arm.

Table 79 Pneumonitis Events in DUO-E (120-day Safety Update DCO [18 October 2023])

	Overall, n (%)			Maintenance/follow-up, n (%)		
	SoC (N = 36)	SoC + D (N = 235)	SoC +D + O (N = 238)	SoC (N = 169)	SoC + D (N = 183)	SoC + D + O (N = 192)
Bronchiolitis [a]	0	0	1 (0.4)	0	0	1 (0.5)
Interstitial lung disease	0	1 (0.4)	3 (1.3)	0	1 (0.5)	3 (1.6)
Pneumonitis	1 (0.4)	4 (1.7)	9 (3.2)	0	3 (1.6)	6 (3.1)
Pneumonitis grouped term	**1 (0.4)**	**5 (2.1)**	**13 (5.5)**	**0**	**4 (2.2)**	**10 (5.2)**

[a.] Bronchiolitis is included in the grouped term used to determine the pneumonitis cases for the important potential risk of pneumonitis for olaparib, but is not included in the AESI grouped term for pneumonitis for durvalumab

Pneumonitis events (Durvalumab Grouped Term)

The MedDRA PTs grouped to define the potential risk of pneumonitis for olaparib and the imAE for durvalumab differ. The following section uses the durvalumab grouped MedDRA PTs.

Results for the durvalumab Pan tumour Pool were generally similar for SoC + D and SoC + D + O in DUO E for the overall phase of the study:

- The imAE criteria for pneumonitis (grouped term) was met by a similar proportion of patients in the durvalumab Pan tumour Pool and SoC + D and SoC + D + O of DUO-E.
- Events of CTCAE maximum Grade 3 or 4 were reported in a similar proportion of patients in the durvalumab Pan tumour Pool and SoC + D and SoC + D + O.
- No patients in the DUO-E study experienced fatal events of pneumonitis. Fatal events in the durvalumab Pan tumour Pool were very rare.
- A similar proportion of patients in the durvalumab Pan tumour Pool and SoC + D and SoC + D + O of DUO-E received high dose steroids.
- A similar proportion of patients in the durvalumab Pan tumour Pool and SoC + D and SoC + D + O of DUO-E discontinued any study treatment.
- The median time to onset for the imAE of pneumonitis (grouped term) in the durvalumab Pan tumour Pool was 56 days (range: 2 to 814 days). In DUO-E, median time to onset was 246.5 days (range: 198 to 295 days) in the SoC + D arm and 85 days (range: 65 to 321 days) in the SoC + D + O arm.

Pneumonitis (Olaparib Grouped Term)

Pneumonitis is a recognised ADR for carboplatin, paclitaxel, and durvalumab. It is a potential risk for olaparib and as such is appropriately reflected in the product labelling.

Pneumonitis is an AESI for durvalumab and olaparib; it is an ADR for durvalumab and a potential risk for olaparib. Note that there are fewer PTs in the grouped term of pneumonitis for durvalumab; all of which are included in the list of PTs in the grouped term of pneumonitis for the categorisation as an AESI for olaparib. The frequency of pneumonitis events in the SoC + D + O arm was higher than has been observed with olaparib monotherapy. The majority of events were Grade 1 or 2 and non-serious. The majority of events recovered or were recovering at DCO. However, given that immune mediated pneumonitis is also an ADR for durvalumab, the cases were low grade, and the majority recovered, when taken together with the proportion of patients reporting pneumonitis in the SoC + D arm in the maintenance phase of DUO-E (3 patients), this study provides important reassurance that the incidence of pneumonitis in olaparib-treated patients did not appear to increase beyond what might be expected.

The incidence of pneumonitis events in the olaparib pooled data (300 mg bd Tablet Pool) was 1.1%. The majority of pneumonitis AEs reported were mild or moderate, non-serious, and resolved without treatment discontinuation.

The below table shows the AEs of pneumonitis in DUO-E and the rates of pneumonitis in the larger pool (combined therapeutic dose pool).

Table 80 Summary of AEs of Pneumonitis Occurring Across the Olaparib Programme

	Olaparib combination/monotherapy arm		**Comparator arm**	
	Number of patients with AEs	**Incidence [a]**	**Number of AEs**	**Incidence [a]**
DUO-E Maintenance [b] N = 192 SoC + D + O	8	4.2%	0	-
Olaparib 300 mg bd Tablet Pool N = 3556 olaparib [b]	40	1.1%	NA	NA

a. The percentage of patients experiencing any event of pneumonitis.

b. As of 12 April 2023 (DUO-E Primary PFS DCO). Comparator arm for DUO-E is standard of care (N = 169).

AE = adverse event; bd = twice daily; DCO = data cut-off; N = total number of patients; NA = not applicable; PBRER = periodic benefit-risk evaluation report; PFS = progression-free survival; SoC + D + O = durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Hepatic events

Results for the durvalumab Pan tumour Pool were generally similar to SoC + D and SoC + D + O in DUO E for the Overall phase of the study:

- The imAE criteria for hepatic events (grouped term) was met by a similar proportion of patients in the SoC + D and SoC + D + O arms of DUO-E, compared with the durvalumab Pan tumour Pool.
- Events of CTCAE maximum Grade 3 or 4 were reported in a similar proportion of patients in the durvalumab Pan tumour Pool and SoC + D and SoC + D + O arms of DUO-E.
- No patients in the DUO-E study experienced fatal hepatic events and fatal events in the durvalumab Pan tumour Pool were very rare.
- A similar proportion of patients in the durvalumab Pan tumour Pool and SoC + D and SoC + D + O of DUO-E received high dose steroids.
- A similar proportion of patients in the durvalumab Pan tumour Pool and SoC + D and SoC + D + O of DUO-E discontinued any study treatment.

- The median time to onset for the imAE of hepatic events (grouped term) in the durvalumab Pan tumour Pool was 31 days (range: 1 to 644 days). In DUO-E, median time to onset was 62.5 days (range: 23 to 656 days) in the SoC + D arm and 253.0 days (range: 21 to 331 days) in the SoC + D + O arm.

Gastrointestinal events (diarrhoea/colitis, intestinal perforation)

Intestinal perforation

No patients met the imAE criteria for intestinal perforation (grouped term) in either SoC, SoC + D or SoC + D + O in DUO-E, or the durvalumab Pan tumour Pool.

Diarrhoea/Colitis

Results for the durvalumab Pan tumour Pool were generally similar to SoC + D and SoC + D + O in DUO E for the Overall phase of the study:

- The imAE criteria for diarrhoea/colitis was met by a similar proportion of patients in the SoC + D and SoC + D + O arms of DUO-E, compared with the durvalumab Pan tumour Pool.
- Events of CTCAE Grade 3 or 4 were reported in a similar proportion of patients in the SoC + D and SoC + D + O arms of DUO-E, compared with the durvalumab Pan tumour Pool.
- No patients had fatal events of diarrhoea/colitis in either SoC, SoC + D or SoC + D + O in DUO-E, or the durvalumab Pan tumour Pool.
- A similar proportion of patients in the and SoC + D and SoC + D + O arms of DUO-E received high dose steroids, compared with the durvalumab Pan tumour Pool.
- Only one patient in the SoC + D arm of DUO-E discontinued any study treatment due to an event of diarrhoea/colitis. The proportion of patients in the durvalumab Pan tumour Pool who discontinued any study treatment due to an event of diarrhoea/colitis was low.
- The median time to onset for the imAE of diarrhoea/colitis in the durvalumab Pan tumour Pool was 69.5 days (range: 1 to 920 days). In DUO-E, median time to onset was 234.5 days (range: 194 to 296 days) in the SoC + D arm and 49.5 days (range: 7 to 99 days) in the SoC + D + O arm.

Endocrinopathies

Hypothyroid events

Results for the durvalumab Pan tumour Pool were generally similar for SoC + D and SoC + D + O in DUO E for the Overall phase of the study:

- The imAE criteria for hypothyroid events (grouped term) was met by a higher proportion of patients in the SoC + D and SoC + D + O arms of DUO-E, compared with the durvalumab Pan tumour Pool which may be explained by the longer median durvalumab exposure compared to the pool.
- Events of CTCAE maximum Grade 3 or 4 were reported in a low and similar proportion of patients in the SoC + D + O arm and the durvalumab Pan tumour Pool.
- No patients had fatal hypothyroid events in either SoC, SoC + D or SoC + D + O in DUO-E, or the durvalumab Pan tumour Pool.
- A higher proportion of patients in the SoC + D and SoC + D + O arms of DUO-E received endocrine therapies for hypothyroid events, compared with the durvalumab Pan tumour Pool.
- No patients discontinued any study treatment due to hypothyroid events in either SoC, SoC + D or SoC + D + O in DUO-E, or the durvalumab Pan tumour Pool.
- The median time to onset for the imAE of hypothyroid events (grouped term) in the durvalumab Pan tumour Pool was 86.0 days (range: 1 to 951 days). In DUO-E, median time to

onset was 127.0 days (range: 15 to 307 days) in the SoC + D arm and 137.0 days (range: 44 to 570 days) in the SoC + D + O arm.

Hyperthyroid events

Results for the durvalumab Pan tumour Pool were generally similar for SoC + D and SoC + D + O in DUO E for the Overall phase of the study:

- The imAE criteria for hyperthyroid events (grouped term) was met by a similar proportion of patients in the SoC + D and SoC + D + O arms of DUO-E, compared with the durvalumab Pan tumour Pool.
- No patients had hyperthyroid events of CTCAE maximum Grade 3 or 4 in the SoC, SoC + D and SoC + D + O of the DUO-E study, or in the durvalumab Pan-tumour Pool.
- No patients had fatal hyperthyroid events in either SoC, SoC + D or SoC + D + O in DUO-E, or the durvalumab Pan tumour Pool.
- A similar proportion of patients in the SoC + D and SoC + D + O arms of DUO-E received endocrine therapies for hyperthyroid events, compared with the durvalumab Pan tumour Pool.
- One patient discontinued any study treatment due to hyperthyroid events in the SoC + D arm of the DUO-E study; no patients discontinued any study treatment due to hyperthyroid events in the SoC, or SoC + D + O arms of the DUO-E study. One patient discontinued any study treatment due to a hyperthyroid event in the durvalumab Pan tumour Pool.
- The median time to onset for the imAE of hyperthyroid events (grouped term) in the durvalumab Pan-tumour Pool was 43.0 days (range: 1 to 253 days). In DUO-E, median time to onset was 44.0 days (range: 42 to 125 days) in the SoC + D arm and 44.0 days (range: 22 to 151 days) in the SoC + D + O arm.

Thyroiditis

Results for the durvalumab Pan tumour Pool were generally similar for SoC + D and SoC + D + O in DUO E for the Overall phase of the study:

- The imAE criteria for thyroiditis (grouped term) was met by a similar proportion of patients in the SoC + D + O arm of DUO-E, compared with the durvalumab Pan tumour Pool. No patients in the SoC + D arm met the imAE criteria for thyroiditis.
- No patients in DUO-E had thyroiditis events of CTCAE maximum Grade 3 or 4 and only 2 patients in the durvalumab Pan tumour Pool had a thyroiditis event of CTCAE maximum Grade 3 or 4.
- No patients had fatal thyroiditis events in either SoC, SoC + D or SoC + D + O in DUO E, or the durvalumab Pan tumour Pool.
- A similar proportion of patients in the SoC + D + O arm of DUO-E received endocrine therapies, compared with the durvalumab Pan tumour Pool.
- No patients in DUO-E and one patient in the durvalumab Pan-tumour Pool discontinued any study treatment due to a thyroiditis event.
- The median time to onset for the imAE of thyroiditis (grouped term) in the durvalumab Pan-tumour Pool was 57.0 days (range: 14 to 217 days). In DUO-E, median time to onset was 170.0 days (range: 44 to 291 days) in the SoC + D + O arm.

Adrenal insufficiency

Results for the durvalumab Pan tumour Pool were generally similar for SoC + D and SoC + D + O in DUO E for the Overall phase of the study:

- The imAE criteria for adrenal insufficiency (grouped term) was met by a similar proportion of patients in the durvalumab Pan-tumour Pool and SoC + D and SoC + D + O.
- No patients in the SoC + D arm of the DUO-E study reported an adrenal insufficiency event of CTCAE maximum Grade 3 or 4; one patient in the SoC + D + O arm reported a CTCAE

maximum Grade 3 or 4 adrenal insufficiency event. The proportion of patients with CTCAE maximum Grade 3 or 4 adrenal insufficiency events in the durvalumab Pan-tumour Pool was low.

- No patients had fatal adrenal insufficiency in either SoC, SoC + D or SoC + D + O in DUO-E, or the durvalumab Pan tumour Pool.
- A similar proportion of patients in the durvalumab Pan-tumour Pool and SoC + D + O arm of DUO E received high dose steroids.
- No patients in DUO-E or the durvalumab Pan-tumour Pool discontinued any study treatment due to an adrenal insufficiency event.
- The median time to onset for the imAE of adrenal insufficiency (grouped term) in the durvalumab Pan-tumour Pool was 157.5 days (range: 20 to 547 days). In DUO-E, time to onset was 286 days for the one patient with an event in the SoC + D arm and 35 days for the one patient with an event in the SoC + D + O arm.

Hypophysitis

No patients met the imAE criteria for hypophysitis (grouped term) in either SoC, SoC + D or SoC + D + O in DUO-E, compared with 4 patients (< 0.1%) the durvalumab Pan tumour Pool.

Type 1 Diabetes Mellitus

One patient in the SoC + D arm in DUO-E met the imAE criteria for Type 1 diabetes mellitus, compared with no patients in either SoC, or SoC + D + O in DUO-E, and 4 patients (< 0.1%) the durvalumab Pan tumour Pool.

Renal events

- No patients in DUO-E met the imAE criteria for renal events (grouped term) compared with a low proportion of patients in the durvalumab Pan-tumour Pool.
- No patients in DUO-E had renal events of CTCAE maximum Grade 3 or 4. The proportion of patients with CTCAE maximum Grade 3 or 4 renal events in the durvalumab Pan-tumour Pool was low.
- No patients had fatal renal events in either SoC, SoC + D or SoC + D + O in DUO-E, or the durvalumab Pan tumour Pool.
- A low proportion of patients in the durvalumab Pan-tumour Pool received high dose steroids.
- No patients in DUO-E and 7 patients in the durvalumab Pan-tumour Pool discontinued any study treatment due to a renal event.
- The median time to onset for the imAE of renal events (grouped term) in the durvalumab Pan-tumour Pool was 84.0 days (range: 4 to 393 days).

Dermatitis/rash events

- Results for the durvalumab Pan tumour Pool were generally similar to SoC + D and SoC + D + O of DUO E for the Overall phase of the study:
- Events of CTCAE maximum Grade 3 or 4 were reported in a higher proportion of patients in the SoC + D and SoC + D + O arms of DUO-E, compared with the durvalumab Pan tumour Pool.
- No patients had fatal dermatitis/rash events in either SoC, SoC + D or SoC + D + O in DUO-E, or the durvalumab Pan tumour Pool.
- A higher proportion of patients in the SoC + D and SoC + D + O arms of DUO-E received high dose steroids, compared with the durvalumab Pan tumour Pool.
- A higher proportion of patients in the SoC + D and SoC + D + O arms of DUO-E discontinued any study treatment, compared with the durvalumab Pan-tumour Pool.

- The median time to onset for the imAE of dermatitis/rash events (grouped term) in the durvalumab Pan-tumour Pool was 54.0 days (range: 4 to 576 days). In DUO-E, median time to onset was 11.0 days (range: 5 to 274 days) in the SoC + D arm and 87.0 days (range: 2 to 308 days) in the SoC + D + O arm.

The imAEs Dermatitis/Rash (grouped term) for the durvalumab Pan-tumour Pool were generally similar to SoC + D and SoC + D + O of DUO-E for the Overall phase of the study, at DCO1 (12 April 2023).

Myocarditis events

No patients met the imAE criteria for myocarditis events (grouped term) in either SoC, SoC + D or SoC + D + O in DUO-E, compared with 5 patients (0.1%) the durvalumab Pan tumour Pool.

Myositis events

Results for the durvalumab Pan tumour Pool were generally similar for SoC + D and SoC + D + O of DUO E for the Overall phase of the study:

- The imAE criteria for myositis events (grouped term) was met by a similar proportion of patients in the durvalumab Pan-tumour Pool and SoC + D and SoC + D + O of DUO E.
- Events of CTCAE maximum Grade 3 or 4 were reported in a similar proportion of patients in the durvalumab Pan-tumour Pool and SoC + D and SoC + D + O of DUO E.
- No patients had fatal myositis events in either SoC, SoC + D or SoC + D + O in DUO-E, or the durvalumab Pan tumour Pool.
- A similar proportion of patients in the durvalumab Pan-tumour Pool and SoC + D and SoC + D + O of DUO E received high dose steroids.
- A similar proportion of patients in the durvalumab Pan-tumour Pool and SoC + D and SoC + D + O of DUO E discontinued any study treatment.
- The median time to onset for the imAE of myositis events (grouped term) in the durvalumab Pan-tumour Pool was 33.5 days (range: 30 to 43 days). In DUO-E, median time to onset was 82.5 days (range: 24 to 141 days) in the SoC + D arm and 261 days for the one patient with an event in the SoC + D + O arm.

There were no additional patients with events of myositis in the DUO-E study between the DCO1 date and the 120-day safety update DCO (18 October 2023).

The review of adjudicated imAEs myositis events (grouped term), revealed that the results for the durvalumab Pan-tumour Pool were generally similar for the SoC + D and SoC + D + O arms for the Overall phase of the DUO-E study. No events of myositis occurred in the Maintenance phase. There were 6 events (2.6%) in the SoC + D arm and 1 event (0.4%) in the SoC + D + O arm of the DUO-E study. Only one event of Grade 3/4 was reported in the SoC + D arm. Nine events (0.2%) of myositis occurred in the durvalumab Pan-tumour Pool, and 3 events (< 0.1%) were Grade 3/4.

Myositis is a known ADR and imAE for durvalumab. The incidence, and severity of the myositis AEs reported in the DUO-E study were consistent with the known safety profile of durvalumab.

Pancreatic events

No patients met the imAE criteria for pancreatic events (grouped term) in any of the treatment arms in DUO-E, compared with 9 patients (0.2%) in the durvalumab Pan tumour Pool.

Myasthenia gravis

One patient in the SoC + D arm of DUO-E met the imAE criteria for myasthenia gravis events (grouped term); there were no events in either SoC or SoC + D + O in DUO-E, compared with 2 patients (< 0.1%) in the durvalumab Pan tumour Pool. The event in the patient in the SoC + D arm of DUO-E was

non-serious and Grade ≤ 3 with an onset date of Day 419. The patient received high dose steroids and the event resolved.

Guillain-Barre syndrome events

No patients met the imAE criteria for Guillain-Barre syndrome events (grouped term) in either SoC, SoC + D or SoC + D + O in DUO-E, compared with one patient (< 0.1%) the durvalumab Pan tumour Pool.

Other/rare miscellaneous events

In DUO-E, PTs for other rare/miscellaneous events (grouped term) that met the imAE criteria were:

- SoC arm: arthralgia (one patient [0.4%] and treated with systemic corticosteroids).
- SoC + D arm: autoimmune haemolytic anaemia (SAE); immune thrombocytopenia (SAE); immune mediated cholangitis (SAE); uveitis; vasculitis (one patient [0.4%] each, and all events treated with systemic corticosteroids).
- SoC + D + O arm: arthritis; autoimmune haemolytic anaemia (SAE); haemolytic anaemia; systemic inflammatory response syndrome (SAE) (one patient [0.4%] each and all events treated with systemic corticosteroids).

Three events, all in the SoC + D arm (PTs of immune thrombocytopenia, immune-mediated cholangitis, and vasculitis) led to discontinuation of study drug/durvalumab in DUO-E. None of the PTs for other rare/miscellaneous events (grouped term) in any treatment arm of DUO-E were fatal.

Immune thrombocytopenia was observed in 1 patient (0.1%) in the SoC + D arm. This (CTCAE Grade 3) event was reported in the chemotherapy phase of the SoC + D arm of DUO-E.

The median time to onset for all 54 rare/miscellaneous imAEs in the durvalumab Pan-tumour Pool was 114.5 days (range: 2 to 631 days). In DUO E, there were 10 rare/miscellaneous imAEs. Median time to onset was 155.0 days for one event in the SoC arm, 53.0 days for 5 events in the SoC + D arm (range: 11 to 174 days) and 381.0 days for 4 events in the SoC + D + O arm (range: 374 to 476 days).

Infusion-related reactions and hypersensitivity/anaphylaxis reactions events

Infusion-related Reactions

Table 81 Infusion-related reaction AESIs, all events and by maximum CTCAE Grade – Overall and maintenance phase (Safety Analysis Set)

	Number (%) of patients [a]					
		CTCAE Grade				
	Any AE	1	2	3	4	5
Overall						
SoC (N = 236)						
Infusion-related reaction (grouped term)	24 (10.2)	4 (1.7)	17 (7.2)	1 (0.4)	2 (0.8)	0
Infusion related reaction	24 (10.2)	4 (1.7)	17 (7.2)	1 (0.4)	2 (0.8)	0
Urticaria	0	0	0	0	0	0
SoC + D (N = 235)						
Infusion-related reaction (grouped term)	15 (6.4)	6 (2.6)	9 (3.8)	0	0	0
Infusion related reaction	14 (6.0)	5 (2.1)	9 (3.8)	0	0	0
Urticaria	1 (0.4)	1 (0.4)	0	0	0	0
SoC + D + O (N = 238)						
Infusion-related reaction (grouped term)	14 (5.9)	4 (1.7)	8 (3.4)	2 (0.8)	0	0
Infusion related reaction	13 (5.5)	4 (1.7)	8 (3.4)	1 (0.4)	0	0
Urticaria	1 (0.4)	0	0	1 (0.4)	0	0
Maintenance Phase						
SoC (N = 169)						
Infusion-related reaction (grouped term)	1 (0.6)	0	0	1 (0.6)	0	0
Infusion related reaction	1 (0.6)	0	0	1 (0.6)	0	0
Urticaria	0	0	0	0	0	0
SoC + D (N = 183)						
Infusion-related reaction (grouped term)	1 (0.5)	0	1 (0.5)	0	0	0
Infusion related reaction	1 (0.5)	0	1 (0.5)	0	0	0
Urticaria	0	0	0	0	0	0
SoC + D + O (N = 192)						
Infusion-related reaction (grouped term)	1 (0.5)	0	1 (0.5)	0	0	0
Infusion related reaction	1 (0.5)	0	1 (0.5)	0	0	0
Urticaria	0	0	0	0	0	0

[a] Each patient was represented once with the maximum reported CTCAE grade for each specific AE of interest.

If a patient had multiple (PT level) events within a specific AE of interest, then the maximum CTCAE grade across those events was counted.

Specific AEs of interest may either be grouped MedDRA PTs or individual MedDRA PTs.

Included AEs with an onset date or that worsened on or after the date of first dose of durvalumab/placebo or olaparib/placebo (overall) or first dose of olaparib/placebo (Maintenance Phase) up until the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurred first.

CTCAE Version 5.0. MedDRA Version 25.1.

AE = Adverse event; AESI = Adverse event of special interest; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; N = Total number of patients; PT = Preferred term; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Hypersensitivity/Anaphylactic Reactions

Hypersensitivity/anaphylactic reaction AESIs (grouped term and PT) of any cause are shown by frequency and grade in the below table.

Hypersensitivity/anaphylactic reaction (grouped term) AESIs were comparable across all 3 treatment arms; the majority of the events were CTCAE Grade 1 or 2 in severity.

Of the AESIs of hypersensitivity/anaphylactic reaction, no patients in the SoC arm, 4 patients in the SoC + D arm, and 4 patients in the SoC + D + O arm had events leading to discontinuation of study treatment in the study overall.

Table 82 Hypersensitivity/Anaphylactic Reaction AESIs, All Events and by Maximum CTCAE Grade – Overall and Maintenance Phase (Safety Analysis Set)

	Number (%) of patients [a]					
		CTCAE Grade				
	Any AE	1	2	3	4	5
Overall						
SoC (N = 236)						
Hypersensitivity/anaphylactic reactions (grouped term)	9 (3.8)	4 (1.7)	1 (0.4)	3 (1.3)	1 (0.4)	0
Anaphylactic reaction	3 (1.3)	0	0	2 (0.8)	1 (0.4)	0
Anaphylactic shock	0	0	0	0	0	0
Drug hypersensitivity	6 (2.5)	4 (1.7)	1 (0.4)	1 (0.4)	0	0
Hypersensitivity	0	0	0	0	0	0
SoC + D (N = 235)						
Hypersensitivity/anaphylactic reactions (grouped term)	8 (3.4)	1 (0.4)	4 (1.7)	2 (0.9)	1 (0.4)	0
Anaphylactic reaction	1 (0.4)	0	0	1 (0.4)	0	0
Anaphylactic shock	1 (0.4)	0	0	0	1 (0.4)	0
Drug hypersensitivity	1 (0.4)	0	0	1 (0.4)	0	0
Hypersensitivity	5 (2.1)	1 (0.4)	4 (1.7)	0	0	0
SoC + D + O (N = 238)						
Hypersensitivity/anaphylactic reactions (grouped term)	14 (5.9)	4 (1.7)	6 (2.5)	3 (1.3)	1 (0.4)	0
Anaphylactic reaction	2 (0.8)	1 (0.4)	0	1 (0.4)	0	0
Anaphylactic shock	1 (0.4)	0	0	0	1 (0.4)	0
Drug hypersensitivity	4 (1.7)	0	3 (1.3)	1 (0.4)	0	0
Hypersensitivity	7 (2.9)	3 (1.3)	3 (1.3)	1 (0.4)	0	0
Maintenance Phase						
SoC (N = 169)						
Hypersensitivity/anaphylactic reactions (grouped term)	2 (1.2)	0	0	1 (0.6)	1 (0.6)	0
Anaphylactic reaction	2 (1.2)	0	0	1 (0.6)	1 (0.6)	0
Anaphylactic shock	0	0	0	0	0	0
Drug hypersensitivity	0	0	0	0	0	0
Hypersensitivity	0	0	0	0	0	0
SoC + D (N = 183)						
Hypersensitivity/anaphylactic reactions (grouped term)	1 (0.5)	0	1 (0.5)	0	0	0
Anaphylactic reaction	0	0	0	0	0	0
Anaphylactic shock	0	0	0	0	0	0
Drug hypersensitivity	0	0	0	0	0	0
Hypersensitivity	1 (0.5)	0	1 (0.5)	0	0	0
SoC + D + O (N = 192)						
Hypersensitivity/anaphylactic reactions (grouped term)	3 (1.6)	2 (1.0)	1 (0.5)	0	0	0
Anaphylactic reaction	0	0	0	0	0	0
Anaphylactic shock	0	0	0	0	0	0
Drug hypersensitivity	0	0	0	0	0	0
Hypersensitivity	3 (1.6)	2 (1.0)	1 (0.5)	0	0	0

[a] Each patient was represented once with the maximum reported CTCAE grade for each specific AE of interest.

If a patient had multiple (PT level) events within a specific AE of interest, then the maximum CTCAE grade across those events was counted.

Specific AEs of interest may either be grouped MedDRA PTs or individual MedDRA PTs.

Included AEs with an onset date or that worsened on or after the date of first dose of durvalumab/placebo or olaparib/placebo (overall) or first dose of olaparib/placebo (Maintenance Phase) up until the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurred first.

CTCAE Version 5.0. MedDRA Version 25.1.

AE = Adverse event; AESI = Adverse event of special interest; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; N = Total number of patients; PT = Preferred term; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Serious adverse event/deaths/other significant events

Serious adverse events regardless of causality

DUO-E study

Table 83 Most common SAEs (Frequency of ≥ 1% in any treatment arm) by System Organ Class and PT – Overall and maintenance phase (Safety Analysis Set)

System organ class/ Preferred term	Number (%) of patients [a]					
	Overall			Maintenance		
	SoC (N = 236)	SoC + D (N = 235)	SoC + D + O (N = 238)	SoC (N = 169)	SoC + D (N = 183)	SoC + D + O (N = 192)
Patients with any SAE	**73 (30.9)**	**73 (31.1)**	**85 (35.7)**	**19 (11.2)**	**22 (12.0)**	**42 (21.9)**
Blood and lymphatic system disorders						
Anaemia	10 (4.2)	1 (0.4)	16 (6.7)	0	0	12 (6.3)
Febrile neutropenia	8 (3.4)	4 (1.7)	7 (2.9)	0	0	2 (1.0)
Neutropenia	3 (1.3)	3 (1.3)	5 (2.1)	0	0	1 (0.5)
Aplasia pure red cell	0	0	3 (1.3)	0	0	3 (1.6)
Infections and infestations						
Urinary tract infection	5 (2.1)	2 (0.9)	6 (2.5)	4 (2.4)	1 (0.5)	3 (1.6)
Sepsis	3 (1.3)	2 (0.9)	4 (1.7)	1 (0.6)	0	1 (0.5)
COVID-19	3 (1.3)	1 (0.4)	4 (1.7)	1 (0.6)	1 (0.5)	1 (0.5)
COVID-19 pneumonia	0	1 (0.4)	3 (1.3)	0	0	3 (1.6)
Pneumonia	0	1 (0.4)	2 (0.8)	0	0	2 (1.0)
Urosepsis	3 (1.3)	1 (0.4)	0	1 (0.6)	0	0
Gastrointestinal disorders						
Diarrhoea	4 (1.7)	0	2 (0.8)	0	0	1 (0.5)
Vomiting	2 (0.8)	5 (2.1)	1 (0.4)	1 (0.6)	1 (0.5)	0
Nausea	2 (0.8)	3 (1.3)	1 (0.4)	0	1 (0.5)	0
Constipation	3 (1.3)	2 (0.9)	0	0	0	0
Respiratory, thoracic, and mediastinal disorders						
Pneumonitis	0	1 (0.4)	3 (1.3)	0	1 (0.5)	2 (1.0)
Pulmonary embolism	4 (1.7)	0	3 (1.3)	0	0	1 (0.5)
General disorders and administration site conditions						
Pyrexia	1 (0.4)	1 (0.4)	3 (1.3)	1 (0.6)	0	1 (0.5)
Vascular disorders						
Deep vein thrombosis	1 (0.4)	2 (0.9)	3 (1.3)	0	0	1 (0.5)
Metabolism and nutrition disorders						
Hyponatraemia	4 (1.7)	5 (2.1)	0	0	1 (0.5)	0
Injury, poisoning and procedural complications						
Fall	3 (1.3)	1 (0.4)	1 (0.4)	0	0	1 (0.5)
Infusion related reaction	3 (1.3)	0	1 (0.4)	0	0	0
Renal and urinary disorders						
Hydronephrosis	2 (0.8)	0	0	2 (1.2)	0	0
Investigations						
Neutrophil count decreased	4 (1.7)	1 (0.4)	0	0	0	0

[a] Number (%) of patients with a SAE, sorted by decreasing order of frequency by system organ class and then by PT for the SoC + D + O arm, the SoC + D arm, and the SoC arm for the study overall.

Included AEs with an onset date or that worsened on or after the date of first dose of study treatment (overall) or first dose of olaparib/placebo (Maintenance Phase) up until the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurred first.

Patients with multiple SAEs were counted once for each system organ class/PT.

Percentages were based on the total numbers of patients in the treatment arm (N).

MedDRA Version 25.1.

AE = Adverse event; COVID-19 = Coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; N = Total number of patients; PT = Preferred term; SAE = Serious adverse event; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Table 84 Most common SAEs by System Organ Class and Preferred Term (Frequency ≥ 1% patients in any treatment group in SoC, SoC + D, and SoC + D + O in DUO-E overall phase) Compared with the durvalumab and olaparib pools (Safety Analysis Set)

System organ class/ Preferred term	Number (%) of patients [a]				
	DUO-E Overall			Durvalumab Pan-tumour Pool (N = 4045)	Olaparib 300 mg bd Tablet Pool (N = 3556)
	SoC (N = 236)	SoC + D (N = 235)	SoC + D + O (N = 238)		
Patients with any SAE	**73 (30.9)**	**73 (31.1)**	**85 (35.7)**	**1448 (35.8)**	**670 (18.8)**
Blood and lymphatic system disorders					
Anaemia	10 (4.2)	1 (0.4)	16 (6.7)	28 (0.7)	146 (4.1)
Febrile neutropenia	8 (3.4)	4 (1.7)	7 (2.9)	0	11 (0.3)
Neutropenia	3 (1.3)	3 (1.3)	5 (2.1)	2 (<0.1)	12 (0.3)
Aplasia pure red cell	0	0	3 (1.3)	0	0
Infections and infestations					
Urinary tract infection	5 (2.1)	2 (0.9)	6 (2.5)	37 (0.9)	22 (0.6)
Sepsis	3 (1.3)	2 (0.9)	4 (1.7)	54 (1.3)	14 (0.4)
COVID-19	3 (1.3)	1 (0.4)	4 (1.7)	0	4 (0.1)
COVID-19 pneumonia	0	1 (0.4)	3 (1.3)	0	3 (0.1)
Urosepsis	3 (1.3)	1 (0.4)	0	11 (0.3)	5 (0.1)
Respiratory, thoracic, and mediastinal disorders					
Pneumonitis	0	1 (0.4)	3 (1.3)	44 (1.1)	10 (0.3)
Pulmonary embolism	4 (1.7)	0	3 (1.3)	31 (0.8)	21 (0.6)
General disorders and administration site conditions					
Pyrexia	1 (0.4)	1 (0.4)	3 (1.3)	52 (1.3)	15 (0.4)
Gastrointestinal disorders					
Diarrhoea	4 (1.7)	0	2 (0.8)	22 (0.5)	5 (0.1)
Vomiting	2 (0.8)	5 (2.1)	1 (0.4)	24 (0.6)	19 (0.5)
Nausea	2 (0.8)	3 (1.3)	1 (0.4)	12 (0.3)	11 (0.3)
Constipation	3 (1.3)	2 (0.9)	0	17 (0.4)	4 (0.1)
Metabolism and nutrition disorders					
Hyponatraemia	4 (1.7)	5 (2.1)	0	18 (0.4)	6 (0.2)
Vascular disorders					
Deep vein thrombosis	1 (0.4)	2 (0.9)	3 (1.3)	2 (<0.1)	7 (0.2)
Injury, poisoning and procedural complications					
Fall	3 (1.3)	1 (0.4)	1 (0.4)	4 (<0.1)	3 (0.1)
Infusion related reaction	3 (1.3)	0	1 (0.4)	7 (0.2)	1 (0.0)
Investigations					
Neutrophil count decreased	4 (1.7)	1 (0.4)	0	0	4 (0.1)

a. Number (%) of patients with an SAE, sorted by system organ class and then by frequency in DUO-E SoC + D + O then the SoC + D arm for the Overall study period. Patients with multiple SAEs were counted once for each system organ class/PT.

For DUO-E, SAEs had an onset date or that worsened on or after the date of first dose of study treatment (overall) or first dose of olaparib/placebo (maintenance phase) up until the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurred first. For the Durvalumab Pan-tumour pool, SAEs had an onset date on or after the date of first dose or pre-treatment AEs that increased in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication (or surgery) or up to and including the date of initiation of the first subsequent therapy (whichever occurred first). For the olaparib 300 mg bd tablet pool, SAEs had an onset date between the date of first dose of continuous treatment and 30 days following the last dose of continuous treatment.

Percentages are based on the total number of patients in the treatment group (N).
Disease progression AEs reported in Study 1108 are not included in this summary.
MedDRA version 25.1
AE = adverse event; bd = twice daily; COVID-19 = Coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in treatment group; PT = preferred term; SAE = serious adverse event; SoC = standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Table 85 Most common SAEs by System Organ Class and Preferred Term (Frequency ≥ 1% Patients in any treatment group in SoC, SoC + D, and SoC + D + O in DUO-E maintenance Phase) compared with the durvalumab and olaparib pools (Safety Analysis Set)

	Number (%) of patients [a]				
	DUO-E Maintenance Phase			**Durvalumab Pan-tumour Pool (N = 4045)**	**Olaparib 300 mg bd Tablet Pool (N = 3556)**
System organ class/ Preferred term	**SoC (N = 169)**	**SoC + D (N = 183)**	**SoC + D + O (N = 192)**		
Patients with any SAE	**19 (11.2)**	**22 (12.0)**	**42 (21.9)**	**1448 (35.8)**	**670 (18.8)**
Blood and lymphatic system disorders					
Anaemia	0	0	12 (6.3)	28 (0.7)	146 (4.1)
Aplasia pure red cell	0	0	3 (1.6)	0	0
Febrile neutropenia	0	0	2 (1.0)	0	11 (0.3)
Infections and infestations					
Urinary tract infection	4 (2.4)	1 (0.5)	3 (1.6)	37 (0.9)	22 (0.6)
COVID-19 pneumonia	0	0	3 (1.6)	0	3 (0.1)
Pneumonia	0	0	2 (1.0)	152 (3.8)	31 (0.9)
Respiratory, thoracic, and mediastinal disorders					
Pneumonitis	0	1 (0.5)	2 (1.0)	44 (1.1)	10 (0.3)
Renal and urinary disorders					
Hydronephrosis	2 (1.2)	0	0	6 (0.1)	3 (0.1)

a. Number (%) of patients with an SAE, sorted by system organ class and then by frequency in DUO-E SoC + D + O then the SoC + D arm for the Maintenance study period. Patients with multiple SAEs were counted once for each system organ class/PT.

For DUO-E, SAEs had an onset date or that worsened on or after the date of first dose of study treatment (overall) or first dose of olaparib/placebo (maintenance phase) up until the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurred first. For the Durvalumab Pan-tumour pool, SAEs had an onset date on or after the date of first dose or pre-treatment AEs that increased in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication (or surgery) or up to and including the date of initiation of the first subsequent therapy (whichever occurred first). For the olaparib 300 mg bd tablet pool, SAEs had an onset date between the date of first dose of continuous treatment and 30 days following the last dose of continuous treatment.

Percentages are based on the total number of patients in the treatment group (N).

Disease progression AEs reported in Study 1108 are not included in this summary.
MedDRA version 25.1.
AE = adverse event; bd = twice daily; COVID-19 = Coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in treatment group; PT = preferred term; SAE = serious adverse event; SoC = standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Deaths

DUO-E Study

Table 86 All deaths in DUO-E and the durvalumab and olaparib pools (Full Analysis Set)

Category	Number (%) of patients				
	DUO-E Overall			Durvalumab Pan-tumour Pool (N = 4045)	Olaparib 300 mg bd Tablet Pool (N = 3556)
	SoC (N = 241)	SoC + D (N = 238)	SoC + D + O (N = 239)		
Total number of deaths	82 (34.0)	65 (27.3)	52 (21.8)	2724 (67.3)	1255 (35.3)
Death related to disease under investigation only [a]	60 (24.9)	51 (21.4)	37 (15.5)	2403 (59.4)	1123 (31.6)
Death related to disease under investigation [a] and an AE with outcome of death [b]	1 (0.4)	0	1 (0.4)	118 (2.9)	10 (0.3)
AE onset prior to subsequent therapy [c, d]	1 (0.4)	0	1 (0.4)	114 (2.8)	NA
AE onset after start of subsequent therapy [e, f]	0	0	0	4 (0.1)	NA
AE with outcome of death only [b]	7 (2.9)	4 (1.7)	7 (2.9)	120 (3.0)	22 (0.6)
AE onset prior to subsequent therapy [c, d]	7 (2.9)	4 (1.7)	4 (1.7)	117 (2.9)	NA
AE onset after start of subsequent therapy [e, f]	0	0	3 (1.3)	3 (0.1)	NA
Death after end of safety follow-up period and not due to disease under investigation [g]	11 (4.6)	8 (3.4)	7 (2.9)	NA	12 (0.3)

Category	Number (%) of patients				
	DUO-E Overall			Durvalumab Pan-tumour Pool (N = 4045)	Olaparib 300 mg bd Tablet Pool (N = 3556)
	SoC (N = 241)	SoC + D (N = 238)	SoC + D + O (N = 239)		
Death with Unknown Reason	1 (0.4)	2 (0.8)	0	44 (1.1)	NA
Other deaths [h]	2 (0.8)	0	0	39 (1.0)	86 (2.4)

a. Death related to disease under investigation was determined by the Investigator.

b. Included AEs with outcome death if they started, or worsened, on or after the date of first dose of any of the investigational study treatments, including durvalumab/placebo or olaparib/placebo, throughout the treatment period and including the safety follow-up period until the later date of 30 days after the last dose of olaparib/placebo and 90 days after last dose of durvalumab/placebo.

c. Included adverse events with an onset date or that worsened on or after the date of first dose of durvalumab/placebo or olaparib/placebo up until the initiation of the first subsequent anti-cancer therapy following last dose of study treatment or until the end of safety follow-up period (latest of either 30 days following last dose of olaparib/ placebo or 90 days following last dose of durvalumab/placebo), whichever occurred first.

d. For Durvalumab Pan-Tumour Pool, AE start date before the initiation of the first subsequent therapy. Durvalumab Pan-Tumour Pool included AEs with an onset date on or after the date of first dose or pre-treatment AEs that increased in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication (or surgery) or up to and including the date of initiation of the first subsequent therapy (whichever occurred first). Disease progression adverse events reported in Study 1108 are not included in this summary.

e. Adverse event start date prior to the end of safety follow-up period (latest of either 30 days following last dose of olaparib/placebo or 90 days following last dose of durvalumab/placebo) and AE start date after the date of initiation of the first subsequent anticancer therapy.

f. For Durvalumab Pan-Tumour Pool, AE start date was after the initiation of the first subsequent therapy.

g. Death not due to disease progression.

h. Patients who died and were not captured in the earlier categories.

Rows are mutually exclusive; patients were only reported in one category.

AE = Adverse event; ITT = Intention-to-treat; N = Total number of patients; NA Not available; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Table 87 Adverse events with outcome of death, by System Organ Class and Preferred Term in SoC, SoC + D and SoC + D + O in DUO-E overall compared with the durvalumab and olaparib pools (Safety Analysis Set)

MedDRA system organ class Preferred term	Number (%) of patients [a]				
	DUO-E Overall			Durvalumab Pan-tumour Pool (N = 4045)	Olaparib 300 mg bd Tablet Pool (N = 3556)
	SoC (N = 236)	SoC + D (N = 235)	SoC + D + O (N = 238)		
Patients with any AE with outcome of death	**8 (3.4)**	**4 (1.7)**	**5 (2.1)**	**231 (5.7)**	**32 (0.9)**
Cardiac disorders					
Cardiac arrest	0	0	2 (0.8)	7 (0.2)	1 (0.0)
Myocardial infarction	0	1 (0.4)	0	7 (0.2)	0
General disorders and administration site conditions					
Death	2 (0.8)	1 (0.4)	0	21 (0.5)	0

MedDRA system organ class Preferred term	Number (%) of patients [a]				
	DUO-E Overall			Durvalumab Pan-tumour Pool (N = 4045)	Olaparib 300 mg bd Tablet Pool (N = 3556)
	SoC (N = 236)	SoC + D (N = 235)	SoC + D + O (N = 238)		
General physical health deterioration	0	1 (0.4)	0	16 (0.4)	0
Multiple organ dysfunction syndrome	0	0	1 (0.4)	0	0
Renal and urinary disorders					
Renal failure	0	1 (0.4)	0	1 (<0.1)	0
Infections and infestations					
COVID-19	1 (0.4)	0	0	0	1 (0.0)
Pneumonia aspiration	1 (0.4)	0	0	2 (<0.1)	1 (0.0)
Sepsis	0	0	1 (0.4)	13 (0.3)	2 (0.1)
Septic shock	1 (0.4)	0	0	6 (0.1)	1 (0.0)
Urosepsis	1 (0.4)	0	0	2 (<0.1)	0
Respiratory, thoracic, and mediastinal disorders					
Acute respiratory failure	0	0	1 (0.4)	7 (0.2)	0
Pulmonary embolism	1 (0.4)	0	0	6 (0.1)	0
Respiratory failure	1 (0.4)	0	0	13 (0.3)	0

a. Number (%) of patients with AEs with outcome of death (including deaths related to disease under investigation and an AE with outcome of death), sorted by decreasing frequency of PT in DUO-E SoC + D + O then SoC + D arm and SoC arm for the Overall study period and then alphabetically for PT. Patients with multiple AEs with outcome of death are counted once for each PT. Patients with events in more than one PT are counted once in each of those PT.

Patients with multiple AEs with outcome of death are counted once for each System organ class/PT.

In DUO-E, deaths included AEs with an onset date or that worsened on or after the date of first dose of study treatment (overall) or first dose of olaparib/placebo (maintenance phase) up until the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurred first. Note that in DUO-E, there were 3 patients in the SoC + D + O arm with an AE with an outcome of death after the start of subsequent therapy but which had a start date prior to the end of the safety follow-up (AEs of cholecystitis acute, cellulitis, and pneumocystis jirovecii pneumonia); these patients are not included in this table.

For the Durvalumab Pan-tumour pool, deaths included AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication (or surgery), or up to and including the date of initiation of the first subsequent therapy (whichever occurred first). Disease progression adverse events reported in Study 1108 are not included in this summary.

For the olaparib 300 mg bd pool, deaths included AEs with an onset date between the date of first dose of continuous treatment and 30 days following the last dose of continuous treatment.

MedDRA version 25.1

AE = adverse event; bd = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in treatment group; PT = preferred term; SoC = standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Between the DCO1 and 120-day safety update DCO dates in the DUO-E study, an additional 48 patients have died, taking the total number of deaths to 247 (94 patients in the SoC arm; 81 patients in the SoC + D arm and 72 patients in in the SoC + D + O arm). The majority of these deaths have been due to disease progression only (43 of the 48 patients who died between the 2 DCO dates).

Laboratory findings

Haematology

Clinically important changes in haematology variables are presented in the below table.

Table 88 Clinically Important Changes from Baseline in Haematology Parameters (Safety Analysis Set)

Parameter	n/N (%) of patients							
	DUO-E Overall						Durvalumab Pan-tumour Pool (N = 4045)	
	SoC (N = 236)		SoC + D (N = 235)		SoC + D + O [a] (N = 238)			
	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4
Haemoglobin (g/L) [a]	83/231 (35.9)	33/231 (14.3)	81/231 (35.1)	39/231 (16.9)	113/238 (47.5)	60/238 (25.2)	209/3868 (5.4)	193/3868 (5.0)
High	0	0	0	0	0	0	0	0
Low	83/231 (35.9)	33/231 (14.3)	81/231 (35.1)	39/231 (16.9)	113/238 (47.5)	60/238 (25.2)	209/3868 (5.4)	193/3868 (5.0)
Leukocytes (10^9/L)	77/231 (33.3)	36/231 (15.6)	81/231 (35.1)	35/231 (15.2)	105/238 (44.1)	49/238 (20.6)	75/3868 (1.9)	22/3868 (0.6)
Platelets (10^9/L)	25/231 (10.8)	13/231 (5.6)	38/231 (16.5)	20/231 (8.7)	40/238 (16.8)	16/238 (6.7)	64/3865 (1.7)	44/3865 (1.1)
Neutrophils (10^9/L)	86/219 (39.3)	51/219 (23.3)	80/209 (38.3)	47/209 (22.5)	111/224 (49.6)	63/224 (28.1)	119/3833 (3.1)	37/3833 (1.0)
Lymphocytes (10^9/L)	43/208 (20.7)	33/208 (15.9)	60/202 (29.7)	23/202 (11.4)	85/215 (39.5)	52/215 (24.2)	748/3828 (19.5)	507/3828 (13.2)
High	0	0	6/202 (3.0)	0	3/215 (1.4)	1/215 (0.5)	11/3828 (0.3)	1/3828 (< 0.1)
Low	43/208 (20.7)	33/208 (15.9)	54/202 (26.7)	23/202 (11.4)	84/215 (39.1)	52/215 (24.2)	738/3828 (19.3)	506/3828 (13.2)

[a] Version 4.03 of the CTCAE grading criteria only assessed Haemoglobin in the low direction, in version 5.0 Haemoglobin is a bi-directional laboratory parameter.

Percentages are based on the total number of patients in the treatment group (N).

Derived from laboratory assessments from the start of treatment and up to and including 90 days following the date of last dose of study medication (or surgery) or up to and including the date of initiation of the first subsequent therapy (whichever occurred first).

Patient's worst (highest CTCAE grade) changes from baseline were used.

For the durvalumab Pan-tumour pool, the worst CTCAE grade is taken across the full duration of the AE regardless of the timing of treatment. For DUO-E, the worst CTCAE grade is taken from the AE onset date until the first subsequent anti-cancer therapy following discontinuation of treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurred first.

All studies used CTCAE version 4.03 except for DUO-E which used version 5.0.

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; N = number of patients; n = number of patients with an event; SoC = standard of care; SoC + D = durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Olaparib 300 mg bd Tablet Pool

Frequency of adverse laboratory findings associated with olaparib treatment in the tablet pool and overall are presented in the below table.

Table 89 Frequency of Adverse Laboratory Findings Associated with Olaparib Treatment in the Tablet Pool and Overall

	Olaparib 300 mg bd Tablet Pool (N = 3556)	**Overall (tablet and capsule) (N = 4499)**
Parameter	**≥ 2 CTCAE grade changes n/N (%)**	**≥ 2 CTCAE grade changes n/N (%)**
Haemoglobin [a]	722/3520 (20.5)	918/4453 (20.6)
Neutrophils [a]	595/3213 (18.5)	716/4138 (17.3)
Platelets [a]	141/3518 (4.0)	195/4451 (4.4)
Lymphocytes [a]	882/3505 (25.2)	1094/4257 (25.7)

	Olaparib 300 mg bd Tablet Pool (N = 3556)	Overall (tablet and capsule) (N = 4499)
Parameter	**≥ 2 CTCAE grade changes n/N (%)**	**≥ 2 CTCAE grade changes n/N (%)**
Leukocytes [a]	684/3506 (19.5)	836/4439 (18.8)
Creatinine [a]	462/3514 (13.1)	589/4446 (13.2)
Erythrocyte MCV [b]	1695/3223 (52.6)	2050/4083 (50.2)

a. Represents patients who had any 2 Grade change (ie, 0 to 2 or higher, 1 to 3 or higher, or 2 to 4).

b. Represents patients who had a change in MCV from low or normal at baseline to > 1 x ULN.

Only includes patients with a baseline value and at least one value on continuous treatment, and this is used as the denominator for percentage calculations.
Baseline is defined as the last result obtained prior to first dose of olaparib.
Derived from laboratory assessments between the start of continuous treatment and 30 days following the date of last dose of continuous treatment.
CTCAE version 5.0.
Only low grading is considered for haemoglobin, leukocytes, and lymphocytes.
bd = twice daily; CTCAE = Common Terminology Criteria for Adverse Events; MCV = mean corpuscular volume, N = total number of patients; n = number of patients with an event; ULN = upper limit of normal.

Clinical chemistry

Table 90 Maximum Overall CTCAE Grade During Treatment for Key Clinical Chemistry Parameters (Safety Analysis Set)

	Maximum overall CTCAE grade during treatment n (%) [a]				
Parameter	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
ALP (U/L) (High)					
SoC (N = 236)	192 (83.5)	34 (14.8)	3 (1.3)	1 (0.4)	0
SoC + D (N = 235)	169 (73.2)	52 (22.5)	9 (3.9)	1 (0.4)	0
SoC + D + O (N = 238)	186 (78.2)	46 (19.3)	5 (2.1)	1 (0.4)	0
ALT (U/L) (High)					
SoC (N = 236)	169 (73.5)	51 (22.2)	7 (3.0)	3 (1.3)	0
SoC + D (N = 235)	147 (63.6)	64 (27.7)	12 (5.2)	7 (3.0)	1 (0.4)
SoC + D + O (N = 238)	145 (60.9)	75 (31.5)	9 (3.8)	7 (2.9)	2 (0.8)
AST (U/L) (High)					
SoC (N = 236)	174 (75.7)	50 (21.7)	5 (2.2)	1 (0.4)	0
SoC + D (N = 235)	158 (68.4)	63 (27.3)	3 (1.3)	6 (2.6)	1 (0.4)
SoC + D + O (N = 238)	168 (70.6)	56 (23.5)	6 (2.5)	6 (2.5)	2 (0.8)
Bilirubin (µmol/L) (High)					
SoC (N = 236)	216 (93.9)	10 (4.3)	4 (1.7)	0	0
SoC + D (N = 235)	216 (93.5)	8 (3.5)	6 (2.6)	1 (0.4)	0
SoC + D + O (N = 238)	214 (89.9)	17 (7.1)	5 (2.1)	1 (0.4)	1 (0.4)
Creatinine (µmol/L) (High)					
SoC (N = 236)	189 (82.2)	7 (3.0)	30 (13.0)	4 (1.7)	0
SoC + D (N = 235)	182 (78.8)	17 (7.4)	31 (13.4)	1 (0.4)	0
SoC + D + O (N = 238)	160 (67.2)	17 (7.1)	57 (23.9)	4 (1.7)	0

[a] Derived from laboratory assessments between the start of treatment and the later date of 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo or until the initiation of the first subsequent therapy following discontinuation of treatment (whichever occurred first).

CTCAE Version 5.0.

ALP = Alkaline phosphatase; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; N = Total number of patients; n = Number of patients; SoC = Standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance; U = Unit.

Durvalumab Pan tumour Pool

Table 91 Clinically Important Changes from Baseline in Clinical Chemistry Parameters (Safety Analysis Set)

Parameter	n/N (%) of patients							
	DUO-E Overall						Durvalumab Pan-tumour Pool (N = 4045)	
	SoC (N = 236)		SoC + D (N = 235)		SoC + D + O (N = 238)			
	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4
Alanine aminotransferase (U/L)	9/230 (3.9)	3/230 (1.3)	18/231 (7.8)	8/231 (3.5)	18/238 (7.6)	9/238 (3.8)	224/3860 (5.8)	145/3860 (3.8)
Aspartate aminotransferase (U/L)	6/230 (2.6)	1/230 (0.4)	9/231 (3.9)	7/231 (3.0)	14/238 (5.9)	8/238 (3.4)	259/3850 (6.7)	235/3850 (6.1)
Alkaline phosphatase (U/L)	2/230 (0.9)	1/230 (0.4)	7/231 (3.0)	1/231 (0.4)	4/238 (1.7)	1/238 (0.4)	192/3840 (5.0)	168/3840 (4.4)
Albumin (g/L)	14/230 (6.1)	1/230 (0.4)	15/230 (6.5)	2/230 (0.9)	15/237 (6.3)	6/237 (2.5)	475/3821 (12.4)	60/3821 (1.6)
Total bilirubin (µmol/L)	2/230 (0.9)	0	7/231 (3.0)	1/231 (0.4)	7/238 (2.9)	2/238 (0.8)	202/3853 (5.2)	103/3853 (2.7)
Corrected calcium (mmol/L)	0	0	0	0	0	0	196/3696 (5.3)	111/3696 (3.0)
High	0	0	0	0	0	0	144/3696 (3.9)	91/3696 (2.5)
Low	0	0	0	0	0	0	54/3696 (1.5)	20/3696 (0.5)
Sodium (mmol/L)	11/230 (4.8)	12/230 (5.2)	14/231 (6.1)	13/231 (5.6)	9/238 (3.8)	9/238 (3.8)	328/3861 (8.5)	325/3861 (8.4)
High	0	1/230 (0.4)	1/231 (0.4)	0	1/238 (0.4)	0	15/3861 (0.4)	6/3861 (0.2)
Low	11/230 (4.8)	11/230 (4.8)	13/231 (5.6)	13/231 (5.6)	8/238 (3.4)	9/238 (3.8)	313/3861 (8.1)	319/3861 (8.3)
Potassium (mmol/L)	10/230 (4.3)	7/230 (3.0)	13/231 (5.6)	9/231 (3.9)	19/238 (8.0)	12/238 (5.0)	295/3853 (7.7)	157/3853 (4.1)
High	6/230 (2.6)	3/230 (1.3)	4/231 (1.7)	0	8/238 (3.4)	0	222/3853 (5.8)	80/3853 (2.1)
Low	4/230 (1.7)	4/230 (1.7)	9/231 (3.9)	9/231 (3.9)	12/238 (5.0)	12/238 (5.0)	77/3853 (2.0)	79/3853 (2.1)
Magnesium (mmol/L)	22/215 (10.2)	6/215 (2.8)	30/215 (14.0)	12/215 (5.6)	32/221 (14.5)	6/221 (2.7)	58/3297 (1.8)	54/3297 (1.6)
High	2/215 (0.9)	2/215 (0.9)	5/215 (2.3)	5/215 (2.3)	2/221 (0.9)	2/221 (0.9)	41/3297 (1.2)	41/3297 (1.2)

Parameter	n/N (%) of patients							
	DUO-E Overall						Durvalumab Pan-tumour Pool (N = 4045)	
	SoC (N = 236)		SoC + D (N = 235)		SoC + D + O (N = 238)			
	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4
Low	21/215 (9.8)	4/215 (1.9)	26/215 (12.1)	7/215 (3.3)	30/221 (13.6)	4/221 (1.8)	18/3297 (0.5)	14/3297 (0.4)
Glucose (mmol/L) [a]	0	0	0	0	1/237 (0.4)	0	546/3826 (14.3)	227/3826 (5.9)
High	0	0	0	0	0	0	500/3826 (13.1)	209/3826 (5.5)
Low	0	0	0	0	1/237 (0.4)	0	57/3826 (1.5)	19/3826 (0.5)
Creatinine (µmol/L)	34/230 (14.8)	4/230 (1.7)	32/231 (13.9)	1/231 (0.4)	60/238 (25.2)	4/238 (1.7)	154/3796 (4.1)	33/3796 (0.9)
Gamma Glutamyl Transferase	10/205 (4.9)	6/205 (2.9)	23/211 (10.9)	10/211 (4.7)	22/216 (10.2)	9/216 (4.2)	187/1765 (10.6)	170/1765 (9.6)
Lipase (U/L)	18/211 (8.5)	9/211 (4.3)	22/211 (10.4)	12/211 (5.7)	16/217 (7.4)	8/217 (3.7)	130/1225 (10.6)	103/1225 (8.4)
Amylase (U/L)	3/219 (1.4)	2/219 (0.9)	14/229 (6.1)	1/229 (0.4)	8/231 (3.5)	3/231 (1.3)	83/1225 (6.8)	66/1225 (5.4)

[a.] Version 4.03 of the CTCAE grading criteria assessed Glucose bi-directionally, in version 5.0 Glucose is only assessed in the low direction.

Percentages are based on the total number of patients in the treatment group (N).
Derived from laboratory assessments from the start of treatment and up to and including 90 days following the date of last dose of study medication (or surgery) or up to and including the date of initiation of the first subsequent therapy (whichever occurred first).
Patient's worst (highest CTCAE grade; highest CTC grade in the direction of high corrected calcium) changes from baseline were used.

For the durvalumab Pan-tumour pool, the worst CTCAE grade was taken across the full duration of the AE regardless of the timing of treatment. For DUO-E, the worst CTCAE grade was taken from the AE onset date until the first subsequent anti-cancer therapy following discontinuation or treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurred first.
All studies used CTCAE version 4.03 except for DUO-E which used version 5.0.

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; N = number of patients; n = number of patients with an event; SoC = standard of care; SoC + D = durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Olaparib 300 mg bd Tablet Pool

Shifts to CTCAE Grade 3 or 4 occurred in a similar proportion (≤ 5% difference) of patients in the SoC + D and SoC + D + O arms of the DUO-E study, compared with the olaparib 300 mg bd Tablet Pool.

In DUO-E overall, 4 of 230 patients (1.7%) in the SoC arm had shifts to CTCAE Grade 3 or 4 in creatinine, compared with one of 231 patients (0.4%) in the SoC + D arm and 4 of 238 patients (1.7%) in the SoC + D + O arm. In the olaparib 300 mg bd Tablet Pool, shifts to CTCAE Grade 3 or 4 occurred in 18 of 3514 patients (0.5%). Although the proportion of patients with shifts in creatinine to

CTCAE Grade 3 or 4 was higher in the SoC + D + O arm compared with the olaparib 300 mg bd Tablet Pool, the proportion in the SoC + D + O arm of DUO-E was low, and the same as the proportion in the SoC arm of DUO-E (1.7%).

The incidence of CTCAE Grade 3 or 4 clinical chemistry parameter values was low (6% or fewer patients with Grade 3 and 1% or fewer with Grade 4 during treatment).

Hepatic function abnormalities

In the study overall, one patient (0.4%) in the SoC + D treatment arm, 4 patients (1.7%) in the SoC + D + O treatment arm, and no patients in the SoC treatment arm met the Hy's Law laboratory criteria (i.e. AST or ALT $\geq 3 \times$ ULN range concurrent with or preceding a bilirubin increase of $\geq 2 \times$ ULN). For one of these 5 patients, DILI could not be ruled out based on confounding factors: One patient in the SoC + D + O arm had an SAE of DILI (coincident with the concurrent AST/ALT and bilirubin elevation) on Day 21 of the study (Chemotherapy Phase); durvalumab treatment was interrupted; no olaparib received. For this patient, concomitant paclitaxel and high dose vitamin C could have contributed to the development of drug-induced liver injury (data on file). The remaining 4 patients who met the Hy's Law laboratory criteria all had alternative explanations for elevations of ALT and bilirubin (bile duct stone causing obstruction; Hepatitis C; immune-mediated cholangitis; and sepsis, pneumonia and COVID-19).

Drug-induced Liver Injury

Two patients had events of drug-induced liver injury during the Chemotherapy Phase; one patient in the SoC + D arm had a CTCAE Grade 3 SAE and one patient in the SoC + D + O arm had a CTCAE Grade 2 SAE. The patient in the SoC + D + O arm who had the event of drug-induced liver injury also met the criteria for potential Hy's Law. One event occurred within the safety follow-up period and one event occurred on-treatment. One of the patients recovered/resolved, the other patient had an AE that was not recovered/not resolved at the time of DCO. Drug-induced liver injury is a PT within the durvalumab AESI grouped term of hepatic events.

DUO-E vs Durvalumab Pan tumour Pool

A low proportion of patients in DUO-E (one patient [0.4%] in the SoC + D arm and 4 patients [1.7%] SoC + D + O arm) and the durvalumab Pan-tumour Pool (131 patients [3.2%]) met the Hy's Law laboratory criteria.

DUO-E vs Olaparib 300 mg bd Pool

The proportion of patients with maximum on treatment combined AST or ALT $\geq 3 \times$ ULN was low and similar in the SoC + D + O arm of DUO-E, and the olaparib 300 mg bd pool.

No patients in the olaparib 300 mg bd pool met the criteria for Hy's law. In total 31 patients had ALT/AST and bilirubin elevations in the olaparib 300 mg bd pool. Among these patients, were 6 participants of the study of patients with normal hepatic function or hepatic impairment (1 patient was in the normal hepatic function group, 2 patients were in the mild impairment group, and 3 patients were in the moderate impairment group). In addition, 25 of these patients had elevated ALP (> 2×ULN). A detailed evaluation of medical history, progression of disease, temporal association for the 25 patients with elevated ALP and other factors showed that all of these patients had alternative explanations for elevations of ALT and bilirubin, generally suggestive of obstructive causes, or cancer disease progression, including disease progression in the liver.

Creatinine clearance

Patients were allowed into the DUO-E study with creatinine clearance CrCl of > 51 mL/min or greater as determined by Cockcroft-Gault formula. This CrCl rate had to be demonstrated again, within 3 days prior to dosing, in order to start olaparib/placebo. Few patients developed severe renal impairment during the study. Kidney failure, defined as glomerular filtration rate of less than 15 mL/min, was seen in one patient in the SoC treatment arm during the study. Severe impairment, defined as glomerular filtration rate at least 15 mL/min to less than 30 mL/min, was seen in 7 patients (3.0%) in the SoC arm, 2 patients (0.9%) in SoC + D arm, and 7 patients (2.9%) in the SoC + D + O arm. Adverse events of blood creatinine increased, dysuria, and nephritis are ADRs for durvalumab, which could contribute to the decreased glomerular filtration rate.

Thyroid function

Hypothyroidism and hyperthyroidism are ADRs for durvalumab. Elevated TSH values greater than the ULN and low TSH values less than the LLN were observed in a higher percentage of patients in the SoC + D and SoC + D + O arms compared with the SoC arm; however, the percentage of patients with elevated TSH values greater than the ULN and low TSH values less than the LLN was similar for the SoC + D and SoC + D + O arms.

Table 92 Abnormal On-Treatment Thyroid Tests (Safety Analysis Set)

	Number (%) of patients						
	DUO-E Overall			DUO-E Maintenance Phase			Durvalumab Pan-tumour Pool (N = 4045)
	SoC (N = 236)	SoC + D (N = 235)	SoC + D + O (N = 238)	SoC (N = 169)	SoC + D (N = 183)	SoC + D + O (N = 192)	
On-treatment elevated TSH > ULN	**44 (18.6)**	**91 (38.7)**	**88 (37.0)**	**31 (18.3)**	**82 (44.8)**	**74 (38.5)**	**1269 (31.4)**
On-treatment elevated TSH > ULN with TSH ≤ ULN at baseline *	**33**	**64**	**68**	**23**	**60**	**59**	**780**
With at least one T3 free/T4 free < LLN [a]	8 (24.2)	32 (50.0)	35 (51.5)	5 (21.7)	30 (50.0)	30 (50.8)	456 (58.5)
With all other T3 free/T4 free ≥ LLN [a]	18 (54.5)	30 (46.9)	32 (47.1)	14 (60.9)	28 (46.7)	28 (47.5)	270 (34.6)
With all T3 free/T4 free missing [a]	7 (21.2)	2 (3.1)	1 (1.5)	4 (17.4)	2 (3.3)	1 (1.7)	54 (6.9)
On-treatment low TSH < LLN	**28 (11.9)**	**62 (26.4)**	**58 (24.4)**	**23 (13.6)**	**55 (30.1)**	**46 (24.0)**	**880 (21.8)**
On-treatment low TSH < LLN with TSH ≥ LLN at baseline *	**21**	**57**	**49**	**17**	**51**	**38**	**709**
With at least one T3 free/T4 free > ULN [a]	7 (33.3)	31 (54.4)	29 (59.2)	6 (35.3)	28 (54.9)	24 (63.2)	310 (43.7)
With all other T3 free/T4 free ≤ ULN [a]	12 (57.1)	23 (40.4)	18 (36.7)	9 (52.9)	20 (39.2)	12 (31.6)	348 (49.1)
With all T3 free/T4 free missing [a]	2 (9.5)	3 (5.3)	2 (4.1)	2 (11.8)	3 (5.9)	2 (5.3)	51 (7.2)
Number of subjects with at least one baseline and post-baseline TSH result *	**221**	**225**	**232**	**168**	**182**	**190**	**3679**
On-treatment elevated TSH > ULN and above baseline [a]	40 (18.1)	84 (37.3)	84 (36.2)	28 (16.7)	79 (43.4)	71 (37.4)	1108 (30.1)
On-treatment decreased TSH < LLN and below baseline [a]	25 (11.3)	58 (25.8)	52 (22.4)	21 (12.5)	51 (28.0)	41 (21.6)	816 (22.2)

[a] Percentage is based on number of patients in the main category above denoted with a *.

Baseline is defined as the last result obtained prior to the start of study treatment.

Derived from laboratory assessments from the start of treatment up to and including 90 days following the date of last dose of study medication (or surgery) or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

LLN = lower limit of normal; N = number of patients; SoC = standard of care; SoC + D = durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; ULN = upper limit of normal.

Vital signs, physical findings, and other observations related to safety

Vital Signs

Summary statistics and change from baseline over time for blood pressure, heart rate, respiratory rate, body temperature, and body weight values showed no notable trends for the SoC, SoC + D or SoC + D + O arms of DUO-E. In the overall phase of DUO-E, there were more AEs of hypotension in the SoC + D + O arm (5.0%) vs the SoC arm (0.8%), although during the maintenance phase the frequency was similar in these 2 arms. The majority of hypotension events were low grade and non-serious.

Electrocardiograms

Electrocardiogram data did not raise any safety concerns in any treatment arm in DUO-E.

Safety in special populations

Intrinsic Factors

Durvalumab

There were no clinically meaningful differences in the safety profile of durvalumab in DUO-E for the SoC + D or SoC + D + O arm, in DUO-E vs durvalumab Pan tumour Pool, with respect to: age or race. As DUO-E only recruited females, the comparison of sex is only applicable in the durvalumab Pan tumour Pool.

Olaparib

In order to have sufficient numbers of patients to perform an assessment of safety in special groups and populations, the olaparib 300 mg bd Tablet Pool has been used as the main data source for olaparib in this section rather than DUO-E. The pooled dataset includes patients with a range of solid tumours, including breast cancer. Intrinsic factors include the effect of sex, age, race, and renal impairment. Sex and renal impairment at baseline was only measured in the olaparib 300 mg bd Tablet Pool and no clinically meaningful differences were observed. It is considered that no dose adjustment is required on the basis of sex, age, and race.

The safety profile of the SoC + D + O arm in the DUO-E study appeared to be consistent with the safety profiles of each of durvalumab and olaparib; thus suggesting that the intrinsic factor effects in DUO-E were comparable with those for the olaparib 300 mg bd Tablet Pool.

Effect of Age

DUO E study

Table 93 DUO-E Study: Summary of Adverse Events by Age (Safety Analysis Set); DCO: 18 October 2023

	Number of patients (%)											
	Age <65			Age 65-74			Age 75-84			Age 85+		
MedDRA Terms	SoC (N = 122)	SoC+D (N = 120)	SoC+D +O (N = 134)	SoC (N = 94)	SoC+D (N = 87)	SoC+D +O (N = 85)	SoC (N = 19)	SoC+D (N = 28)	SoC+D +O (N = 18)	SoC (N = 1)	SoC+D (N = 0)	SoC+D +O (N = 1)
Total AEs	122 (100)	118 (98.3)	133 (99.3)	94 (100)	86 (98.9)	85 (100)	19 (100)	28 (100)	18 (100)	1 (100)	0	1 (100)

MedDRA Terms	Number of patients (%)											
	Age <65			Age 65-74			Age 75-84			Age 85+		
	SoC (N = 122)	SoC+D (N = 120)	SoC+D +O (N = 134)	SoC (N = 94)	SoC+D (N = 87)	SoC+D +O (N = 85)	SoC (N = 19)	SoC+D (N = 28)	SoC+D +O (N = 18)	SoC (N = 1)	SoC+D (N = 0)	SoC+D +O (N = 1)
Serious AEs – Total	34 (27.9)	36 (30.0)	46 (34.3)	35 (37.2)	30 (34.5)	34 (40.0)	5 (26.3)	13 (46.4)	6 (33.3)	0	0	0
Fatal	2 (1.6)	0	1 (0.7)	5 (5.3)	1 (1.1)	2 (2.4)	1 (5.3)	3 (10.7)	2 (11.1)	0	0	0
Hospitalization/prolong existing hospitalization	33 (27.0)	36 (30.0)	41 (30.6)	31 (33.0)	26 (29.9)	30 (35.3)	5 (26.3)	11 (39.3)	5 (27.8)	0	0	0
Life-threatening	5 (4.1)	0	9 (6.7)	7 (7.4)	1 (1.1)	7 (8.2)	0	2 (7.1)	2 (11.1)	0	0	0
Disability/incapacity	3 (2.5)	0	1 (0.7)	2 (2.1)	2 (2.3)	1 (1.2)	0	0	2 (11.1)	0	0	0
Other (medically significant)	8 (6.6)	6 (5.0)	18 (13.4)	11 (11.7)	10 (11.5)	15 (17.6)	1 (5.3)	4 (14.3)	5 (27.8)	0	0	0
AE leading to discontinuation of any study treatment	19 (15.6)	25 (20.8)	26 (19.4)	20 (21.3)	16 (18.4)	27 (31.8)	4 (21.1)	6 (21.4)	7 (38.9)	0	0	1 (100)
Psychiatric disorders [a]	18 (14.8)	24 (20.0)	23 (17.2)	25 (26.6)	14 (16.1)	17 (20.0)	5 (26.3)	4 (14.3)	8 (44.4)	0	0	0
Nervous system disorders [a]	88 (72.1)	82 (68.3)	92 (68.7)	72 (76.6)	61 (70.1)	70 (82.4)	13 (68.4)	19 (67.9)	16 (88.9)	1 (100)	0	1 (100)
Accidents and injuries [b]	10 (8.2)	11 (9.2)	17 (12.7)	17 (18.1)	15 (17.2)	17 (20.0)	2 (10.5)	5 (17.9)	2 (11.1)	0	0	0
Cardiac disorders [a]	9 (7.4)	9 (7.5)	10 (7.5)	7 (7.4)	5 (5.7)	7 (8.2)	2 (10.5)	4 (14.3)	3 (16.7)	0	0	0
Vascular disorders [a]	23 (18.9)	21 (17.5)	30 (22.4)	19 (20.2)	19 (21.8)	20 (23.5)	2 (10.5)	6 (21.4)	3 (16.7)	0	0	0
Cerebrovascular disorders [c]	0	0	0	0	0	0	0	0	0	0	0	0
Infections and infestations [a]	63 (51.6)	61 (50.8)	80 (59.7)	47 (50.0)	40 (46.0)	46 (54.1)	5 (26.3)	16 (57.1)	12 (66.7)	0	0	1 (100)
Anticholinergic syndrome [c]	0	0	0	0	0	0	0	0	0	0	0	0
Quality of life decreased [c]	0	0	0	0	0	0	0	0	0	0	0	0

MedDRA Terms	Number of patients (%)											
	Age <65			Age 65-74			Age 75-84			Age 85+		
	SoC (N = 122)	SoC+D (N = 120)	SoC+D +O (N = 134)	SoC (N = 94)	SoC+D (N = 87)	SoC+D +O (N = 85)	SoC (N = 19)	SoC+D (N = 28)	SoC+D +O (N = 18)	SoC (N = 1)	SoC+D (N = 0)	SoC+D +O (N = 1)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures [d]	19 (15.6)	22 (18.3)	24 (17.9)	20 (21.3)	21 (24.1)	25 (29.4)	6 (31.6)	3 (10.7)	8 (44.4)	0	0	0

a. Summary of system organ class
b. Summary of standard medical query list of preferred terms for accidents and injuries
c. Summary of preferred term
d. Summary of the following: Orthostatic Hypotension [PT], Fall [PT], Loss of Consciousness [PT], Syncope [PT], Dizziness [PT], Ataxia [PT], Fractures [high level group term] and Dizziness postural [PT]

Table presents number (%) of patients with adverse events in each category. Patients with multiple adverse events in the same category are counted only once in that category. Patients with adverse events in more than one category are counted once in each of those categories.

Includes adverse events with an onset date or that worsen on or after the date of first dose of study treatment up until the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurred first.

MedDRA version 25.1.

Almost all patients, in each age group (< 65, ≥ 65 to < 75, and ≥ 75 years) experienced an AE. There were comparatively few patients in the ≥ 75 years age group so these results should be interpreted with caution.

Overall the safety profiles across the < 65 years and 65 to 74 years age groups were generally comparable, however, there were differences of at least 10% frequency between the < 65 years and 65 to 74 year categories in the following treatment arms:

- SoC: Psychiatric disorders
- SoC + D +O: AEs leading to discontinuation of any study treatment, Nervous system disorders and Sum of postural hypotension, falls, blackouts, syncope, dizziness, ataxia and fracture.

Overall, there were no safety concerns identified following review of the adverse events reported across the different age categories.

Effect of Race

DUO E study

Overall, no notable differences in AE categories were observed in the SoC + D + O or SoC + D arms vs the SoC arm by race.

Almost all patients, in each race group (White, Black or African American, Asian, Other, and Not Reported) experienced an AE. The assessment of safety in the Black or African American, and Other races groups is limited due to the small number of patients in these categories (Black or African American: N = 9 SoC; N = 11 SoC + D; N = 14 SoC + O + D. Other races: N = 12 SoC; N = 14 SoC + D; N = 19 SoC + O + D).

In the DUO-E study overall, compared with the SoC and SoC + D + O arms where a similar proportion of SAEs occurred in each race group, in the SoC + D arm, a higher proportion of Black or African American patients (54.5%) experienced events compared with the White (26.9%), Asian (35.2%), and

Other (28.6%) race groups. However, due to the small number of patients in the Black or African American race group, these results should be interpreted with caution.

Effect of Renal Impairment

DUO-E study

In DUO-E, the eligibility criteria required that patients must have CrCl of ≥ 51 mL/minute within 3 days prior to dosing in order to receive olaparib/placebo (estimated using either the Cockcroft-Gault equation, a 24-hour urine test or another validated test as per local practice).

Extrinsic Factors

The safety profile of SoC, durvalumab, and olaparib was assessed in relation to the following extrinsic factors: geographic region (North America, RoW) and baseline Eastern Cooperative Oncology Group (ECOG/WHO) performance status (0; ≥ 1).

Effect of Geographic Region

For DUO-E, there were few differences in the AE categories reported in durvalumab-treated patients by geographic region.

Table 94 DUO-E (Overall Study Phase) and Durvalumab Pan-tumour Pool: Number (%) of Patients Reporting at Least One AE in Any Category by Geographical Region

AE category	Number (%) of patients [a]			
	DUO-E (Overall)			Durvalumab Pan-tumour Pool (N1 = 1014) (N2 = 3031)
	SoC (N1 = 68) (N2 = 168)	SoC + D (N1 = 66) (N2 = 169)	SoC + D + O [b] (N1 = 65) (N2 = 173)	
Any AE				
Asia	68 (100)	66 (100)	65 (100)	932 (91.9)
Rest of the world	168 (100)	166 (98.2)	172 (99.4)	2894 (95.5)
Any AE of CTCAE Grade 3 or 4 [c]				
Asia	46 (67.6)	36 (54.5)	46 (70.8)	366 (36.1)
Rest of the world	82 (48.8)	90 (53.3)	114 (65.9)	1389 (45.8)
Any AE with outcome = death				
Asia	0	1 (1.5)	1 (1.5)	30 (3.0)
Rest of the world	8 (4.8)	3 (1.8)	4 (2.3)	201 (6.6)
Any SAE (including events with outcome = death) [d]				
Asia	22 (32.4)	25 (37.9)	25 (38.5)	298 (29.4)
Rest of the world	51 (30.4)	48 (28.4)	60 (34.7)	1150 (37.9)
Any AE leading to discontinuation of any study treatment				
Asia	5 (7.4)	8 (12.1)	10 (15.4)	86 (8.5)
Rest of the world	16 (9.5)	20 (11.8)	22 (12.7)	311 (10.3)
Any AE leading to discontinuation of durvalumab/placebo				
Asia	5 (7.4)	7 (10.6)	6 (9.2)	86 (8.5)
Rest of the world	14 (8.3)	19 (11.2)	16 (9.2)	311 (10.3)

a. Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.

b. Olaparib was only administered during the Maintenance phase of DUO-E.

c. All CTCAE grades per patient/treatment period, not just the maximum, were considered when identifying whether there was a grade 3 or 4.

d. Seriousness, as assessed by the investigator. An AE with missing seriousness was considered serious.

For DUO-E, included AEs with an onset date or that worsened on or after the date of first dose of study treatment (overall) or first dose of olaparib/placebo (maintenance phase) up until the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurred first.

Durvalumab Pan-Tumour Pool included AEs with an onset date on or after the date of first dose or pre-treatment AEs that increased in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication (or surgery) or up to and including the date of initiation of the first subsequent therapy (whichever occurred first). Disease progression AEs reported in Study 1108 were not included in this summary.

MedDRA version 25.1.

All studies used CTCAE version 4.03 except for DUO-E which used version 5.0. For DUO-E, the worst CTCAE grade was taken from the AE onset date until the first subsequent anti-cancer therapy following discontinuation of treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurred first. For Durvalumab Pan-Tumour Pool, the worst CTCAE grade is taken across the full duration of the AE regardless of the timing of treatment.

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of patients; N1 = Total number of Asia patients, N2 = Total number of Rest of the world patients; SAE = serious adverse event; SoC = standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Effect of ECOG Performance Status

In DUO-E study no notable differences in AE categories were observed in SoC + D + O vs SoC in the proportion of patients with baseline ECOG score of 1 compared to patients with baseline ECOG score of 0. Serious AEs and AEs with outcome of death were reported in a similar percentage of patients with ECOG status ≥ 1 compared with ECOG status of 0.

DUO-E Results by PD-L1 status

Approximately two-thirds of the 709 patients in the SAS were PD-L1 positive (478 patients were PD-L1 positive; 214 patients were PD-L1 negative; and 17 patients were PD-L1 status unknown). The results by PD-L1 status were based on DCO 12 April 2023 and should be interpreted with caution due to the *post-hoc* nature of the analysis.

Table 95 Treatment Emergent AEs by Category and PD-L1 Status – Patient Level – DUO-E Overall (Safety Analysis Set); DCO1: 12 April 2023

AE Category [a]	Number (%) of patients					
	PD-L1 positive			PD-L1 negative		
	SoC (N = 159)	SoC + D (N = 169)	SoC +D + O (N = 150)	SoC (N = 74)	SoC + D (N = 59)	SoC +D + O (N = 81)
Any AE	159 (100.0)	167 (98.8)	150 (100.0)	74 (100.0)	58 (98.3)	80 (98.8)
Any AE of CTCAE Grade ≥ 3	89 (56.0)	89 (52.7)	100 (66.7)	42 (56.8)	35 (59.3)	55 (67.9)
Any AE with maximum CTCAE Grade 3 or 4 [b]	84 (52.8)	86 (50.9)	96 (64.0)	40 (54.1)	34 (57.6)	54 (66.7)
Any AE with outcome of death	5 (3.1)	3 (1.8)	4 (2.7)	3 (4.1)	1 (1.7)	1 (1.2)
Any SAE (including events with outcome of death)	47 (29.6)	55 (32.5)	52 (34.7)	25 (33.8)	17 (28.8)	29 (35.8)
Any AE leading to discontinuation of durvalumab/placebo [c]	14 (8.8)	19 (11.2)	14 (9.3)	5 (6.8)	7 (11.9)	7 (8.6)
Any AE leading to discontinuation of olaparib/placebo [c]	3 (1.9)	10 (5.9)	17 (11.3)	2 (2.7)	1 (1.7)	4 (4.9)
Any AE leading to discontinuation of SoC [c]	22 (13.8)	22 (13.0)	18 (12.0)	10 (13.5)	9 (15.3)	12 (14.8)
Any AE leading to dose interruption of durvalumab/placebo [d]	68 (42.8)	78 (46.2)	94 (62.7)	21 (28.4)	29 (49.2)	33 (40.7)
Any AE leading to dose interruption of olaparib/placebo [d]	16 (10.1)	25 (14.8)	73 (48.7)	15 (20.3)	10 (16.9)	32 (39.5)
Any AE leading to dose interruption of SoC [d]	57 (35.8)	62 (36.7)	58 (38.7)	24 (32.4)	20 (33.9)	25 (30.9)

a. Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.
b. Maximum CTCAE Grade of 3 or 4 was derived at patient level, and excluded patients who experienced Grade 3 or 4 events with a Grade 5 event.
c. AEs on the AE CRF form with Action taken = 'Drug permanently discontinued'. For SoC, AEs were counted as leading to discontinuation of treatment if action taken was equal to 'Drug permanently discontinued' for at least one agent.
d. AEs on the AE CRF form with Action taken = 'Drug interrupted'. For durvalumab/placebo, this included dose interruption during infusion as indicated in the exposure CRF form as well as dose that skipped or delayed. For SoC, AEs were counted as leading to dose interruption if action taken was equal to 'Drug interrupted' for at least one agent.

Included AEs with an onset date or that worsened on or after the date of first dose of study treatment (overall) or first dose of olaparib/placebo (maintenance phase) up until the initiation of the first subsequent anticancer therapy following discontinuation of study treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurred first.

Table 96 Treatment Emergent AEs by Category and PD-L1 Status – Patient Level – DUO-E Maintenance Phase (Safety Analysis Set); DCO1: 12 April 2023

AE Category [a]	Number (%) of patients					
	PD-L1 positive			PD-L1 negative		
	SoC (N = 110)	SoC + D (N = 137)	SoC + D + O (N = 125)	SoC (N = 58)	SoC + D (N = 41)	SoC + D + O (N = 61)
Any AE	90 (81.8)	117 (85.4)	122 (97.6)	52 (89.7)	36 (87.8)	56 (91.8)
Any AE of CTCAE Grade ≥ 3	12 (10.9)	21 (15.3)	52 (41.6)	16 (27.6)	8 (19.5)	25 (41.0)
Any AE with maximum CTCAE Grade 3 or 4 [b]	10 (9.1)	21 (15.3)	49 (39.2)	16 (27.6)	8 (19.5)	25 (41.0)
Any AE with outcome of death	2 (1.8)	0	3 (2.4)	0	0	0
Any SAE (including events with outcome of death)	7 (6.4)	16 (11.7)	26 (20.8)	12 (20.7)	5 (12.2)	15 (24.6)
Any AE leading to discontinuation of durvalumab/placebo [c]	2 (1.8)	7 (5.1)	13 (10.4)	2 (3.4)	2 (4.9)	3 (4.9)
Any AE leading to discontinuation of olaparib/placebo [c]	3 (2.7)	9 (6.6)	17 (13.6)	2 (3.4)	1 (2.4)	4 (6.6)
Any AE leading to discontinuation of SoC [c]	1 (0.9)	2 (1.5)	1 (0.8)	0	0	0
Any AE leading to dose interruption of durvalumab/placebo [d]	9 (8.2)	28 (20.4)	47 (37.6)	9 (15.5)	7 (17.1)	19 (31.1)
Any AE leading to dose interruption of olaparib/placebo [d]	15 (13.6)	23 (16.8)	72 (57.6)	15 (25.9)	9 (22.0)	30 (49.2)
Any AE leading to dose interruption of SoC [d]	0	1 (0.7)	2 (1.6)	1 (1.7)	0	0

a. Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.
b. Maximum CTCAE Grade of 3 or 4 was derived at patient level, and excluded patients who experienced Grade 3 or 4 events with a Grade 5 event.
c. AEs on the AE CRF form with Action taken = 'Drug permanently discontinued'. For SoC, AEs were counted as leading to discontinuation of treatment if action taken was equal to 'Drug permanently discontinued' for at least one agent.
d. AEs on the AE CRF form with Action taken = 'Drug interrupted'. For durvalumab/placebo, this included dose interruption during infusion as indicated in the exposure CRF form as well as dose that skipped or delayed. For SoC, AEs were counted as leading to dose interruption if action taken was equal to 'Drug interrupted' for at least one agent.

Included AEs with an onset date or that worsened on or after the date of first dose of study treatment (overall) or first dose of olaparib/placebo (maintenance phase) up until the initiation of the first subsequent anticancer therapy following discontinuation of study treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurred first. CTCAE version 5.0. Source: Table 14.3.2.1.1D.

DUO-E Results by MMR Status (as randomised)

Subgroup analyses of the secondary efficacy endpoints were not pre-planned at the time of the primary PFS analysis, however a post-hoc subgroup analysis by MMR status was performed. In the FAS, there were 80.1% of patients (575/718) who were pMMR and 19.9% of patients (143/718) who were dMMR.

Table 97 Duration of Exposure for Durvalumab/Placebo in DUO-E Overall, by MMR Status per IVRS (Safety Analysis Set); DCO1: 12 April 2023

		pMMR Status			dMMR Status		
		SoC (N = 190)	SoC + D (N = 191)	SoC + D + O (N = 191)	SoC (N = 46)	SoC + D (N = 44)	SoC + D + O (N = 47)
Durvalumab/ placebo	Total treatment exposure (weeks) [a]						
	n	190	191	191	46	44	47
	Mean (SD)	44.7 (25.87)	47.0 (30.01)	55.4 (32.37)	40.6 (31.89)	62.5 (37.88)	69.1 (32.54)
	Median (Min–Max)	41.7 (0.7-143.0)	41.7 (0.9-134.0)	53.1 (0.7-144.3)	29.0 (3.0-119.3)	64.3 (3.0-138.0)	64.9 (7.0-138.1)
	Total treatment years [b]	162.749	171.997	202.960	35.836	52.712	62.253

a. Intended exposure (weeks) = [(minimum of (last dose date where dose > 0 mg + C days, date of death, date of DCO) – first dose date + 1 day)]/7 where C was equal to the scheduled number of days between doses minus one. C was equal to '20' if the last dose date fell into the chemotherapy phase and '27' if the last dose date fell into the maintenance phase.
b. Total treatment years = sum of treatment duration (in days) for all patients per treatment group/365.25.

Note that the terms ‘intended exposure’ and ‘total treatment exposure’ are interchangeable.

Note: MMR status (proficient vs deficient) was as recorded in IVRS.

Table 98 Duration of Exposure for Durvalumab/Placebo and Olaparib/Placebo in DUO-E Maintenance Phase, by MMR Status per IVRS (Safety Analysis Set); DCO1: 12 April 2023

		pMMR Status			dMMR Status		
		SoC (N = 144)	**SoC + D (N = 150)**	**SoC + D + O (N = 151)**	**SoC (N = 25)**	**SoC + D (N = 33)**	**SoC + D + O (N = 41)**
Durvalumab/ placebo	Total treatment exposure (weeks) [a]						
	n	144	150	151	25	33	41
	Mean (SD)	32.2 (22.74)	34.5 (26.41)	43.7 (28.02)	38.3 (31.30)	55.4 (30.80)	54.5 (28.28)
	Median (Min–Max)	24.0 (4.0-124.3)	24.7 (0.0-115.0)	38.9 (0.0-125.0)	36.0 (4.0-100.4)	55.9 (8.0-118.1)	48.0 (2.9-117.3)
	Total treatment years [b]	88.893	99.211	126.505	18.357	35.036	42.831
Olaparib/ placebo	Total treatment exposure (weeks) [c]						
	N	144	150	151	25	33	41
	Mean (SD)	31.8 (22.98)	34.7 (26.21)	43.9 (28.15)	37.9 (31.68)	52.8 (31.45)	51.3 (29.96)
	Median (Min–Max)	24.1 (0.9-124.3)	26.9 (1.6-115.0)	40.0 (1.4-125.0)	34.3 (1.9-100.4)	53.4 (8.0-118.1)	46.0 (1.3-117.3)
	Total treatment years [b]	87.784	99.619	127.154	18.144	33.394	40.271

a. Intended exposure (weeks) = [(minimum of (last dose date where dose > 0 mg + C days, date of death, date of DCO) – first dose date + 1 day)]/7 where C was equal to the scheduled number of days between doses minus one. C was equal to ‘20’ if the last dose date fell into the chemotherapy phase and ‘27’ if the last dose date fell into the maintenance phase.

b. Total treatment years = sum of treatment duration (in days) for all patients per treatment group/365.25.

c. Intended exposure (weeks) = [(minimum of (last dose date where dose > 0 mg, date of death, date of DCO) - first dose date +1) / 7.

Note that the terms ‘intended exposure’ and ‘total treatment exposure’ are interchangeable.

Note: MMR status (proficient vs deficient) was as recorded in IVRS.

Table 99 Treatment Emergent AEs by Category – Patient Level – dMMR Status (Safety Analysis Set

AE Category [a]	Number (%) of patients					
	DUO-E Overall			DUO-E Maintenance Phase		
	SoC N=46	SoC + D N=44	SoC + D + O N=47	SoC N=25	SoC + D N=33	SoC + D + O N=41
Any AE	46 (100.0)	44 (100.0)	47 (100.0)	22 (88.0)	31 (93.9)	40 (97.6)
Any AE of CTCAE Grade ≥ 3	29 (63.0)	23 (52.3)	31 (66.0)	2 (8.0)	7 (21.2)	15 (36.6)
Any AE with maximum CTCAE Grade 3 or 4 [b]	28 (60.9)	23 (52.3)	30 (63.8)	2 (8.0)	7 (21.2)	14 (34.1)
Any AE with outcome of death	1 (2.2)	0 (0)	1 (2.1)	0 (0)	0 (0)	1 (2.4)
Any SAE (including events with outcome of death)	15 (32.6)	13 (29.5)	16 (34.0)	2 (8.0)	4 (12.1)	7 (17.1)
Any AE leading to discontinuation of durvalumab/placebo [c]	5 (10.9)	5 (11.4)	3 (6.4)	1 (4.0)	3 (9.1)	3 (7.3)
Any AE leading to discontinuation of olaparib/placebo [c]	1 (2.2)	4 (9.1)	5 (10.6)	1 (4.0)	4 (12.1)	5 (12.2)
Any AE leading to discontinuation of SoC [c]	4 (8.7)	5 (11.4)	6 (12.8)	0 (0)	1 (3.0)	0 (0)
Any AE leading to dose interruption of durvalumab/placebo [d]	18 (39.1)	23 (52.3)	32 (68.1)	1 (4.0)	11 (33.3)	13 (31.7)
Any AE leading to dose interruption of olaparib/placebo [d]	5 (10.9)	10 (22.7)	22 (46.8)	5 (20.0)	10 (30.3)	21 (51.2)
Any AE leading to dose interruption of SoC [d]	15 (32.6)	13 (29.5)	19 (40.4)	0 (0)	0 (0)	1 (2.4)

[a] Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.

[b] Maximum CTCAE Grade of 3 or 4 was derived at patient level, and excluded patients who experienced Grade 3 or 4 events with a Grade 5 event.

[c] AEs on the AE CRF form with Action taken = 'Drug permanently discontinued'. For SoC, AEs are counted as leading to discontinuation of treatment if action taken was equal to 'Drug permanently discontinued' for at least one agent.

[d] AEs on the AE CRF form with Action taken = 'Drug interrupted'. For durvalumab/placebo, this includes dose interruption during infusion as indicated in the exposure CRF form as well as dose that skipped or delayed. For SoC, AEs are counted as leading to dose interruption if action taken was equal to 'Drug interrupted' for at least one agent.

Includes AEs with an onset date or that worsen on or after the date of first dose of study treatment (overall) or first dose of olaparib/placebo (maintenance phase) up until the initiation of the first subsequent anticancer therapy following discontinuation of study treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurred first.

AE = adverse event; CRF = case report form; CTCAE = Common Terminology Criteria for Adverse Events (version 5.0); dMMR = mismatch repair deficient; N = total number of patients; SAE = serious adverse event; SoC = standard of care; SoC + D = durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Table 100 Treatment Emergent AEs by Category – Patient Level – pMMR Status (Safety Analysis Set)

AE Category [a]	Number (%) of patients					
	DUO-E Overall			DUO-E Maintenance Phase		
	SoC N=190	SoC + D N=191	SoC + D + O N=191	SoC N=144	SoC + D N=150	SoC + D + O N=151
Any AE	190 (100.0)	188 (98.4)	190 (99.5)	121 (84.0)	127 (84.7)	144 (95.4)
Any AE of CTCAE Grade ≥ 3	104 (54.7)	106 (55.5)	129 (67.5)	26 (18.1)	23 (15.3)	64 (42.4)
Any AE with maximum CTCAE Grade 3 or 4 [b]	98 (51.6)	102 (53.4)	125 (65.4)	24 (16.7)	23 (15.3)	62 (41.1)
Any AE with outcome of death	7 (3.7)	4 (2.1)	4 (2.1)	2 (1.4)	0 (0)	2 (1.3)
Any SAE (including events with outcome of death)	58 (30.5)	60 (31.4)	69 (36.1)	17 (11.8)	18 (12.0)	35 (23.2)
Any AE leading to discontinuation of durvalumab/placebo [c]	14 (7.4)	21 (11.0)	19 (9.9)	3 (2.1)	6 (4.0)	13 (8.6)
Any AE leading to discontinuation of olaparib/placebo [c]	4 (2.1)	7 (3.7)	16 (8.4)	4 (2.8)	6 (4.0)	16 (10.6)
Any AE leading to discontinuation of SoC [c]	28 (14.7)	26 (13.6)	25 (13.1)	1 (0.7)	1 (0.7)	1 (0.7)
Any AE leading to dose interruption of durvalumab/placebo [d]	72 (37.9)	89 (46.6)	99 (51.8)	17 (11.8)	27 (18.0)	55 (36.4)
Any AE leading to dose interruption of olaparib/placebo [d]	26 (13.7)	26 (13.6)	88 (46.1)	25 (17.4)	23 (15.3)	85 (56.3)
Any AE leading to dose interruption of SoC [d]	68 (35.8)	72 (37.7)	66 (34.6)	1 (0.7)	1 (0.7)	1 (0.7)

[a] Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.

[b] Maximum CTCAE Grade of 3 or 4 was derived at patient level, and excluded patients who experienced Grade 3 or 4 events with a Grade 5 event.

[c] AEs on the AE CRF form with Action taken = 'Drug permanently discontinued'. For SoC, AEs are counted as leading to discontinuation of treatment if action taken was equal to 'Drug permanently discontinued' for at least one agent.

[d] AEs on the AE CRF form with Action taken = 'Drug interrupted'. For durvalumab/placebo, this includes dose interruption during infusion as indicated in the exposure CRF form as well as dose that skipped or delayed. For SoC, AEs are counted as leading to dose interruption if action taken was equal to 'Drug interrupted' for at least one agent.

Includes AEs with an onset date or that worsen on or after the date of first dose of study treatment (overall) or first dose of olaparib/placebo (maintenance phase) up until the initiation of the first subsequent anticancer therapy following discontinuation of study treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurred first.

AE = adverse event; CRF = case report form; CTCAE = Common Terminology Criteria for Adverse Events (version 5.0); N = total number of patients; pMMR = mismatch repair proficient; SAE = serious adverse event; SoC = standard of care; SoC + D = durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Table 101 Most Common Adverse Events (Frequency ≥ 10% in Any Treatment Arm in DUO-E Safety Analysis Set Population Overall) by MMR Status per IVRS; DCO1: 12 April 2023

PT	Number (%) of patients [a]					
	pMMR Status			dMMR Status		
	SoC (N = 190)	SoC + D (N = 191)	SoC + D + O (N = 191)	SoC (N = 46)	SoC + D (N = 44)	SoC + D + O (N = 47)
Patients with any AE	**190 (100.0)**	**188 (98.4)**	**190 (99.5)**	**46 (100.0)**	**44 (100.0)**	**47 (100.0)**
Anaemia	103 (54.2)	93 (48.7)	120 (62.8)	25 (54.3)	18 (40.9)	27 (57.4)
Nausea	83 (43.7)	70 (36.6)	108 (56.5)	22 (47.8)	26 (59.1)	22 (46.8)
Alopecia	99 (52.1)	95 (49.7)	102 (53.4)	19 (41.3)	23 (52.3)	19 (40.4)
Fatigue	66 (34.7)	67 (35.1)	77 (40.3)	21 (45.7)	15 (34.1)	16 (34.0)
Constipation	65 (34.2)	48 (25.1)	64 (33.5)	16 (34.8)	16 (36.4)	14 (29.8)
Diarrhoea	55 (28.9)	62 (32.5)	59 (30.9)	11 (23.9)	12 (27.3)	8 (17.0)
Vomiting	33 (17.4)	37 (19.4)	49 (25.7)	10 (21.7)	12 (27.3)	12 (25.5)
Neuropathy peripheral	57 (30.0)	49 (25.7)	45 (23.6)	9 (19.6)	12 (27.3)	15 (31.9)
Peripheral sensory neuropathy	49 (25.8)	49 (25.7)	49 (25.7)	17 (37.0)	11 (25.0)	11 (23.4)
Arthralgia	45 (23.7)	53 (27.7)	41 (21.5)	13 (28.3)	18 (40.9)	17 (36.2)
Decreased appetite	35 (18.4)	35 (18.3)	39 (20.4)	11 (23.9)	7 (15.9)	16 (34.0)
Neutrophil count decreased	53 (27.9)	37 (19.4)	43 (22.5)	10 (21.7)	7 (15.9)	7 (14.9)
Neutropenia	23 (12.1)	29 (15.2)	38 (19.9)	8 (17.4)	7 (15.9)	11 (23.4)
COVID-19	25 (13.2)	30 (15.7)	39 (20.4)	7 (15.2)	6 (13.6)	9 (19.1)
Urinary tract infection	45 (23.7)	26 (13.6)	41 (21.5)	5 (10.9)	7 (15.9)	7 (14.9)
Asthenia	18 (9.5)	19 (9.9)	37 (19.4)	6 (13.0)	4 (9.1)	9 (19.1)
Abdominal pain	32 (16.8)	32 (16.8)	34 (17.8)	7 (15.2)	6 (13.6)	6 (12.8)
Platelet count decreased	31 (16.3)	29 (15.2)	32 (16.8)	6 (13.0)	7 (15.9)	8 (17.0)
Dizziness	26 (13.7)	26 (13.6)	33 (17.3)	5 (10.9)	6 (13.6)	7 (14.9)
Headache	27 (14.2)	20 (10.5)	30 (15.7)	8 (17.4)	10 (22.7)	9 (19.1)
Hypomagnesaemia	32 (16.8)	26 (13.6)	32 (16.8)	6 (13.0)	12 (27.3)	6 (12.8)
White blood cell count decreased	34 (17.9)	22 (11.5)	33 (17.3)	6 (13.0)	7 (15.9)	5 (10.6)
Pruritus	24 (12.6)	29 (15.2)	30 (15.7)	5 (10.9)	7 (15.9)	7 (14.9)
Thrombocytopenia	14 (7.4)	25 (13.1)	31 (16.2)	4 (8.7)	5 (11.4)	4 (8.5)

PT	Number (%) of patients [a]					
	pMMR Status			dMMR Status		
	SoC (N = 190)	SoC + D (N = 191)	SoC + D + O (N = 191)	SoC (N = 46)	SoC + D (N = 44)	SoC + D + O (N = 47)
Back pain	20 (10.5)	16 (8.4)	30 (15.7)	2 (4.3)	3 (6.8)	5 (10.6)
Cough	18 (9.5)	23 (12.0)	28 (14.7)	7 (15.2)	12 (27.3)	5 (10.6)
Hypothyroidism	6 (3.2)	32 (16.8)	29 (15.2)	2 (4.3)	5 (11.4)	4 (8.5)
Myalgia	35 (18.4)	27 (14.1)	25 (13.1)	9 (19.6)	5 (11.4)	5 (10.6)
Alanine aminotransferase increased	15 (7.9)	25 (13.1)	23 (12.0)	3 (6.5)	5 (11.4)	7 (14.9)
Oedema peripheral	15 (7.9)	23 (12.0)	22 (11.5)	6 (13.0)	6 (13.6)	8 (17.0)
Pain in extremity	27 (14.2)	22 (11.5)	26 (13.6)	8 (17.4)	9 (20.5)	3 (6.4)
Dyspnoea	22 (11.6)	20 (10.5)	24 (12.6)	4 (8.7)	9 (20.5)	5 (10.6)
Insomnia	28 (14.7)	18 (9.4)	26 (13.6)	5 (10.9)	6 (13.6)	3 (6.4)
Rash	21 (11.1)	31 (16.2)	22 (11.5)	6 (13.0)	10 (22.7)	6 (12.8)
Hypokalaemia	15 (7.9)	20 (10.5)	27 (14.1)	5 (10.9)	7 (15.9)	1 (2.1)
Dysgeusia	22 (11.6)	18 (9.4)	24 (12.6)	4 (8.7)	6 (13.6)	3 (6.4)
Stomatitis	16 (8.4)	17 (8.9)	20 (10.5)	2 (4.3)	2 (4.5)	5 (10.6)
Pyrexia	12 (6.3)	18 (9.4)	18 (9.4)	7 (15.2)	3 (6.8)	6 (12.8)
Blood creatinine increased	10 (5.3)	7 (3.7)	19 (9.9)	3 (6.5)	3 (6.8)	5 (10.6)
Infusion related reaction	22 (11.6)	13 (6.8)	13 (6.8)	2 (4.3)	1 (2.3)	0

[a] Number (%) of patients with AEs, sorted in decreasing frequency of PT in DUO-E for the Safety Analysis Set population (SoC + D + O then SoC + D then SoC). Patients with multiple AEs were counted once for each system organ class and PT. Patients with adverse events in more than one preferred term were counted once in each of those preferred terms.

Included AEs with an onset date or that worsened on or after the date of first dose of study treatment (overall) or first dose of olaparib/placebo (maintenance phase) up until the initiation of the first subsequent anticancer therapy following discontinuation of study treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurs first.

Percentages are based on the total number of patients in the treatment group (N).

Note: MMR status (proficient vs deficient) was as recorded in IVRS.

MedDRA version 25.1.

Table 102 Most Common Adverse Events (Frequency ≥ 10% in Any Treatment Arm in DUO-E Safety Analysis Set Population) in DUO-E Maintenance Phase by MMR Status per IVRS; DCO1: 12 April 2023

PT	Number (%) of patients [a]					
	pMMR Status			dMMR Status		
	SoC (N = 44)	SoC + D (N = 150)	SoC + D + O (N = 151)	SoC (N = 25)	SoC + D (N = 33)	SoC + D + O (N = 41)
Patients with any AE	**121 (84.0)**	**127 (84.7)**	**144 (95.4)**	**22 (88.0)**	**31 (93.9)**	**40 (97.6)**
Nausea	22 (15.3)	14 (9.3)	63 (41.7)	3 (12.0)	8 (24.2)	16 (39.0)
Anaemia	16 (11.1)	13 (8.7)	56 (37.1)	1 (4.0)	3 (9.1)	14 (34.1)
Fatigue	18 (12.5)	9 (6.0)	35 (23.2)	1 (4.0)	4 (12.1)	8 (19.5)
Vomiting	14 (9.7)	8 (5.3)	32 (21.2)	2 (8.0)	5 (15.2)	7 (17.1)
Diarrhoea	16 (11.1)	23 (15.3)	30 (19.9)	4 (16.0)	5 (15.2)	4 (9.8)
COVID-19	17 (11.8)	15 (10.0)	28 (18.5)	3 (12.0)	6 (18.2)	6 (14.6)
Decreased appetite	5 (3.5)	9 (6.0)	18 (11.9)	1 (4.0)	0	10 (24.4)
Urinary tract infection	23 (16.0)	10 (6.7)	22 (14.6)	0	4 (12.1)	3 (7.3)
Abdominal pain	15 (10.4)	17 (11.3)	19 (12.6)	3 (12.0)	3 (9.1)	4 (9.8)
Back pain	11 (7.6)	10 (6.7)	19 (12.6)	0	1 (3.0)	4 (9.8)
Arthralgia	12 (8.3)	24 (16.0)	18 (11.9)	4 (16.0)	10 (30.3)	4 (9.8)
Cough	12 (8.3)	13 (8.7)	19 (12.6)	2 (8.0)	9 (27.3)	2 (4.9)
Neutropenia	1 (0.7)	5 (3.3)	19 (12.6)	0	1 (3.0)	2 (4.9)

[a] Number (%) of patients with AEs, sorted in decreasing frequency of PT in DUO-E for the Safety Analysis Set population (SoC + D + O then SoC + D then SoC). Patients with multiple AEs were counted once for each system organ class and PT. Patients with adverse events in more than one preferred term were counted once in each of those preferred terms.

Included AEs with an onset date or that worsened on or after the date of first dose of study treatment (overall) or first dose of olaparib/placebo (maintenance phase) up until the initiation of the first subsequent anticancer therapy following discontinuation of study treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurs first.

Percentages are based on the total number of patients in the treatment group (N).

Note: MMR status (proficient vs deficient) was as recorded in IVRS. MedDRA version 25.1.

Table 103 Most Common SAEs by System Organ Class and Preferred Term (Frequency ≥ 1% Patients in Any Treatment Arm in SoC, SoC + D, and SoC + D + O in DUO-E Safety Analysis Set Population Overall Phase) by MMR Status per IVRS; DCO1: 12 April 2023

System organ class/ Preferred term	Number (%) of patients [a]					
	pMMR Status			dMMR Status		
	SoC (N = 190)	SoC + D (N = 191)	SoC + D + O (N = 191)	SoC (N = 46)	SoC + D (N = 44)	SoC + D + O (N = 47)
Patients with any SAE	**58 (30.5)**	**60 (31.4)**	**69 (36.1)**	**15 (32.6)**	**13 (29.5)**	**16 (34.0)**
Blood and lymphatic system disorders						
Anaemia	7 (3.7)	1 (0.5)	13 (6.8)	3 (6.5)	0	3 (6.4)
Febrile neutropenia	6 (3.2)	4 (2.1)	5 (2.6)	2 (4.3)	0	2 (4.3)
Neutropenia	1 (0.5)	3 (1.6)	4 (2.1)	2 (4.3)	0	1 (2.1)
Aplasia pure red cell	0	0	3 (1.6)	0	0	0
Infections and infestations						
Urinary tract infection	4 (2.1)	2 (1.0)	5 (2.6)	1 (2.2)	0	1 (2.1)
Sepsis	3 (1.6)	1 (0.5)	2 (1.0)	0	1 (2.3)	2 (4.3)
COVID-19	2 (1.1)	1 (0.5)	3 (1.6)	1 (2.2)	0	1 (2.1)
COVID-19 pneumonia	0	1 (0.5)	3 (1.6)	0	0	0
Urosepsis	2 (1.1)	1 (0.5)	0	1 (2.2)	0	0
Respiratory, thoracic, and mediastinal disorders						
Pneumonitis	0	1 (0.5)	2 (1.0)	0	0	1 (2.1)
Pulmonary embolism	3 (1.6)	0	2 (1.0)	1 (2.2)	0	1 (2.1)
General disorders and administration site conditions						
Pyrexia	1 (0.5)	0	3 (1.6)	0	1 (2.3)	0
Gastrointestinal disorders						
Diarrhoea	3 (1.6)	0	2 (1.0)	1 (2.2)	0	0
Vomiting	1 (0.5)	5 (2.6)	1 (0.5)	1 (2.2)	0	0
Nausea	1 (0.5)	2 (1.0)	1 (0.5)	1 (2.2)	1 (2.3)	0
Constipation	3 (1.6)	2 (1.0)	0	0	0	0
Metabolism and nutrition disorders						
Hyponatraemia	2 (1.1)	4 (2.1)	0	2 (4.3)	1 (2.3)	0
Vascular disorders						
Deep vein thrombosis	1 (0.5)	2 (1.0)	2 (1.0)	0	0	1 (2.1)
Injury, poisoning and procedural complications						
Fall	3 (1.6)	1 (0.5)	1 (0.5)	0	0	0
Infusion related reaction	3 (1.6)	0	1 (0.5)	0	0	0
Investigations						
Neutrophil count decreased	4 (2.1)	1 (0.5)	0	0	0	0

[a] Number (%) of patients with an SAE, sorted by system organ class and then by frequency in DUO-E SoC + D + O then the SoC + D arm for the Overall study period for the Safety Analysis Set population. Patients with multiple SAEs were counted once for each system organ class/PT. Included AEs with an onset date or that worsened on or after the date of first dose of study treatment (overall) or first dose of olaparib/placebo (maintenance phase) up until the initiation of the first subsequent anticancer therapy following discontinuation of study treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurred first.

Antidrug antibody-related adverse events

In DUO-E, 17 patients, out of 405 (4.2%) patients assessed were positive for durvalumab ADA at any timepoint (8 of 198 [4.0%] in the SoC + D arm, and 9 of 207 [4.3%] in the SoC + D + O arm); of these, most patients were positive for durvalumab ADA at baseline only (6 of 8 patients in the SoC + D arm and all 9 patients in the SoC + D + O arm). There were 2 patients in the SoC + D arm who were positive for treatment-emergent durvalumab ADA post-baseline only; both patients were classified as persistently ADA positive because the last available assessment was ADA-positive (Day 182 for the first patient and Day 85 for the second one) rather than duration of the ADA response being ≥ 16 weeks duration. The first patient was also positive for neutralising antibodies on Day 182; this was the only patient positive for neutralising antibodies in the DUO-E study.

In both DUO-E and the durvalumab pan-tumour pool, the incidence and types of AEs reported in patients positive for durvalumab ADA were broadly comparable to those reported in patients who were negative for durvalumab ADA. There were no new types of events or events clearly suggestive or indicative of immune complex disease. For patients who were positive for durvalumab ADA, the AEs

observed were consistent with those observed in patients treated with durvalumab in previous studies. Overall, immunogenicity had no apparent impact on safety.

The ADA evaluable patients were patients in the Safety Analysis Set who received at least one dose of durvalumab and had non-missing baseline ADA and at least one post-baseline ADA result

In DUO-E, serum samples for ADA and ADA-neutralising antibodies for durvalumab at scheduled visits as per the CSP were collected for the majority of patients (> 80% on the SoC + D and SoC + D + O arms). Samples were measured for the presence of ADAs and ADA-neutralising antibodies for durvalumab using validated assays.

Safety related to drug-drug interactions and other interactions

Durvalumab is an immunoglobulin, therefore, no formal pharmacokinetic drug-drug interaction studies have been conducted. The mechanism of action of durvalumab involves binding to PD L1, and therefore significant pharmacodynamic drug interactions with the commonly administered concomitant medications are not expected. Despite this, appropriate clinical monitoring was conducted to evaluate any potential drug-drug interactions.

Clinical studies of olaparib in combination with other anticancer agents, including DNA damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity. CYP3A4/5 are the enzymes primarily responsible for the metabolism of olaparib, therefore concomitant use of strong CYP3A inhibitors is not recommended. If strong or moderate CYP3A inhibitors must have co-administered, the dose of olaparib should be reduced. Co administration of olaparib with a strong CYP3A inducer can substantially diminish the clinical efficacy of olaparib and as such is not recommended. If moderate CYP3A inducers must be co-administered, prescribers should be aware of a potential decreased efficacy of olaparib. In vitro, olaparib has been shown to be a weak inhibitor of OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K and therefore olaparib may increase the exposure of substrates to these. Caution should be exercised if olaparib is administered in combination with any statin. Based on limited in vitro data, olaparib may reduce the exposure to substrates of 2B6 (and potentially substrates of CYP2C9, CYP2C19 and Pgp). The efficacy of some hormonal contraceptives may be reduced if co-administered with olaparib.

Discontinuation due to adverse events

Adverse events leading to discontinuation

Table 104 Most common (Frequency ≥ 1% of patients in any treatment arm in DUO-E overall and maintenance phase) adverse events leading to discontinuation of any study treatment or SoC by System Organ Class and Preferred Term in DUO-E overall and maintenance (Safety Analysis Set)

	Number (%) of patients [a]					
	DUO-E Overall			**DUO-E Maintenance Phase**		
PT	**SoC (N = 236)**	**SoC + D (N = 235)**	**SoC + D + O [b] (N = 238)**	**SoC (N = 169)**	**SoC + D (N = 183)**	**SoC + D + O (N = 192)**
Patients with any AE leading to discontinuation [c]	**44 (18.6)**	**49 (20.9)**	**58 (24.4)**	**7 (4.1)**	**11 (6.0)**	**27 (14.1)**
Anaemia	6 (2.5)	5 (2.1)	10 (4.2)	0	2 (1.1)	8 (4.2)
Neuropathy peripheral	5 (2.1)	6 (2.6)	8 (3.4)	0	1 (0.5)	0
Infusion related reaction	10 (4.2)	5 (2.1)	5 (2.1)	1 (0.6)	0	0
Pneumonitis	0	2 (0.9)	5 (2.1)	0	2 (1.1)	3 (1.6)

PT	Number (%) of patients [a]					
	DUO-E Overall			DUO-E Maintenance Phase		
	SoC (N = 236)	SoC + D (N = 235)	SoC + D + O [b] (N = 238)	SoC (N = 169)	SoC + D (N = 183)	SoC + D + O (N = 192)
Neutropenia	1 (0.4)	0	5 (2.1)	1 (0.6)	0	2 (1.0)
Drug hypersensitivity	0	0	3 (1.3)	0	0	0
Peripheral sensory neuropathy	3 (1.3)	2 (0.9)	2 (0.8)	1 (0.6)	0	0
Interstitial lung disease	0	1 (0.4)	2 (0.8)	0	1 (0.5)	2 (1.0)
Fatigue	1 (0.4)	3 (1.3)	1 (0.4)	0	1 (0.5)	0
Rash maculo-papular	0	3 (1.3)	1 (0.4)	0	1 (0.5)	1 (0.5)
Hypersensitivity	0	3 (1.3)	0	0	0	0

a. Number (%) of patients with an AE leading to discontinuation of any study treatment or SoC, sorted by decreasing frequency of PT in DUO-E SoC + D + O then SoC + D arm and SoC arm for the Overall study period.

b. Olaparib was only administered during the Maintenance phase of DUO-E.

c. Action taken = study treatment permanently discontinued.

Includes AEs with an onset date or that worsened on or after the date of first dose of study treatment (overall) or first dose of olaparib/placebo (maintenance phase) up until the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurred first.
MedDRA version 25.1.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in treatment group; PT = preferred term; SoC = standard of care; SoC + D =Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Table 105 Most common (Frequency ≥ 1% of patients in any treatment arm in DUO-E overall and maintenance phase) adverse events leading to discontinuation of durvalumab/placebo treatment by System Organ Class and Preferred Term in DUO E and the Pan-tumour Pool (Safety Analysis Set)

System organ class/ Preferred term	Number (%) of patients [a]						
	DUO-E Overall			DUO-E Maintenance Phase			Durvalumab Pan-tumour Pool (N = 4045)
	SoC (N = 236)	SoC + D (N = 235)	SoC + D + O [b] (N = 238)	SoC (N = 169)	SoC + D (N = 183)	SoC + D + O (N = 192)	
Patients with any AE leading to discontinuation	**19 (8.1)**	**26 (11.1)**	**22 (9.2)**	**4 (2.4)**	**9 (4.9)**	**16 (8.3)**	**397 (9.8)**
Respiratory, thoracic, and mediastinal disorders							
Pneumonitis	0	1 (0.4)	4 (1.7)	0	1 (0.5)	2 (1.0)	36 (0.9)
Interstitial lung disease	0	1 (0.4)	2 (0.8)	0	1 (0.5)	2 (1.0)	8 (0.2)
Blood and lymphatic system disorders							
Anaemia	5 (2.1)	4 (1.7)	2 (0.8)	0	2 (1.1)	2 (1.0)	6 (0.1)

a. Number (%) of patients with an AE leading to discontinuation of durvalumab/placebo, sorted by decreasing frequency of system organ class and then PT in DUO-E SoC + D + O then SoC + D arm and SoC arm for the Overall study period. Patients with multiple AEs leading to discontinuation of durvalumab/placebo were counted once for each system organ class/PT.

b. Olaparib was only administered during the Maintenance phase of DUO-E.

For DUO-E, includes AEs with an onset date or that worsened on or after the date of first dose of study treatment (overall) or first dose of olaparib/placebo (maintenance phase) up until the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo, whichever occurred first. For the durvalumab Pan-tumour pool, includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increased in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication (or surgery) or up to and including the date of initiation of the first subsequent therapy, whichever occurred first.
For the durvalumab Pan-tumour pool, disease progression AEs reported in Study 1108 are not included in this summary. Percentages are based on the total numbers of subjects in the treatment group (N).
MedDRA version 25.1
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in treatment group; PT = preferred term; SoC = standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Table 106 Most common (Frequency ≥ 1% of patients in any treatment arm in DUO-E maintenance phase) adverse events leading to discontinuation of olaparib/placebo by System Organ Class and Preferred Term in DUO-E maintenance phase and the olaparib pool (Safety Analysis Set)

System organ class/ Preferred term	Number (%) of patients [a]			
	DUO-E Maintenance Phase			Olaparib 300 mg bd Tablet Pool (N = 3556)
	SoC (N = 169)	SoC + D (N = 183)	SoC + D + O (N = 192)	
Patients with any AE leading to discontinuation [b]	**5 (3.0)**	**10 (5.5)**	**21 (10.9)**	**331 (9.3)**
Blood and lymphatic system disorders				
Anaemia	0	2 (1.1)	7 (3.6)	73 (2.1)
Neutropenia	1 (0.6)	0	2 (1.0)	12 (0.3)
Respiratory, thoracic, and mediastinal disorders				
Pneumonitis	0	1 (0.5)	3 (1.6)	9 (0.3)

a. Number (%) of patients with an AE leading to discontinuation of olaparib/placebo, sorted by decreasing frequency of system organ class and then PT in DUO-E SoC + D + O then SoC + D arm and SoC arm. Patients with multiple AEs leading to discontinuation of olaparib/placebo were counted once for each system organ class/preferred term.

b. Action taken = drug permanently discontinued.

For DUO-E, includes AEs with an onset date or that worsened on or after the date of first dose of olaparib/placebo (maintenance phase) up until the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurred first. For the olaparib 300 mg bd pool, includes AEs with an onset date between the date of first dose of continuous treatment and 30 days following the last dose of continuous treatment.

MedDRA version 25.1.
AE = adverse event; bd = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in treatment group; PT = preferred term; SoC = standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Dose modifications due to adverse events

Dose modifications of durvalumab/placebo in DUO-E and the durvalumab Pan tumour Pool

Table 107 Adverse events leading to dose delay/interruption of durvalumab/placebo (≥ 2% in any treatment arm of DUO-E) in DUO-E overall and maintenance and the durvalumab Pan tumour Pool (Safety Analysis Set)

System organ class Preferred term	Number (%) of patients [a]						
	DUO-E Overall			DUO-E Maintenance			Durvalumab Pan-tumour Pool (N = 4045)
	SoC (N = 236)	SoC + D (N = 235)	SoC + D + O (N = 238)	SoC (N = 169)	SoC + D (N = 183)	SoC + D + O (N = 192)	
Patients with any AE leading to dose delay/interruption of durvalumab/placebo	**90 (38.1)**	**112 (47.7)**	**131 (55.0)**	**18 (10.7)**	**38 (20.8)**	**68 (35.4)**	**1121 (27.7)**
Blood and lymphatic system disorders							
Anaemia	22 (9.3)	20 (8.5)	32 (13.4)	2 (1.2)	1 (0.5)	16 (8.3)	40 (1.0)
Neutropenia	11 (4.7)	13 (5.5)	16 (6.7)	0	1 (0.5)	4 (2.1)	9 (0.2)
Thrombocytopenia	5 (2.1)	13 (5.5)	15 (6.3)	0	0	1 (0.5)	15 (0.4)
Infections and infestations							
COVID-19	12 (5.1)	13 (5.5)	26 (10.9)	6 (3.6)	9 (4.9)	17 (8.9)	1 (< 0.1)
Urinary tract infection	3 (1.3)	3 (1.3)	5 (2.1)	2 (1.2)	1 (0.5)	1 (0.5)	19 (0.5)
Investigations							
Platelet count decreased	14 (5.9)	18 (7.7)	13 (5.5)	1 (0.6)	0	1 (0.5)	4 (0.1)
Neutrophil count decreased	19 (8.1)	10 (4.3)	8 (3.4)	2 (1.2)	0	2 (1.0)	7 (0.2)
White blood cell count decreased	5 (2.1)	1 (0.4)	4 (1.7)	1 (0.6)	0	1 (0.5)	2 (< 0.1)
Alanine aminotransferase increased	4 (1.7)	5 (2.1)	2 (0.8)	0	2 (1.1)	2 (1.0)	47 (1.2)
Blood creatinine increased	5 (2.1)	1 (0.4)	2 (0.8)	0	0	2 (1.0)	25 (0.6)
Respiratory, thoracic and mediastinal disorders							
Dyspnoea	1 (0.4)	2 (0.9)	5 (2.1)	1 (0.6)	1 (0.5)	2 (1.0)	32 (0.8)
Endocrine disorders							
Hypothyroidism	0	6 (2.6)	5 (2.1)	0	4 (2.2)	2 (1.0)	33 (0.8)

[a] Number (%) of patients with AEs leading to dose delay or interruption of durvalumab/placebo, sorted in decreasing frequency of system organ class and then preferred term in DUO-E SoC + D + O then SoC + D arm and SoC arm for the Overall study period. Patients with multiple AEs leading to discontinuation of durvalumab/placebo were counted once for each system organ/preferred term.

For DUO-E, includes AEs with an onset date or that worsened on or after the date of first dose of study treatment (overall) or first dose of olaparib/placebo (maintenance phase) up until the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurred first. For the durvalumab Pan-tumour pool, includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increased in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy, whichever occurred first.
Dose modification is a standardised reason of dose interrupted (dose interrupted, dose delayed, dose omitted) or dose reduced.
For the durvalumab Pan-tumour pool, disease progression AEs reported in Study 1108, Study 6, Study 10, and Study 11 are not included in this summary.
MedDRA version 25.1 (DUO-E), version 23.1 (durvalumab Pan-tumour pool).
AE = adverse event; COVID-19 = Coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients; SoC = standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance;
SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Note that "interruption" is used when an AE resulted in an interruption in the study drug administration schedule, i.e. in a delay of the cycle. It is also used for cases where administration of an investigational product was temporarily stopped mid administration due to an AE(s). Therefore, an interruption for durvalumab/placebo includes interruptions and delays.

Dose modifications of olaparib/placebo in DUO-E study and the olaparib pool

Table 108 Adverse events leading to dose interruption of olaparib/placebo (≥ 2% in any treatment arm of DUO-E) in DUO-E maintenance phase and the olaparib pool (Safety Analysis Set)

System organ class / Preferred term	Number (%) of patients [a]			
	DUO-E Maintenance Phase			Olaparib 300 mg bd Tablet Pool (N = 3556)
	SoC (N = 169)	SoC + D (N = 183)	SoC + D + O (N = 192)	
Patients with any AE leading to dose interruption[b]	**30 (17.8)**	**33 (18.0)**	**106 (55.2)**	**1350 (38.0)**
Blood and lymphatic system disorders				
Anaemia	2 (1.2)	1 (0.5)	37 (19.3)	575 (16.2)
Neutropenia	0	1 (0.5)	9 (4.7)	138 (3.9)
Thrombocytopenia	0	0	4 (2.1)	57 (1.6)
Infections and infestations				
COVID-19	9 (5.3)	8 (4.4)	21 (10.9)	8 (0.2)
Urinary tract infection	4 (2.4)	0	1 (0.5)	14 (0.4)
Gastrointestinal disorders				
Nausea	3 (1.8)	2 (1.1)	12 (6.3)	169 (4.8)
Vomiting	1 (0.6)	2 (1.1)	7 (3.6)	145 (4.1)
Diarrhoea	0	1 (0.5)	4 (2.1)	62 (1.7)
General disorders and administration site conditions				
Fatigue	0	0	5 (2.6)	92 (2.6)

a. Number (%) of patients with an AE leading to dose interruption of olaparib/placebo, sorted in decreasing frequency of system organ class and then preferred term in DUO-E SoC + D + O then SoC + D arm and SoC arm. Patients with multiple AEs leading to discontinuation of olaparib/placebo were counted once for each system organ class/preferred term.

b. For the olaparib 300 mg bd pool, action taken, drug interrupted. Dose reduced and interrupted.

For DUO-E, includes AEs with an onset date or that worsened on or after the date of first dose of olaparib/placebo (maintenance phase) up until the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurred first. For the olaparib 300 mg bd pool, includes AEs with an onset date between the date of first dose of continuous treatment and 30 days following the last dose of continuous treatment.

MedDRA version 25.1

AE = adverse event; bd = twice daily; COVID-19 = Coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients; SoC = standard of care; SoC + D = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab maintenance; SoC + D + O = Durvalumab in combination with standard of care platinum-based chemotherapy followed by durvalumab and olaparib maintenance.

Table 109 Adverse events leading to dose reduction of olaparib/placebo (≥ 1% in SoC or SoC + D + O and SoC + D of DUO-E) in DUO-E maintenance phase and the olaparib pool (Safety Analysis Set)

System organ class/Preferred term	Number (%) of patients [a]			
	DUO-E Maintenance Phase			Olaparib 300 mg bd Tablet Pool (N = 3556)
	SoC (N = 169)	SoC + D (N = 183)	SoC + D + O (N = 192)	
Patients with any AE leading to dose reduction	4 (2.4)	13 (7.1)	63 (32.8)	778 (21.9)
Blood and lymphatic system disorders				
Anaemia	0	1 (0.5)	25 (13.0)	387 (10.9)
Neutropenia	0	0	5 (2.6)	42 (1.2)
Gastrointestinal disorders				
Nausea	0	0	6 (3.1)	101 (2.8)
Vomiting	1 (0.6)	0	2 (1.0)	47 (1.3)
Diarrhoea	0	0	2 (1.0)	16 (0.4)
General disorders and administration site conditions				
Fatigue	0	0	5 (2.6)	83 (2.3)
Investigations				
Blood creatinine increased	0	2 (1.1)	4 (2.1)	24 (0.7)
Creatinine renal clearance decreased	1 (0.6)	0	3 (1.6)	6 (0.2)
White blood cell count decreased	0	0	2 (1.0)	27 (0.8)
Renal and urinary disorders				
Renal failure	0	1 (0.5)	3 (1.6)	2 (0.1)
Renal impairment	0	2 (1.1)	2 (1.0)	6 (0.2)
Acute kidney injury	0	2 (1.1)	1 (0.5)	1 (0.0)
Nervous system disorders				
Neuropathy peripheral	0	0	2 (1.0)	3 (0.1)
Metabolism and nutrition disorders				
Decreased appetite	0	0	2 (1.0)	14 (0.4)

a. Number (%) of patients with AEs leading to dose reduction, sorted in decreasing frequency of preferred term in SoC + D + O then SoC + D. Patients with multiple AEs are counted once for each preferred term.

For DUO-E, includes adverse events with an onset date or that worsened on or after the date of first dose of olaparib/placebo up until the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurred first.

For the olaparib 300 mg bd Tablet Pool. includes Adverse Events with an onset date between the date of first dose of continuous treatment and 30 days following the last dose of continuous treatment.
Percentages are based on the total numbers of patients in the treatment group (N).
MedDRA version 25.1
AE = adverse event; bd = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients; SoC = standard of care.

Post marketing experience

Durvalumab Post-marketing Data

Total post-marketing exposure of durvalumab since launch to 30 April 2023 is estimated to be approximately 118467 patient years (Imfinzi PBRER, 30 April 2023). No new safety concerns were identified based on the post-marketing safety reports.

Olaparib Post-marketing Data

Total post-marketing exposure of olaparib since launch to 15 June 2023 is estimated to be approximately 167556 patient years (Lynparza PBRER, 15 June 2023). No new safety concerns were identified based on the post-marketing safety reports.

2.5.1. Discussion on clinical safety

The safety profile of durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab as monotherapy or in combination with olaparib in patients with newly diagnosed advanced or recurrent endometrial cancer is based on data from the ongoing pivotal study D9311C00001 (DUO-E), using a DCO of 12 April 2023 (unless otherwise specified) with supportive pooled safety data of different studies of both durvalumab and olaparib.

The safety assessment is based on data from 709 patients that received study treatment in the DUO-E study (236 patients in the SoC arm, 235 patients in the SoC + D arm, and 238 patients in the SoC + D + O arm). In the maintenance phase, there were 169 patients in the SoC arm, 183 patients in the SoC + D arm, and 192 patients in the SoC + D + O arm. The assessment of safety is also supported by data from the safety pool with the data from durvalumab pan-tumour pool (N=4045), olaparib 300 mg bd tablet pool (N=3556), olaparib monotherapy combined therapeutic dose pool (N=4499) and data from the olaparib entire clinical programme (N = 21793 as of 15 June 2023). It is important to note that pooled safety data represents a heterogeneous group of patients with different indications and regimens compared with participants in DUO-E.

In the study overall, intended **duration of exposure** to standard of care chemotherapy (carboplatin and paclitaxel) was similar in all treatment arms with a median of 6 infusions received. The intended duration of exposure of durvalumab was longer on the SoC + D + O arm, compared with SoC + D (excluding total duration of dose delays), with over half of patients reaching 9 months of treatment in the SoC and SoC + D arm and 13 months of treatment in the SoC + D + O arm. When compared to the durvalumab pan-tumour pool, the median total duration of exposure to durvalumab was longer in DUO-E. With regards to olaparib/placebo, the median intended treatment duration (excluding total duration of dose interruptions) was of 25 weeks in the SoC arm, 33 in the SoC + D arm and 40 in the SoC + D + O arm and similar to the total actual treatment duration. In the SoC + D + O arm, for olaparib, there was a greater difference between intended exposure and actual exposure at planned dose compared with the SoC and SoC + D treatment arms, reflecting the greater number of dose reductions/interruptions of olaparib (dose reductions: 7.7 SoC vs 9.8 SoC + D vs 37% SoC + D + SoC + D + O; dose interruptions: 33% vs 28% vs 65%, respectively).

Overall, in all 3 treatment arms, the **most commonly reported AEs** (all grades/Grade 3 or 4) were haematologic and gastrointestinal events.

The most common (> 20%) adverse reactions in SoC + D + O were anaemia (61.8%), nausea (54.6%), fatigue (54.2%), neuropathy peripheral (51.7%), alopecia (50.8%), neutropenia (39.5%), constipation (32.8%), thrombocytopenia (29.8%), diarrhoea (28.2%), vomiting (25.6%), arthralgia (24.4%), rash (23.5%), abdominal pain (23.5%), decreased appetite (23.1%) and leukopenia

(20.2%).The most common (> 2%) NCI CTCAE Grade ≥ 3 adverse reactions were neutropenia (25.2%), anaemia (23.5%), leukopenia (6.7%), thrombocytopenia (5.9%), fatigue (5.5%), febrile neutropenia (3.4%), nausea (2.9%), aspartate aminotransferase increased / alanine aminotransferase increased (2.9%) and neuropathy peripheral (2.5%).The type and incidence of AEs were generally comparable between SoC + D + O and SoC and the differences were generally consistent with the established durvalumab and olaparib safety profiles to date. In the maintenance phase, the AEs reported at a higher frequency (difference of ≥ 5% patients) in the SoC + D + O arm than in the SoC arm were consistent with the known safety profile of olaparib.

The incidence of the most common AEs in the DUO-E study was generally higher than in the durvalumab Pan tumour Pool, which appears reasonable since the pooled studies did not include patients who received SoC.

AE of maximum CTCAE Grade 3 or 4 were reported across all treatment arms in more than 50% of patients. In the study overall, AEs of maximum CTCAE Grade 3 or 4 were similar between the SoC + D (53.6%) and SoC arms (54.2%) but reported for more patients in the SoC + D + O arm (67.2%). Anaemia and neutropenia occurred at a higher frequency (≥5% difference) in SoC + D + O compared with SoC and SoC + D; no maximum CTCAE Grade 3 or 4 AEs were reported with a ≥5% higher frequency in SoC + D arm compared with SoC. In the maintenance phase the incidence was of 16.9%, 16.0% and 41.7% for SoC + D, SoC and SoC + D + O arms, respectively. The most common AEs of maximum CTCAE Grade 3 or 4 (> 5%) in the SoC arm were neutrophil count decreased (15.3%), anaemia (14.8%) and neutropenia (5.9%); in the SoC + D arm were anaemia (16.2%), neutrophil count decreased (11.5%) and neutropenia (8.5%); and in SoC + D + O arm were anaemia (23.5%), neutrophil count decreased (13.4%), neutropenia (11.8%). In the maintenance phase, only in the SoC + D + O arm anaemia (18.8%) was reported at a ≥ 5% greater frequency.

AE of Grade 3 or 4 of ≥2% in any treatment arm were consistent with the known safety profiles of chemotherapy and olaparib. Higher incidence of maximum CTCAE Grade 3 or 4 AEs was observed for SoC + D in the overall phase of DUO-E compared with the durvalumab Pan tumour Pool, these AEs in the SoC + D arm were mainly due to the contribution of chemotherapy. The higher incidence of maximum Grade 3 or 4 events in SoC + D + O was driven by AEs such as anaemia, neutropenia and neutrophil count decreased which were observed at a much lower incidence in the durvalumab Pan tumour Pool and are ADRs normally associated with chemotherapy and olaparib. In the maintenance phase of DUO-E, anaemia was the only CTCAE Grade ≥ 3 AE reported with a ≥ 5% higher frequency in the SoC + D + O arm compared with the SoC arm; no CTCAE Grade ≥ 3 AEs were reported with a ≥ 5% higher frequency in SoC + D arm compared with SoC.

Higher incidence of maximum CTCAE Grade 3 or 4 AEs was observed for SoC + D in the overall phase of DUO-E compared with the durvalumab Pan tumour Pool. These AEs reported at a maximum Grade 3 or 4 in the SoC + D arm were mainly due to the contribution of chemotherapy. The incidence of maximum CTCAE Grade 3 or 4 AEs was similar for SoC + D in the maintenance phase of DUO-E compared with the durvalumab Pan tumour Pool.

The incidence of maximum CTCAE Grade 3 or 4 AEs was higher for SoC + D + O in both the overall and maintenance phase of DUO-E compared with the durvalumab Pan tumour Pool. The incidence of CTCAE ≥ 3 AEs was similar for the maintenance phase of SoC + D + O in DUO-E compared with the olaparib 300 mg bd Tablet Pool and it is consistent with the adverse drug reaction (ADR) profile normally associated with chemotherapy and olaparib.

AESIs

AESIs of olaparib include myelodysplastic syndrome and acute myeloid leukaemia (MDS/AML), new primary malignancies (NPM) and pneumonitis. AESIs of durvalumab include AEs with a potential

inflammatory or immune-mediated mechanism (i.e. pneumonitis, hepatic events, diarrhoea/colitis, intestinal perforations, adrenal insufficiency, Type 1 diabetes mellitus, hyperthyroid events, hypophysitis, hypothyroid events, thyroiditis, renal events, dermatitis/rash, pancreatic events, myocarditis, myasthenia gravis, Guillain-Barre syndrome, myositis, infusion/hypersensitivity reactions, and other rare/miscellaneous). Among these, immune-mediated AEs (imAEs) were identified based on programmatic rules that considered interventions involving systemic steroid therapy, immunosuppressant use, and/or endocrine therapy.

PRCA has been reflected in section 4.4 'Warnings and Precautions' of the SmPC for both Imfinzi and Lynparza. It warns that if PRCA is confirmed, treatment with durvalumab and olaparib should be discontinued.

MDS/AML is categorised as an important identified risk of olaparib. No events of MDS/AML were reported within any of the 3 treatment arms at either the DCO1 or 120-day safety update DCO date.

Haematological toxicity.

Following review of all available data, **autoimmune haemolytic anaemia (AIHA)** and **pure red aplasia (PRCA)** are considered to be a potential risk associated with the combination of durvalumab and olaparib. AIHA is not considered a potential risk for either durvalumab or olaparib monotherapy, however haemolytic anaemia is considered a potential risk for durvalumab. While there have not been any reports of AIHA in the olaparib monotherapy pool, there has been a single report of AIHA in the durvalumab Pan tumour pool.

There were 2 reports of AIHA and a single report of haemolytic anaemia for the combination of durvalumab and olaparib, and a single report of AIHA in the SoC + D arm. For 3 of these cases where the event was serious. Three events of AIHA were observed in the DUO-E study (1 in the SoC + D arm and 2 in the SoC + D + O arm). One event occurred on treatment in the SoC + D arm and two events in the follow-up period. At time of reporting, two events had resolved and one event was not resolved. According to the MAH, there has been one previous report of AIHA in the durvalumab Pan tumour Pool and no events previously observed for the olaparib 300 mg bd Tablet Pool. All 3 events in the DUO-E study were CTCAE Grade 3 and were considered related to study treatment. Two of the three events were also SAEs. By the update DCO date all AIHA/haemolytic anaemia events were 'recovered/resolved' or 'resolved with sequelae'. A warning has been included in section 4.4 of the SmPC due to the (potential) risk of AIHA with the combination of durvalumab and olaparib. Considering the cases of AIHA observed in the DUO-E study and that AIHA is not regarded as a risk for olaparib or durvalumab monotherapy, it is accepted that AIHA is not included as an ADR for the combination in section 4.8 of the SmPC of Imfinzi and Lynparza.

After safety review of study DUO-E, no update to the safety concerns or to the risk minimisation measures have been proposed by the MAH except from a SmPC update to add a warning for durvalumab or olaparib regarding PCRA and AIHA. Only for PRCA, the MAH proposed to update section 4.8 of the SmPC for both Imfinzi and Lynparza.

Haemolytic anaemia is considered a potential risk for durvalumab. One patient in the SoC + D + O arm, had a CTCAE Grade 3 SAE of haemolytic anaemia in the follow-up period. The event was considered related to durvalumab, and at the time of reporting, the event had resolved with sequelae.
NPMs is an important potential risk for olaparib. In DUO-E, NPMs were reported for a similar number of patients in the SoC + D arm (1 patient [0.4%]), SoC + D + O arm (2 patients [0.8%]) and the SoC arm (3 patients [1.3%]). There was only one event occurring in the maintenance phase in the SoC + D + O arm and the overall incidence was less than 1.5% and balanced across all treatment arms.

Pneumonitis is a recognised ADR for carboplatin, paclitaxel and durvalumab and a potential risk for olaparib. A warning is included in the SmPC of Lynparza in section 4.4. In the study overall, there were more pneumonitis events in the SoC + D (4 [1.7%]) and SoC + D + O (12 [5%]) arms than the SoC arm (1 [0.4%]). In the DUO-E study, olaparib was only administered during the Maintenance Phase and most of the events occurred during the maintenance phase. The frequency of pneumonitis events in the SoC + D + O arm was higher than has been observed with olaparib monotherapy (1.1% in the olaparib pooled data), which is not unexpected taking into account the added effect of durvalumab. However, since other (potential) confounder factors were present in several patients out of the 13 cases of pneumonitis reported in the SoC + D + O arm, it is difficult to ascertain whether it could be related to olaparib treatment and therefore it is accepted that pneumonitis is not included as ADR for the combination in section 4.8 of the Lynparza SmPC.In the overall phase of the DUO-E study, consistent with the durvalumab mechanism of action, the incidence of **imAEs** was higher in the SoC + D (28.1%) and SoC + D + O (23.5%) arms than in the SoC arm (6.8%). The major contributors to imAE frequency were hypothyroidism (2.5% SoC vs 14.5% SoC + D vs 11.8% SoC + D + O) and dermatitis/rash (3.4% vs 6.4% vs 6.3%). Overall, imAEs were generally CTCAE Grades 1 or 2 and non-serious; no imAEs had an event outcome of death. In the maintenance phase, imAEs were similar in the SoC + D and SoC + D + O arms (14.8% and 14.1%, respectively) and were reported for more patients than in the SoC arm (3.6%). There was little change by the 120-day safety update DCO date.

Infusion-related reactions: In DUO-E, infusion-related reactions (grouped term) were comparable across all 3 treatment arms; 15 patients (6.4%) in SoC + D, 14 patients (5.9%) in SoC + D + O and 24 patients (10.2%) in SoC in the Overall study phase. The majority were of CTCAE Grade 1 or 2. Of the AESIs of infusion-related reaction, 10 patients in the SoC arm, 5 patients in the SoC + D arm, and 6 patients in the SoC + D + O arm had events leading to discontinuation of study treatment in the study overall and all events were resolved by the date of DCO. In the Maintenance phase of DUO-E, one patient in the SoC + D arm, 3 patients in the SoC + D + O arm and 2 patients in the SoC arm had AESIs of infusion-related reactions. Events in the SoC + D and SoC + D + O arms in the Maintenance phase were all CTCAE Grade ≤2 (all were events of hypersensitivity). Of the 2 patients with AESIs of infusion-related reactions in the SoC arm Maintenance phase, one event was CTCAE Grade 3 and one was CTCAE Grade 4 (both were events of anaphylactic reaction).

Hypersensitivity/anaphylactic reaction (grouped term) AESIs was slightly higher in the SoC + D + O arm compared with the SoC + D and SoC arms (14 [5.9%] vs 8 [3.4%] vs 9 [3.8%], respectively). The majority of the events were CTCAE Grade 1 or 2. Of the AESIs of hypersensitivity/anaphylactic reaction, no patients in the SoC arm, 4 patients in the SoC + D arm, and 4 patients in the SoC + D + O arm had events leading to discontinuation of study treatment in the study overall.

Serious adverse event (**SAEs**) were reported by approximately a third of patients across all treatment arms. SAEs regardless of causality were reported for a similar number of patients in the SoC and SoC + D arms with a slightly higher incidence in the SoC + D + O arm (30.9% vs 31.1% vs 35.7%, respectively). The PTs most commonly reported as SAEs (≥2% patients in any treatment arm) were anaemia (4.2% SoC vs 0.4 SoC + D vs 6.7% SoC + D + O), febrile neutropenia (3.4% vs 1.7% vs 2.9%), urinary tract infection (2.1% vs 0.9% vs 2.5%), hyponatraemia (1.7% vs 2.1% vs 0) and vomiting (0.8% vs 2.1% vs 0.4%). In the Maintenance Phase, although the frequency of SAEs was lower than in the overall study, more patients in the SoC + D + O arm had SAEs compared with either the SoC + D or SoC arms (21.9% vs 12% vs 11.2%, respectively), anaemia being the most commonly reported in the SoC + D + O arm.

The frequency of any SAEs (frequency ≥ 2% in DUO-E) reported in the overall study phase in the SoC + D arm was similar to the durvalumab Pan tumour Pool, with the exception of a higher incidence (a difference of ≥ 1%) of AEs for: febrile neutropenia, neutropenia, hyponatraemia, vomiting, and nausea

in the SoC + D arm of DUO-E. The type of SAEs reported in the maintenance phase of SoC + D arm were generally consistent with the known safety profile of durvalumab. The frequency of SAEs (a difference ≥ 2%) reported in the maintenance phase of SoC + D + O was similar compared with the olaparib 300 mg bd Tablet Pool, with the exception of a higher incidence (a difference of ≥ 1%) of AEs of: anaemia, aplasia pure red cell, urinary tract infection, and COVID-19 pneumonia.

The number of patients with AEs with outcome of **death** in the DUO-E study was of 3.4% (n=8) in the SoC, 1.7% (n=4) in the SoC + D arm and 2.1% (n=5) in the SoC + D + O arm. None of these events was considered causally related to study treatment by the investigator. Of these, 5 patients died during the maintenance phase of the DUO-E (3 patients in the SoC + D + O arm and 2 patients in the SoC arm). Up to the updated DCO (18 October 2023), an additional 48 patients have died, being the total number of deaths of 247 (94 patients in the SoC arm; 81 patients in the SoC + D arm and 72 patients in in the SoC + D + O arm). The majority of these deaths were due to disease progression (43/48). Five patients died after end of safety follow-up period: 2 patients in the SoC (cause unknown), 2 patients in the SoC + D (due to cardiac arrest and septic shock) and 1 patient in the SoC + D + O arm (cause unknown).

Clinical laboratory data were consistent with the known safety profiles and background disease state. Overall, no new safety concerns were identified from the haematology results. No clinically meaningful changes from baseline or trends in clinical laboratory chemistry values over time were observed in any treatment arm in DUO-E. Increases in creatinine are considered an ADR for carboplatin, paclitaxel, durvalumab, and olaparib. In total, 4 patients (1.7%) in the SoC + D + O treatment arm, one patient (0.4%) in the SoC + D treatment arm, and no patients in the SoC treatment arm had laboratory values consistent with potential Hy's Law. For one of these 5 patients, Hy's Law could not be ruled out based on confounding factors. Two patients had events of drug-induced liver injury during the chemotherapy phase; one patient in the SoC + D arm and other in the SoC + D + O arm. The patient in the SoC + D + O arm who had the event of drug-induced liver injury also met the criteria for potential Hy's Law. Of note, drug-induced liver injury is an ADR for olaparib reported in the post-marketing setting.

With regards to **special populations**, in the DUO-E study overall, compared with the SoC and SoC + D arms where a similar proportion of CTCAE Grade 3 or 4 AEs occurred in each age group, in the SoC + D + O arm, a higher proportion of patients aged ≥ 65 to < 75 (71.8%), and ≥ 75 years (68.4%) experienced events compared with the < 65 years group (64.2%). Overall, the safety profiles across the < 65 years and 65 to 74 years age groups were generally comparable, however, there were differences of at least 10% frequency between the < 65 years and 65 to 74 year categories in some TEAEs (SoC: Psychiatric disorders; SoC + D +O: AEs leading to discontinuation of any study treatment, nervous system disorders and sum of postural hypotension, falls, blackouts, syncope, dizziness, ataxia and fracture). In the DUO-E study overall, for the SoC + D and SoC + D + O arms, the greatest proportion of AEs with an outcome of death occurred in the ≥ 75 years age group; however, in the SoC arm there was no notable difference between the ≥ 65 to < 75 years and ≥ 75 years age groups. For SAEs, the greatest proportion of SAEs occurred in the ≥ 65 to < 75 years age group in the SoC and SoC + D + O arms, while in the SoC + D arm, a similar proportion of patients experienced SAEs in the ≥ 65 to < 75 years and ≥ 75 years age groups. Overall, there were no safety concerns identified following review of the adverse events reported across the different age categories. It is important to note that there were few patients ≥ 75 years age group so these results should be interpreted with caution.

Safety data were analysed by PD-L1 expression and MMR status, and were generally comparable to the safety profile of the overall ITT population. The number of patients with **AEs leading to discontinuation** of the study treatment was of 18.6% in the SoC, 20.9% in the SoC + D and 24.4%

in the SoC + D + O. Discontinuation of durvalumab/placebo due to AEs was similar across the treatment arms. Regarding olaparib/placebo there were more discontinuations due to an AE in the SoC + D + O arm. The frequency of discontinuation of SoC was similar across the treatment arms.

The most common AE (≥ 2% in any treatment arm) leading to discontinuation of any study treatment were anaemia, infusion related reactions, neuropathy peripheral and pneumonitis. No AEs leading to discontinuation of any study treatment occurred at a ≥ 5% difference between the treatment arms.

In the study overall, AEs leading to dose delay/interruptions of durvalumab/placebo were higher in the SoC + D and SoC + D + O arms compared to the SoC arm (48% vs 55% vs 38%). There were more AEs leading to dose interruptions and dose reductions of olaparib/placebo in the SoC + D + O arm compared with either the SoC + D or SoC arms.

Immunogenicity: There were no new types of events or events clearly suggestive or indicative of immune complex disease. For patients who were positive for durvalumab antidrug antibody (ADA), the AEs observed were consistent with those observed in patients treated with durvalumab in previous studies. However, due to the limited number of ADA-positive patients, a formal analysis of the impact of ADAs on the safety of durvalumab is difficult.

ADRs: The frequencies of known ADRs for olaparib observed in DUO-E are consistent within the known safety profile of olaparib. No new ADRs were identified specific for durvalumab and olaparib based on the DUO-E study data. The frequency and severity of durvalumab ADRs in SoC + D and SoC + D + O of DUO-E are consistent with the durvalumab Pan-tumour Pool. Pure red cell aplasia (PRCA) has been identified as an ADR for the combination of olaparib + durvalumab. Three individual reports of **PRCA** were observed in the SoC + D + O arm of DUO-E study (1.3%). One event occurred on treatment and two events occurred in the follow-up period. At time of reporting, one of the three events of PRCA had resolved, and the patient went on to receive subsequent chemotherapy. Two events were not resolved. All 3 events were CTCAE Grade 3 SAEs and all were considered related to study treatment. All events were recorded as recovered or recovering following discontinuation of treatment with both olaparib and durvalumab (with the exception of one in which the patient died due to disease progression) and routine medical management.

PRCA is not considered to be an ADR for either durvalumab or olaparib monotherapy (no events of PRCA have been observed in the large, pooled monotherapy datasets for either durvalumab or olaparib and the event has only been observed when durvalumab and olaparib are used together). This AE is already reported in sections 4.4 and 4.8 of the SmPC. The event of PRCA has been identified as an ADR for the combination of olaparib plus durvalumab and therefore included in section 4.8 of the SmPC for both products with the frequency of "Common". The frequency has been derived from DUO-E data and reflects 3 patients from 238 (1.3%) treated with durvalumab and olaparib in combination.

The reported ADRs in section 4.8 of the Imfinzi and Lynparza SmPCs have been revised.

2.5.2. Conclusions on clinical safety

In the DUO-E study overall, SoC +D and SoC + D + O demonstrated a manageable safety profile for the treatment of patients with newly diagnosed advanced or recurrent endometrial cancer. In addition to AEs attributable to SoC, the type, frequency, and severity of AEs in SoC +D and SoC + D + O arms were generally consistent with the established safety profile of durvalumab and olaparib given separately.

A new ADR (PRCA) has been identified for the combination of durvalumab and olaparib which has been added to section 4.8 of both Imfinzi and Lynparza SmPCs.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The WSA submitted an updated RMP version 10.1 for Imfinzi and version 30.1 for Lynparza with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 10.3 for Imfinzi and version 30.2 for Lynparza are acceptable.

The CHMP endorsed the Risk Management Plan version 10.3 for Imfinzi and 30.2 for Lynparza with the following content:

Safety concerns

Imfinzi

There are no safety concerns.

Lynparza

Table 110 Summary of Safety Concerns

Important identified risks	Myelodysplastic syndrome/acute myeloid leukaemia
Important potential risks	New primary malignancies Effects on embryofoetal survival and abnormal development
Missing information	Long term exposure to/potential toxicity to olaparib

Pharmacovigilance plan

Imfinzi

Not applicable.

Lynparza

Not applicable.

Risk minimisation measures

Imfinzi

Not applicable as there are no safety concerns.

Lynparza

Table 111 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
MDS/AML	Routine risk minimisation measures: • SmPC Section 4.4 and 4.8 • PL Section 2 and 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up targeted safety questionnaire • Cumulative assessment (provided within each annual PBRER)
New primary malignancy	None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up targeted safety questionnaire
Effects on embryofoetal survival and abnormal development	Routine risk minimisation measures: • SmPC Sections 4.4, 4.6 • PL Section 2	Routine
Long term exposure to/potential toxicity to olaparib	None	Routine

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the Imfinzi SmPC and sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the Lynparza SmPC have been updated. The Annex II and the Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the WSA and has been found acceptable for the following reasons: as part of this extension of indication for the treatment of endometrial cancer no substantial changes to the PIL have been proposed by the MAH. Therefore, the MAH´s justification to not undertake further consultation with target patient groups is considered acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The recommended indication reflecting the data evaluated is:

Imfinzi

Endometrial Cancer

IMFINZI in combination with carboplatin and paclitaxel is indicated for the first-line treatment of adults with primary advanced or recurrent endometrial cancer who are candidates for systemic therapy, followed by maintenance treatment with:

- IMFINZI as monotherapy in endometrial cancer that is mismatch repair deficient (dMMR)
- IMFINZI in combination with olaparib in endometrial cancer that is mismatch repair proficient (pMMR).

Lynparza

Endometrial cancer

Lynparza in combination with durvalumab is indicated for the maintenance treatment of adult patients with primary advanced or recurrent endometrial cancer that is mismatch repair proficient (pMMR) whose disease has not progressed on first-line treatment with durvalumab in combination with carboplatin and paclitaxel.

3.1.2. Available therapies and unmet medical need

Patients with advanced (stage III/IV) or recurrent EC may receive a combination of surgery, radiotherapy, and systemic therapy depending on the extent of disease and local practices. Patients with stage III and IVA disease with no residual tumour after surgery are considered to have high-risk EC and generally receive adjuvant chemotherapy with carboplatin and paclitaxel, which can be given with concurrent or subsequent radiation therapy (NCCN 2023, Oaknin et al. 2022).

The current SoC for first-line treatment of patients with stage III and IVA EC with residual tumour after surgery, stage IVB disease, or as 1L therapy for recurrent disease comprises platinum-based chemotherapy, with the combination of carboplatin and paclitaxel as the preferred regimen, based on the results from study GOG 209 (Miller et al. 2020, Oaknin et al. 2022, NCCN 2023). Recently, studies evaluating the addition of immune checkpoint inhibitors pembrolizumab (study NRG-GY018 [NCT03914612] Eskander et al. 2023) or dostarlimab (study RUBY Part 1 [NCT03981796] Mirza et al. 2023), initiated in combination with SoC chemotherapy and continued as maintenance monotherapy, have reported statistically significant PFS improvements vs SoC chemotherapy for the first-line treatment of patients with advanced or recurrent EC. Recently, based on the results from the RUBY study, dostarlimab in combination with carboplatin and paclitaxel has been authorized in the EU for the treatment of adult patients with dMMR/MSI-H primary advanced or recurrent EC who are candidates for systemic therapy.

For patients who progress following prior platinum-based chemotherapy, pembrolizumab (as monotherapy or in combination with lenvatinib) and dostarlimab (as monotherapy for dMMR status patients) are approved and recommended by both the NCCN and ESMO guidelines as second-line treatment for patients who have progressed following prior treatment and who have no satisfactory

alternative treatment options (NCCN 2023, Oaknin et al. 2022). The choice of treatment is mainly guided by a patient's dMMR or pMMR status.

3.1.3. Main clinical studies

The current application is based on the results from the DUO-E study, a phase III, randomised, multicentre, double-blind study of first-line platinum-based chemotherapy in combination with durvalumab, followed by maintenance durvalumab with or without olaparib in patients with newly diagnosed advanced or recurrent endometrial cancer. Patients with histologically confirmed, advanced (stage III or IV) or recurrent high-grade epithelial endometrial cancer (all histologies except for sarcomas) were randomised 1:1:1 to receive either paclitaxel + carboplatin or paclitaxel + carboplatin in combination with durvalumab 1120 mg Q3W followed by durvalumab 1500 mg Q4W maintenance treatment or the same combination adding olaparib to durvalumab during maintenance treatment. Randomisation was stratified by MMR status, disease status and geographic region.

The primary endpoint is PFS by investigator assessment for both the SoC + D vs SoC and the SoC + D + O vs SoC comparisons. OS and other supportive endpoints such as PFS2, ORR, DoR, TFST, TSST, TDT and patient reported outcomes were included as secondary endpoints.

A total of 718 patients (ITT population) were randomized in the study: 241 to the SoC arm, 238 to the SoC + D arm and 239 to the SoC + D + O treatment arm.

3.2. Favourable effects

As of the DCO date (12 April 2023), the study met its primary objective reporting a statistically significant improvement in PFS, in the ITT population, for both comparisons. With regards to the indication of SoC + D followed by D maintenance monotherapy in patients with dMMR tumours, the benefit is considered established based on the already available results. In addition to positive results for PFS (HR 0.42; 95% CI: 0.22, 0.80), a positive trend in OS has been identified (HR 0.34; 95% CI: 0.13, 0.79), although OS is based on an IA on a very limited number of events. For the SoC + D followed by D + O maintenance phase indication in the pMMR subpopulation, a clear benefit in terms of PFS has been shown over SoC (HR 0.57; 95% CI: 0.44, 0.73; median PFS of 15.0 months vs 9.7 months, respectively). Additionally, a positive trend for OS has been identified (HR 0.69; 95% CI: 0.47, 1.00) although with, still, a low number of reported events. Other secondary endpoints showed the same trend in favour of the experimental arms. Several pre-planned sensitivity analyses were performed and they were consistent with the PFS primary analysis.

3.3. Uncertainties and limitations about favourable effects

At the time of the primary analysis, OS data were not sufficiently mature and, while a detrimental effect seems unlikely, results of the second IA and the final analysis from study D9311C00001 (DUO-E) will be provided, once available, to better characterise the efficacy of the proposed regimens and rule out a (potential) detrimental effect (Annex II condition PAES).

The study design and the inclusion of a heterogeneous population in terms of the presence of different biomarkers (MMR, HRR, PDL-1) that may be key for the effect of the treatment have been considered a limitation of the study to establish the benefit-risk of these combinations in the overall population.

3.4. Unfavourable effects

Up to the DCO of 12 April 2023, the most frequently reported AEs (≥ 30%) in any arm were anaemia (54.2% SoC vs 47.2% SoC + D vs 61.8% SoC + D + O), alopecia (50% vs 50.2% vs 50.8%), nausea

(44.5% vs 40.9% vs 54.6%), fatigue (36.9% vs 34.9% vs 39.1%), constipation (34.3% vs 27.2% vs 32.8%), diarrhoea (28% vs 31.5% vs 28.2%) and arthralgia (24.6% vs 30.2% vs 24.4%).

In the study overall, AEs of maximum CTCAE Grade 3 or 4 were similar between the SoC + D (53.6%) and SoC (54.2%) arms but reported for more patients in the SoC + D + O arm (67.2%). The most frequently reported maximum Grade 3 or 4 AEs (≥ 5%) in all 3 treatment arms were anaemia, neutrophil count decreased, and neutropenia.

In the study overall, SAEs regardless of causality were reported for approximately a third of patients across all treatment arms. The most common SAEs were anaemia (4.2% SoC vs 0.4 SoC + D vs 6.7% SoC + D + O), febrile neutropenia (3.4% vs 1.7% vs 2.9%), urinary tract infection (2.1% vs 0.9% vs 2.5%), hyponatraemia (1.7% vs 2.1% vs 0) and vomiting (0.8% vs 2.1% vs 0.4%).

The number of AEs with an outcome of death was of 3.4% (n=8) in the SoC, 1.7% (n=4) in the SoC + D arm and 2.1% (n=5) in the SoC + D + O arms. None of the events was considered causally related to study treatment by the investigator.

Discontinuation of any study treatment due to AEs occurred in 18.6% in the SoC arm, 20.9% in the SoC + D arm and 24.4% in the SoC + D + O arm. The most common AE leading to discontinuation of any study treatment were anaemia, infusion related reactions, neuropathy peripheral and pneumonitis.

No AESIs of MDS/AML were reported within any of the 3 treatment arms. New primary malignancies (NPMs) were reported for a similar number of patients in the SoC + D arm (1 patient [0.4%]), SoC + D + O arm (2 patients [0.8%]) and the SoC arm (3 patients [1.3%]). There was one event of NPM during the maintenance phase in the SoC + D + O arm and the overall incidence was less than 1.5% and balanced across all treatment arms.

In the overall study, there were more pneumonitis events in the SoC + D (4 [1.7%]) and SoC + D + O (12 [5%]) arms than the SoC arm (1 [0.4%]). Most of the events occurred during the maintenance phase. The incidence of imAEs was similar in the SoC + D and SoC + D + O arms and higher compared with the SoC arm. The major contributors to the overall imAE frequency were hypothyroidism and dermatitis/rash.

Adverse events of PRCA (3 patients), AIHA (2 patients), and haemolytic anaemia (one patient) were reported for patients in the SoC + D + O arm.

3.5. Uncertainties and limitations about unfavourable effects

The causality of olaparib in occurrence of rare cases of NPM could not be firmly established. However, uncertainties remain on the potential risks of NPM with olaparib. NPM is already an important potential risk in the RMP and follow-up targeted safety questionnaire as routine risk minimisation measure.

3.6. Effects Table

Table 112: Effects Table for durvalumab (Imfinzi), in combination with platinum-based chemotherapy, followed by durvalumab as monotherapy or in combination with olaparib (Lynparza), for the first-line treatment of adults with advanced or recurrent endometrial cancer (data cut-off: 12 April 2023)

Effect	Short description	Unit	Treatment SoC+D (n=238)	Treatment SoC+D+O (n=239)	Control SoC (n=241)	Uncertainties / Strength of evidence	References
	Favourable Effects						
pMMR population			**SoC + D**	**SoC + D + O (n=191)**	**SoC (n=192)**		
PFS by investigator	Progression Free Survival assessed by Investigator	Median, months (95% CI)		15.0 (12.4, 18.0)	9.7 (9.2, 10.1)	HR (95% CI): 0.57 (0.44, 0.73). 57% events in SoC+D+O and 77.1% in SoC	DUO-E study CSR
OS	Overall Survival	Median, months (95% CI)		NR (NR, NR)	25.9 (25.1, NR)	HR (95% CI): 0.69 (0.47, 1.00). 24.1% events in SoC+D+O and 33.3% in SoC	DUO-E study CSR
dMMR population			**SoC + D (n=46)**	**SoC + D + O**	**SoC (n=49)**		
PFS by investigator	Progression Free Survival assessed by Investigator	Median, months (95% CI)	NR (NR, NR)		7.0 (6.7, 14.8)	HR (95% CI): 0.42 (0.22, 0.80). 32.6% events in SoC + D and 51% in SoC	DUO-E study CSR
OS	Overall Survival	Median, months (95% CI)	NR (NR, NR)		23.7 (16.9, NR)	HR (95% CI): 0.34 (0.13, 0.79). 15.2% events in SoC+D and 36.7% in SoC	DUO-E study CSR
	Unfavourable Effects						
			N=235	**N=238**	**N=236**		
Grade 3 or 4 AEs	High-grade AEs	%	53.2	65.5	53.4		
Grade 5 AEs	AEs leading to death	%	1.7	2.1	3.4		
SAEs	Serious AEs	%	31.1	35.7	30.9		
AEs discontinuation	AEs leading to discontinuation of any treatment	%	20.9	24.4	18.6		
imAEs	Any immune-mediated AEs	%	28.1	23.5	6.8		

Abbreviations:

Notes: See Figures

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Results from the DUO-E study have shown a statistically significant improvement in terms of PFS, for the combination of chemotherapy and durvalumab, followed by maintenance treatment by either durvalumab monotherapy or combined with olaparib in 1L treatment of patients with advanced or recurrent endometrial carcinoma, compared to chemotherapy. These results have been confirmed by several secondary endpoints and sensitivity analyses.

However, the contribution of olaparib to SoC+D in dMMR patients is considered negligible. Moreover, in the subgroup of patients with pMMR the benefit of SoC+D over SoC is considered modest. The indication was therefore restricted by MMR status (i.e. SoC+D for dMMR and SoC+D+O for pMMR). The benefit is considered established for SoC+D in patients with dMMR tumours, based on the already available results. In addition to positive results for PFS (HR 0.42; 95% CI: 0.22, 0.80), a positive trend in OS has been identified (HR 0.34; 95% CI: 0.13, 0.79), although this trend is based on an IA of 7 (15.2%) events in the SoC + D arm and 18 (36.7%) events in the SoC arm. This will require further characterisation with updated OS results (which are to be provided as an annex II PAES). These results are supported by the biological rationale of dMMR status being a predictive factor for the efficacy of anti-PD1 compounds, already highlighted by published results with other anti-PD1 medicinal products. For the SoC + D + O indication in the pMMR subpopulation, a clear benefit in terms of PFS has been shown over SoC (HR 0.57; 95% CI: 0.44, 0.73; median PFS of 15.0 months vs 9.7 months, respectively). Additionally, a positive trend for OS has been identified (HR 0.69; 95% CI: 0.47, 1.00), although more mature data will be required to further confirm these results and rule out a (potential) detrimental effect in the long-term (annex II PAES).

Overall, the safety profile of durvalumab plus chemotherapy followed by durvalumab as monotherapy or in combination with olaparib during the maintenance phase was generally consistent with the established safety profile of durvalumab, olaparib and carboplatin/paclitaxel. However, the addition of olaparib to durvalumab during the maintenance phase entails an increase in Grade 3-4 AEs and SAEs. Moreover, a new ADR (PRCA) has been identified for the combination of durvalumab plus olaparib and reflected in section 4.8 of the SmPC for both Imfinzi and Lynparza.

3.7.2. Balance of benefits and risks

To date, the combination of paclitaxel and carboplatin is considered the standard of care in this disease setting. Recently, the addition of dostarlimab to the above-mentioned chemotherapy regimen has been authorized within the UE in the subpopulation of dMMR/MSI-H patients.

Based on the results from the DUO-E study, the combination of chemotherapy and durvalumab, followed by maintenance treatment with durvalumab monotherapy has demonstrated a statistically significant and clinically relevant benefit in PFS for the 1L treatment of advanced or recurrent endometrial carcinoma which is dMMR.

The combination of chemotherapy and durvalumab, followed by maintenance treatment with durvalumab and olaparib has also demonstrated an improvement in PFS which can be considered of clinical relevance for the treatment of primary advanced or recurrent endometrial carcinoma which is pMMR.

Overall, the identified toxicity profile is considered acceptable and manageable although the addition of olaparib to durvalumab in the maintenance phase entails an increased toxicity.

Overall, the B/R balance of Imfinzi and Lynparza in the new claimed indications is considered positive.

3.8. Conclusions

The overall B/R of Imfinzi in combination with carboplatin and paclitaxel for the first line treatment of adults with primary advanced or recurrent endometrial cancer who are candidates for systemic therapy, followed by maintenance treatment with durvalumab as monotherapy in endometrial cancer that is mismatch repair deficient (dMMR) or in combination with olaparib in endometrial cancer that is mismatch repair proficient (pMMR) and of Lynparza in combination with durvalumab for the maintenance treatment of adult patients with primary advanced or recurrent endometrial cancer that is mismatch proficient (pMMR) whose disease has not progressed on first-line treatment with durvalumab in combination with carboplatin and paclitaxel is positive.

The CHMP considers the following measures necessary to address issues related to efficacy:

Imfinzi

Post-authorisation efficacy study (PAES): In order to further characterise the long-term efficacy of durvalumab in combination with carboplatin and paclitaxel for the first line treatment of adults with primary advanced or recurrent endometrial cancer who are candidates for systemic therapy, followed by maintenance treatment with durvalumab as monotherapy in endometrial cancer that is mismatch repair deficient (dMMR) or in combination with olaparib in endometrial cancer that is mismatch repair proficient (pMMR), the MAH should submit the results of the second interim OS analysis and the final OS analysis from study D9311C00001 (DUO-E), a phase III randomised double-blind placebo-controlled multicentre study.

Lynparza

Post-authorisation efficacy study (PAES): In order to further characterise the long-term efficacy of olaparib in combination with durvalumab for the maintenance treatment of adult patients with primary advanced or recurrent endometrial cancer that is mismatch proficient (pMMR) whose disease has not progressed on first-line treatment with durvalumab in combination with carboplatin and paclitaxel, the MAH should submit the results of the second interim OS analysis and the final OS analysis from study D9311C00001 (DUO-E), a phase III randomised double-blind placebo-controlled multicentre study.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include Imfinzi (durvalumab) in combination with carboplatin and paclitaxel for the first line treatment of adults with primary advanced or recurrent endometrial cancer who are candidates for systemic therapy, followed by maintenance treatment with durvalumab as monotherapy in endometrial cancer that is mismatch repair deficient (dMMR) or in combination with olaparib in endometrial cancer that is mismatch repair proficient (pMMR) and to include Lynparza (olaparib) in combination with durvalumab for the maintenance treatment of adult patients with primary advanced or recurrent endometrial cancer that is mismatch proficient (pMMR) whose disease has not progressed on first-line treatment with durvalumab in combination with carboplatin and paclitaxel, based on the results from pivotal Phase III study, D9311C00001 (DUO-E). As a consequence sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the Imfinzi SmPC and sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the Lynparza SmPC are updated. The Annex II, the Package Leaflet and the Risk Management Plan (version 10.3 for Imfinzi and version 30.2 for Lynparza) are updated in accordance.

The worksharing procedure leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the worksharing procedure, amendments to Annexes I, II and IIIB and to the Risk Management Plan are recommended.

This recommendation is subject to the following new conditions:

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Obligation to conduct post-authorisation measures

The WSA shall complete, within the stated timeframe, the below measures:

Imfinzi

Description	Due date
Post-authorisation efficacy study (PAES): In order to further characterise the long-term efficacy of durvalumab in combination with carboplatin and paclitaxel for the first line treatment of adults with primary advanced or recurrent endometrial cancer who are candidates for systemic therapy, followed by maintenance treatment with durvalumab as monotherapy in endometrial cancer that is mismatch repair deficient (dMMR) or in combination with olaparib in endometrial cancer that is mismatch repair proficient (pMMR), the MAH should submit the results of the second interim OS analysis and the final OS analysis from study D9311C00001 (DUO-E), a phase III randomised double-blind placebo-controlled multicentre study.	Second interim OS analysis: December 2025 Final OS analysis: December 2026

Lynparza

Description	Due date
Post-authorisation efficacy study (PAES): In order to further characterise the long-term efficacy of olaparib in combination with durvalumab for the maintenance treatment of adult patients with primary advanced or recurrent endometrial cancer that is mismatch proficient (pMMR) whose disease has not progressed on first-line treatment with durvalumab in combination with carboplatin and paclitaxel, the MAH should submit the results of the second interim OS analysis and the final OS analysis from study D9311C00001 (DUO-E), a phase III randomised double-blind placebo-controlled multicentre study.	Second interim OS analysis: December 2025 Final OS analysis: December 2026