22 May 2025
EMA/196723/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Imfinzi

International non-proprietary name: Durvalumab

Procedure No. EMEA/H/C/004771/II/0073

Note

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

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List of abbreviations

Abbreviation	Explanation
ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
AEPI	Adverse event of possible interest
AESI	Adverse event of special interest
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
BCG	Bacillus Calmette-Guérin vaccine
BICR	Blinded Independent Central Review
BSC	Best supportive care
BTC	Biliary tract cancer
Cis	Cisplatin
CD80	Cluster of differentiation 80
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CPS	Combined positive score
CrCl	Creatinine clearance
CRF	Case report form
CRR	Complete response rate
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTx	Chemotherapy
Durva	Durvalumab
DCO	Data cut-off
dd-MVAC	Dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin
DFS	Disease-free survival
DoR	Duration of response
DSS	Disease-specific survival
EAU	European Association of Urology
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EFS24	Proportion of patients alive and event free at 24 months
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer - Quality of Life Questionnaire - 30 Core
ES-SCLC	Extensive-stage small cell lung cancer
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
GC or G+C	Gemcitabine plus cisplatin
GCP	Good Clinical Practice
G/Gem	Gemcitabine
GHS	Global health status
HCC	Hepatocellular carcinoma
HR	Hazard ratio
HRQoL	Health-related quality of life
IA	Interim analysis
IA-1	Interim analysis 1
IA-2	Interim analysis 2
IC(s)	Immune cell(s)
ICH	International Council for Harmonization
imAE	Immune-mediated adverse event
ISS	Integrated Summary of Safety
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive voice response system

Abbreviation	Explanation
KM	Kaplan-Meier
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MFS	Metastasis-free survival
MIBC	Muscle invasive bladder cancer
MIUC	Muscle-invasive urothelial carcinoma
MRI	Magnetic resonance imaging
MTP	Multiple testing procedure
MVAC	Methotrexate, vinblastine, doxorubicin, and cisplatin
N	Total number of patients
nAb	Neutralizing antibody
NAC	Neoadjuvant chemotherapy
NCCN	National Comprehensive Cancer Network
NE	Not evaluable
NMIBC	Non-muscle-invasive bladder cancer
NR	Not reached
NSCLC	Non-small-cell lung cancer
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
OS5	Overall survival at 5 years
pCR	Pathologic complete response
PD-1	Programmed cell death 1
PDCO	Pediatric Committee
PD-L1	Programmed cell death ligand-1
PD-L2	Programmed cell death ligand-2
PFS	Progression-free survival
PFS2	Time from randomization to subsequent progression or recurrence post-EFS event
PI	Prescribing information
PIP	Pediatric investigational plan
PK	Pharmacokinetic(s)
PRO	Patient-reported outcome
QoL	Quality of life
QxW	Every x weeks
RECIST 1.1	Response Evaluation Criteria for Solid Tumors version 1.1
SAE	Serious adverse event
SAP	Statistical Analysis Plan
sBLA	Supplemental Biologics License Application
SCLC	Small cell lung cancer
SEERs	Surveillance, Epidemiology, and End Results
SmPC	Summary of Product Characteristics
SoC	Standard of care
TC	Tumor cell
TCC	Transitional cell carcinoma
TURBT	Transurethral resection of bladder tumor
UC	Urothelial carcinoma
US	United States
USPI	United States prescribing information
vs	Versus
WHO	World Health Organization

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 14 October 2024 an application for a variation.

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 to include IMFINZI in combination with cisplatin-based chemotherapy as neoadjuvant treatment, followed by IMFINZI as monotherapy adjuvant treatment after radical cystectomy, for the treatment of adults with muscle invasive bladder cancer (MIBC), based on an ongoing pivotal study D933RC00001 (NIAGARA); this is a phase 3, randomized, open-label, multi-center, global study to determine the efficacy and safety of durvalumab in combination with gemcitabine + cisplatin for neoadjuvant treatment followed by durvalumab alone for adjuvant treatment in patients with muscle-invasive bladder cancer. As a consequence, sections 4.1, 4.2, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly. The RMP version 13 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes and update the PI according to the Excipients Guideline.

The variation 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 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (P/0301/2023) was completed.

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 MAH 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 MAH received Scientific Advice from the CHMP on 26 April 2018 (EMEA/H/SA/2752/9/2018/II). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Boje Kvorning Pires Ehmsen Co-Rapporteur: Carolina Prieto Fernandez

Timetable	Actual dates
Submission date	14 October 2024
Start of procedure:	2 November 2024
CHMP Rapporteur Assessment Report	20 December 2024
PRAC Rapporteur Assessment Report	2 January 2025
PRAC members comments	8 January 2025
CHMP Co-Rapporteur Assessment	8 January 2025
PRAC Outcome	16 January 2025
CHMP members comments	20 January 2025
Updated CHMP Rapporteur(s) (Joint) Assessment Report	22 January 2025
Request for supplementary information (RSI)	30 January 2025
CHMP Rapporteur Assessment Report	22 April 2025
PRAC Rapporteur Assessment Report	23 April 2025
PRAC members comments	30 April
Updated PRAC Rapporteur Assessment Report	2 May 2025
PRAC Outcome	8 May 2025
CHMP members comments	12 May 2025
Updated CHMP Rapporteur Assessment Report	14 May 2025
Opinion	22 May 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Resectable muscle invasive bladder cancer (MIBC), stage T2N0-1M0 to T4aN0-1M0 (corresponding to AJCC Stage II or IIa, 8th edition) and transitional cell and mixed transitional/nontransitional cell histologies (TCC) of the bladder.

The claimed therapeutic indication

IMFINZI in combination with cisplatin-based chemotherapy as neoadjuvant treatment, followed by IMFINZI as monotherapy adjuvant treatment after radical cystectomy, is indicated for the treatment of adults with muscle invasive bladder cancer (MIBC).

The final approved indication is:

IMFINZI in combination with gemcitabine and cisplatin as neoadjuvant treatment, followed by IMFINZI as monotherapy adjuvant treatment after radical cystectomy, is indicated for the treatment of adults with resectable muscle invasive bladder cancer (MIBC).

Epidemiology and risk factors

In Europe, bladder cancer is estimated to be the fifth most common newly diagnosed cancer with an estimated 224,777 new cases and the eighth most common cause of cancer death with 70,383 cancer-related deaths reported in 2022. In Europe, the age-standardized incidence rate (per 100,000 persons) is 21.1 for males and 5.0 for females. The age-standardized mortality rate (per 100,000 person/years) is 5.4 for men and 1.2 for women (GLOBOCAN 2022).

Urothelial carcinoma (also known as transitional cell carcinoma) is the most common type of cancer of the bladder, ureter, urethra, and renal pelvis, and accounts for approximately 90% of primary malignancies of the urinary tract (NCCN Guidelines 2024). Urothelial carcinoma of the bladder is generally divided into MIBC and non-muscle invasive bladder cancer (NMIBC) based on invasion of the muscularis propria.

The most important risk factor for developing bladder cancer is tobacco smoking, which accounts for approximately 50% of cases, followed by occupational exposure to aromatic amines and ionising radiation (Powles et al. 2021 ESMO Clinical Practice Guideline).

Clinical presentation, diagnosis and stage/prognosis

MIBC accounts for approximately 25% to 30% of newly diagnosed bladder cancer (Babjuk et al. 2019, Boccardo and Palmeri 2006, Burger et al. 2013). The prognosis of urothelial bladder cancer depends on multiple factors, but the TNM stage at diagnosis is the single most important prognostic factor for urinary bladder carcinoma. The 5-year overall survival for pT1 is 75%, pT2 is 50%, and pT3 is 20% (ncbi.nlm.nih.gov/books/NBK536923). The number of positive lymph nodes is associated with increased risk of cancer-specific death (HR 1.9, 95% CI 1.04-3.46 for N1 disease; HR 4.3, 95% CI 2.25-8.34 for ≥ 2 LNs) (Tarin et al. 2012 doi: 10.1016/j.eururo.2012.01.049).

Even with the use of neoadjuvant chemotherapy (NAC), disease recurrence rates after cystectomy are still very high and occur in approximately 40% to 45% of patients within 3 years (Pfister et al. 2022).

Approximately 55% of patients who were treated with adjuvant nivolumab in the high risk setting experienced disease recurrence or death within 36 months (Galsky et al. 2023).

Table 1 provides a summary of efficacy outcomes in prospective randomised studies in patients with MIBC/MIUC (muscle invasive urothelial cancer) in the neoadjuvant or adjuvant setting.

Table 1 Summary of Efficacy Outcomes Based on Prospective Randomised Studies in Patients with MIBC/MIUC

Study name / Study population	Treatment arms	Number of patients	DFS/PFS		OS	
SWOG-8710 Muscle-invasive bladder cancer (cT2N0M0-T4aN0M0) Grossman et al 2003	Neoadjuvant MVAC + radical cystectomy	153	Not reported		Median OS: 77 months (95% CI: 55 – 104)	
	Radical cystectomy alone	154	Not reported		Median OS: 46 months (95% CI: 25 – 60)	
GETUG/AFU V05 VESPER Muscle-invasive bladder cancer (cT2N0M0 or pT3-pT4 or pN+) Pfister et al 2022 Pfister et al 2024	Neoadjuvant dd-MVAC + radical cystectomy	218	Not reported; 3-year PFS rate: 66%	PFS HR: 0.70 (95% CI: 0.51 – 0.96) p = 0.025	OS5 66% (95% CI: 60 – 73)	HR: 0.71 (95% CI: 0.52 – 0.97)
	Neoadjuvant GC + radical cystectomy	219	Not reported; 3-year PFS rate: 56%		OS5 57% (95% CI: 50 – 64)	
CheckMate-274 High risk muscle-invasive urothelial carcinoma (ypT2-pT4a or ypN+ after prior chemotherapy; pT3-pT4a or pN+ if no prior chemotherapy) Galsky et al 2023 Galsky et al 2024	Adjuvant nivolumab	353 (ITT)	DFS 36 months: 45.0% Median DFS: 22 months (95% CI: 18.8 – 36.9)	HR: 0.71 (95% CI: 0.58 – 0.86) [a]	Median OS: 69.5 months (95% CI: 58.1 – NE)	HR: 0.76 (95% CI: 0.61 – 0.96)
	Adjuvant placebo	356 (ITT)	DFS 36 months: 34.9% Median DFS: 10.9 months (95% CI: 8.3 – 15.2)		Median OS: 50.1 months (95% CI: 38.2 – NE)	
AMBASSADOR High risk muscle-invasive urothelial carcinoma (≥ pT2 and/or pN+ or margins+ after prior chemotherapy, or pT3 and/or pN+ or margins+ if no prior chemotherapy) Apolo et al 2024	Adjuvant pembrolizumab	354	Median DFS: 29.0 months (95% CI: 21.8 – NE)	HR: 0.69 (95% CI: 0.55 – 0.87; p = 0.0013)	Median OS: 50.9 months (95% CI: 43.9 – NE)	HR: 0.98 (95% CI: 0.76 – 1.26; p = 0.88)
	Observation	348	Median DFS: 14.0 months (95% CI: 9.7 – 20.20)		Median OS: 55.8 months (95% CI: 53.3 – NE)	

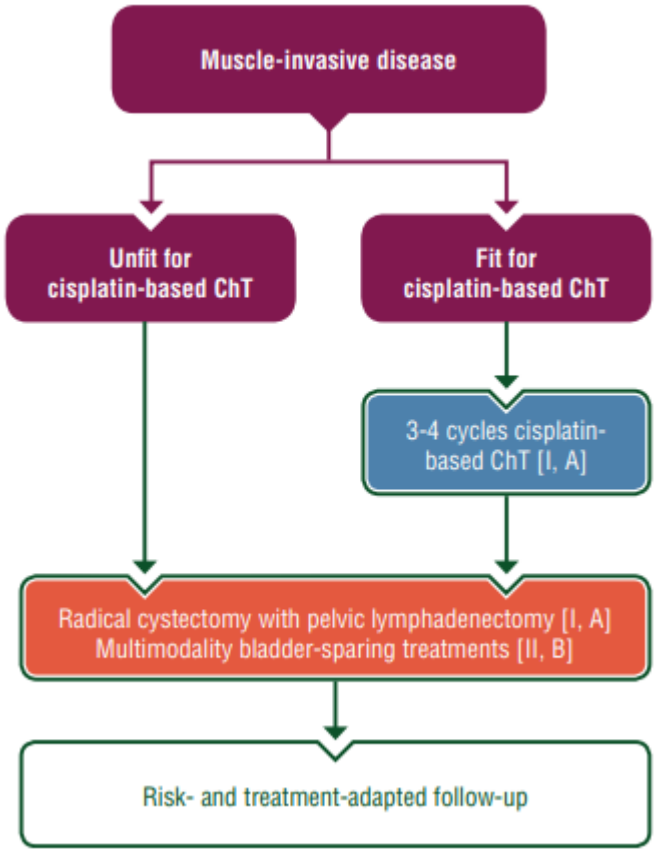
[a] Updated analysis results following prior statistically significant result (see Table 4).

Management

According to the current 2021 ESMO Clinical Practice Guideline on bladder cancer, neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy (RC) with pelvic lymph node dissection is the standard of care for resectable MIBC staged cT2-T4a, N0-1, M0 (AJCC Stage II or IIIa).

The use of cisplatin-based neoadjuvant chemotherapy for bladder cancer is supported by a meta-analysis of 11 randomised trials, showing a 5% absolute increase in 5-year OS and a 9% absolute increase in 5-year DFS compared with radical cystectomy alone (Advanced Bladder cancer Meta-analysis collaboration 2005 DOI: 10.1016/j.eururo.2005.04.006). Cisplatin-gemcitabine or accelerated methotrexate, vinblastine, adriamycin and cisplatin (MVAC) are the most widely given neoadjuvant regimens and the optimal number of treatment cycles to be given, has not been established (2021 ESMO Clinical Guideline on bladder cancer). Adjuvant chemotherapy for patients who have received neoadjuvant chemotherapy is currently not recommended.

Figure 1. Current ESMO treatment recommendations:



Other approved PD-L1/PD-1 inhibitors in bladder cancer

Anticancer agents that inhibit PD-L1 (atezolizumab, durvalumab, and avelumab), and inhibitors of PD-1 (nivolumab and pembrolizumab), have demonstrated clinical activity in advanced urothelial carcinoma (kobi al. 2023).

Pembrolizumab (EMEA/H/C/003820/II/0150, 25 July 2024), avelumab (EMEA/H/C/004338/II/0018, 10 December 2020), and nivolumab (EMEA/H/C/003985/II/0137, 25 April 2024) are currently approved in the EU for the treatment of urothelial cancer.

Unmet medical need

Despite the advancements in the treatment of MIBC, there remains an unmet medical need for additional treatment options to improve long-term survival outcomes in this patient population.

2.1.2. About the product

Durvalumab is a human monoclonal antibody of the immunoglobulin G1 kappa subclass that inhibits binding of PD-L1 (B7 homolog 1, CD274) to PD-1 (CD279) and CD80 (B7 1 Blockade of PDL1/PD1 and PDL1/CD80 interactions releases the inhibition of T cells and promotes an antitumour immune response, without inducing antibody dependent cell mediated cytotoxicity.

The addition of immunotherapy to chemotherapeutic agents has resulted in improved response rates relative to chemotherapy alone in a variety of cancer types and different approaches for combining PD-1 pathway blockers with other agents has been explored in treatment-naïve patients (Langer et al 2016). The rationale for the present study was that PD-L1 inhibition through exposure to durvalumab, in combination with chemotherapeutics such as gemcitabine plus cisplatin (G+C), might increase both the

long-term response rate and the frequency of response by preventing the MIBC tumour cells from evading immune-mediated antitumour response, as well as by averting intrinsic resistance.

Current approvals of durvalumab in the EU

Durvalumab is currently approved in the EU for the treatment of locally advanced, unresectable, NSCLC in adult patients whose tumours express PD L1 on ≥1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy (EMEA/H/C/004771/0000). Durvalumab is also approved in combination with standard-of-care platinum-based chemotherapy as 1L treatment of extensive stage small cell lung cancer (ES SCLC; EMEA/H/C/004771/II/0014/G), in combination with gemcitabine and cisplatin for 1L treatment of unresectable or metastatic biliary tract cancer (BTC) (EMEA/H/C/004771/II/0046), in combination with tremelimumab for advanced HCC (EMEA/H/C/004771/II/0045), and also in monotherapy (EMEA/H/C/004771/II/0057), and in combination with tremelimumab and platinum-based chemotherapy for metastatic NSCLC with no sensitising EGFR mutations or ALK positive mutations (EMEA/H/C/004771/II/0041). Recently, durvalumab has also been approved the for the treatment of adults with resectable NSCLC at high risk of recurrence and no EGFR mutations or ALK (EMEA/H/C/004771/II/0064) and for the treatment of adults with limited-stage small cell lung cancer (LSSCLC) whose disease has not progressed following platinum-based chemoradiation therapy (EMEA/H/C/004771/II/0069).

2.1.3. General comments on compliance with GCP

The MAH claims that the clinical study program was carried out in accordance with GCP, as documented by the ICH 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

Durvalumab is an IgG1 monoclonal antibody, a protein being extensively degraded in the patient's body by regular proteolytic mechanisms before excretion. Durvalumab is expected to biodegrade in the environment and does not pose a significant risk to the environment. Thus, according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00 corr2), durvalumab is exempt from the submission of Environmental Risk Assessment studies as the product and excipients do not pose a significant risk to the environment.

2.2.2. Conclusion on the non-clinical aspects

The updated data submitted in this application, do not lead to a significant increase in environmental exposure further to the use of durvalumab. Considering the above data, durvalumab is not expected to pose a risk to the environment. The justification for not performing any ERA studies is accepted.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH 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.

Table 2: Tabular overview of all clinical studies

Type of study	Study identifier	Objective(s) of the study	Study design and type of control	Test products, dosage regimen, route of administration	No. of subjects randomized/ treated	Healthy subjects or diagnosis of patients	Duration of treatment	Study status [b]; type of report
Controlled Clinical Studies								
Efficacy and safety	D933RC00001 (NIAGARA) Refer to Interim CSR (16Sep2024)	Efficacy, safety, tolerability, PK, immunogenicity, symptoms, and HRQoL	Phase III, randomized, open-label, parallel-group, no treatment control, global study	D+G+C arm: Neoadjuvant durvalumab 1500 mg plus gemcitabine /cisplatin IV Q3W for 4 cycles, then adjuvant durvalumab 1500 mg IV Q4W for 8 cycles postcystectomy G+C arm: Neoadjuvant gemcitabine/cisplatin IV Q3W for 4 cycles then no adjuvant therapy post-cystectomy	D + G+C: 533/530 G+C: 530/526	Muscle-invasive bladder cancer	4 cycles Q3W prior to surgery for all patients, followed by up to 8 cycles Q4W after surgery in the durvalumab + chemotherapy arm.	Ongoing; interim
Efficacy and safety	D4191C00001 (PACIFIC) Refer to Interim CSR (21Jul2017) Refer to CSR Addendum 1 (17Aug2018)	Efficacy, safety, tolerability, PK, immunogenicity, symptoms and HRQoL	Phase III, randomized, double-blind, placebo-controlled, multicenter, global study	Durvalumab IV 10 mg/kg Q2W for up to 12 months Placebo IV Q2W for up to 12 months	Total: 713/709 Durvalumab 476/475 Placebo 237/234	Adult patients with locally advanced, unresectable, Stage III NSCLC, whose disease has not progressed after platinum-based concurrent chemo-radiation therapy	Maximum of 12 months, or until progressive disease, initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, treatment discontinuation criteria are met	Complete; Interim; Addendum 1

Type of study	Study identifier	Objective(s) of the study	Study design and type of control	Test products, dosage regimen, route of administration	No. of subjects randomized/ treated	Healthy subjects or diagnosis of patients	Duration of treatment	Study status [b]; type of report
Efficacy and safety	D4191C00004 (ARCTIC) Refer to Final CSR (29Apr2019)	Efficacy, safety, tolerability, PK, immunogenicity, symptoms and HRQoL	Phase III, randomized, open-label, multicenter, global study	**Sub-study A:** Durvalumab IV 10 mg/kg Q2W up to 12 months SoC IV or oral **Sub-study B:** Durvalumab + Tremelimumab durvalumab IV 20 mg/kg plus tremelimumab IV 1 mg/kg Q4W up to 12 weeks, then durvalumab IV 10 mg/kg Q2W from Week 16 for 34 weeks Durvalumab IV 10 mg/kg Q2W up to 12 months Tremelimumab IV 10 mg/kg Q4W for 24 weeks, then Q12W for 24 weeks SoC IV or oral	**Sub-study A:** Total: 126/125 Durvalumab 62/62 SoC 64/63 **Sub-study B:** Total: 469/460 Durvalumab + Tremelimumab Total: 174/173 Durvalumab 117/117 Tremelimumab 60/60 SoC 118/110	Adult patients with recurrent or progressive NSCLC (Stage IIIb-IV) after having received at least 2 prior systemic treatment regimens, including 1 platinum-based chemotherapy regime for NSCLC. Tumor samples must be assessed as PDL1-high (ie, TC ≥ 25% for Substudy A) or PD-L1-low/negative (ie, TC < 25% for Substudy B)	Maximum of 12 months, or until progressive disease, initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, treatment discontinuation criteria are met	Complete; Final
Efficacy and safety	D419AC00001 (MYSTIC) Refer to Final CSR (12Jun2019)	Efficacy, safety, PK, immunogenicity, symptoms and HRQoL	Phase III, randomized, open-label, multicenter, global study	Durvalumab IV 20 mg/kg Q4W Durvalumab + Tremelimumab Durvalumab IV 20 mg/kg Q4W for 4 doses/cycles plus tremelimumab IV 1 mg/kg for 4 doses/cycles, then durvalumab IV 20 mg/kg from Week 16	Total: 1118/1092 Durvalumab 374/369 Durvalumab + Tremelimumab 372/371 SoC 372/352	Adult patients with advanced or metastatic NSCLC (Stage IV) not amendable to curative surgery or radiation and with no prior chemotherapy or any other	Until progressive disease, or treatment discontinuation criteria are met	Complete; Final

Type of study	Study identifier	Objective(s) of the study	Study design and type of control	Test products, dosage regimen, route of administration	No. of subjects randomized/ treated	Healthy subjects or diagnosis of patients	Duration of treatment	Study status [b]; type of report
				SoC IV		systemic therapy for advanced or metastatic NSCLC		
Efficacy and safety	D4193C00002 (EAGLE) Refer to Final CSR (20May2019)	Efficacy, safety, tolerability, and symptoms and HRQoL	Phase III, randomized, open-label, multicenter, global study	Durvalumab IV 10 mg/kg Q2W Durvalumab + Tremelimumab durvalumab IV 20 mg/kg Q4W for 4 doses then IV 10 mg/kg Q2W beginning 4 weeks after last combination dose, plus tremelimumab IV 1 mg/kg Q4W for 4 doses SoC IV	Total: 736/723 Durvalumab 240/237 Durvalumab + Tremelimumab 247/246 SoC 249/240	Adult patients with PD-L1-positive or negative, recurrent or metastatic SCCHN who have progressed during or after only one palliative systemic treatment regimen that contained a platinum agent or who have progressed within 6 months of last platinum dose	Until progressive disease, or initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, treatment discontinuation criteria are met	Complete; Final
Efficacy and safety	D419LC00001 (KESTREL) Refer to Final CSR (28Apr2021)	Efficacy, safety, tolerability, immunogenicity, PK, disease related symptoms and HRQoL	Phase III, randomized, open-label, comparative, multicenter, global study	Durvalumab + tremelimumab arm: Durvalumab IV 1500 mg Q4W plus tremelimumab IV 75 mg for 4 doses Durvalumab arm: Durvalumab IV 1500 mg Q4W SoC: Six 3-week cycles consisting of a platinum (cisplatin 100 mg/m^2 of body surface area or carboplatin AUC of 5	Total: 823/806 Durvalumab + tremelimumab arm: 413/408 Durvalumab arm: 204/202 SoC arm: 206/196	Adult patients with R/M SCCHN who were not amenable to local curative therapy with surgery or radiation and who had not received prior systemic therapy for R/M disease, unless it was given as part of multimodali	Until progressive disease, initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or other discontinuation criteria were met	Complete Final

Type of study	Study identifier	Objective(s) of the study	Study design and type of control	Test products, dosage regimen, route of administration	No. of subjects randomized/ treated	Healthy subjects or diagnosis of patients	Duration of treatment	Study status [b]; type of report
				mg/mL/min IV) on Day 1, 5FU 1000 mg/m^2/day on Days 1 through 4 of every 3-week cycle, and weekly cetuximab (400 mg/m^2 on Day 1 of Cycle 1, and then 250 mg/m^2 weekly for up to six 3-week cycles and 250 mg/m^2 IV weekly for maintenance until progressive disease		ty treatment for locally advanced or locally recurrent disease.		
Efficacy and safety	D419BC00001 (DANUBE) Refer to Final CSR (13Aug2020)	Efficacy, safety, tolerability, immunogenicity, PK, and disease related symptoms and HRQoL	Phase III, randomized, open-label, comparative, multicenter, global study	D monotherapy: Durvalumab IV 1500 mg Q4W D +T Durvalumab IV 1500 mg Q4W plus tremelimumab IV 75 mg for up to 4 doses, followed by D monotherapy (1500 mg IV Q4W) until confirmed disease progression SoC (cisplatin + gemcitabine or carboplatin + gemcitabine): **Cisplatin + gemcitabine 28-day cycle:** Cisplatin (70 mg/m^2 IV on Day 2 of every 28-day cycle) + gemcitabine (1000 mg/m^2 IV on Days 1, 8, and 15 of each 28-day cycle), for up to 6 cycles.	Total: 1032/ 998 D monotherapy 346/345 D+T 342/340 SoC 344/313	Adult patients with unresectable, Stage IV transitional cell carcinoma of the urothelium (including renal pelvis, ureters, urinary bladder, and urethra) not previously treated with first-line chemotherapy for advanced disease	Until confirmed progressive disease or other discontinuation criteria were met	Complete; Final

Type of study	Study identifier	Objective(s) of the study	Study design and type of control	Test products, dosage regimen, route of administration	No. of subjects randomized/ treated	Healthy subjects or diagnosis of patients	Duration of treatment	Study status [b]; type of report
				Cisplatin + gemcitabine 21day cycle: Cisplatin (70 mg/m^2 IV on Day 1 of every 21day cycle) + gemcitabine (1000 to 1250 mg/m^2 IV on Days 1 and 8 o each 21-day cycle) for up to 6 cycles. **Carboplatin + gemcitabine:** carboplatin (AUC o 4.5 to 5 on Day 1 of each 21-day cycle) + gemcitabine (1000 mg/m^2 IV o Days 1 and 8 of each 21day cycle), for up to 6 cycles.				
Efficacy and safety	D419CC00002 (HIMALAYA) Refer to Final CSR (19Jan2022)	Efficacy, safety, tolerability, immunogenicity, PK, disease related symptoms and HRQoL	Phase III, randomized, openlabel, comparative, multicenter, global study	D arm: Durvalumab IV 1500 mg Q4W T300+D arm Durvalumab IV 1500 mg Q4W plus tremelimumab IV 300 mg for 1 dose T75+D Arm Durvalumab IV 1500 mg Q4W plus tremelimumab IV 75 mg for 4 doses S arm: Sorafenib 400 mg BID	Total: 1324/1302 D arm 389/388 T300+D arm 393/389 T75+D Arm 153/152 S arm: 389/374	Adult patients with unresectable HCC who are not eligible for locoregional therapy and have not received prior systemic therapy for HCC (first-line setting)	Until progressive disease, or unacceptable toxicity, withdrawal of consent, or other discontinuation criteria were met	Complete; Final
Efficacy and safety	D419QC00001 (CASPIAN) Refer to Interim CSR	Efficacy, PK, immunogenicity, symptoms and HRQoL, safety, and tolerability	Phase III, randomized, open-label, comparative, multicente	**Arm 1:** During chemotherapy durvalumab IV 1500 mg Q3W for 4 doses (Weeks 0, 3, 6, 9)	Arm 1 268/266 Arm 2 268/265	Adult patients with ESSCLC eligible to receive 1L treatment	Arms 1+2: Until progressive disease, or unacceptable toxicity, withdrawal of consent,	Complete; Final; Interim

Type of study	Study identifier	Objective(s) of the study	Study design and type of control	Test products, dosage regimen, route of administration	No. of subjects randomized/ treated	Healthy subjects or diagnosis of patients	Duration of treatment	Study status [b]; type of report
	(05Sep2019) Refer to Final CSR (26Aug2020)		r, global study	+ tremelimumab IV 75 mg Q3W for 4 doses (Weeks 0, 3, 6, 9), and SoC IV Q3W for 4 doses (Weeks 0, 3, 6, 9) <u>Post-Chemotherapy</u> durvalumab IV 1500 mg Q4W from Week 12 to progressive disease tremelimumab IV 75 mg once at Week 16 **Arm 2:** <u>During chemotherapy</u> durvalumab IV 1500 mg Q3W for 4 doses (Weeks 0, 3, 6, 9) and SoC IV Q3W for 4 doses (Weeks 0, 3, 6, 9) <u>Post-Chemotherapy</u> durvalumab IV 1500 mg Q4W from Week 12 to progressive disease **Arm 3:** SoC IV Q3W for 4 doses (Weeks 0, 3, 6, 9) and, if clinically indicated, Q3W on Weeks 12 and 15	<u>Arm 3</u> 269/266		or discontinuation criteria are met <u>Arm 3:</u> Up to 6 cycles post-randomization	
Efficacy and safety	D933AC00001 (TOPAZ-1) Refer to final CSR (21Feb2022)	Efficacy, PK, immunogenicity, safety, tolerability, diseaserelated symptoms, and HRQoL	Phase III, randomized, double-blind, placebo-controlled, multi-regional study	**Combination therapy:** Durvalumab IV 1500 mg or placebo Q3W for up to 8 doses in combination with cisplatin 25 mg/m^2 and gemcitabine 1000 mg/m^2	Total: 685/680, Durvalumab plus cisplatin/gemcitabine 341/338 Placebo plus cisplatin/gemcitabine 344/342	Adult patients with previously untreated, unresectable locally advanced or metastatic BTC (IHCC,	Combination therapy for up to 8 cycles followed by monotherapy until clinical progression (or RECIST 1.1-	Complete; Final

Type of study	Study identifier	Objective(s) of the study	Study design and type of control	Test products, dosage regimen, route of administration	No. of subjects randomized/ treated	Healthy subjects or diagnosis of patients	Duration of treatment	Study status [b]; type of report
				(each administered on Days 1 and 8, Q3W) for up to 8 cycles. Following the gemcitabine/cisplatin treatment period, patients received monotherapy: **Durvalumab Monotherapy:** Durvalumab IV 1500 mg or placebo Q4W until clinical progression or RECIST 1.1-defined progressive disease or another discontinuation criterion was met		EHCC, or GBC)	defined radiological progressive disease), unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met	
Efficacy and safety	D9311C00001 (DUO-E) Refer to Interim CSR (21Sep2023)	Efficacy, safety, tolerability, PK, immunogenicity, symptoms and HRQoL	Phase III double-blind, randomized, placebo-controlled, multicenter study	Durvalumab 1120 mg durvalumab/placebo Q3W for a maximum of 6 cycles, followed by 1500 mg durvalumab/placebo Q4W (IV) Olaparib 300 mg bd (oral)	Total: 718/709 Durvalumab 238/235 Olaparib 239/238 Placebo 241/236	Patients with newly diagnosed advanced or recurrent endometrial cancer	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	Ongoing; interim (PFS analysis and interim OS analysis)
Efficacy and safety	D419MC00004 (POSEIDON) Refer to Final CSR (06Sep2021)	Efficacy, safety, tolerability, PK, immunogenicity, and symptoms and HRQoL	Phase III, randomized, openlabel, comparative, multicenter, global study	**Arm 1:** Durvalumab + Tremelimumab + SoC durvalumab IV 1500 mg Q3W for 4 doses + SoC then durvalumab IV 1500 mg Q4W	Total: 1013/997 Arm 1 338/330 Arm 2 338/334	Adult patients with metastatic NSCLC with tumors that lack activating EGFR mutations	Arms 1+2: Until progressive disease, or unacceptable toxicity, withdrawal of consent, or	Complete; Final

Type of study	Study identifier	Objective(s) of the study	Study design and type of control	Test products, dosage regimen, route of administration	No. of subjects randomized/ treated	Healthy subjects or diagnosis of patients	Duration of treatment	Study status [b]; type of report
				until progressive disease AND tremelimumab IV 75 mg Q3W for 4 doses and 1 additional dose at Week 16 **Arm 2:** Durvalumab + SoC durvalumab IV 1500 mg Q3W for 4 doses + SoC then durvalumab IV 1500 mg Q4W until progressive disease **Arm 3:** SoC abraxane + carboplatin, pemetrexed + cisplatin or carboplatin, or gemcitabine + cisplatin or carboplatin	Arm 3 337/333	and ALK fusions eligible to receive 1L treatment	discontinuation criteria are met Arm 3: Up to 6 doses post-randomization	
Efficacy and safety	D4193C00001 (HAWK) Refer to Final CSR (03Oct2017) Refer to CSR Addendum 1 (10Jan2019)	Efficacy, safety, tolerability, diseaserelated symptoms and HRQoL	Phase II, single-arm, multicenter, global study	Durvalumab IV 10 mg/kg Q2W for up to 26 doses	NA/112	Adult patients with PD-L1-positive R/M SCCHN	For up 12 months, with an option for re-treatment (for up to a further 12 months)	Complete; Final, Addendum 1
Efficacy and safety	D4191C00003 (ATLANTIC) Refer to Final CSR (20Sep2016)	Efficacy, safety, tolerability, PK, and immunogenicity	Phase II, openlabel, multicenter study	Durvalumab IV 10 mg/kg Q2W for up to 12 months	Total: NA/444 Cohort 1 NA/111 Cohort 2 NA/265	Adult patients with NSCLC (Stage IIIb-IV) whose disease has progressed or recurred after both a	Maximum of 12 months, or until progressive disease, initiation of alternative cancer therapy,	Complete; Final

Type of study	Study identifier	Objective(s) of the study	Study design and type of control	Test products, dosage regimen, route of administration	No. of subjects randomized/ treated	Healthy subjects or diagnosis of patients	Duration of treatment	Study status [b]; type of report
					Cohort 3 NA/68	platinum-based therapy and at least 2 prior systemic treatment regimens Cohort 1: EGFR/ALK+ and PD-L1 high (TC ≥ 25%) Cohort 2: EGFR/ALK wild type/unknown and PD-L1 high (TC ≥ 25%) Cohort 3: EGFR/ALK wild type unknown and PD-L1 high (TC ≥ 90%)	unacceptable toxicity, withdrawal of consent, treatment discontinuation criteria are met	
Efficacy and safety	CD-ON-MEDI4736-1108 (Study 1108) Refer to 3rd Interim CSR (28Jun2017) Refer to Final CSR (24May2018)	Safety, tolerability, efficacy, PK, and immunogenicity	Phase I/II, firstin-human, open-label, multicenter, global study	**Dose escalation:** Durvalumab IV 0.1 mg/kg Q2W 0.3 mg/kg Q2W 1 mg/kg Q2W 3 mg/kg Q2W 10 mg/kg Q2W 15 mg/kg Q3W **Dose exploration:** Durvalumab IV 20 mg/kg Q4W **Dose expansion:** Durvalumab IV 10 mg/kg Q2W	Durvalumab NA/1001	Adult patients with advanced solid tumors	Maximum of 12 months, or until progressive disease, initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, treatment discontinuation criteria are met	Complete; 3rd Interim; Final

Type of study	Study identifier	Objective(s) of the study	Study design and type of control	Test products, dosage regimen, route of administration	No. of subjects randomized/ treated	Healthy subjects or diagnosis of patients	Duration of treatment	Study status [b]; type of report
Safety	D4190C00002 (Japan Study 02) Refer to Final CSR (24Oct2018)	Safety, tolerability, PK, immunogenicity, and efficacy	Phase I, openlabel, multicenter study	**Durvalumab monotherapy:** 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 **Combination therapy:** Dose-expansion phase durvalumab IV 20 mg/kg Q4W for 12 months AND tremelimumab IV 1 mg/kg Q4W for 4 doses	**Dose escalation** NA/22 **Dose expansion** durvalumab: NA/124 Durvalumab + Tremelimumab: 127/124	Dose escalation: Adults in Japan with advanced solid tumors refractory to standard therapy Dose expansion: Adult patients with confirmed BTC, EC or SCCHN whose disease has progressed with at least 1 platinum-based therapy	Maximum of 12 months, or until progressive disease, initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, treatment discontinuation criteria are met	Complete; Final
Efficacy and safety	D4193C00003 (CONDOR) Refer to Final CSR (19Oct2017) Refer to Addendum 1 CSR (08Jan2019)	Efficacy and HRQoL	Phase II, randomized, open-label, multicenter, global study	Durvalumab monotherapy durvalumab IV 10 mg/kg Q2W Tremelimumab monotherapy tremelimumab IV 10 mg/kg Q4W for 7 doses followed by 10 mg/kg Q12W for 2 doses Combination therapy durvalumab IV 20 mg/kg Q4W for 4 doses then IV 10 mg/kg Q2W until 12 months or progressive diseas AND	Total: 267/263 Durvalumab: 67/65 Tremelimumab: 67/65 Durvalumab + Tremelimumab: 133/133	Adult patients with recurrent or metastatic SCCHN	Maximum of 12 months, or until progressive disease, initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, treatment discontinuation criteria are met	Complete; Final, Addendum 1

Type of study	Study identifier	Objective(s) of the study	Study design and type of control	Test products, dosage regimen, route of administration	No. of subjects randomized/ treated	Healthy subjects or diagnosis of patients	Duration of treatment	Study status [b]; type of report
				tremelimumab IV 1 mg/kg Q4W for 4 doses				
Efficacy and safety	D4190C00022 (Study 22) Refer to Final CSR (20Aug2021)	Safety, tolerability, efficacy, and biomarkers	Phase I/II, randomized, open-label, multiple-part, global study	Part 1 T75+D: tremelimumab IV 75 mg (1 mg/kg) × 4 doses + durvalumab IV 1500 mg (20 mg/kg) Q4W Part 2A and China Cohort D: durvalumab monotherapy IV 1500 mg (20 mg/kg) Q4W T: tremelimumab monotherapy IV 750 mg (10 mg/kg) Q4W × 7 doses followed by Q12W T75+D: tremelimumab IV 75 mg (1 mg/kg) × 4 doses + durvalumab IV 1500 mg (20 mg/kg) Q4W Part 2B T300+D: tremelimumab IV 300 mg (4 mg/kg) × 1 dose + durvalumab IV 1500 mg (20 mg/kg) Q4W Part 3 D: durvalumab monotherapy IV 1500 mg (20 mg/kg) Q4W T: tremelimumab monotherapy IV 750 mg (10 mg/kg) Q4W × 7 doses followed by Q12W	433/426 Part 1 40/40 Parts 2 and 3 332/326 China Cohort 14/13 Part 4 47/47	Adult patients with advanced hepatocellular carcinoma	Until treatment discontinuation criteria are met	Complete; Final

Type of study	Study identifier	Objective(s) of the study	Study design and type of control	Test products, dosage regimen, route of administration	No. of subjects randomized/ treated	Healthy subjects or diagnosis of patients	Duration of treatment	Study status [b]; type of report
				T75+D: tremelimumab IV 75 mg (1 mg/kg) × 4 doses + durvalumab IV 1500 mg (20 mg/kg) Q4W T300+D: tremelimumab IV 300 mg (4 mg/kg) × 1 dose + durvalumab IV 1500 mg (20 mg/kg) Q4W <u>Part 4</u> D1120+B: durvalumab IV 1120 mg (15 mg/kg) + bevacizumab IV 15 mg/kg Q3W				

[a] Note: Except for the NIAGARA CSR, these CSRs may have previously been submitted to the application but are listed here for purposes of the safety pool and/or population PK analysis.

[b] Status pertains to the status of the CSR. Follow-up data may be collected for individual studies.

1L, first line; ALK, anaplastic lymphoma kinase; AUC, area under the concentration curve; BID, twice-daily; BTC, biliary tract carcinoma; C, cisplatin; CSR, Clinical Study Report; D, durvalumab; EC, esophagus carcinoma; EGFR, epidermal growth factor receptor; EHCC, extrahepatic cholangiocarcinoma; ES-SCLC, extensivestage small cell lung cancer; G, gemcitabine; GBC, gallbladder cancer; HCC, hepatocellular carcinoma; HRQoL, healthrelated quality of life; IHCC, intrahepatic cholangiocarcinoma; IV, intravenous; NA, not applicable; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand 1; PK, pharmacokinetic(s); Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; Q12W, every 12 weeks; RECIST 1.1, Response Evaluation Criteria in Solid Tumors Version 1.1; R/M, recurrent/metastatic; S, sorafenib; SCCHN, squamous cell carcinoma of the head and neck; SoC, standard-of-care; T, tremilimumab; TC, tumor cells.

2.3.2. Clinical Pharmacology

The clinical pharmacology data was provided supporting the use of neoadjuvant IMFINZI (durvalumab) in combination with gemcitabine plus cisplatin prior to radical cystectomy, followed by adjuvant durvalumab monotherapy in adult patients with MIBC.

The PK, pharmacodynamics, and immunogenicity of durvalumab have been previously well characterized and are summarized in the respective current prescribing information.

New PK and immunogenicity data are pertaining only to the pivotal study for the current submission (Study D933RC00001, hereafter referred to as NIAGARA), in order to support the proposed indication, dosage, and duration of treatment.

Bioanalytical methods

IMFINZI (durvalumab) is an approved product and the overall view of the formulation development process, and the summary of biopharmaceutic studies and associated analytical methods were submitted in previous submissions to the agency.

PK and ADA sampling: Samples for durvalumab PK analysis were collected during the neoadjuvant period pre-dose (ie, within 60 minutes of the start of durvalumab infusion) at Cycles 1, 2, and 4, and post-dose end of infusion (within 10 minutes after end of durvalumab infusion) at Cycle 1. In the adjuvant period, durvalumab PK samples were collected pre-dose at Cycles 2 and 5. Samples for ADA analysis were collected pre-dose during the neoadjuvant period at Cycles 1, 2, and 4 and pre-dose during the adjuvant period at Cycles 2 and 5. PK and ADA samples were collected at FU approximately 3 months after EOT.

The bioanalytical methods used for the determination of durvalumab serum concentration, the detection of ADA to durvalumab, and the detection of nAb to durvalumab in human serum in the NIAGARA study are listed in Table 3.

Table 3 Overview of Bioanalytical Methods Used in the Pivotal NIAGARA Study

Measurement	Laboratory	Method number
Durvalumab	1	X
ADA	A	Y
nAb	I	Z

Assay parameters for durvalumab serum concentrations, ADA, and nAb methods used in the NIAGARA study are provided in Table 4, Table 5, Table 6.

Table 4 Summary of Durvalumab Serum Concentration Assay Parameters in the NIAGARA Study

Method number	XYZ
Report number	183708
LLOQ (ng/mL)	50.00
Range (ng/mL)	50.00 to 1600.00
Inter-assay %RE range	-17.1 to 0.0
Inter-assay %CV range	9.23 to 12.8
Intra-assay %RE range	-19.8 to -7.0
Intra-assay %CV range	3.4 to 9.9

Summary of method performance in NIAGARA is presented in Table 5.

Table 5 Summary Method Performance of a Bioanalytical Method to Measure Durvalumab in Human Serum

Method performance in Study D933RC00001 (NIAGARA) Bioanalytical Report: 188063		
Assay passing rate	128 of 135 (94.8%), including ISR	Table 1 of Report 188063
Standard curve performance	• Cumulative bias range: -5.7 to 7.4% • Cumulative precision: ≤ 6.5% CV	Table 9 and Table 10 of Report 188063
QC performance	• Cumulative bias range: -3.8 to 11.3% • Cumulative precision: ≤ 11.3% CV • TE: ≤ 22.6% [a]	Table 11 and Table 12 of Report 188063
Method reproducibility	Incurred sample re-analysis was performed on 6.71% (198) study samples and 89.4% of the samples met the pre-specified criteria.	Table 17 and Table 18 of Report 188063
Study sample analysis/stability	Two samples were tested, but not reported, which were outside of the established stability of 721 days at 70°C ± 10°C	Heading 1.2.1.2 of Report 183708 Addendum 2
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ: 11 Performance during accuracy and precision runs: Not applicable	

Table 6 Summary of Anti Durvalumab Antibody Assay Parameters in the NIAGARA Study

Method number	XYZ
Screening assay cut point[a]	1.59
Screening assay false-positive rate (%)	5
Assay LOD (ng/mL)[b]	8.22
Assay detectable range (ng/mL)	8.22 to 100000
Assay drug tolerance	Assay can detect ≥82.3 ng/mL positive control in the presence of ≤ 100µg/mL of durvalumab [c]
Inter-assay precision (%CV)	15.6 to 27.0 [d]
Intra-assay precision (%CV)	1.94 to 3.80
Confirmatory assay cut point (% inhibitioin)[e]	29.4
Confirmatory assay false-positive rate (%)	0.1
Validaton report number	XXX
Synopsis of amendment history	Addendum 1: Additional Stability

[a] Cut point was established in each validation study by statistical analysis of SN ratios of RLU responses of the individual naïve samples from patients with cancer without drug normalized relative to the pooled serum matrix blank RLU signal.

[b] Represents screening assay sensitivity.

[c] Additional drug tolerance evaluation was performed at the AstraZeneca South San Francisco bioanalytical laboratory. According to the Report G-IM-0143, the assay can detect ≥ 100 ng/mL positive control in the presence of ≤ 161 µg/mL of durvalumab (≤ 182 µg/mL in the screening tier).

[d] The overall precision of the raw response for each positive control level (high positive control, low positive control), and re-adjusted low positive control was ≤ 23.0% and met the target criterion of ≤ 25.0%. The overall precision of the raw response for negative control was 27.0%, which was greater than the target criterion of ≤ 25.0%. High negative control response was observed in 2 runs. The runs were performed on the same day and met the final acceptance criteria of cut point factor (1.59 signal to background ratio) < low positive control signal to noise. All other runs demonstrated comparable negative control response; therefore, overall precision of the raw response for negative control was found to be acceptable.

[e] Confirmatory cut point was established for each disease state matrix by statistical analysis of the percent inhibition levels of the responses of individual naïve samples from patients with cancer tested, both with and without drug. A 0.1% false-positive rate was used for mesothelioma and other cancer indications.

Drug tolerance for the screening assay was evaluated using samples prepared at various concentrations of surrogate ADA and durvalumab in 2 assay runs. ADA1 and ADA3 were tested at 8 concentrations levels (2000, 1000, 500, 250, 100, 40, 16, and 0 ng/mL). Each ADA concentration was tested in the presence of each concentration of durvalumab at 0, 10, 100, and 182 µg/mL (G-IM-0143).

Drug tolerance results for the screening assay are summarized below and are shown in two different ways. Table 7 presents the lowest detectable ADA levels in the presence of each durvalumab concentration in the screening assay. Table 8 presents the highest tolerated durvalumab concentration with the corresponding ADA level in the screening assay. Data was derived by linear regression between 2 data points flanking the cut point, and reported as the mean of 2 assay runs.

Table 7 Lowest detectable ADA levels in the screening assay

IMFINZI® Drug Level (µg/mL)	Goat polyclonal anti-IMFINZI® (ADA1) ng/mL	Monoclonal anti-TM A8LO_ComHit3 (ADA3) ng/mL
182	622	76
100	265*	27
10	67*	2

*These values are averages of two assay runs (265 ng/mL is average of 221 and 309 ng/mL; 67 ng/mL is average of 91 and 43 ng/mL) and are slightly different from the values reported in validation (82.30 ng/mL and 27.43 ng/mL respectively, V-IM-0077[2]), which were values generated from a single assay run.

Table 8 Highest tolerated Imfinzi concentrations in the screening assay

Surrogate ADA concentration (ng/mL)	Tolerated IMFINZI® concentration (µg/mL)	
	Goat polyclonal anti-IMFINZI® (ADA1)	Monoclonal anti-TM A8LO_ComHit3 (ADA3)
2,000	≥182	≥182
1,000	≥182	≥182
500	164	≥182
250	107	≥182
100	48	≥182
40	10	138

Table 9 Summary of Anti-durvalumab neutralizing antibody assay parameters in the NIAGARA Study

Method number	XYZ
Assay cut point[a]	1.20
Assay false-positive rate (%)	1
Assay LOD (ng/mL)[b]	220.69
Assay drug tolerance	Assay can detect ≥ 2000 ng/mL of positive control in the presence of 1000 µg/mL of durvalumab in 100% serum
Inter-assay precision (%CV)	7.91 to 18.3 (based on SN ratio)
Intra-assay precision (%CV) range	2.3 to 10.3
Validaton report number	XXX
Synopsis of amendment history	NA

[a] Cut point was established by statistical analysis of SN ratios of RLU responses of the individual naïve samples from patients with cancer without drug normalized relative to the pooled serum matrix blank RLU signal.

[b] Represents assay sensitivity.

Pharmacokinetics

At EFS IA2, PK data (serum concentrations of durvalumab) were available for a total of 507 patients in the PK Analysis Set. Results are provided in Table 10. Given the timing of assessments, the PK of durvalumab in NIAGARA was consistent with expectations based on previously reported PK data from studies of durvalumab (monotherapy and in combination with chemotherapy).

Table 10 Summary of durvalumab concentrations over time in the NIAGARA Study (PK Analysis set)

Analysis timepoint	Mean (SD) µg/mL	Median (min, max) µg/mL	%CV	Geometric mean µg/mL [a]	Geometric %CV [a]	Number BLQ/n
Neoadjuvant 1500 mg Q3W IV (N = 507)						
Cycle 1, Day 1/Week 1 - Pre-Infusion	BLQ	BLQ (BLQ, 505 [b])	NA	BLQ	NA	477/488 [b]
Cycle 1, Day 1/Week 1 - Post-Infusion	473.2 (121.9)	457.3 (0.236, 1140)	25.76	451.8	45.61	12/490
Cycle 2, Day 1/Week 4 - Pre-Infusion	116.4 (59.4)	109.3 (50.1, 719)	51.05	109.3	32.7	1/344
Cycle 4, Day 1/Week 10 - Pre-Infusion	227.9 (72.23)	215.8 (52.1, 551)	31.7	216.8	33.27	1/244
Adjuvant 1500 mg Q4W IV (N = 507)						
Cycle 2, Day 1/Week 5 - Pre-Infusion	107.9 (39.79)	101.7 (26, 235)	36.88	100.7	39.39	0/303
Cycle 5, Day 1/Week 17 - Pre-Infusion	203.8 (80.85)	196.3 (1.63, 724)	39.68	186.9	52.07	0/239
Follow up (N = 507)						
3 months approx. after EOT	50.74 (40.49)	42.78 (0.322, 236)	79.79	35.2	127.9	19/283

[a] Calculated using log transformed data

[b] There were 11 patients with quantifiable durvalumab concentrations at the Cycle 1, Day 1 pre-infusion timepoint; the reasons for this are unknown.

N, number of patients in the PK Analysis Set; n, number of evaluable PK samples collected at timepoint; number BLQ, number of evaluable PK samples collected at timepoint that were BLQ.

Pharmacokinetics Across Studies

The PK of durvalumab monotherapy has been previously well characterized in patients with solid tumors, and these results have been summarized (data not shown). In all studies, only sparse sampling was performed for the assessment of PK.

Table 11 shows the observed durvalumab trough and peak concentrations in the NIAGARA study compared with the D pan-tumor pool (the pooled safety dataset of patients treated with durvalumab (D) across multiple tumor types (pan-tumor) in clinical trials, including the NIAGARA study) in the PK analysis set (patients who received at least one dose oof IP per the protocol for whom any postdose data were available and who did not violate or deviate from the protocol in ways that would significantly affect the PK analyses). The observed geometric mean durvalumab concentrations at the Cycle 1, Day 1 post-infusion timepoint were similar for the NIAGARA neoadjuvant 1500 mg Q3W dosing regimen and the D

pan-tumor 1500 mg fixed dose and 20 mg/kg Q4W dosing regimens. The observed Ctrough geometric mean durvalumab concentrations were higher for the NIAGARA neoadjuvant dosing regimen compared with dosing regimens across the D pan-tumor pool (Cycles 2 and 4 pre-infusion timepoints) and compared with the NIAGARA adjuvant (1500 mg Q4W) dosing regimen (Cycle 2 pre-infusion timepoint). Although pre-infusion concentrations of the 1500 mg Q3W dose during the NIAGARA neoadjuvant period were shown to be slightly higher compared to 1500 mg Q4W (D pan-tumor pool and NIAGARA Q4W adjuvant dosing regimens), the relative increase in dose intensity of durvalumab is supported by the fact that durvalumab has a flat exposure-safety relationship with dose levels prescribed clinically, and PK modeling reveals no clinically meaningful differences in drug levels between these dosing regimens (see EMEA/H/C/004771/II/0045 and EMEA/H/C/004771/II/0057 for further details of population PK and ERES relationship analyses).

Table 11 Summary of serum durvalumab concentrations in the NIAGARA Study and the D Pan-Tumour pool (PK Analysis Set)

Visit - timepoint		Geometric mean, µg/mL [a] (geometric %CV [a]) [number BLQ/n]			
	NIAGARA study (N = 507)	D pan-tumor pool [b]			
		1500 mg Q4W IV (N = 959)	20 mg/kg Q4W IV (N = 424)	10 mg/kg Q2W IV (N = 2520)	Total (N = 3903)
Neoadjuvant 1500 mg Q3W IV					
Cycle 1, Day 1 - Pre-infusion	BLQ [477/488]	BLQ [729/756]	BLQ [408/416]	BLQ [1870/1955]	BLQ [3007/3127]
Cycle 1, Day 1 - Post-infusion	451.8 (45.61) [12/490]	448.7 (36.37) [15/523]	445.6 (38.08) [5/376]	202.0 (46.62) [50/2267]	253.1 (59.83) [70/3166]
Cycle 2, Day 1 – Pre-infusion	109.3 (32.70) [1/344]	73.0 (56.27) [5/823]	64.5 (86.82) [0/24]	81.5 (63.89) [1/1199]	77.8 (61.51) [6/2046]
Cycle 4, Day 1 - Pre-infusion	216.8 (33.27) [1/244]	121.8 (74.46) [0/536]	114.1 (63.44) [2/206]	135.1 (61.92) [1/297]	123.9 (69.11) [3/1039]
Adjuvant 1500 mg Q4W IV					
Cycle 2, Day 1 - Pre-infusion	100.7 (39.39) [0/303]	140.3 (78.82) [2/205]	129.7 (60.50) [0/150]	171.8 (57.50) [2/803]	159.8 (63.13) [4/1158]
Cycle 5, Day 1 - Pre-infusion	186.9 (52.07) [0/239]	NA	79.2 (3.53) [0/2]	184.1 (67.75) [1/536]	183.6 (67.88) [1/538]
Follow up					
3 months approx. after EOT	35.2 (127.93) [19/283]	16.4 (306.25) [20/257]	18.2 (334.51) [12/107]	18.7 (186.73) [27/625]	18.0 (226.78) [59/989]

[a] Calculated using log transformed data

[b] The D pan-tumor pool includes data from 13 studies: HIMALAYA, Study 22, Study 1108, HAWK, Japan Study 02, DANUBE, KESTREL, ATLANTIC, PACIFIC, MYSTIC, ARCTIC, CONDOR, and EAGLE (see Appendix Section 5, Table 9 for an overview of the studies in the D pan-tumor pool).

N, number of patients in the PK Analysis Set; n, number of evaluable PK samples collected at timepoint; number BLQ, number of evaluable PK samples collected at timepoint that were BLQ.

The chemotherapy combination studies of CASPIAN (EMEA/H/C/004771/II/0014/G), POSEIDON (EMEA/H/C/004771/II/0041), and TOPAZ-1 (EMEA/H/C/004771/II/0046) had dosing regimens that were similar to the neoadjuvant period in the NIAGARA study. The geometric mean durvalumab Ctrough concentration of 109.3 µg/mL (n = 344, geometric %CV = 32.70) observed at Cycle 2, Day 1 in the NIAGARA study (see Table 4) was similar to the geometric mean Ctrough concentrations observed at Cycle 2, Day 1 in the CASPIAN study (109.5 µg/mL [n = 237, geometric %CV = 64.55]), POSEIDON study (91.53 µg/mL [n = 285, geometric %CV = 100.58]) and TOPAZ-1 study (88.39 µg/mL [n = 250, geometric %CV = 56.57]).

Immunogenicity: At EFS IA2, immunogenicity data were analyzed for 453 ADA-evaluable patients (ie, 453 of 530 patients were included in the ADA Analysis Set). Overall, the durvalumab ADA prevalence (percentage of ADA-evaluable patients who were ADA-positive at any time) was 8.2% (37 of 453 patients). The ADA incidence (percentage of ADA-evaluable patients who were TE-ADA-positive) was 1.8% (8 of 453 patients). Six of 453 patients (1.3%) were positive for nAb to durvalumab. The median of maximum ADA titers to durvalumab in TE-ADA-positive patients was 8.0, close to the minimum required dilution of 1. **The presence of ADAs had no apparent impact on the PK.** However, the low numbers of ADA-positive patients precluded definitive conclusions.

Absorption

NA. Durvalumab is administered by I.V. infusion.

Distribution

NA. Durvalumab is a monoclonal antibody.

Elimination

NA. Only 10 min after end of infusion and C_{trough} samples were collected in NIAGARA.

Dose proportionality and time dependencies

NA. Only one dose level was used in NIAGARA.

Special populations

Not evaluated in NIAGARA

Pharmacokinetic interaction studies

NA

Pharmacokinetics using human biomaterials

NA

2.3.3. Pharmacodynamics

No new pharmacodynamics data are available to that reported in previous submissions for durvalumab registration.

Mechanism of action

PD-L1 is expressed on both tumor cells and tumor associated immune cells in the tumor microenvironment, and expression of PD-L1 can be induced by inflammatory signals. Programmed cell death ligand 1 blocks T cell function and activation through interactions with its receptors PD-1 and CD80 (B7.1). Durvalumab (Imfinzi) is a fully human high affinity IgG1 kappa mAb that binds to PD-L1 and selectively blocks the interaction of PD-L1 with PD 1 and CD80 while leaving PD-1/PD-L2 interaction intact (Stewart et al 2015). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of T cells and promotes an antitumor immune response, without inducing antibody dependent cell mediated cytotoxicity.

Primary and secondary pharmacology

Prior population PK analyses have been conducted for multiple submissions (e.g., CASPIAN (EMEA/H/C/004771/II/0014/G), POSEIDON (EMEA/H/C/004771/II/0041), TOPAZ-1 (EMEA/H/C/004771/II/0046), and HIMALAYA), which have evaluated various intrinsic and extrinsic covariates, including tumour types. These analyses have showed there is no clinically meaningful PK difference among different tumour types.

Immunogenicity

Table 12 Overview of Durvalumab Administration, Dosing Regimen, Anti-drug Antibody Sampling Timepoints, and Immunogenicity Results in the NIAGARA Study

Study number (name) **DCO date**	**Route of administration and dosage regimen**	**Durvalumab ADA sampling timepoints**	**Durvalumab ADA results**
D933R00001 **(NIAGARA)** DCO: 29Apr2024 (IA2)	Durvalumab 1500 mg + G+C Q3W IV for 4 cycles followed by surgery. Post-surgery patients received durvalumab 1500 mg Q4W IV for 8 additional cycles.	Neoadjuvant phase: Pre-dose at Cycles 1, 2, and 4. Post-surgery (adjuvant) phase: Pre-dose at Cycles 2 and 5.	ADA prevalence was 8.2% (37/453[a]). ADA incidence was 1.8% (8/453 [a]). 6/453 [a] patients (1.3%) were nAb positive.

[a] The denominator for calculation of percentage was the number of ADA-evaluable patients. ADA-evaluable patients consisted of patients in the safety analysis set with a non-missing durvalumab baseline ADA result and at least one non-missing durvalumab postbaseline ADA result.

Table 13 Summary of ADA Responses to Durvalumab in the NIAGARA Study and D Pan tumor Pool (Safety Analysis Set)

ADA category	Number of patients (%)	
	NIAGARA study[a] 1500 mg Q3W IV or 1500 mg Q4W IV (N = 530)	D pan-tumor pool [b] 10 mg/kg Q2W, 20 mg/kg Q4W or 1500 mg Q4W IV (N = 4045)
ADA-evaluable patients [c]	**453**	**3069**
ADA prevalence (ADA positive at any visit) [d]	37 (8.2)	191 (6.2)
Median of maximum titer	4.0	4.0
ADA incidence (TE-ADA positive) [e]	8 (1.8)	84 (2.7)
Median of maximum titer	8.0	4.0
Treatment-boosted ADA [f]	1 (0.2)	2 (0.1)
Median of maximum titer	128.0	12.0
Treatment-induced ADA (positive postbaseline only)	7 (1.5)	82 (2.7)
Median of maximum titer	8.0	4.0
ADA positive at baseline only	29 (6.4)	92 (3.0)
Median of maximum titer	2.0	4.0
ADA positive postbaseline and positive at baseline	1 (0.2)	17 (0.6)
Median of maximum titer	128.0	8.0
Persistently positive ADA [g]	4 (0.9)	67 (2.2)
Median of maximum titer	64.0	4.0
Transiently positive ADA [h]	4 (0.9)	32 (1.0)
Median of maximum titer	5.0	4.0
nAb positive at any visit	6 (1.3)	16 (0.5)
Median of maximum titer	3.0	16.0

a Overall study period: neoadjuvant (D + G+C Q3W), post-surgery, and adjuvant (D monotherapy Q4W) periods.
b The D pan-tumor pool integrates data from 13 studies: HIMALAYA, Study 22, Study 1108, HAWK, Japan Study 02, DANUBE, KESTREL, ATLANTIC, PACIFIC, MYSTIC, ARCTIC, CONDOR, and EAGLE (see Appendix Section 5, Table 9 for an overview of the studies in the D pan-tumor pool).
c ADA-evaluable patients consisted of patients in the safety analysis set (N) with a non-missing durvalumab baseline ADA result and at least one non-missing durvalumab postbaseline ADA result.
d ADA prevalence is defined as the proportion of patients with positive ADA result at any time, baseline or postbaseline.
ADA incidence is defined as the proportion of patients who were TE-ADA-positive. This category consists of patients with treatment-induced ADA and patients with treatment-boosted ADA.
e Treatment-boosted ADA is defined as baseline-positive ADA titer that was boosted to ≥ 4-fold during the study period.
f Persistently positive is defined as having at least 2 postbaseline 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. This category includes patients meeting these criteria who were ADA-positive at baseline.
g Transiently positive is defined as having at least one postbaseline ADA-positive measurement and not fulfilling the conditions for persistently positive. This category includes patients meeting these criteria who were ADA-positive at baseline.
h The denominator for calculation of percentage for ADA categories is the number of ADA-evaluable patients in the group. If a patient had > 1 titer result, the maximum titer result was used to calculate median, min and max whether it was baseline or postbaseline.

2.3.4. PK/PD modelling

No new modelling or update of previous models were presented.

2.3.5. Discussion on clinical pharmacology

Clinical pharmacology data is based on the new PK and immunogenicity data of the pivotal study NIAGARA and 13 supportive monotherapy studies in the D Pan-tumour and individual PK data from 3 monotherapy studies (CASPIAN (EMEA/H/C/004771/II/0014/G), POSEIDON, and TOPAZ-1) to support the proposed indication, dosage and duration of treatment. A population PK and exposure-response analyses were performed with the pooled data from previous submissions. However, no update has been performed within the current variation.

The intended dosing regimen is 1500 mg in combination with chemotherapy every 3 weeks for 4 cycles prior to surgery (neoadjuvant), followed by 1500 mg every 4 weeks as monotherapy after surgery (adjuvant) the same posology that was used in the pivotal study.

Bioanalytical Method used for Pharmacokinetics

The bioanalytical method was validated in 2016. Subsequently, 3 amendments were issued covering blinded analysis of samples from sponsor (MedImmune), long term stability (721 days at -80°C) and submission of additional precision and accuracy tables per request by the new sponsor (AstraZeneca). The same method was used in the CASPIAN (EMEA/H/C/004771/II/0014/G) and HIMALAYA studies (EMEA/H/C/004771/II/0045, EMEA/H/C/004771/II/0057), which were also combination studies. In the CASPIAN study, durvalumab was co-administered with etoposide and either carboplatin or cisplatin. In the HIMALAYA study durvalumab was co-administered with tremelimumab. Hence, the bioanalytical method is considered well-established. Review of analysis plan, data audits and report audits were performed by QA. However, no audits during critical stages of analytical procedures or sample receipt were documented. Incurred sample reproducibility was assessed in NIAGARA in 198 samples (6.91%). The test met an acceptable rate of reproducibility. The percentage of samples included for ISR is below 10% which is acceptable as a similar percentage was successfully tested in both the CASPIAN and HIMALAYA clinical studies. The ISR assessment and the assay passing rate of >90% show that the bioanalytical method is robust and reliable.

Bioanalytical Methods used for Immunogenicity

The validation of methods for testing immunogenicity including nAbs was assessed in procedure Imfinzi II-69. Drug tolerance as assessed in study G-IM-0143 by MedImmune indicates there may be an issue with the screening assay used in the NIAGARA study. When goat polyclonal anti-durvalumab antibodies are tested, the surrogate ADA concentration should be 1000 ng/mL, if the drug tolerance is above 182 µg/mL. This may preclude detection of ADAs during the neoadjuvant Q3W phase. However, during the adjuvant phase in which durvalumab is administered Q4W, this appears to be less of an issue.

Immunogenicity was assessed in NIAGARA study with 453 ADA-evaluable patients and compared to the results from the 3069 ADA-evaluable patients in the D pan-tumour pool. In the NIAGARA study, the ADA prevalence was 8.2% and the incidence was 1.8%. The results were similar to the prevalence and incidence of ADA reported in the durvalumab pan-tumour pool (6.2% and 2.7% respectively). On the other hand, % of patients with neutralizing ADA was higher in comparison to the % reported in the D-pan-tumour pool (1.3% and 0.5% respectively). However, these results were comparable to other studies in the durvalumab clinical development program. Furthermore, the impact of immunogenicity on pharmacokinetics has been assessed and no apparent effect on durvalumab serum concentration is observed in ADA positive patients, although the large imbalance between ADA positive and negative patients (8 vs 408) did not allow a proper statistical comparison. Predicted individual durvalumab serum concentration-time profiles by ADA category in the NIAGARA study showed no apparent effect of ADA on the PK of durvalumab. Therefore, there seems not to be immunogenicity concerns following the administration of durvalumab in the studied population.

Pharmacokinetics

Sparse sampling for PK was performed in the NIAGARA study before the first dose, within 10 minutes after the first infusion and thereafter only pre-dose sampling was conducted in cycles 2 and 4 for the neoadjuvant phase and in cycle 2 and 5 in the adjuvant period supplemented at follow up approximately 3 months after end of treatment. Considering that the pharmacokinetics of durvalumab is well-established, this is acceptable.

The interindividual variability was moderate (CV% 32.7 - 52.07 during the study).

Similar to previous analysis, no covariate showed a substantial impact on model parameters CLss and V1. Therefore, the analysis suggests that PK in patients from NIAGARA study is similar to the PK in other patients from other studies included in the population PK model. Overall, no clinically relevant Exposure-Response relationship was observed between durvalumab exposure and efficacy and safety endpoints. The results are in accordance with previous reported durvalumab exposure-response analysis in other approved indications. No changes were introduced to section 5.2 of the SmPC, which is supported.

2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology properties of the combination of durvalumab with gemcitabine plus cisplatin prior to radical cystectomy, followed by durvalumab as monotherapy after surgery for the treatment of adult patients with resectable MIBC have been sufficiently studied based on the limited PK evidence collected in the Phase 3 trial NIAGARA.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

Durvalumab is approved for use at a fixed dose of 1500 mg utilizing both Q3W and Q4W dosing schedules. The fixed dose regimen utilized in the NIAGARA study is aligned with the approved durvalumab dose regimen in ES SCLC, advanced biliary tract cancer, and metastatic NSCLC.

The Q3W dosing schedule utilized in the NIAGARA study (in which durvalumab 1500 mg was administered at a Q3W dosing interval for the first 4 cycles prior to radical cystectomy) was chosen to conform to the Q3W chemotherapy schedule in the neoadjuvant period of the study. After surgery the dosing schedule reverted to a 1500 mg Q4W timeframe, which is the standard fixed dosing regimen supported by in vitro data, nonclinical activity, clinical PK/pharmacodynamics, biomarkers, efficacy and safety (as well as tolerability) data across multiple studies in multiple tumor types.

This proposed durvalumab dosing regimen for patients with resectable MIBC is also supported by evidence of clinically meaningful efficacy and a manageable safety profile following the use of this dosing regimen in the NIAGARA study.

Based on previously reported data, no dose adjustment is necessary based on intrinsic or extrinsic factors (age, renal and hepatic function, race, region, and ECOG performance status).

Weight Adjustment

Guidance for applying weight-based dosing modifications (to 20 mg/kg) if a patient's weight decreased to ≤ 30 kg was provided to Investigators in the NIAGARA study. This guidance is standardized in all fixed-dose durvalumab clinical studies based on previously conducted population PK analyses and simulations.

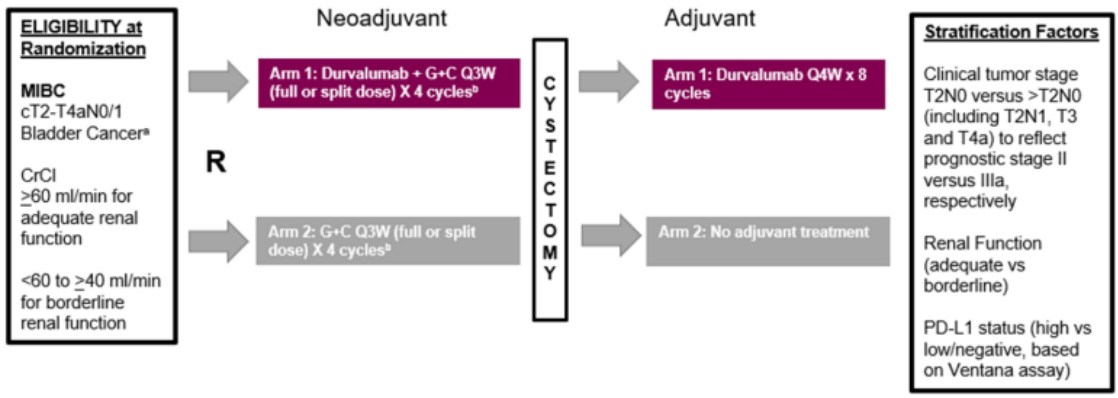
In the NIAGARA study, the body weight of all the patients remained above 30 kg at all assessed timepoints, and therefore the safety profile of the fixed dose regimen in patients with extremely low body weight (≤ 30 kg) could not be evaluated. Nevertheless, as aligned with standard approved dosing regimens, it is recommended that patients with a body weight of 30 kg or less receive weight-based dosing, equivalent to durvalumab 20 mg/kg in combination with chemotherapy, followed by durvalumab 20 mg/kg Q4W as monotherapy until weight increases to greater than 30 kg.

2.4.2. Main study

NIAGARA

NIAGARA (Study D933R00001) is an ongoing Phase III, randomized, open-label, multi-center, global study to determine the efficacy and safety of neoadjuvant durvalumab in combination with gemcitabine and cisplatin prior to radical cystectomy for muscle invasive bladder cancer (MIBC), followed by adjuvant durvalumab (D + G+C arm), compared with neoadjuvant gemcitabine and cisplatin prior to radical cystectomy and no adjuvant treatment (G+C arm). Globally 1063 patients were randomized in a 1:1 ratio.

Figure 2 Flow Chart of Study Design



[a] Enrollment of patients with T2N0 disease was limited to approximately 40% of the targeted global population (for both treatment arms).
[b] Patients with borderline renal function received split-dose G+C and were limited to up to 20% of the targeted global population.
R = Randomization.

Study participants

Inclusion criteria

The main inclusion criteria were:

Age ≥ 18 years at the time of screening.

1. Patients with histologically or cytologically documented muscle-invasive TCC (also known as UC) of the bladder.
2. Patients with transitional cell and mixed transitional/non-transitional cell histologies (adenocarcinoma, squamous cell)/variant transitional (e.g., micropapillary, plasmacytoid, sarcomatoid, nested variant, lymphoepitheliod, nested variant) histologies. Patients with pure non-transitional cell variant histologies and any small cell histology were not eligible.

3. Patients with clinical tumour stage T2-T4aN0/1M0 according to the AJCC Staging Manual (AJCC Cancer Staging Manual, 8th Edition) TCC of the bladder. cN1 disease was defined as the presence of a single lymph node in the true pelvis (perivesical, obturator, internal and external iliac, and sacral lymph node); lymph node must have measured < 20 mm in the short axis (small volume metastasis) and have been resectable, as per the planned lymphadenectomy procedure. Lymph nodes with < 10 mm short axis diameter were considered non-pathological per RECIST 1.1. (Note, criterion changed during CSP amendment 3)
4. A single tumour (T)-stage was determined by the Investigator and was used for documentation of baseline disease characteristics and also for registering the patient for randomization (ie, for stratification purposes). Clinical staging, specifically for the determination of the cT, was a composite of combined results obtained from a pathological assessment of the tumour (from a TURBT sample, confirming muscle invasion), an examination under anesthesia procedure (performed after the completion of the TURBT procedure), and results from a CT/MRI image (Note, criterion changed during CSP amendment 2). Patients also had to meet the following additional criteria:
5. Had to be planning and per the judgment of the Investigator medically fit for treatment with neoadjuvant therapy prior to radical cystectomy (i.e., patients were not to be randomized if they were not eligible or could not receive any neoadjuvant treatment)
6. Had to be planning and per the judgment of the Investigator medically fit to undergo a radical cystectomy at time of enrolment and randomization.
7. Have not received prior systemic chemotherapy or immunotherapy for treatment of MIBC. (Prior local intravesical chemotherapy was allowed regardless of time frame. Prior local intravesical immunotherapy (e.g. BCG) was allowed if completed at least 6 weeks prior to the initiation of study treatment.)
8. ECOG PS of 0 or 1 at enrolment.
9. Tumour PD-L1 status, with IHC assay confirmed by a reference laboratory, had to be known prior to randomization. As such, all patients had to give valid written consent to provide a newly acquired MIBC tumour biopsy during screening (preferred) or provide an available archival MIBC tumour sample taken ≤ 3 months prior to screening. Tumour lesions submitted had to be when the patient was determined to have MIBC (ie, non-MIBC samples were not acceptable). Samples with limited tumour content were not acceptable. The tumour specimens submitted to evaluate PD-L1 status were to be of sufficient quantity to allow for PD-L1 IHC, retrospective evaluation of muscle-invasive disease, and other exploratory biomarker analyses and was preferred in formalin-fixed paraffin-embedded blocks.
10. Adequate organ and marrow function.

Exclusion criteria

The main exclusion criteria were:

1. Evidence of lymph node (N2-3) or metastatic TCC/UC (M1), extravesical TCC/UC that invades the pelvic and/or abdominal wall for bladder cancer (T4b), pure non-urothelial histology, any small cell histology or primary non-bladder (i.e., ureter, urethral, or renal pelvis) TCC/UC of the urothelium. Patients with cN1 and additional radiologically suspected lymph node metastasis within or outside the pelvis should be excluded if the short axis is ≥10 mm as per IV contrast enhanced CT or MRI scan. If an enlarged lymph node ≥10 and <15 mm can be confirmed pathologically (e.g., by biopsy) as a non-cancer [benign] lesion and/or by positron emission tomography-CT, the patient may be considered eligible.

2. Per the judgement of the Investigator, if a nephronureterctomy is required at the time of randomization for tumor of the mid ureter, renal pelvis, or collecting system.

3. If a ureteral tumor is present proximal to common iliacs that would require ureterectomy in addition to the planned cystectomy.

4. Inoperable tumor(s) with fixation to the pelvic wall on clinical exam.

6. Active or prior documented autoimmune or inflammatory disorders, with the exception of vitiligo or alopecia, hypothyroidism stable on hormone replacement, any chronic skin condition that does not require systemic therapy. Patients without active disease in the last 5 years and patients with celiac disease controlled by diet alone could be included, but only after consultation with Astra Zeneca.

7. Uncontrolled intercurrent illness.

8. History of a myocardial infarction within 6 months prior to randomization due to potential cardiotoxic effects observed with gemcitabine.

9. History of another primary malignancy, except for prostate cancer of stage ≤T2cN0M0 without biochemical recurrence or progression, malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of investigational product (IP) and of low potential risk for recurrence, adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease, adequately treated carcinoma in situ without evidence of disease.

12. Active infection. Active tuberculosis or hepatitis B or C or HIV infection, or use of immuno-suppresive medication within 14 days of the first dose of durvalumab except systemic corticosteroids when used in physiological doses or as premedication.

14. New York Heart Association Class III or IV heart failure.

18. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable.

22. Prior pelvic radiotherapy treatment within 2 years of randomization to study.

Treatments

Durvalumab

This study utilized a fixed intravenous dose for durvalumab treatment (1500 mg Q3W) + G+C (up to 4 cycles) prior to radical cystectomy, followed by durvalumab monotherapy (1500 mg Q4W) for an additional 8 cycles post-surgery.

Gemcitabine + Cisplatin

G+C was dosed intravenously at 1000 mg/m^2 on Days 1 and 8 Q3W (gemcitabine) + 70 mg/m^2 on Day 1 Q3W (cisplatin) for patients with adequate renal function (creatinine clearance ≥ 60 mL/min) and at 1000 mg/m^2 on Days 1 and 8 Q3W (gemcitabine) + 35 mg/m^2 on Days 1 and 8 Q3W (cisplatin) for patients with borderline renal function (creatinine clearance ≥ 40 mL/min to < 60 mL/min).

A RECIST 1.1 tumour assessment was performed at baseline and upon completion of neoadjuvant therapy (prior to surgery). After surgery, RECIST 1.1 tumour assessments were performed every 12 weeks for the first 24 months, then every 24 weeks for 36 months, and then every 52 weeks thereafter until progression, the end of study, or death.

Table 14 Study treatments

	Treatment 1	Treatment 2
Study treatment name:	Durvalumab (MEDI4736)	Gemcitabine and cisplatin[a]
Dosage formulation:	500-mg vial solution for infusion after dilution, 50 mg/mL	As sourced locally
Route of administration:	IV	IV
Dosing instructions:	1500 mg IV q3w (neoadjuvant)[b] 1500 mg IV q4w (adjuvant, post-radical cystectomy)	Day 1 and Day 8 (gemcitabine 1000 mg/m^2 IV) of each 21-day cycle (neoadjuvant) Day 1 and Day 8 (cisplatin 35mg/m^2 IV) or Day 1 (cisplatin 70 mg/m^2 IV) each 21-day cycle (neoadjuvant)
Packaging and labelling:	Study treatment will be provided in 500-mg vials. Each vial will be labeled in accordance with GMP Annex 13 and per country regulatory requirements.[c]	Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labeling. Label text will be translated into local language.
Provider:	AstraZeneca	Sourced locally by site[a]

[a] Under certain circumstances when local sourcing is not feasible, G+C treatment may be supplied centrally through AstraZeneca.
[b] Dosing of durvalumab will occur prior to the dosing of G+C chemotherapy
[c] Label text prepared for durvalumab (MEDI4736) will show the product name as "MEDI4736" or "durvalumab (MEDI4736)" depending upon the agreed product name used in the approved study master label document. All naming conventions are correct during this transitional period.
G+C Gemcitabine and cisplatin; GMP Good Manufacturing Practice; IV Intravenous(ly); q3w Every 3 weeks; q4w Every 4 weeks.

A large randomized Phase III has not been conducted to directly compare a 21 day and a 28 day G+C regimen in the neoadjuvant setting for urothelial carcinoma. The 21- day G+C regimen, used in the NIAGARA study, is incorporated in the current NCCN bladder cancer guidelines (NCCN 2023) for the neoadjuvant setting,

Split-dose rationale

Some patients with MIBC may be unable to tolerate the standard dose regimen of cisplatin due to impaired or borderline renal function (Dash et al 2006). For patients with borderline renal function or minimal dysfunction, a split-dose intravenous regimen of 1000 mg/m^2 IV Q3W gemcitabine plus 35 mg/m^2 IV cisplatin on Day 1 and Day 8 Q3W has been considered a reasonable option for patients who would otherwise have no option for treatment with neoadjuvant chemotherapy. This modified regimen has shown potential for an improvement in tolerability compared with other current treatment options for patients with borderline renal function, the potential to avoid dosing delays, reduced toxicity, and comparable benefit to the standard G+C dose in patients with adequate renal function (Abdelhafez and Williams 2017, Hussain et al 2012).

PD-L1 testing

Table 15 PD-L1 Status defined by scoring of Ventana PD-L1 (SP263) Assay

PD-L1 Interpretation	Staining description
PD-L1 status was determined by the percentage of tumor cells with any membrane staining above background by the percentage of tumor-associated ICs with staining (IC+) at any intensity above background. The percent of tumor area occupied by any tumor-associated ICs (Immune Cells Present, ICP) was used to determine IC+, (which was the percent area of ICP exhibiting PD-L1 positive IC staining) is also evaluated.	
High	PD-L1 status was considered high if any of the following were met: • ≥ 25% of TCs exhibit membrane staining • ICP > 1% and IC+ ≥ 25% • ICP = 1% and IC+ = 100%
Low/Negative	PD-L1 status was considered low/negative if: • None of the criteria for PD-L1 high status were met

Tumour assessments

Tumour assessments occur every 12 weeks ±7 days after the date of radical cystectomy for the first 24 months, then every 24 weeks ±7 days for 36 months, and then every 52 weeks (annually) thereafter until unequivocal progression, the end of study, death, study discontinuation, or Sponsor decision, whichever comes first.

Objectives and endpoints

Dual primary endpoint: pCR

Pathological complete response (pCR) rate is defined as the proportion of patients whose pathological staging was T0N0M0 as assessed per central pathology review using specimens obtained via radical cystectomy following the neoadjuvant treatment and was calculated among patients within the ITT population. pCR is assessed by central pathology review.

Dual primary endpoint: EFS

Event Free Survival (EFS) is defined as the time from randomization to the first recurrence of disease after radical cystectomy, the time of first documented progression in patients who are medically precluded from a radical cystectomy, or time of expected surgery in patients who refuse to undergo a radical cystectomy or failure to undergo a radical cystectomy in patients with residual disease, or the time of death due to any cause, whichever occurs first.

EFS is being assessed using CT/MRI and pathology testing performed according to local standards and as clinically indicated.

Table 16 Objectives and endpoints

Objectives	Endpoints
Primary	
To assess the efficacy of durvalumab + G+C combination therapy (neoadjuvant)/ durvalumab alone (adjuvant) (D + G+C) compared to G+C combination therapy (neoadjuvant)/no adjuvant (G+C) in terms of pCR and EFS in MIBC patients	• pCR using assessments per central pathology review • EFS using assessments per BICR or by central pathology review if a biopsy is required for a suspected new lesion
Secondary	
To assess the efficacy of D + G+C vs G+C in terms of EFS at 24 months in MIBC patients	• EFS24 using assessments per BICR or by central pathology review if a biopsy is required for a suspected new lesion
To assess the efficacy of D + G+C compared to G+C in terms of pathologic response at radical cystectomy and EFS in MIBC patients	• pCR using assessments per local pathology review • Proportion of patients who achieve < P2 per local pathology review • EFS using assessments per local Investigator or local biopsy review if a biopsy is required for a suspected new lesion • EFS24 using assessments per local Investigator or local biopsy review if a biopsy is required for a suspected new lesion

Objectives	Endpoints
To assess the efficacy of D + G+C vs G+C in MIBC patients	• MFS and DSS per Investigator assessments or Investigator biopsy review if a biopsy is required for a suspected new lesion • OS • OS at 5 years • DFS in patients who undergo radical cystectomy • Proportion of patients who undergo radical cystectomy • PFS2 as defined by local standard clinical practice
To assess the efficacy of D + G+C vs G+C in terms of pCR and EFS in MIBC patients in the PD-L1-high subgroup. *Note, objective added in CSP amendment 2 (see Section 9.9.1)*	• pCR using assessments per central pathology review • EFS using assessments per BICR or by central pathology review if a biopsy is required for a suspected new lesion
To assess disease-related symptoms, physical function, and other HRQoL in D + G+C vs G+C using the EORTC QLQ-C30 questionnaire	• Adjusted mean change from baseline and time to definitive clinically meaningful deterioration in EORTC QLQ-C30 scale/item scores (prioritized domains: fatigue and pain, physical functioning, and GHS/QoL)
To assess the PK of durvalumab when used in combination with G+C	• Serum concentration of durvalumab and noncompartmental PK parameters (such as peak and trough concentrations, as data allow; sparse sampling)
To investigate the immunogenicity of durvalumab when used in combination with G+C	• Presence of ADAs for durvalumab (confirmatory results: positive or negative)
Safety	
To assess the safety and tolerability profile of D + G+C vs G+C in MIBC patients	• AEs, laboratory findings, vital signs, and ECGs
Exploratory	
To assess patient-reported treatment-related symptoms or tolerability of D + G+C vs G+C using PRO-CTCAE	• PRO-CTCAE (items preselected based on systemic treatment arms) – descriptive summary of responses
To assess overall health status and overall severity of disease-related symptoms in patients in D + G+C vs G+C using the PGIC and PGIS questionnaires, respectively	• PGIC and PGIS – descriptive summary of responses
To explore the impact of treatment and disease state on health state utility using the EQ-5D-5L	• The EQ-5D-5L health state utility index will be used to derive health state utility based on patient-reported data
To evaluate tumor-based biomarkers and associations with efficacy parameters, potentially including, but not limited to, microsatellite stability, tumor mutational burden, and other immune-related biomarkers	• Association of tumor-based assessments with efficacy and clinical parameters[a]
To evaluate circulatory-based and urine-based biomarkers and associations with efficacy parameters, including, but not limited to, circulating tumor DNA	• Association of circulating tumor DNA, whole blood gene expression, and urine biomarkers with efficacy and clinical parameters[a]

[a] Results of this endpoint will not be reported in the CSR.

Primary and secondary objectives changed during CSP amendment 4 to include all MIBC in the analyses (in an ITT manner), rather than only including patients with adequate renal function.

Exploratory endpoint to assess healthcare resource use (HOSPAD) was removed during CSP amendment 5.

Table 17 Definition of efficacy endpoints and analysis methods

Endpoint	Definition	Analysis
pCR [a]	The proportion of patients whose pathological staging was T0N0M0 as assessed using specimens obtained via radical cystectomy following the neoadjuvant treatment. pCR was assessed per central pathology review (dual primary endpoint) and local pathology review (secondary endpoint).	Logistic regression adjusted for the stratification factors, odds ratio and the corresponding CI
EFS [a]	Time from randomization to the first recurrence of disease after radical cystectomy, the time of first documented progression in patients who were medically precluded from a radical cystectomy, or time of expected surgery in patients who refused to undergo a radical cystectomy or failure to undergo a radical cystectomy in participants with residual disease, or the time of death due to any cause, whichever occurred first.	Stratified log-rank test to obtain the p-value, stratified Cox PH model to obtain the HR and the corresponding CI
OS [a] and OS5 [a]	The time from the date of randomization until death due to any cause, regardless of whether the patient withdrew from randomized therapy or received another anticancer therapy (ie, date of death or censoring – date of randomization + 1). 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. The Kaplan-Meier estimate of OS at 5 years after randomization.	Stratified log-rank test for OS. Kaplan-Meier estimates of survival rate at 5 years
Proportion of patients who achieve < P2	The proportion of patients whose pathological staging at radical cystectomy was P0 (T0N0M0)/Pa/P1/Cis as assessed per local pathology review using specimens obtained via radical cystectomy following the neoadjuvant treatment.	Logistic regression adjusted for the stratification factors
EFS24	The Kaplan-Meier estimate of EFS at 24 months after randomization, as assessed per BICR or by central pathology review if a biopsy was required for a suspected new lesion, and per local Investigator or local biopsy review if a biopsy was required for a suspected new lesion.	Kaplan-Meier estimates of EFS rate at 24 months by treatment
MFS	The time from date of randomization until the first recognition of distant metastases or death, whichever occurred first. Patients who were alive and free from metastases were censored at the time of the latest date of assessment from their last evaluable disease assessment.	Stratified log-rank test
DSS	The time from the date of randomization until death due to bladder cancer. Any patient not known to have died due to bladder cancer at the time of analysis was censored based on the last recorded date on which the patient was known to be alive.	Stratified log-rank test
DFS	The time from the date of radical cystectomy to the first recurrence of disease post radical cystectomy, or death due to any cause, whichever occurred first. DFS was assessed in patients who underwent radical cystectomy and were disease free at adjuvant baseline visit per BICR assessment.	Stratified log-rank test
Proportion of patients who undergo cystectomy	The proportion patients who underwent radical cystectomy after the neoadjuvant treatment.	Point estimate and 95% CI
PFS2	The time from the date of randomization to the earliest date of progression which occurred on subsequent therapy following an EFS event or death.	Stratified log-rank test

[a] Alpha controlled within a multiple testing procedure (for details see SAP Section 4.2.1, Appendix 16.1.9).

Table 18 Populations for analysis

Population/Analysis Set	Description
Enrolled	All patients who signed the ICF.
Full analysis set (FAS)	All randomized patients. Patients who were randomized but did not subsequently receive treatment were included in the FAS in the treatment arm to which they were randomized. The analysis of data using the FAS follows the principles of intention to treat.
Safety analysis set	All randomized patients who received at least one dose of study treatment. Safety data were not formally analyzed but summarized according to actual treatment received.
PK analysis set	All patients who received at least one dose of IP per the protocol for whom any postdose data were available and who did not violate or deviate from the protocol in ways that would significantly affect the PK analyses.
ADA analysis set	All patients who received at least one dose of IP per the protocol for whom baseline and at least one non-missing postbaseline ADA result were available.
Cystectomy population	All patients in FAS who underwent radical cystectomy and were disease free at adjuvant baseline. Treatment arms were compared on the basis of randomized study treatment, regardless of the treatment actually received. This analysis set was used for DFS only.
PD-L1 high analysis set	The subset of patients in the FAS whose PD-L1 status was PD-L1 high as defined by VENTANA PD-L1 (SP263) Assay at baseline by IVRS (Table 2)

Sample size

The study was sized to characterise the pCR rate and EFS benefit of D + G+C vs G+C in MIBC patients who had not received prior systemic chemotherapy:

- It was assumed that the pCR for patients (ITT population) in the G+C arm was 35% (Grossman et al 2003). pCR was assumed to be 50% for the D + G+C arm. With 525 patients in each arm, the study would have at least 95% power to demonstrate a statistically significant difference at a 2-sided alpha level of 0.1%.
- The assumed EFS treatment effect under the alternative hypothesis was an average HR of 0.733 for D + G+C vs G+C. With 451 EFS events, the study would have at least 90% power to demonstrate a statistically significant difference at a 2-sided overall alpha level of 4.90%. Two interim analyses were planned at approximately 67% and 91% of the target events. The smallest treatment difference that could be statistically significant was an average HR of 0.82.

Randomisation

This study randomised approximately 1050 patients globally in a 1:1 ratio to receive durvalumab + G+C combination therapy every 3 weeks (q3w) (Arm 1) or G+C combination therapy q3w (Arm 2) for 4 cycles of neoadjuvant chemotherapy prior to radical cystectomy. Following radical cystectomy and during adjuvant therapy, patients in Arm 1 received durvalumab monotherapy every 4 weeks (q4w) for 8 additional cycles, and patients in Arm 2 received no adjuvant treatment.

Randomisation was stratified by:

- Tumor stage (T2N0) versus >T2N0 [including T2N1, T3 and T4a])

- Renal function (adequate renal function versus borderline renal function). Creatinine clearance [CrCl] ≥60 mL/min vs. borderline renal function: CrCl ≥40 mL/min to <60 mL/min)
- PD-L1 status (high versus low/negative).

Blinding (masking)

The study was open-labelled. Hence, no blinding procedure was utilized although EFS was BICR assessed.

Analysis sets

Full analysis set (FAS) (ITT population)

The FAS will include all randomized patients. Unless otherwise specified, the FAS will be used for all efficacy analyses (including PROs). Treatment arms will be compared on the basis of randomized study treatment, regardless of the treatment actually received. Patients who were randomized but did not subsequently go on to receive study treatment are included in the analysis in the treatment arm to which they were randomized.

Cystectomy population

The Cystectomy population will include all patients in FAS who undergo radical cystectomy and were disease free at adjuvant baseline. Unless otherwise specified, the analysis set will be used for DFS only. Treatment arms will be compared on the basis of randomized study treatment, regardless of the treatment actually received.

PD-L1-high analysis set

The PD-L1-high analysis set will include the subset of patients in the FAS whose PD-L1 status is PD-L1-high as defined by Ventana SP263 assay.

Statistical methods

Table 19 Summary of outcome variables and analysis populations

Outcome variable	Populations
Efficacy data	
pCR rate	Full analysis set (ITT population) PD-L1-high analysis set
EFS	Full analysis set (ITT population) PD-L1-high analysis set
Proportion of patients who achieve <P2, EFS24, MFS, DSS, OS, OS5, PFS2, proportion of patients who undergo radical cystectomy	Full analysis set (ITT population)
PROs	Full analysis set (ITT population)
DFS	Cystectomy population
Demography	Full analysis set (ITT population)
PK data	PK analysis set
Safety data	
Exposure	Safety analysis set
AEs	Safety analysis set
ECOG performance status	Safety analysis set
Laboratory measurements	Safety analysis set
Vital signs	Safety analysis set

AE Adverse event; DFS Disease-free survival; DSS Disease-specific survival; ECOG Eastern Cooperative Oncology Group; EFS Event-free survival; EFS24 Proportion of patients alive and event free at 24 months; ITT Intent-to-treat; MFS Metastasis-free survival; OS5 Proportion of patients alive at 5 years; pCR Pathologic complete response; PFS2 Time from the date of randomization to the earliest date of progression which occurs on subsequent therapy following an EFS event or death; PK Pharmacokinetic; PRO Patient-reported outcome.

Dual primary endpoints:

- The dual primary **pCR** is the pCR assessment in MIBC patients per central pathology review.

  pCR was also assessed per local pathology review.

- The dual primary **EFS** is the EFS assessment in MIBC patients per BICR or by central pathology review if a biopsy is required for a suspected new lesion

  - A recurrence of disease includes local (pelvic) recurrence of UC, urinary tract recurrence of UC, or distant metastasis of UC. In the event that progression is confirmed via biopsy or subsequent scans (the confirmation of suspected new lesions initially identified in the scans if applicable), the date of recurrence will be the earliest date among the initial detection of radiological unequivocal new lesion, or the pathological confirmation of new lesion if biopsy is performed to confirm suspected new lesion post cystectomy, or the death due to any causes.

  - Patients who are suspected of having microscopic disease (i.e., no evidence on imaging) or who have documented macroscopic disease (confirmed by imaging) at the completion of neoadjuvant therapy and who refuse to proceed with a radical cystectomy, are declared as progressed, with EFS being declared at the time of expected surgery.

  - For patients who fulfil criteria for a complete clinical response, refuse an initial radical cystectomy and are entered in a noncystectomy extension phase, EFS is defined as time to the first recurrence of disease following a delayed radical cystectomy (if performed). For patients who are medically precluded from or refuse a delayed radical cystectomy, EFS is confirmed at time of unequivocal progression.

Censoring of EFS

EFS was assessed using CT/MRI and pathology testing performed according to local standards and as clinically indicated. The EFS assessment was done by BICR or by central pathology review if a biopsy is required for a suspected new lesion, and by local investigator or local biopsy review if a biopsy is required for a suspected new lesion.

Patients who took subsequent therapy prior to their last evaluable RECIST assessment or progression or death were not censored at their last evaluable RECIST assessment prior to taking the subsequent therapy. Additionally, if the patient progressed or experienced recurrent disease or died directly preceded by 2 or more consecutive missed visits, the patient was still to be counted as having an EFS event. For both of these situations a sensitivity analysis was performed.

Patients who have not progressed or experienced recurrent disease or died at the time of analysis were censored at the time of the latest date of assessment from their last evaluable disease assessment. For the purpose of EFS, the date of surgery was considered as disease assessment date. If the patient had no evaluable visits or did not have baseline disease assessment (i.e., a baseline scan) prior to neoadjuvant treatment, they were censored at Day 1 unless they died within 112 days of randomization. If an adjuvant baseline scan was not recorded, it was considered that no lesions were presented following surgery.

The EFS time was always derived based on assessment dates and not visit dates.

The pCR was compared between the D + G+C and G+C arms using logistic regression models adjusted for the stratification factors (renal function [adequate vs borderline], tumor stage [T2 vs > T2] and PD-L1 status [high vs low/negative]) as covariates in the model based on patients in the FAS. The results of the analysis were presented in terms of an OR together with its associate profile likelihood 99.9% and 95% CI and p-value.

Table 20 Analysis methods and sensitivity analyses of EFS (source SAP, version 6)

EFS	Stratified log-rank test to obtain the p-value, stratified Cox PH model to obtain the hazard ratio and the corresponding confidence interval: Dual primary analysis using BICR or by central pathology review if a biopsy is required for a suspected new lesion: • Arm 1 versus Arm 2 (FAS) Secondary analysis using BICR or by central pathology review if a biopsy is required for a suspected new lesion: • Arm 1 versus Arm 2 (PD-L1 High Population) Sensitivity analysis for primary and secondary using BICR or by central pathology review if a biopsy is required for a suspected new lesion: o Arm 1 versus Arm 2 (FAS): Excluding the PD-L1 stratification factor from the stratified log-rank test and stratified Cox PH model ▪ Subsequently add TC1 or TC25 separately (2 models) as categorical covariates in the model o Using a KM plot of time to censoring where the censoring indicator of the primary analysis is reversed – attrition bias (FAS) o Interval censored analysis – evaluation time bias (FAS) o Analysis where subjects who take subsequent anti-cancer therapy prior to the EFS event will be censored at their last evaluable assessment prior to taking the subsequent therapy – attrition bias (FAS) o Analysis using the 2 missed visit censoring rules – attrition bias (FAS) o Analysis using alternative censoring rules – no adjuvant baseline (FAS) o Sensitivity analysis to assess impact of COVID-19 deaths (FAS)

Subgroup analyses:

Subgroup analyses were conducted comparing EFS between arms in the following subgroups of patients in the FAS including, but not limited to:

- Sex (male versus female)
- Histology
- Age at randomization (<65 years versus ≥65 years)
- Lymph node positive (N0 versus N1)
- Tumor stage (T2N0 versus >T2N0) at baseline per IVRS
- All visible tumor removed during the TUBRT procedure prior to study entry (Yes versus No)
- PD-L1 status (high, low/negative) per IVRS
- Race (white versus non-white)

- TC25 (TC≥ 25% versus TC<25%) and TC1 (TC≥1% versus TC<1%)

Timepoints of primary endpoint analyses (and multiplicity control)

The dual primary endpoint of pCR (FAS) was tested at 1 timepoint (final analysis of pCR; approximately 6 months after the last patient was randomized to the study). The dual primary endpoint of EFS (FAS) was to be tested at 3 timepoints:

- at the time of the final analysis for pCR.
- IA-2 - when approximately 410 EFS events (39% maturity) had occurred across the 2 arms in the FAS, or in April 2024, whichever occurred first.
- final analysis - when the first of the following conditions were met: – Approximately 451 EFS events in patients in the FAS across 2 arms (43% maturity); or – June 2025, approximately 45 months after the last patient was randomized to the study.

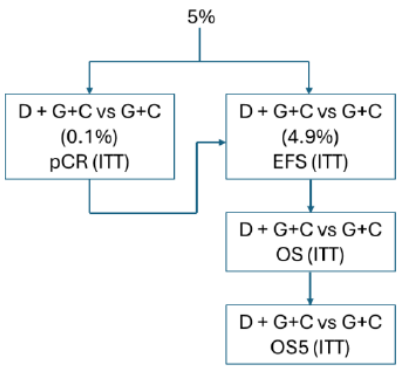
If an interim analysis for EFS was not positive, the study was to continue until the next interim or final analysis as planned. If EFS was positive at an interim analysis the study was to be unblinded and any further analyses of EFS would be descriptive only.

Multiple testing procedure (For details on OS and OS5, please refer to the section on secondary endpoints)

In order to strongly control the type I error at the 5% 2-sided alpha level, a multiple testing procedure with gatekeeping strategy was used across the dual primary endpoints (pCR rate and EFS). If the higher-level hypothesis in the multiple testing procedure was rejected for superiority, the following hypothesis was then tested as shown in Figure 2. Hypotheses were tested using a multiple testing procedure with an alpha-exhaustive recycling strategy (Burman et al 2009). With this approach, hypotheses were tested in a predefined order by first splitting the 5% alpha into 0.1% and 4.9% for pCR and EFS for D + G+C vs G+C, respectively, in the ITT population as outlined in Figure 2.

OS was planned to be tested at 2 interim time points and a final time point in accordance with the hierarchical multiple testing strategy. The first interim analysis of OS was conducted at the time when the IA-2 EFS analysis was conducted (was tested only if EFS was positive via the multiple testing procedure). A second interim analysis will be conducted at the time when the final EFS analysis is conducted. Per the SAP, OS5 will be formally tested (per the MTP) at the final analysis of the study, approximately 5 years after the last patient is randomized to the study. A descriptive analysis of OS5 has been conducted at the IA-2 DCO. The other prespecified secondary analyses were not included in the multiple testing procedure, so are non-confirmatory, with p-values interpreted at a nominal 5% significance level.

Figure 3 NIAGARA Study: Multiple testing procedure for controlling the Type I Error rate



Details on the alpha spending for EFS (Source SAP, version 6)

The alpha level allocated to the EFS was controlled at the interim and final time points using the Lan DeMets Alpha-spending function that approximates an O'Brien Fleming approach, where the alpha level applied at the interim depends on the proportion of information available. The first interim analysis has been performed with 301 events and the 2-sided alpha of 0.69%.

Below is a table describing the statistical treatment of the above secondary variables:

Table 21 Statistical treatment of variables

Endpoint Analysed	Notes
EFS24	Hazard ratio using the KM estimates of EFS24 (following approach by Klein et al. 2007): Secondary analysis using BICR or by central pathology review if a biopsy is required for a suspected new lesion: • Arm 1 versus Arm 2 (Patients with adequate renal function) • Arm 1 versus Arm 2 (ITT population) Secondary analysis per local Investigator or Investigator biopsy review if a biopsy is required for a suspected new lesion: • Arm 1 versus Arm 2 (Patients with adequate renal function) • Arm 1 versus Arm 2 (ITT population)
Proportion of patients who achieve <P2	Logistic regression adjusted for the stratification factors using central pathology review (Patients with adequate renal function, ITT)
OS5	Hazard ratio using the KM estimates (following approach by Klein et al. 2007) (Patients with adequate renal function, ITT)
Proportion of patients who undergo cystectomy	Point estimate and 95% CI (Patients with adequate renal function, ITT)
DSS	Stratified log-rank test (Patients with adequate renal function, ITT)
DFS	Stratified log-rank test (Patients with adequate renal function in the cystectomy population, Cystectomy population)
MFS	Stratified log-rank test (Patients with adequate renal function, ITT)
PFS2	Stratified log-rank test (Patients with adequate renal function, ITT)
EORTC QLQ-C30 endpoints	Average change from baseline using a MMRM analysis
Time to definitive/sustained clinically meaningful deterioration (EORTC QLQ-C30)	Stratified log-rank test

Results

Participant flow and recruitment

First patient enrolled: 16 November 2018.

Last patient enrolled: 23 August 2021.

IA-1 : April 2022

EFS IA-2 and OS IA-1: 29 April 2024

Table 22 Key Dispoisition characteristics (All Patients, IA-2, 29-Apr-2024)

	Number (%) of patients		
	D + G+C	**G+C**	**Total**
Patients randomized	533 (100)	530 (100)	1063 (100)
Patients who received study treatment [a]	530 (99.4)	526 (99.2)	1056 (99.3)
Patients who did not receive study treatment [a]	3 (0.6)	4 (0.8)	7 (0.7)
Patients ongoing neoadjuvant treatment at DCO [b, c]	0	0	0
Patients who completed neoadjuvant treatment [b, c]	417 (78.7)	389 (74.0)	806 (76.3)
Patients who discontinued neoadjuvant treatment [b, c, d]	113 (21.3)	137 (26.0)	250 (23.7)
Patients who entered non-cystectomy extension phase [b]	6 (1.1)	0	6 (0.6)
Patients who underwent cystectomy [a]	470 (88.2)	446 (84.2)	916 (86.2)
Radical cystectomy	469 (88.0)	441 (83.2)	910 (85.6)
Partial cystectomy	1 (0.2)	5 (0.9)	6 (0.6)
Patients who did not undergo cystectomy as planned [a]	63 (11.8)	84 (15.8)	147 (13.8)
Patients who started adjuvant treatment [b]	383 (72.3)	0	383 (36.3)
Patients ongoing adjuvant treatment at DCO [b]	0	0	0
Patients who completed adjuvant treatment [b, e]	288 (54.3)	0	288 (27.3)
Patients who discontinued adjuvant treatment [b, d]	95 (17.9)	0	95 (9.0)
Patients ongoing study at DCO [a, f]	379 (71.1)	333 (62.8)	712 (67.0)

a Percentages are calculated from the number of patients randomized. In NIAGARA, the full analysis set includes all randomized patients.

b Percentages for ***adjuvant treatment*** are calculated from the number of patients who received ***neoadjuvant*** treatment.

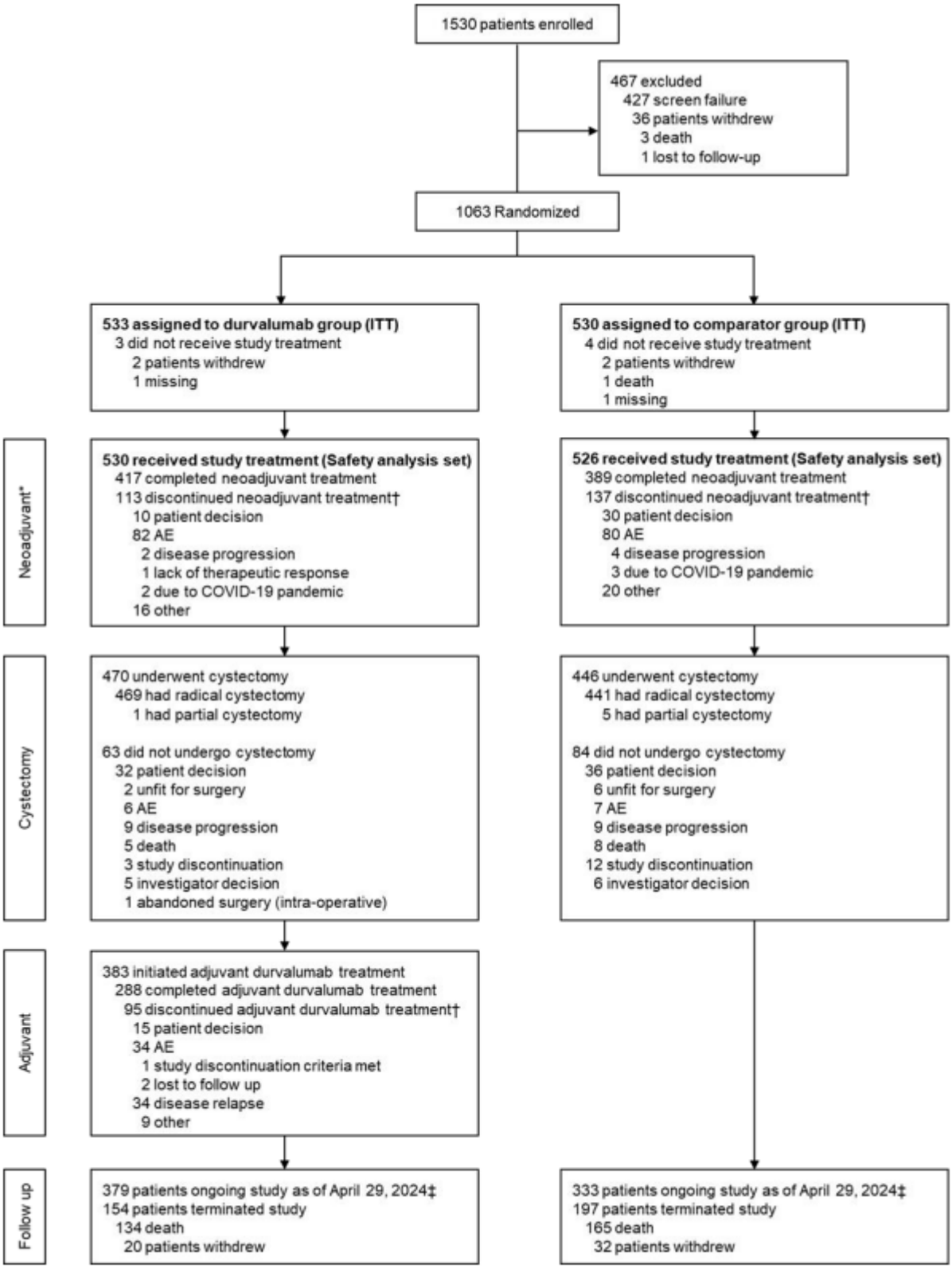
c Neoadjuvant treatment includes non-cystectomy extension phase. Only patients who discontinued all constituent treatments (including SoC) were included as discontinued study treatment.

d 287 (53.8%) of the 533 patients completed all 8 cycles of adjuvant durvalumab.

e Patients ongoing study consist of those randomized patients still receiving treatment, those randomized patients who have completed treatment and are in safety follow-up or those randomized patients who are still in survival follow-up regardless of whether they were administered treatment or not.

f DCO: 29 April 2024.

Figure 4 CONSORT Diagram



*Neoadjuvant treatment includes the non-cystectomy extension phase.

Conduct of the study

Protocol Amendments

Table 23 Rapporteur's summary on substantial protocol amendments:

Date of amendment	Description of change	Brief rationale
23 April 2019	Primary/secondary endpoints updated to reflect EFS assessments by BICR with the addition of central pathology review.	
9 December 2019	Patients in either treatment arm who have a complete clinical response at the completion of neoadjuvant treatment and refuse a radical cystectomy, are allowed to transition into the non-cystectomy extension phase with assessments mirroring those in the adjuvant phase. For patients in the D+G+C arm, this would include additional cycles of durvalumab monotherapy. Definition of EFS updated accordingly, as required by FDA Limit on recruitment of patients with T2 disease to approximately 40% in both treatment arms.	To align with previously published studies describing the distribution of patients with T2 and >T2 disease for patients receiving neoadjuvant chemotherapy and to ensure that the statistical asssumptions for pCR rates between the experimental and control groups are maintained.
20 July 2020	Randomization will be stratified by clinical tumor stage T2N0 versus >T2N0 (including T2N1, T3 and T4a) to reflect prognostic stage II vs. IIIa, respectively. The study population now includes patients with cN1 disease, patients with N2 and N3 disease are not eligible.	In accordance with current NCCN guidelines, patients with stage IIIa disease are now considered for neoadjuvant chemotherapy/radical cystectomy.
1 June 2021	Updated study objectives and study population: the primary analysis for pCR and EFS will be performed on the ITT population instead of patients in the adequate renal function cohort; now	Regulatory advice

	reflected as the primary study objective. Overall survival (OS) added as a secondary endpoint.	
22 June 2023	Changed number of events for final EFS analysis and also added calendar-based assessment timepoints for EFS IA2 and FA. In accordance with these changes, the study power and critical value were also updated, as were the information fraction values at the interim analyses.	To account for the slowing down of EFS events after 2 years
29 January 2024	Removal of "However, if the patient progresses or experiences recurrent disease or dies after 2 or more missed visits, the patient will be censored at the time of the latest evaluable disease assessment." Addition of sensitivity analyses:"Analysis where subjects who take subsequent anticancer therapy prior to the EFS event will be censored at their last evaluable assessment prior to taking the subsequent therapy - attrition bias (ITT)"	The "two missed visits rule" is removed from the primary endpoint EFS to minimize loss of relevant events.

Protocol Deviations

Table 24 Important protocol deviations (Full analysis set, IA-2, 29-Apr-2024)

	Number (%) of patients		
	D + G+C (N = 533)	G+C (N = 530)	Total (N = 1063)
Number of patients with at least 1 important protocol deviation	47 (8.8)	37 (7.0)	84 (7.9)
Lack of evidence of postmenopausal status or positive urinary or serum pregnancy test for female pre-menopausal patients	1 (0.2)	0	1 (0.1)
Written ICF not obtained prior to performing any CSP-related procedures	1 (0.2)	0	1 (0.1)
Patients without histologically or cytologically documented muscle-invasive TCC of the bladder that did not have a clinical stage of T2-T4aN0/1M0. Patients were also to meet the following additional criteria:- Patients who were not planning to or could not receive neoadjuvant therapy - Patients who were not planning to undergo radical cystectomy - Received prior systemic chemotherapy or immunotherapy for treatment of MIBC	1 (0.2)	2 (0.4)	3 (0.3)
Sample used for tumor PD-L1 status were not from a MIBC sample confirmed by pathology at the site, or PD-L1 status was not known / incorrect prior to randomization, or MIBC tumor sample was not within 3 months prior to screening (more than 106 days from screening visit date)	1 (0.2)	3 (0.6)	4 (0.4)
Inadequate organ and marrow function (as defined in protocol)	1 (0.2)	0	1 (0.1)
Evidence of lymph node (N2-3) or metastatic TCC/UC(M1), extravesical TCC/UC that invaded the pelvic and/or abdominal wall for bladder cancer (T4b), or primary non-bladder (ie, ureter, urethral, or renal pelvis) TCC/UC of the urothelium determined by CT or MRI	4 (0.8)	3 (0.6)	7 (0.7)
Prior pelvic radiotherapy treatment within 2 years of randomization to study	1 (0.2)	0	1 (0.1)
Active infection including tuberculosis, HBV, HCV, or HIV determined by criteria outlined in CSP	2 (0.4)	0	2 (0.2)
Failure to collect samples for pCR analysis unless clinically contraindicated	2 (0.4)	0	2 (0.2)
Missed baseline ePRO assessments (C1D1) or patient compliance below 85%	9 (1.7)	16 (3.0)	25 (2.4)
Missing on study key safety assessment for clinical chemistry, hematology, or TSH prior to treatment	1 (0.2)	0	1 (0.1)
Disease assessments not done according to CSP	3 (0.6)	4 (0.8)	7 (0.7)
CrCl was incorrectly calculated causing the patient to be stratified incorrectly	1 (0.2)	1 (0.2)	2 (0.2)
Tumor staging incorrectly entered into IVRS/IWRS causing patient to be stratified incorrectly	17 (3.2)	9 (1.7)	26 (2.4)
Patient received concomitant medication defined as prohibited in the CSP (including other anticancer agents and on study radiotherapy)	4 (0.8)	1 (0.2)	5 (0.5)
Proven recurrence, either by RECIST 1.1-defined radiological progression or positive tumor biopsy from suspected recurrence following radical cystectomy	3 (0.6)	0	3 (0.3)
Number of patients with at least 1 COVID-19 related important protocol deviation	2 (0.4)	4 (0.8)	6 (0.6)
Tumor staging incorrectly entered into IVRS/IWRS causing patient to be stratified incorrectly	0	4 (0.8)	4 (0.4)
Patient received concomitant medication defined as prohibited in the CSP (including other anticancer agents and on study radiotherapy)	2 (0.4)	0	2 (0.2)

The same patient may have had more than 1 important protocol deviation.
DCO: 29 April 2024

Baseline data

Table 25 Demographic and patient characteristics (Full Analysis Set, IA-2, 29-Apr-2024)

Demographic characteristic	D + G+C (N = 533)	G+C (N = 530)	Total (N = 1063)
Age, years			
n	533	530	1063
Mean (StD)	64.1 (8.93)	64.6 (8.94)	64.4 (8.94)
Median (Min, Max)	65.0 (34, 84)	66.0 (32, 83)	65.0 (32, 84)
Age group (years), n (%)			
< 50	33 (6.2)	35 (6.6)	68 (6.4)
≥ 50 - < 65	225 (42.2)	206 (38.9)	431 (40.5)
≥ 65 - < 75	217 (40.7)	226 (42.6)	443 (41.7)
≥ 75	58 (10.9)	63 (11.9)	121 (11.4)
Total	533 (100.0)	530 (100.0)	1063 (100.0)
Sex, n (%)			
Male	437 (82.0)	433 (81.7)	870 (81.8)
Female	96 (18.0)	97 (18.3)	193 (18.2)
Total	533 (100.0)	530 (100.0)	1063 (100.0)
Race, n (%)			
White	354 (66.4)	358 (67.5)	712 (67.0)
Black or African American	6 (1.1)	4 (0.8)	10 (0.9)
Asian	152 (28.5)	145 (27.4)	297 (27.9)
Other	7 (1.3)	1 (0.2)	8 (0.8)
Missing	14 (2.6)	22 (4.2)	36 (3.4)
Total	533 (100.0)	530 (100.0)	1063 (100.0)
Ethnic group, n (%)			
Hispanic or Latino	44 (8.3)	41 (7.7)	85 (8.0)
Not Hispanic or Latino	483 (90.6)	477 (90.0)	960 (90.3)
Missing	6 (1.1)	12 (2.3)	18 (1.7)
Total	533 (100.0)	530 (100.0)	1063 (100.0)
Weight (kg)			
Mean (StD)	77.6 (17.02)	76.6 (16.01)	77.1 (16.53)
Median (Min, Max)	76.0 (38, 157)	75.0 (35, 125)	75.7 (35, 157)
Weight group (kg), n (%)			
< 70	193 (36.2)	180 (34.0)	373 (35.1)
≥ 70 - < 90	210 (39.4)	251 (47.4)	461 (43.4)
≥ 90	130 (24.4)	99 (18.7)	229 (21.5)
Smoking status, n (%)			
Non-smoker	144 (27.0)	120 (22.6)	264 (24.8)
Smoker	377 (70.7)	399 (75.3)	776 (73.0)
Ex-smoker	255 (47.8)	269 (50.8)	524 (49.3)
Current smoker	122 (22.9)	130 (24.5)	252 (23.7)
Missing	12 (2.3)	11 (2.1)	23 (2.2)
Region, n (%)			
Asia	151 (28.3)	143 (27.0)	294 (27.7)
Europe	265 (49.7)	287 (54.2)	552 (51.9)
North America and Australia	66 (12.4)	62 (11.7)	128 (12.0)
South America	51 (9.6)	38 (7.2)	89 (8.4)

DCO: 29 April 2024

Table 26 Tumour Stage (Full Analysis Set)

	Number (%) of subjects		
Tumor stage (per eCRF)	**D+G+C (N = 533)**	**G+C (N = 530)**	**Total (N = 1063)**
T2N0	229 (43.0)	226 (42.6)	455 (42.8)
> T2N0	304 (57.0)	304 (57.4)	608 (57.2)
T2N1	6 (1.1)	14 (2.6)	20 (1.9)
T3	241 (45.2)	222 (41.9)	463 (43.6)
T4	57 (10.7)	68 (12.8)	125 (11.8)

T2 includes T2, T2a, and T2b; T3 includes T3, T3a, and T3b in combination with N0/N1; T4 includes T4 and T4a in combination with N0/N1.

Table 27 Disease Characteristics at Study Entry (Full Analysis Set , IA-2, 29-Apr-2024)

Disease characteristics	Number (%) of patients		
	D + G+C (N = 533)	G+C (N = 530)	Total (N = 1063)
WHO/ECOG performance status			
Normal activity	418 (78.4)	415 (78.3)	833 (78.4)
Restricted activity	115 (21.6)	115 (21.7)	230 (21.6)
Tumor stage (per IVRS)			
T2N0	215 (40.3)	213 (40.2)	428 (40.3)
> T2N0	318 (59.7)	317 (59.8)	635 (59.7)
Renal function (per IVRS) [a]			
Adequate renal function	432 (81.1)	430 (81.1)	862 (81.1)
Borderline renal function	101 (18.9)	100 (18.9)	201 (18.9)
PD-L1 status (per IVRS) [b]			
High [c]	389 (73.0)	388 (73.2)	777 (73.1)
Low/Negative [d]	144 (27.0)	142 (26.8)	286 (26.9)
Renal function (per eCRF)			
Adequate renal function	431 (80.9)	431 (81.3)	862 (81.1)
Borderline renal function	102 (19.1)	99 (18.7)	201 (18.9)
PD-L1 status (per laboratory data)			
High [c]	388 (72.8)	388 (73.2)	776 (73.0)
Low/Negative [d]	145 (27.2)	142 (26.8)	287 (27.0)
TC1 (per laboratory data) [e]			
TC ≥ 1%	291 (54.6)	281 (53.0)	572 (53.8)
TC < 1%	242 (45.4)	249 (47.0)	491 (46.2)
TC25 (per laboratory data) [f]			
TC ≥ 25%	152 (28.5)	153 (28.9)	305 (28.7)
TC < 25%	381 (71.5)	377 (71.1)	758 (71.3)
Primary tumor location			
Bladder	533 (100.0)	530 (100.0)	1063 (100.0)
Histology type			
Urothelial (transitional cell) carcinoma	457 (85.7)	441 (83.2)	898 (84.5)
Urothelial (transitional cell) carcinoma with squamous differentiation	38 (7.1)	49 (9.2)	87 (8.2)
Urothelial (transitional cell) carcinoma with glandular differentiation	10 (1.9)	15 (2.8)	25 (2.4)

Table 28 Disease Characteristics at Study Entry (Full Analysis Set, IA-2, 29-Apr-2024)

Disease characteristics	Number (%) of patients		
	D + G+C (N = 533)	G+C (N = 530)	Total (N = 1063)
Urothelial (transitional cell) carcinoma with variant histology	28 (5.3)	25 (4.7)	53 (5.0)
Regional lymph nodes			
N0	505 (94.7)	500 (94.3)	1005 (94.5)
N1	28 (5.3)	30 (5.7)	58 (5.5)
Distant metastasis			
M0	533 (100.0)	530 (100.0)	1063 (100.0)

[a] One patient in the D + G+C arm was mis-stratified to adequate renal function and one patient in the G+C arm was mis-stratified to borderline renal function per IVRS.

[b] One patient in the D + G+C arm was mis-stratified to the PD-L1 high group according to IVRS and should belong to PD-L1 low group per central laboratory data.

[c] PD-L1 high status was considered high if any of the following are met: ≥ 25% of tumor cells exhibit membrane staining; ICP > 1% and IC+ ≥ 25%; ICP = 1% and IC+ = 100%.

[d] PD-L1 low/negative status was considered low/negative if: none of the criteria for PD-L1 high status are met.

[e] TC1 was defined as TC ≥ 1% vs TC < 1%.

[f] TC25 was defined as TC ≥ 25% vs TC < 25%.

CrCl for borderline renal function: ≥ 40 mL/min to < 60 mL/min; CrCl for adequate renal function: ≥ 60 mL/min.
DCO: 29 April 2024

Numbers analysed

Table 29 Analysis Set (All Patients, IA-2, 29-Apr-2024)

	Number (%) of patients		
	D + G+C	G+C	Total
Patients randomized	533	530	1063
Patients included in the full analysis set [a]	533	530	1063
Cystectomy population [b]	352	337	689
Patients excluded from the cystectomy population	178	189	367
Patients included in the PD-L1 high analysis set [c]	389	388	777
Patients included in the safety analysis set [d]	530	526	1056
Patients excluded from the safety analysis set	3	4	7
Did not receive treatment	3	4	7
Patients included in the PK analysis set [e]	507	0	507
Patients excluded from the PK analysis set	23	526	549
Did not receive treatment or postdose PK data not available	23	526	549
Patients included in the ADA analysis set [f]	453	0	453
Patients excluded from the ADA analysis set	77	526	603
Did not receive treatment or postdose ADA data not available	77	526	603

[a] Full analysis set - all randomized patients.

[b] Cystectomy population - all randomized patients who underwent radical cystectomy and were disease free at adjuvant baseline per BICR.

[c] Patients in the full analysis set whose PD-L1 status was PD-L1 high as defined by VENTANA PD-L1 (SP263) Assay at baseline (Table 2).

[d] Safety analysis set - all patients who received any amount of study treatment.

[e] PK analysis set - all patients who received any amount of study treatment and postdose PK data were available.

[f] ADA analysis set - all patients who received any amount of study treatment, baseline and postdose ADA data were available.

DCO: 29 April 2024

Outcomes and estimation

Dual primary endpoint: EFS

Table 30 Dual Primary Endpoint: EFS per BICR or by Central Pathology (Full Analysis Set, IA-2, 29-Apr-2024)

EFS status	D + G+C (N = 533)	G+C (N = 530)
Total EFS events, n (%)	187 (35.1)	246 (46.4)
Progression in patients precluding radical cystectomy	9 (1.7)	9 (1.7)
Refused or failure to undergo radical cystectomy in patients with residual disease	40 (7.5)	60 (11.3)
Recurrence of disease after radical cystectomy	69 (12.9)	87 (16.4)
Death in the absence of other EFS events	67 (12.6)	85 (16.0)
Partial cystectomy medically not justified	1 (0.2)	5 (0.9)
Failure to undergo delayed cystectomy	1 (0.2)	0
Censored patients, n (%)	346 (64.9)	284 (53.6)
Event-free at time of analysis	337 (63.2)	265 (50.0)
No neo-adjuvant baseline data	3 (0.6)	3 (0.6)
Lost to follow-up	0	0
Withdrawal by patient	6 (1.1)	16 (3.0)
Other	0	0
25th percentile EFS (months) [a]	13.4	8.6
Median EFS (months) [a]	NR	46.1
75th percentile EFS (months) [a]	NR	NR
EFS rate at 6 months (%) [a]	87.7	82.4
95% CI for EFS rate at 6 months (%) [a]	84.5 - 90.2	78.8 - 85.4
EFS rate at 12 months (%) [a]	76.0	69.9
95% CI for EFS rate at 12 months (%) [a]	72.0 - 79.4	65.7 - 73.7
EFS rate at 24 months (%) [a]	67.8	59.8
95% CI for EFS rate at 24 months (%) [a]	63.6 - 71.7	55.4 - 64.0
EFS rate at 36 months (%) [a]	63.7	53.6
95% CI for EFS rate at 36 months (%) [a]	59.3 - 67.7	49.0 - 57.9
Hazard ratio [b,c]	0.68	
95.877% CI for hazard ratio [b,c]	0.554 - 0.824	
95% CI for hazard ratio [b]	0.558 - 0.817	
2-sided p-value [d]	< 0.0001	

[a] Calculated using the Kaplan-Meier technique.

[b] Based on stratified Cox PH model; the stratification factors are tumor stage (T2N0 vs > T2N0), renal function (adequate vs borderline) and PD-L1 status (high vs low/negative) per IVRS, with ties handled by the Efron approach.

[c] A hazard ratio < 1 favors D + G+C to be associated with a longer EFS than G+C.

[d] p-value calculated using a stratified log-rank test, and the stratification factors are the same as the ones indicated in [b]

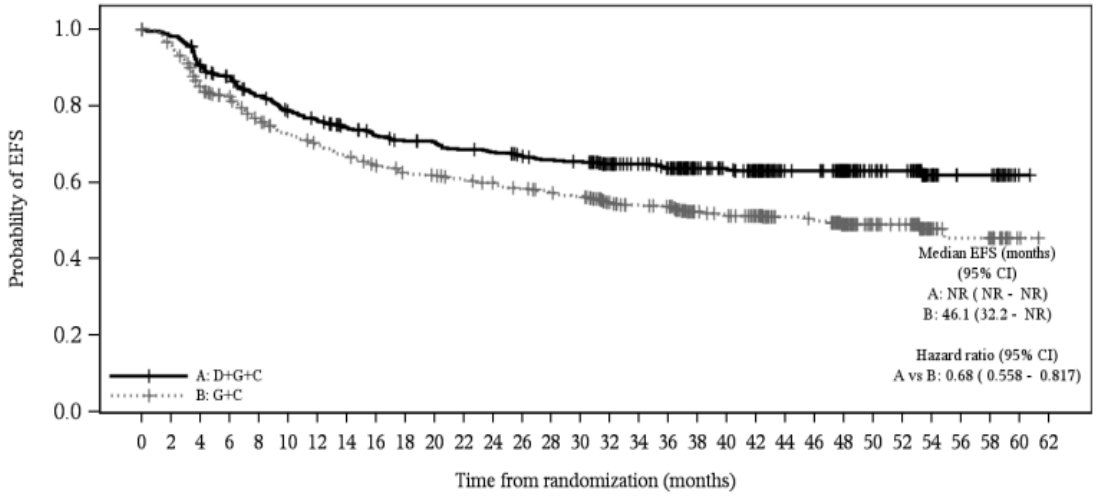
[e] Based on a Lan-DeMets alpha spending function with O'Brien Fleming boundary with the observed number of events; the boundaries for declaring statistical significance are 0.04123 for a 4.9% overall alpha.

For a definition of EFS, see Table 6.

EFS analysis was based on assessments per the BICR or by central pathology review if a biopsy was required for a suspected new lesion.

DCO: 29 April 2024

Table 31 EFS Kaplan Meier Plot, per BICR or by Central Pathology (Full Analysis Set, IA-2, 29-Apr-2024)



Number of patients at risk																												Number of randomized patients/ number of events
A:	533	519	475	454	424	401	386	370	356	348	344	335	330	321	315	312	282	269	255	214	202	180	141	140	115	86	81	32	20	20	1	0	533/187
B:	530	498	437	416	381	358	343	328	313	300	296	288	281	273	264	259	228	219	214	177	172	159	132	129	94	69	62	24	18	16	2	0	530/246

For a definition of EFS, see Table 6. Median EFS calculated using the Kaplan-Meier technique.

Hazard ratio based on stratified Cox PH model; the stratification factors are tumor stage (T2N0 vs > T2N0), renal function (adequate vs borderline) and PD-L1 status (high vs low/negative) per IVRS, with ties handled by the Efron approach.

A hazard ratio < 1 favors D + G+C to be associated with a longer EFS than G+C.

DCO: 29 April 2024

Dual primary endpoint: pCR

Table 32 Dual Primary Endpoint: pCR Rate Based on Central Pathology (Full Analysis Set, Final Analysis)

pCR by central pathology	D + G+C (N = 533)	G+C (N = 530)
Patients with pCR, n (%)	180 (33.8)	137 (25.8)
95% CI (%) [a]	29.8 – 38.0	22.2 – 29.8
Odds ratio [b]	1.49	
99.9% CI for odds ratio [b]	0.946 – 2.354	
95% CI for odds ratio [b]	1.138 – 1.958	
2-sided p-value [b]	0.0038 [c]	

[a] 95% CIs are calculated using the Clopper Pearson method.

[b] Odds ratio and the corresponding CI, and p-value are obtained using logistic regression adjusted for the stratification factors (renal function [adequate vs borderline], tumor stage [T2N0 vs > T2N0] and PD-L1 status [high vs low/negative] per IVRS).

[c] Threshold for significance, p = 0.001.

An odds ratio > 1 favors D + G+C over G+C.

DCO: 14 January 2022

Table 33 Dual Primary Endpoint: pCR Rate Based on Central Pathology (Full Analysis Set, Updated Analysis, DCO 29-Apr-2024)

pCR by central pathology	D + G+C (N = 533)	G+C (N = 530)
Patients with pCR, n (%)	199 (37.3)	146 (27.5)
95% CI (%) [a]	33.2 - 41.6	23.8 - 31.6
Odds ratio [b]	1.60	
95% CI for odds ratio [b]	1.227 - 2.084	
2-sided p-value [b,c]	0.0005	

[a] 95% CIs are calculated using the Clopper Pearson method.

[b] Odds ratio and the corresponding CI, and p-value are obtained using logistic regression adjusted for the stratification factors (renal function [adequate vs borderline], tumor stage [T2N0 vs > T2N0] and PD-L1 status [high vs low/negative] per IVRS).

[c] This is an updated analysis of the primary endpoint and as such is an exploratory analysis with a nominal p-value.

An odds ratio > 1 favors D + G+C over G+C.

Table 34 pCR Rate Based on Local Pathology (Full Analysis Set, Final Analysis)

pCR by local pathology	D + G+C (N = 533)	G+C (N = 530)
Patients with pCR, n (%)	212 (39.8)	170 (32.1)
95% CI (%) [a]	35.6 – 44.1	28.1 – 36.2
Odds ratio [b]	1.41	
95% CI for odds ratio [b]	1.095 – 1.823	
2-sided p-value [b]	0.0080	

[a] 95% CIs are calculated using the Clopper Pearson method.

[b] Odds ratio and the corresponding CI, and p-value are obtained using logistic regression adjusted for the stratification factors (renal function [adequate vs borderline], tumor stage [T2N0 vs > T2N0] and PD-L1 status [high vs low/negative] per IVRS).

An odds ratio > 1 favors D + G+C over G+C.

DCO: 14 January 2022

Secondary endpoint: OS

Table 35 Overall Survival (Full Analysis Set, IA-2, 29-Apr-2024)

Overall survival status	D + G+C (N = 533)	G+C (N = 530)
Death, n (%)	136 (25.5)	169 (31.9)
Censored patients, n (%)	397 (74.5)	361 (68.1)
Still in survival follow-up [a]	379 (71.1)	333 (62.8)
Terminated prior to death [b,c]	18 (3.4)	28 (5.3)
Withdrawal by patient	18 (3.4)	28 (5.3)
Lost to follow-up	0	0
Other	0	0
25th percentile OS (months) [d]	41.9	24.1
Median OS (months) [d]	NR	NR
75th percentile OS (months) [d]	NR	NR
Survival rate at 6 months (%) [d]	96.2	95.6
95% CI for OS rate at 6 months (%) [d]	94.2 - 97.5	93.4 - 97.0
Survival rate at 12 months (%) [d]	89.5	86.5
95% CI for OS rate at 12 months (%) [d]	86.6 - 91.9	83.3 - 89.2
Survival rate at 24 months (%) [d]	82.2	75.2
95% CI for OS rate at 24 months (%) [d]	78.7 - 85.2	71.3 - 78.8
Survival rate at 36 months (%) [d]	76.6	69.8
95% CI for OS rate at 36 months (%) [d]	72.7 - 80.0	65.5 - 73.6
Survival rate at 60 months (%) [d]	71.1	63.9
95% CI for OS rate at 60 months (%) [d]	66.3 - 75.3	58.9 - 68.5
Hazard ratio (D + G+C vs G+C) [e,f]	0.75	
98.457% CI for hazard ratio [e,h]	0.563 - 0.985	
95% CI for hazard ratio [e]	0.594 - 0.934	
2-sided p-value [g]	0.0106	

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

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

[c] Withdrawal by patient includes withdrawal by parent/guardian.

[d] Calculated using the Kaplan-Meier technique.

[e] Based on stratified Cox PH model; the stratification factors were renal function (adequate vs borderline), tumor stage (T2N0 vs > T2N0), and PD-L1 status (high vs low/negative) per IVRS, with ties handled by the Efron approach.

[f] A hazard ratio < 1 favors D + G+C to be associated with a longer OS than G+C.

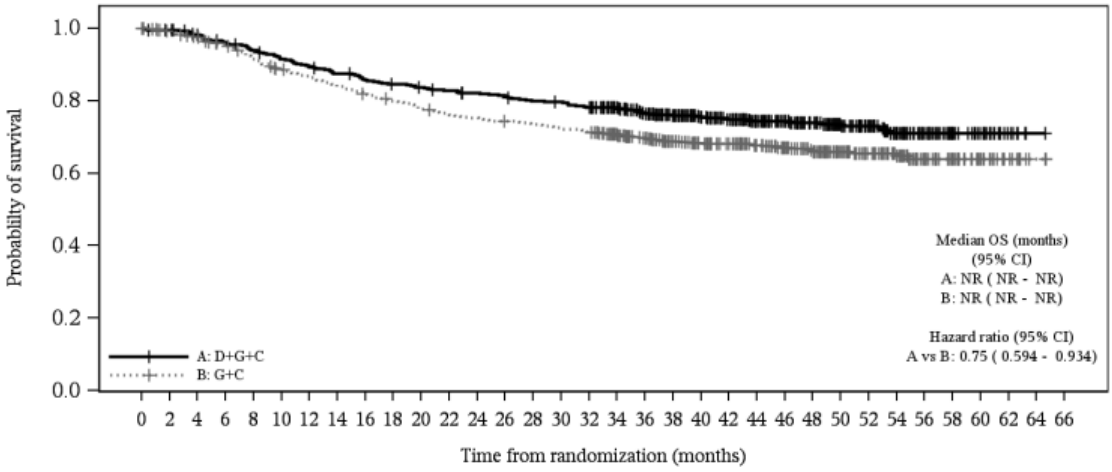
[g] Based on a stratified log-rank test, and the stratification factors are the same as the ones indicated in [e].

[h] Based on a Lan-DeMets alpha spending function with O'Brien Fleming boundary with the observed number of events, the boundaries for declaring statistical significance are 0.01543 for a 4.9% overall alpha.

For a definition of OS, see Table 6.

DCO: 29 April 2024

Figure 5 Overall Survival Kaplan-Meier Plot (Full Analysis Set, IA-2, 29-Apr-2024)



Number of patients at risk																													Number of randomized patients/ number of events
A:	533	528	517	505	492	478	468	457	446	440	434	428	423	418	410	408	400	375	349	321	295	271	238	207	182	152	125	96	68	34	21	7	1	0	533/136
B:	530	516	507	490	467	450	438	425	413	402	392	383	378	373	368	363	358	334	311	281	259	239	215	194	174	141	113	90	60	38	21	10	2	0	530/169

For a definition of OS, see Table 6. Median OS calculated using the Kaplan-Meier technique.

HR based on stratified Cox PH model; the stratification factors were tumor stage (T2N0 vs > T2N0), renal function (adequate vs borderline) and PD-L1 status (high vs low/negative) per IVRS, with ties handled by the Efron approach.

A hazard ratio < 1 favors D + G+C to be associated with a longer OS than G+C.

DCO: 29 April 2024

Secondary endpoint: metastasis-free survival (MFS)

Table 36 Metastasis-free Survival (Full Analysis Set, IA-2, 29-Apr-2024)

MFS status	D + G+C (N = 533)	G+C (N = 530)
Total MFS events, n (%)	152 (28.5)	201 (37.9)
Distant metastasis	54 (10.1)	77 (14.5)
Death in the absence of distant metastasis	98 (18.4)	124 (23.4)
Censored patients, n (%)	381 (71.5)	329 (62.1)
Metastasis-free at time of analysis [a]	363 (68.1)	303 (57.2)
Lost to follow-up	0	0
Withdrawn consent	18 (3.4)	26 (4.9)
Other	0	0
25th percentile MFS (months) [b]	24.2	15.0
MFS survival (months) [b]	NR	NR
75th percentile MFS (months) [b]	NR	NR
MFS rate at 6 months (%) [b]	95.1	93.9
95% CI for MFS at 6 months [b]	92.8 - 96.6	91.3 - 95.7
MFS rate at 12 months (%) [b]	84.5	80.1
95% CI for MFS at 12 months [b]	80.9 - 87.4	76.1 - 83.4
MFS rate at 24 months (%) [b]	75.1	65.1
95% CI for MFS at 24 months [b]	71.0 - 78.8	60.6 - 69.3
MFS rate at 36 months (%) [b]	69.9	59.3
95% CI for MFS at 36 months [b]	65.5 - 73.9	54.6 - 63.7
Hazard ratio [c,d]	0.67	
95% CI for hazard ratio	0.541 - 0.826	
2-sided p-value [e]	0.0002	

[a] Includes patients who do not have distant metastasis at data cut-off.

[b] Calculated using the Kaplan-Meier technique.

[c] Based on stratified Cox PH model; the stratification factors are renal function (adequate vs borderline), tumor stage (T2N0 vs > T2N0), and PD-L1 status (high vs low/negative) per IVRS, with ties handled by the Efron approach.

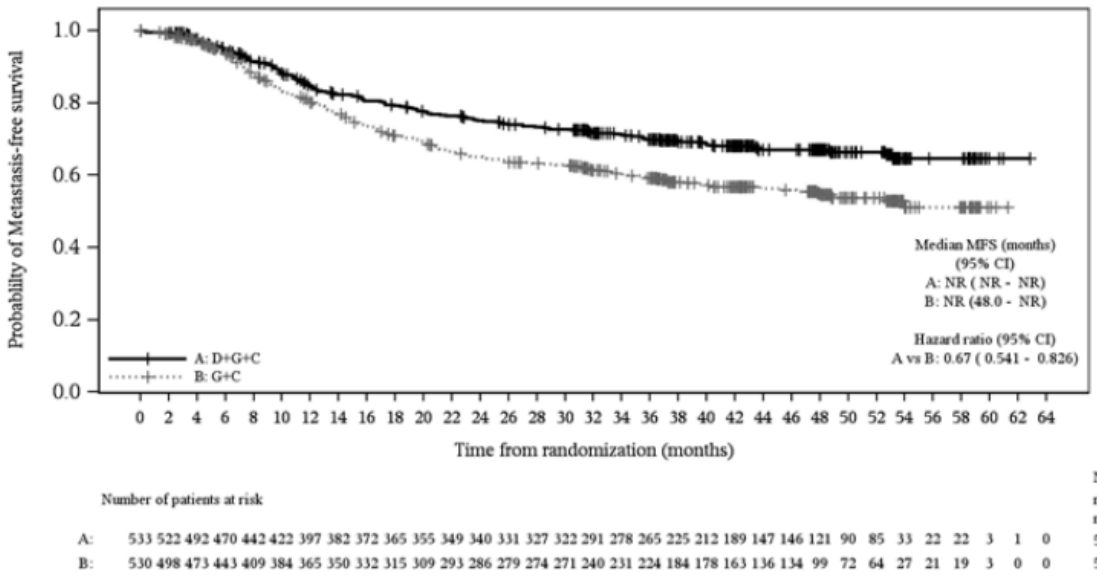
[d] A hazard ratio < 1 favors D + G+C to be associated with a longer MFS than G+C.

[e] p-value is based on a stratified log-rank test, and the stratification factors are the same as the ones indicated in [c]. p-value is nominal as this endpoint is not included in the MTP.

For a definition of MFS, see Table 6.

DCO: 29 April 2024

Figure 6 Metastasis-free Survival Kaplan Meier Plot (Full Analysis Set, IA-2, 29-Apr-2024)



Number of patients at risk																												Number of randomized patients/ number of events
A:	533	522	492	470	442	422	397	382	372	365	355	349	340	331	327	322	291	278	265	225	212	189	147	146	121	90	85	33	22	22	3	1	0	533/152
B:	530	498	473	443	409	384	365	350	332	315	309	293	286	279	274	271	240	231	224	184	178	163	136	134	99	72	64	27	21	19	3	0	0	530/201

For a definition of MFS, see Table 6. Median MFS is calculated using the Kaplan-Meier technique.
HR based on stratified Cox PH model; the stratification factors are tumor stage (T2N0 vs > T2N0), renal function (adequate vs borderline) and PD-L1 status (high vs low/negative) per IVRS, with ties handled by the Efron approach.
A hazard ratio < 1 favors D + G+C to be associated with a longer MFS than G+C.
DCO: 29 April 2024

Secondary endpoint: DFS

Table 37 Disease free survival (DFS) for patients who underwent radical cystectomy, per BICR or by central pathology review (Full analysis set)

Disease-free survival status	D+G+C (N=469)	G+C (N=441)
Total disease-free survival events, n (%)	132 (28.1)	166 (37.6)
Disease recurrence	69 (14.7)	87 (19.7)
Death	63 (13.4)	79 (17.9)
Censored patients, n (%)	337 (71.9)	275 (62.4)
Disease-free at time of analysis	333 (71.0)	265 (60.1)
Lost to follow-up	0	0
Withdrawn consent	4 (0.9)	10 (2.3)
Other	0	0
25th percentile disease-free survival (months) [a]	21.2	13.9
Median disease-free survival (months) [a]	NR	NR
75th percentile disease-free survival (months) [a]	NR	NR
Disease-free survival rate at 6 months (%) [a]	88.0	85.8
95% CI for disease-free survival rate at 6 months (%) [a]	84.6 - 90.6	82.1 - 88.8
Disease-free survival rate at 12 months (%) [a]	81.7	76.7
95% CI for disease-free survival rate at 12 months (%) [a]	77.8 - 85.0	72.3 - 80.4

Disease-free survival status	D+G+C (N=469)	G+C (N=441)
Disease-free survival rate at 24 months (%) [a]	73.2	68.2
95% CI for disease-free survival rate at 24 months (%) [a]	68.8 - 77.0	63.5 - 72.5
Disease-free survival rate at 36 months (%) [a]	70.5	61.5
95% CI for disease-free survival rate at 36 months (%) [a]	65.9 - 74.5	56.5 - 66.1
Hazard ratio [b c]	0.70	
95% CI for hazard ratio	0.554 - 0.877	
2-sided p-value [d]	0.0020	

C = Cisplatin, D = Durvalumab, G = Gemcitabine, CI = Confidence interval, DCO = Data cut-off, NR = Not reached
DFS for patients who underwent radical cystectomy is defined as the time from the date of radical cystectomy to the first recurrence of disease post radical cystectomy, or death due to any cause, whichever occurs first. DFS analysis will be based on assessments per the BICR or by central pathology review if a biopsy is required for a suspected new lesion regardless of disease free at adjuvant baseline.
[a] Calculated using the Kaplan-Meier technique.
[b] Based on stratified Cox proportional hazard model; the stratification factors are tumor stage [T2N0 versus >T2N0], renal function [adequate versus borderline] and PD-L1 status [high versus low/negative] per IVRS, with ties handled by the Efron approach.
[c] A hazard ratio < 1 favours D+G+C to be associated with a longer event-free survival than G+C.
[d] Calculated using a stratified log rank test; the stratification factors are tumor stage [T2N0 versus >T2N0], renal function [adequate versus borderline] and PD-L1 status [high versus low/negative] per IVRS.

Table 38 Summary of cystectomy (Full Analysis set, IA-2, 29-Apr-2024)

	D + G+C (N = 533)	G+C (N = 530)	Total (N = 1063)
Patients who did not undergo cystectomy as planned, n (%)	63 (11.8)	84 (15.8)	147 (13.8)
Patient decision	32 (6.0)	36 (6.8)	68 (6.4)
Unfit for surgery (eg. Performance status decline)	2 (0.4)	6 (1.1)	8 (0.8)
AE	6 (1.1)	7 (1.3)	13 (1.2)
Disease progression	9 (1.7)	9 (1.7)	18 (1.7)
Death	5 (0.9)	8 (1.5)	13 (1.2)
Study discontinuation	3 (0.6)	12 (2.3)	15 (1.4)
Investigator decision to not perform surgery	5 (0.9)	6 (1.1)	11 (1.0)
Abandoned procedure (intra-operative)	1 (0.2)	0	1 (0.1)
Patients who underwent cystectomy, n (%)	470 (88.2)	446 (84.2)	916 (86.2)
Partial cystectomy	1 (0.2)	5 (0.9)	6 (0.6)
Radical cystectomy	469 (88.0)	441 (83.2)	910 (85.6)
Randomization to cystectomy (days)			
Median (min, max)	112.0 (42, 221)	112.0 (29, 404)	112.0 (29, 404)
Last dose of neoadjuvant therapy to cystectomy (days)			
Median (min, max)	39.0 (8, 118)	38.0 (12, 333)	38.0 (8, 333)
Patients underwent cystectomy within 56 days after last dose of neoadjuvant chemotherapy, n (%) [a]	424 (90.2)	399 (89.5)	823 (89.8)

[a] Percentages calculated from the number of patients underwent cystectomy.
DCO: 29 April 2024

Table 39 Time to Radical Cystectomy (Full Analysis set, IA-2, 29-Apr-2024)

Time to cystectomy status	Number (%) of patients	
	D + G+C (N = 533)	G+C (N = 530)
Patients with radical cystectomy, n (%)	469 (88.0)	441 (83.2)
Censored patients, n (%)	64 (12.0)	89 (16.8)
Terminated prior cystectomy [a]	14 (2.6)	22 (4.2)
No cystectomy after discontinuation/completion of neoadjuvant period [b]	48 (9.0)	61 (11.5)
Patients with partial cystectomy [c]	1 (0.2)	5 (0.9)
Patients randomized but not treated [d]	1 (0.2)	1 (0.2)
25th percentile time to cystectomy (weeks) [e]	14.7	14.3
Median time to cystectomy (weeks) [e]	16.3	16.1
75th percentile time to cystectomy (weeks) [e]	18.4	18.3
Hazard ratio [f,g]	0.94	
95% CI for hazard ratio [f]	0.823 - 1.068	
2-sided p-value [h]	0.3358	

[a] Includes deaths occurring prior to cystectomy.

[b] Includes patients who discontinued the study before undergoing cystectomy, as well as those who discontinued neo-adjuvant treatment or completed it but did not proceed to cystectomy.

[c] Includes patients who underwent partial cystectomy.

[d] Includes patients who were randomized but did not receive treatment and are still on the study.

[e] Calculated using the Kaplan-Meier technique.

[f] Based on stratified Cox PH model; the stratification factors are renal function (adequate vs borderline), tumor stage (T2N0 vs > T2N0), and PD-L1 status (high vs low/negative) per IVRS, with ties handled by the Efron approach.

[g] Hazard ratio < 1 is associated with longer time to cystectomy in D + G+C than in G+C.

[h] p-value is based on a stratified log-rank test, and the stratification factors are the same as the ones indicated in [f]. p-value is nominal as this endpoint is not included in the MTP.

DCO: 29 April 2024

Patient Reported Outcomes (PROs)

Patient-reported symptoms, functioning, and health related quality of life (HRQoL) were collected using the EORTC QLQ-C30. The questionnaire was to be collected on Day 1 of every Cycle and administered before discussion of disease progression and dosing.

Adjusted mean change from baseline and TTD in the EORTC QLQ-C30 scales were secondary endpoints. Prioritized scales were GHS/QoL, physical functioning, fatigue, and pain. Baseline compliance with the EORTC QLQ-C30 was 69.8% in the D + G+C arm and 72.8% in the G+C arm. Compliance generally decreased in both arms throughout the study.

A trend towards deterioration from baseline was observed in the first 25 weeks for all scales in both arms followed by a decrease in the deterioration or a return to baseline levels thereafter. No between arm differences were observed in the change from baseline in the priority domains (GHS/QoL, physical functioning, fatigue, and pain), but the overall change from baseline favoured the D + G+C arm for GHS/QoL.

Ancillary analyses

Table 40 Event-free survival per BICR or by Central Pathology Review, by Tumour Stage Subgroup (T2N0 and > T2N0) (Full Analysis Set)

Event-free survival status	T2N0		> T2N0	
	D + G+C (N = 215)	G+C (N = 213)	D + G+C (N = 318)	G+C (N = 317)
Total event-free survival events, n (%)	78 (36.3)	88 (41.3)	109 (34.3)	158 (49.8)
Progression in subjects precluding radical cystectomy	2 (0.9)	3 (1.4)	7 (2.2)	6 (1.9)
Refused or failure to undergo radical cystectomy in subjects with residual disease	24 (11.2)	24 (11.3)	16 (5.0)	36 (11.4)
Recurrence of disease after radical cystectomy	30 (14.0)	27 (12.7)	39 (12.3)	60 (18.9)
Death in the absence of other EFS events	22 (10.2)	30 (14.1)	45 (14.2)	55 (17.4)
Partial cystectomy medically not justified	0	4 (1.9)	1 (0.3)	1 (0.3)
Failure to undergo delayed cystectomy	0	0	1 (0.3)	0
Censored subjects, n (%)	137 (63.7)	125 (58.7)	209 (65.7)	159 (50.2)
Event-free at time of analysis	134 (62.3)	117 (54.9)	203 (63.8)	148 (46.7)
No neo-adjuvant baseline data	1 (0.5)	1 (0.5)	2 (0.6)	2 (0.6)
Lost to follow-up	0	0	0	0
Withdrawal by subject	2 (0.9)	7 (3.3)	4 (1.3)	9 (2.8)
Other	0	0	0	0
25th percentile event-free survival (months) [a]	12.0	8.1	14.4	9.1
Median event-free survival (months) [a]	NR	NR	NR	32.7
75th percentile event-free survival (months) [a]	NR	NR	NR	NR
Event-free survival rate at 6 months (%) [a]	84.0	82.5	90.1	82.3
95% CI for event-free survival rate at 6 months (%) [a]	78.4 - 88.3	76.6 - 87.1	86.3 - 92.9	77.6 - 86.1
Event-free survival rate at 12 months (%) [a]	74.8	70.8	76.7	69.3
95% CI for event-free survival rate at 12 months (%) [a]	68.4 - 80.2	64.0 - 76.6	71.6 - 81.0	63.8 - 74.2
Event-free survival rate at 24 months (%) [a]	67.9	64.1	67.8	57.0
95% CI for event-free survival rate at 24 months (%) [a]	61.1 - 73.8	57.0 - 70.3	62.2 - 72.7	51.2 - 62.4
Event-free survival rate at 36 months (%) [a]	63.4	59.8	63.7	49.4
95% CI for event-free survival rate at 36 months (%) [a]	56.4 - 69.6	52.5 - 66.2	57.8 - 68.9	43.4 - 55.0
HR [b c]	0.81		0.60	
95% CI for HR [b]	0.594 - 1.096		0.472 - 0.770	
2-sided p-value [d]	0.1691		< 0.0001	

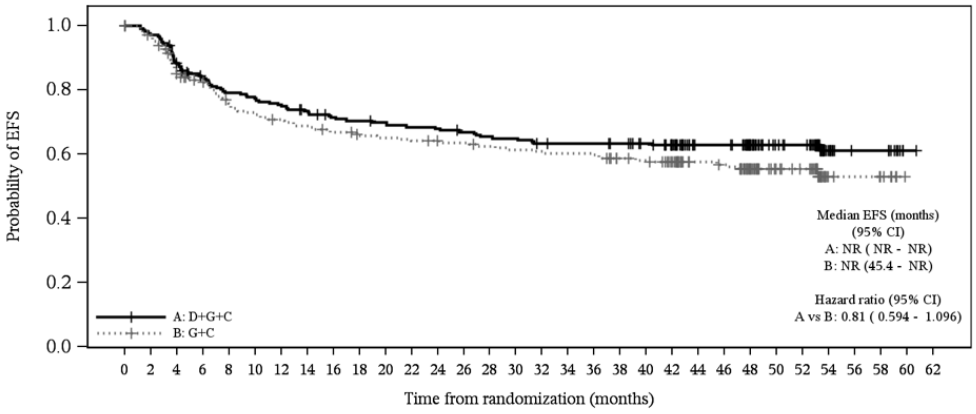
[a] Calculated using the Kaplan-Meier technique.

[b] Based on stratified Cox proportional hazard model; the stratification factors are renal function [adequate versus borderline] and PD-L1 status [high versus low/negative] per IVRS, with ties handled by the Efron approach.

[c] A HR < 1 favors D + G+C to be associated with a longer event-free survival than G+C.

[d] Calculated using a stratified log-rank test; the stratification factors are renal function [adequate versus borderline] and PD-L1 status [high versus low/negative] per IVRS.

Figure 7 EFS Kaplan-Meier Plot, per BICR or by Central Pathology Review, Tumour Stage T2N0 Subgroup (Full Analysis Set)



Number of patients at risk																											Number of randomized patients/ number of events
A:	215	208	187	174	164	160	155	150	144	142	140	137	136	133	130	129	125	124	124	122	117	107	88	88	72	55	52	18	10	10	1	0	215/78
B:	213	201	173	164	149	142	138	134	129	125	124	122	120	119	115	113	112	111	110	103	101	92	78	76	55	39	35	9	8	6	0	0	213/88

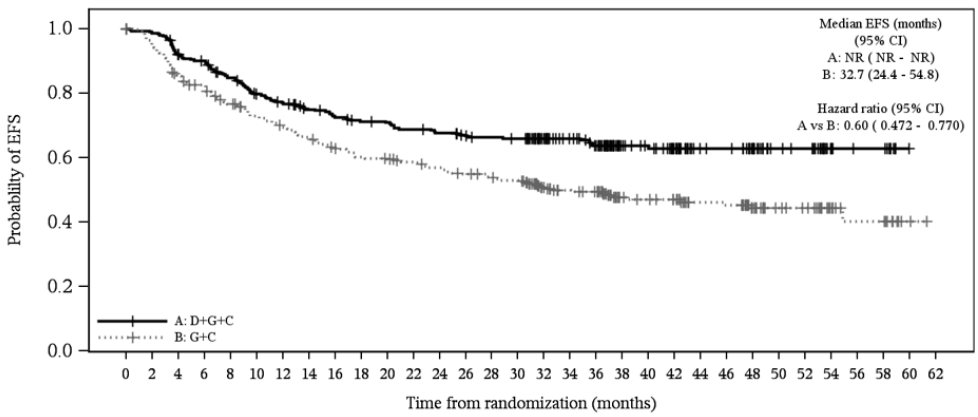
EFS is defined as the time from randomization to the first recurrence of disease after radical cystectomy, the time of first documented progression in subjects who are medically precluded from a radical cystectomy or time of expected surgery in subjects who refuse to undergo a radical cystectomy, or failure to undergo a radical cystectomy in subjects with residual disease or the time of death due to any cause, whichever occurs first.

Median EFS is calculated using the Kaplan-Meier technique.

HR based on stratified Cox proportional hazard model; the stratification factors are renal function [adequate vs borderline] and PD-L1 status [high versus low/negative] per IVRS, with ties handled by the Efron approach.

A HR < 1 favors D + G+C to be associated with a longer event-free survival than G+C.

Figure 8 EFS Kaplan Meier Plot, per BICR or by Central Pathology Review, tumour stage > T2N0 Subgroup (Full Analysis Set)



Number of patients at risk																											Number of randomized patients/ number of events
A:	318	311	288	280	260	241	231	220	212	206	204	198	194	188	185	183	157	145	131	92	85	73	53	52	43	31	29	14	10	10	0	0	318/109
B:	317	297	264	252	232	216	205	194	184	175	172	166	161	154	149	146	116	108	104	74	71	67	54	53	39	30	27	15	10	10	2	0	317/158

EFS is defined as the time from randomization to the first recurrence of disease after radical cystectomy, the time of first documented progression in subjects who are medically precluded from a radical cystectomy or time of expected surgery in subjects who refuse to undergo a radical cystectomy, or failure to undergo a radical cystectomy in subjects with residual disease or the time of death due to any cause, whichever occurs first.

Median EFS is calculated using the Kaplan-Meier technique.

HR based on stratified Cox proportional hazard model; the stratification factors are renal function [adequate vs borderline] and PD-L1 status [high versus low/negative] per IVRS, with ties handled by the Efron approach.

A HR < 1 favors D + G+C to be associated with a longer event-free survival than G+C.

Table 41 Overall Survival, by Tumour Stage Subgroup (T2N0 and > T2N0) (Full Analysis Set)

Overall survival status	T2N0		> T2N0	
	D + G+C (N = 215)	G+C (N = 213)	D + G+C (N = 318)	G+C (N = 317)
Death, n (%)	56 (26.0)	60 (28.2)	80 (25.2)	109 (34.4)
Censored subjects, n (%)	159 (74.0)	153 (71.8)	238 (74.8)	208 (65.6)
Still in survival follow-up [a]	152 (70.7)	140 (65.7)	227 (71.4)	193 (60.9)
Terminated prior to death [b c]	7 (3.3)	13 (6.1)	11 (3.5)	15 (4.7)
Withdrawal by subject	7 (3.3)	13 (6.1)	11 (3.5)	15 (4.7)
Lost to follow-up	0	0	0	0
Other	0	0	0	0
25th percentile overall survival (months) [d]	43.6	35.8	39.6	20.1
Median overall survival (months) [d]	NR	NR	NR	NR
75th percentile overall survival (months) [d]	NR	NR	NR	NR
Survival rate at 6 months (%) [d]	94.8	96.6	97.1	94.9
95% CI for overall survival rate at 6 months (%) [d]	90.8 - 97.1	93.1 - 98.4	94.6 - 98.5	91.8 - 96.8
Survival rate at 12 months (%) [d]	89.1	88.8	89.8	85.1
95% CI for overall survival rate at 12 months (%) [d]	84.1 - 92.6	83.6 - 92.4	85.9 - 92.7	80.6 - 88.6
Survival rate at 24 months (%) [d]	81.5	79.2	82.7	72.6
95% CI for overall survival rate at 24 months (%) [d]	75.5 - 86.1	72.9 - 84.2	78.1 - 86.5	67.3 - 77.3
Survival rate at 36 months (%) [d]	77.6	74.7	75.9	66.6
95% CI for overall survival rate at 36 months (%) [d]	71.3 - 82.6	68.1 - 80.1	70.7 - 80.3	61.0 - 71.6
Survival rate at 60 months (%) [d]	71.4	68.9	71.1	60.4
95% CI for overall survival rate at 60 months (%) [d]	64.1 - 77.5	61.5 - 75.1	64.4 - 76.7	52.9 - 67.0
HR (D + G+C vs G+C) [e f]	0.89		0.67	
95% CI for HR [e]	0.620 - 1.288		0.498 - 0.888	
2-sided p-value [g]	0.5465		0.0055	

[a] Includes subjects known to be alive at data cut-off.

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

[c] Withdrawal by subject include withdrawal by Parent/Guardian.

[d] Calculated using the Kaplan-Meier technique.

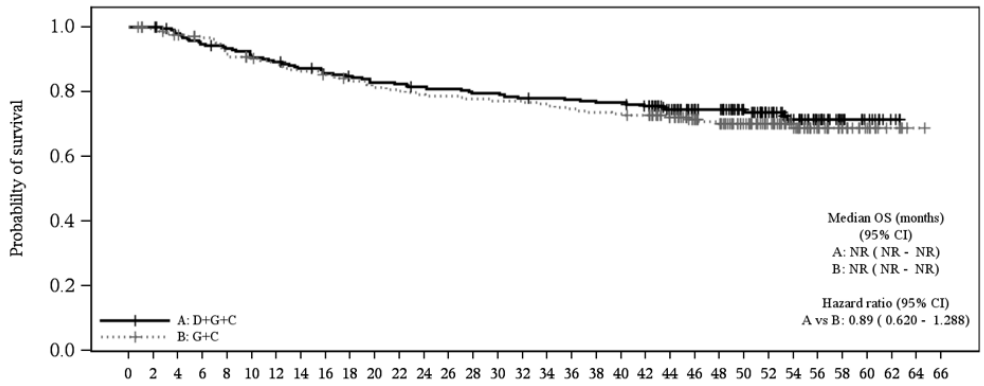
[e] Based on stratified Cox proportional hazard model; the stratification factors are renal function [adequate versus borderline] and PD-L1 status [high versus low/negative] per IVRS, with ties handled by the Efron approach.

[f] A HR < 1 favors D + G+C to be associated with a longer overall survival than G+C.

[g] P-value is based on a stratified log-rank test, and the stratification factors are the same as the ones indicated in e.

Overall survival is defined as the time from the date of randomization until death due to any cause regardless of whether the subject withdraws from randomized therapy or receives another anticancer therapy (ie, date of death or censoring – date of randomization + 1).

Figure 9 Overall Survival, Kaplan Meier Plot, Tumour Stage T2N0 Subgroup (Full Analysis Set)



Number of patients at risk																															Number of randomized patients/ number of events
A:	215	215	208	201	197	191	188	183	179	176	172	171	168	167	164	164	161	160	159	157	157	153	135	115	111	93	74	57	38	15	10	3	0	0	215/56
B:	213	209	203	197	187	182	178	173	170	165	161	159	157	156	154	153	153	151	148	146	145	143	129	111	105	85	67	53	33	19	12	5	1	0	213/60

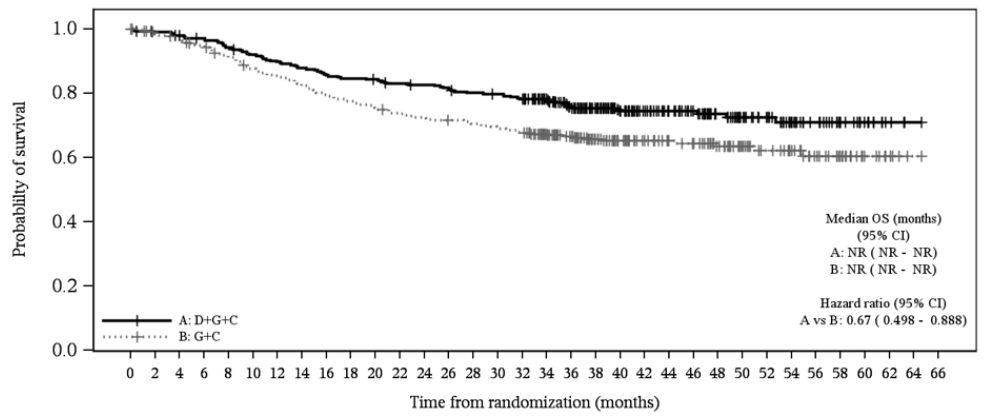
Overall survival is defined as the time from the date of randomization until death due to any cause regardless of whether the subject withdraws from randomized therapy or receives another anticancer therapy (ie, date of death or censoring – date of randomization + 1).

Median OS is calculated using the Kaplan-Meier technique.

HR based on stratified Cox proportional hazard model; the stratification factors are renal function [adequate vs borderline] and PD-L1 status [high versus low/negative] per IVRS, with ties handled by the Efron approach.

A HR < 1 favors D + G+C to be associated with a longer overall survival than G+C.

Figure 10 Overall Survival Kaplan Meier plot, Tumour Stage > T2N0 subgroup (Full Analysis Set)



Number of patients at risk																															Number of randomized patients/ number of events
A:	318	313	309	304	295	287	280	274	267	264	262	257	255	251	246	244	239	215	190	164	138	118	103	92	71	59	51	39	30	19	11	4	1	0	318/80
B:	317	307	304	293	280	268	260	252	243	237	231	224	221	217	214	210	205	183	163	135	114	96	86	83	69	56	46	37	27	19	9	5	1	0	317/109

Overall survival is defined as the time from the date of randomization until death due to any cause regardless of whether the subject withdraws from randomized therapy or receives another anticancer therapy (ie, date of death or censoring – date of randomization + 1).

Median OS is calculated using the Kaplan-Meier technique.

HR based on stratified Cox proportional hazard model; the stratification factors are renal function [adequate vs borderline] and PD-L1 status [high versus low/negative] per IVRS, with ties handled by the Efron approach.

A HR < 1 favors D + G+C to be associated with a longer overall survival than G+C.

Sensitivity analyses

Table 42 EFS, Sensitivity analyses, per BICR or central pathology (Full Analysis set, IA-2, 29-Apr-2024)

Group	N	Number (%) of patients with events	Median (months)	Comparison		
				Hazard ratio [b]	95% CI	2-sided p-value
FAS (per Table 21)						
D + G+C	533	187 (35.1)	NR	0.68	0.558 - 0.817	< 0.0001
G+C	530	246 (46.4)	46.1			
Evaluation-time bias [a]						
D + G+C	533	187 (35.1)	NR	0.68	0.560 - 0.820	< 0.0001
G+C	530	246 (46.4)	47.1			
Subsequent anticancer therapy [b]						
D + G+C	533	175 (32.8)	NR	0.70	0.571 - 0.851	0.0004
G+C	530	221 (41.7)	54.8			
Analysis using the 2 missed visit rule [c]						
D + G+C	533	167 (31.3)	NR	0.68	0.553 - 0.828	0.0001
G+C	530	219 (41.3)	NR			
No adjuvant baseline scan [d]						
D + G+C	533	179 (33.6)	NR	0.67	0.550 - 0.811	< 0.0001
G+C	530	240 (45.3)	47.8			
Excluding the PD-L1 stratification factor [e]						
D + G+C	533	187 (35.1)	NR	0.68	0.562 - 0.823	0.0001
G+C	530	246 (46.4)	46.1			
Including TC1 as a categorical covariate [f]						
D + G+C	533	187 (35.1)	NR	0.68	0.560 - 0.820	0.0001
G+C	530	246 (46.4)	46.1			
Including TC25 as a categorical covariate [g]						
D + G+C	533	187 (35.1)	NR	0.67	0.556 - 0.814	< 0.0001
G+C	530	246 (46.4)	46.1			

[a] For those patients who missed two consecutive visits prior to EFS events, EFS was interval censored.

[b] The analysis was performed by repeating the primary EFS analysis except that the patients who took subsequent therapy prior to EFS event were censored at the last evaluable assessment prior to taking anticancer therapy.

[c] The analysis was performed by repeating the primary EFS analysis except that patients who progressed or experienced recurrence disease or died directly preceded by 2 or more consecutive missed visits were censored at time of the latest evaluable disease assessment prior to the consecutive missed visits.

[d] The analysis was performed by repeating the EFS analysis using the alternative censoring rules, ie, if the patient had radical cystectomy and there was no scan within 120 days following the date of radical cystectomy and prior to the start of adjuvant treatment (D + G+C arm) or within the 120 days, regardless of timing relative to the first study visit (G+C arm), they were censored at the date of radical cystectomy unless they died within 120 days of radical cystectomy.

[e] The analysis was performed by repeating the primary EFS analysis except for removing the PD-L1 stratification factor from the stratified log-rank test and stratified Cox PH model (ie, the model was adjusted only for the stratification factors for tumor stage [T2N0 versus > T2N0)] and renal function [adequate vs borderline]).

[f] The analysis was performed by repeating the primary EFS analysis except for removing the PD-L1 stratification factor from the stratified log-rank test and stratified Cox PH model (ie, the model was adjusted only for the stratification factors for tumor stage [T2N0 versus > T2N0)] and renal function [adequate vs borderline]) and including TC1 as a categorical covariate in the model.

[g] The analysis was performed by repeating the primary EFS analysis except for removing the PD-L1 stratification factor from the stratified log-rank test and stratified Cox PH model (ie, the model was adjusted only for the stratification factors for tumor stage [T2N0 versus > T2N0)] and renal function [adequate vs borderline]) and including TC25 as a categorical covariate in the model.

[h] A hazard ratio < 1 favors D + G+C to be associated with a longer EFS than G+C.

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Table 43 Event-free survival, sensitivity analyses, per BICR or by central pathology review (Full Analysis set)

Group	N	Number (%) of patients with events	Median (months)	Comparison		
				Hazard ratio [b]	95% CI	2-sided p-value
Evaluation-time bias [a]						
D+G+C	533	187 (35.1)	NR	0.68	0.560 - 0.820	<0.0001
G+C	530	246 (46.4)	47.1			
Subsequent anti-cancer therapy [b]						
D+G+C	533	175 (32.8)	NR	0.70	0.571 - 0.851	0.0004
G+C	530	221 (41.7)	54.8			
Analysis using the 2 missed visit rule [c]						
D+G+C	533	167 (31.3)	NR	0.68	0.553 - 0.828	0.0001
G+C	530	219 (41.3)	NR			
No adjuvant baseline scan [d]						
D+G+C	533	179 (33.6)	NR	0.67	0.550 - 0.811	<0.0001
G+C	530	240 (45.3)	47.8			
Excluding the PD-L1 stratification factor [e]						
D+G+C	533	187 (35.1)	NR	0.68	0.562 - 0.823	0.0001
G+C	530	246 (46.4)	46.1			
Including TC1 as a categorical covariate [f]						
D+G+C	533	187 (35.1)	NR	0.68	0.560 - 0.820	0.0001
G+C	530	246 (46.4)	46.1			
Including TC25 as a categorical covariate [g]						
D+G+C	533	187 (35.1)	NR	0.67	0.556 - 0.814	<0.0001
G+C	530	246 (46.4)	46.1			

C = Cisplatin, D = Durvalumab, G = Gemcitabine, CI = Confidence interval
[a] For those patients who missed two consecutive missed visits prior to EFS events, EFS was interval censored.
[b] The analysis was performed by repeating the primary EFS analysis except that patients who took subsequent therapy prior to EFS event were censored at the last evaluable assessment prior to taking anti-cancer therapy.
[c] The analysis was performed by repeating the primary EFS analysis except that patients who progressed or experienced recurrence disease or died directly preceded by 2 or more consecutive missed visits were censored.
[d] The analysis was performed by repeating the EFS analysis using the alternative censoring rules, i.e., if the patient had radical cystectomy and there was no scan within 120 days following the date of radical cystectomy and prior to the start of adjuvant treatment (Arm 1) or within the 120 days,regardless of timing relative to the first study visit (Arm 2),they were censored at the date of radical cystectomy unless they died within 120 days of radical cystectomy.
[e] The analysis was performed by repeating the primary EFS analysis except for removing the PD-L1 stratification factor from the stratified log-rank test and stratified Cox PH model (i.e. the model was adjusted only for the stratification factors for tumor stage [T2N0 versus >T2N0]
and renal function [adequate vs borderline]).
[f] The analysis was performed by repeating the primary EFS analysis using the same model in [e] and including TC1 as a categorical covariate in the model.
[g] The analysis was performed by repeating the primary EFS analysis using the same model in [e] and including TC25 as a categorical covariate in the model.
[h] A hazard ratio < 1 favours D+G+C to be associated with a longer event free survival than G+C

Subgroup analyses

PD-L1 expression

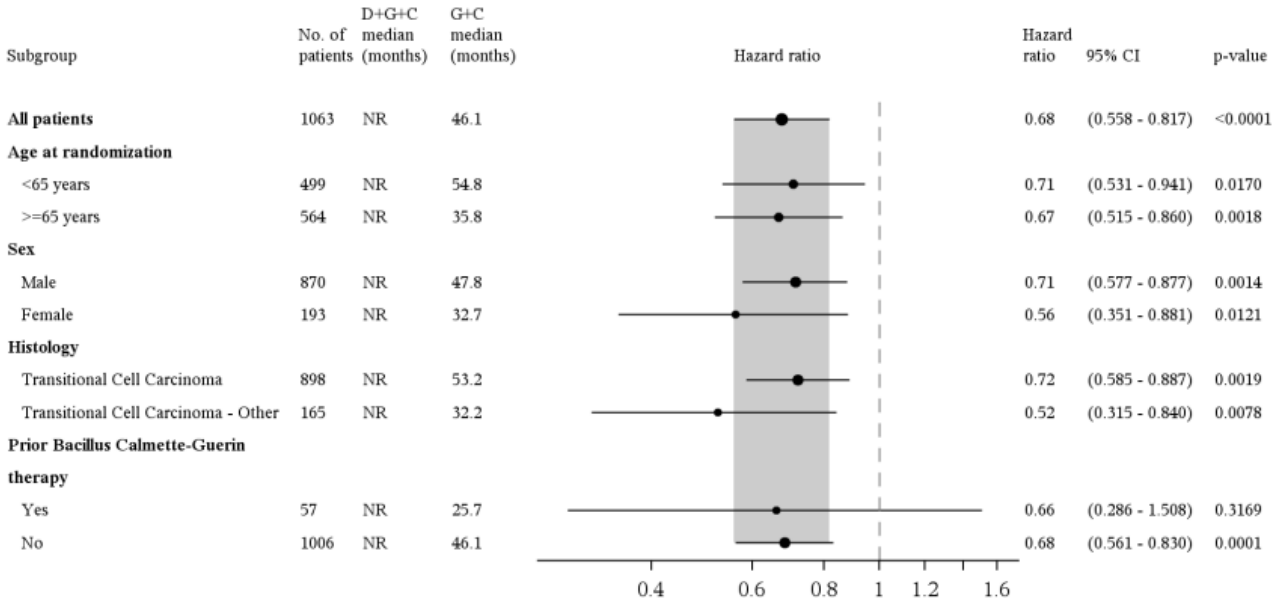
Central testing of PD-L1 status with the VENTANA (SP) Assay was performed in two different central laboratories. During monitoring of PD-L1 testing and prior to unblinding the study, >25% differences in PD-L1 prevalence were observed between the two testing laboratories. The prevalence differences were related to the IC scoring component of the TC/IC 25% algorithm in both screened and randomized patients. Prevalence differences in PD-L1 positivity between testing laboratories were not seen in the tumor cells. Differences were not observed when using the TC ≥ 25% component of the TC/IC 25% algorithm. Differences were also not observed for the TC ≥1% algorithm that was derived from raw TC percentage and binned TC percentage scores, that were recorded by pathologists in an exploratory fashion while scoring TC/IC 25%.

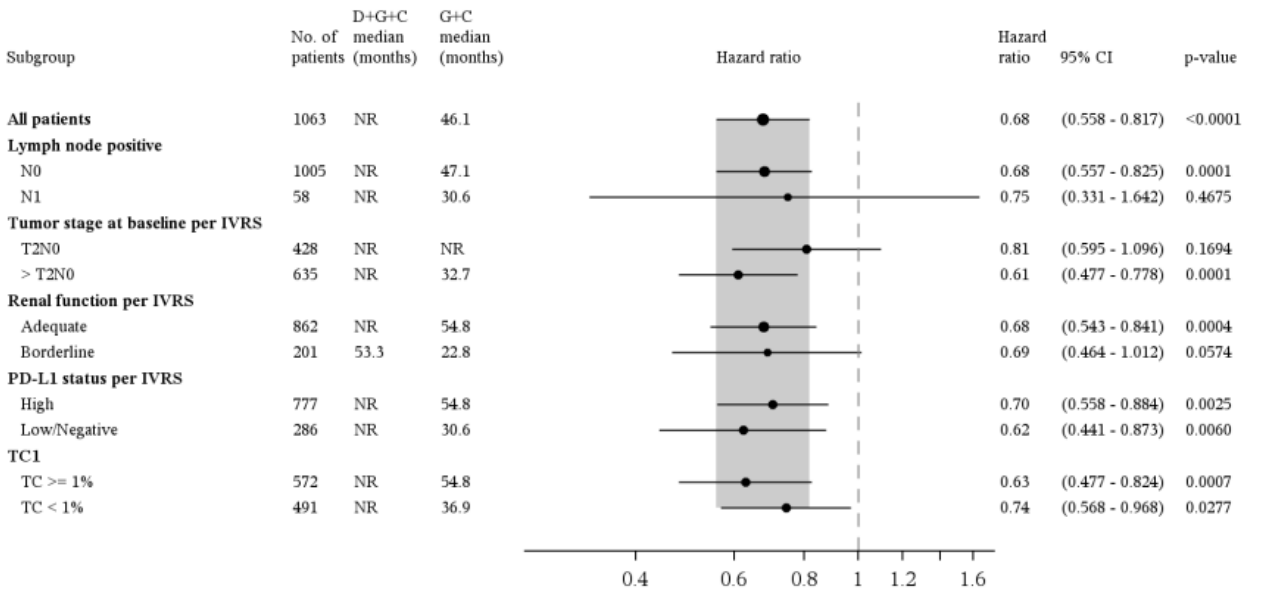
Exploratory multivariate analyses performed by the MAH did not reveal any regional or biological factors that could explain the observed differences in prevalence between the labs.

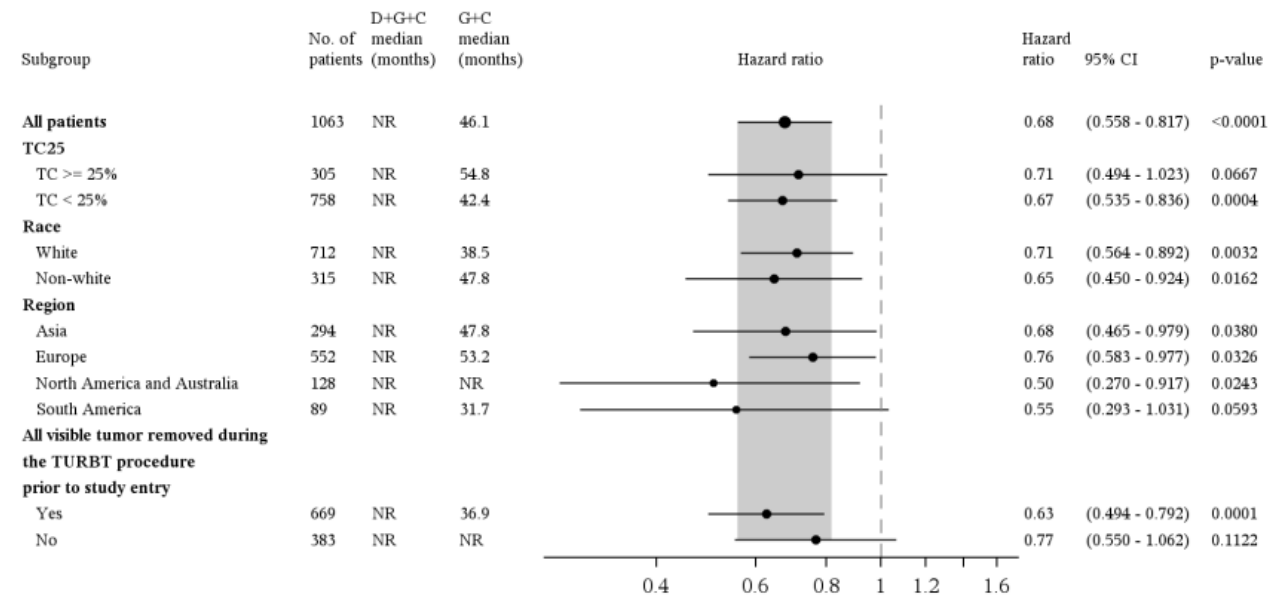
Because the TC component of the algorithm does not show inter-laboratory variability in prevalence, additional subgroup analyses of the primary endpoints and key secondary endpoint of OS were performed according to TC-only scoring algorithms, i.e. using the TC25% and TC1% cutoffs to help assess the efficacy data based on PD-L1 status.

Additional sensitivity analyses of the primary EFS endpoint were prespecified in the SAP Edition 6.0 in which PD-L1 was removed from the stratification variables in the stratified log-rank test and stratified Cox PH model, or either TC1% or TC25% was included as a categorical covariate.

Figure 11 Forest Plot for subgroup analyses, EFS per BICR or central pathology (Full Analysis set)







The plot is hazard ratio and 95% CI. Size of circle is proportional to the number of events. Grey band represents the 95% CI for the overall (all patients) hazard ratio.

All patients row analysis was performed using stratified Cox PH model; the stratification factors are tumor stage (T2N0 versus > T2N0), renal function (adequate versus borderline) and PD-L1 status (high versus low/negative) per IVRS.

The subgroup analysis was performed using an unstratified Cox PH model, with treatment as only covariate and ties handled by Efron approach.

A HR < 1 favors D + G+C to be associated with a longer EFS than G+C.

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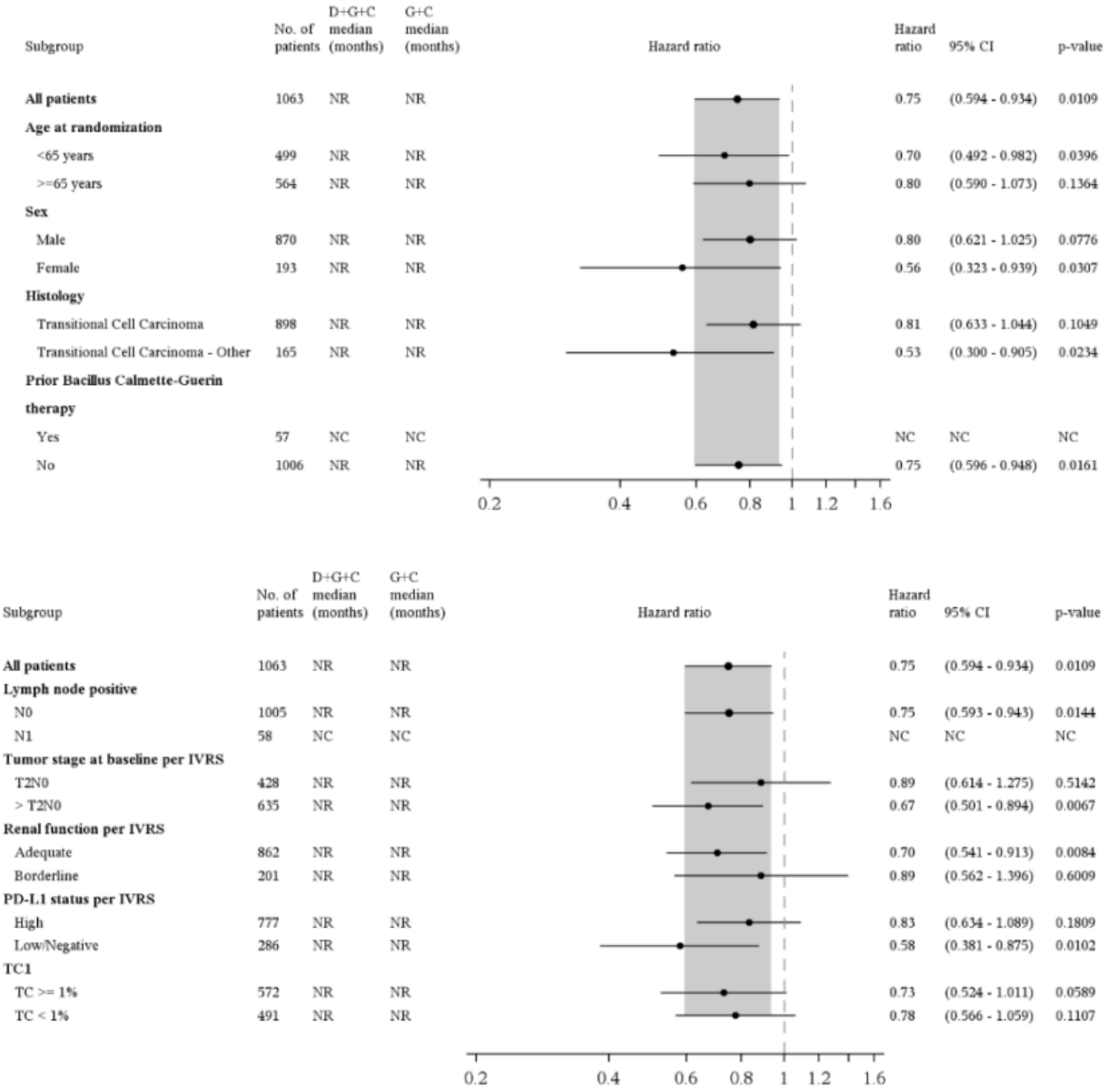
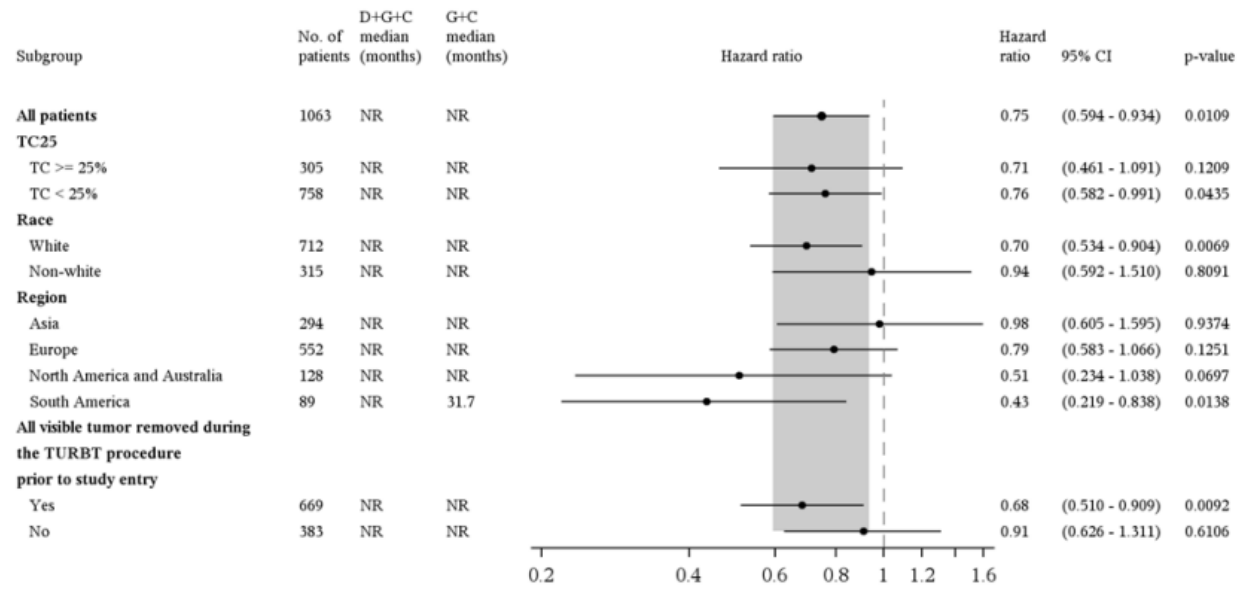
Figure 12 Forest plot for subgroup analyses, OS (Full Analysis Set, IA-2, 29-Apr-2024, Posthoc)





The plot is hazard ratio and 95% CI. Size of circle is proportional to the number of events. Grey band represents the 95% CI for the overall (all patients) hazard ratio.

All patients row analysis was performed using stratified Cox PH model; the stratification factors are tumor stage (T2N0 vs > T2N0), renal function (adequate vs borderline) and PD-L1 status (high vs low/negative) per IVRS.

The subgroup analysis was performed using an unstratified Cox PH model, with treatment as only covariate and ties handled by Efron approach.

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Immunogenicity

In patients who received durvalumab, the anti-drug antibodies (ADA) prevalence was 8.2% (37 of 453 patients), ADA incidence was 1.8% (8 of 453 patients) and 1.3% (6 of 453 patients) were neutralizing antibodies (nAb) positive. The presence of ADAs had no apparent impact on the PK or safety of durvalumab, supporting a low immunogenicity risk of durvalumab; however, the low numbers of ADA-positive patients preclude definitive conclusions being drawn.

Summary of main study

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 sections below).

Table 44 Summary of Efficacy for NIAGARA Study

Title: A Phase III, Randomized, Open-Label, Multi-Center, Global Study to Determine the Efficacy and Safety of Durvalumab in Combination with Gemcitabine+Cisplatin for Neoadjuvant Treatment Followed by Durvalumab Alone for Adjuvant Treatment in Patients with resectable Muscle-Invasive Bladder Cancer (**NIAGARA**).	
Study identifier	(Study D933R00001) EudraCT Number: 2018-001811-59 NCT Number: NCT03732677
Design	Phase III, randomized, open-label, multi-center, parallel-group global study comparing neoadjuvant durvalumab + gemcitabine+cisplatin combination therapy followed by adjuvant durvalumab monotherapy with gemcitabine+cisplatin neoadjuvant therapy.

	Duration of main phase:		Four 3-week neoadjuvant treatment cycles followed by eight 4-week adjuvant treatment cycles, with follow-up until final data cut-off
	Duration of Run-in phase:		Not applicable
	Duration of Extension phase:		Patients still in study at final data cut-off may be transitioned to an extension study for survival follow-up
Hypothesis	Superiority		
Treatments groups	Durvalumab + gemcitabine+cisplatin (D + G+C)		Durvalumab 1500 mg in combination with gemcitabine+cisplatin (every 3 weeks for 4 cycles) prior to cystectomy followed by durvalumab 1500 mg monotherapy (every 4 weeks for 8 cycles) post-cystectomy (N=533)
	Gemcitabine+cisplatin (G+C)		Gemcitabine+cisplatin (every 3 weeks for 4 cycles) prior to cystectomy, without adjuvant treatment post-cystectomy (N=530)
Endpoints and definitions	Dual primary endpoint: Pathological Complete Response	pCR	The proportion of patients whose pathological staging was T0N0M0 as assessed per central pathology review using specimens obtained via radical cystectomy following the neoadjuvant treatment.
	Dual primary endpoint: Event-Free Survival	EFS	The time from randomization to - the first recurrence of disease after radical cystectomy or - the time of first documented progression in patients who were medically precluded from a radical cystectomy or - the time of expected surgery in patients who refused to undergo a radical cystectomy or - failure to undergo a radical cystectomy in patients with residual disease, or - the time of death due to any cause, whichever occurred first.
	Key secondary endpoint (alpha controlled): Overall Survival	OS	The time from the date of randomization until death due to any cause
Database lock	24 May 2024		

Results and Analysis

Analysis description	**Primary Analysis: EFS Interim Analysis 2 (maturity 40.7%) /OS Interim Analysis 1 (maturity 28.7%)**
Analysis population and time point description	Full analysis set (ITT population) Pre-specified EFS interim analysis 2 (planned when approximately 410 events had occurred or in April 2024, whichever occurred first) and OS interim analysis 1 were performed with a 29 April 2024 cut-off date, along with other secondary endpoints

Descriptive statistics and estimate variability	Treatment group	D + C + G	C + G
	Number of subject	533	530
	Total **EFS** events, n (%) 25th-75th percentile (months)	187 (35.1%) 13.4 – Not reached	246 (46.4%) 8.6 – Not reached
	Dual Primary Endpoint: **pCR** (Final Analysis of pCR) Patients with pCR, n (%)	180 (33.8%)	137 (25.8%)
	Total **OS** events, n (%) 25th-75th percentile (months)	136 (25.5%) 41.9 – Not reached	169 (31.9%) 24.1 – Not reached
Effect estimate per comparison	Dual primary endpoint: **EFS** (maturity 40.7%)	Comparison groups	D+C+G vs. D+G *
		Hazard ratio	0.68
		95% confidence interval	0.558 – 0.817
		P-value [a]	<0.0001 [a]
	Dual Primary Endpoint: **pCR** (Final Analysis of pCR)	Comparison groups	D+C+G vs. D+G
		Odds ratio	HR 1.49
		95% Confidence interval	1.138 – 1.958
		P-value [b]	0.0038
	Key Secondary Endpoint: **OS** (maturity 28.7%)	Comparison groups	D+C+G vs. D+G
		Hazard ratio	0.75
		95% Confidence interval	0.594 – 0.934

		P-value [c]	0.0106 [b]
Notes	*Note that only the EFS result for the subgroup with stage >T2N0 (59.7% of ITT) reached statistical significance. [a] Threshold for significance: p = 0.0412 [b] Threshold for significance: p = 0.001 [c] Threshold for significance: p = 0.0154		

2.4.3. Discussion on clinical efficacy

The scope of this variation is to support the extension of indication of durvalumab for the perioperative treatment of resectable muscle invasive bladder cancer (MIBC) in adults, based on the results from the pivotal trial NIAGARA. The MAH applied for the following indication:

IMFINZI in combination with cisplatin-based chemotherapy as neoadjuvant treatment, followed by IMFINZI as monotherapy adjuvant treatment after radical cystectomy, is indicated for the treatment of adults with muscle invasive bladder cancer (MIBC).

The wording of the indication is further discussed below.

Design and conduct of clinical studies

Study design

NIAGARA is an ongoing Phase III, randomised, open-label, multicenter, global study in which adult patients with MIBC, who were eligible for radical cystectomy, were randomized 1:1 to receive neoadjuvant durvalumab in combination with gemcitabine and cisplatin prior to radical cystectomy, followed by adjuvant durvalumab (D+G+C arm), or neoadjuvant gemcitabine and cisplatin prior to radical cystectomy with no adjuvant treatment (G+C arm). All radiological assessments are performed by BICR.

Patients with resectable MIBC, classified as T2N0-1M0 to T4aN0-1M0 (corresponding to AJCC Stage II or IIIa, 8th edition), were eligible for study enrollment. Patients had to have ECOG Performance status 0 or 1. The resectability criteria are in accordance with international guidelines (ESMO 2021, AJCC 2017). The inclusion and exclusion criteria appropriately reflect the target population. However, the restriction to include no more than 40% of patients with stage T2 disease does not appear to align with the expected proportion of this stage in a real-world population of newly diagnosed patients with non-metastatic MIBC, which is expected to be closer to 80% (John et al. 2021). However, this limitation does not impact the the conclusion of the B/R assessment (see further below).

The comparator arm received 4 cycles of neoadjuvant chemotherapy (gemcitabine and cisplatin), which is an acceptable standard of care, in accordance with the 2021 ESMO Clinical Practice Guideline on bladder cancer. The combination of gemcitabine and cisplatin for the neoadjuvant phase is considered acceptable as it is one of the two standards of care recommended in the 2021 ESMO Clinical Practice Guideline on bladder cancer for this setting; the other being accelerated methotrexate, vinblastine, adriamycin and cisplatin (accelerated MVAC). Split-course cisplatin was used for patients with borderline renal function, which is considered appropriate and was endorsed in a Scientific Advice by CHMP (EMEA/H/SA/2752/9/2018/II). Durvalumab was administered at a fixed dose in 4 cycles prior to radical cystectomy and in 8 cycles post radical cystectomy, corresponding to 1 year of perioperative durvalumab treatment. Additionally, the 2021 ESMO Clinical Practice Guideline on bladder cancer does not recommend

the use of adjuvant chemotherapy in patients who have received neoadjuvant chemotherapy, so the absence of adjuvant treatment in the comparator arm is also endorsed.

Patients were stratified at randomization according to clinical tumour stage (T2N0 vs. > T2N0), renal function (normal vs. borderline) and PD-L1 expression status (high vs. low, TC1% (TC ≥ 1% vs TC < 1%) and TC25% (TC ≥ 25% vs TC < 25%)).

Scientific advice

The MAH received Scientific Advice (SA) in 2018 (EMEA/H/SA/2752/9/2018/II) prior to initiation of the NIAGARA study but did not follow all the CHMP recommendations. The CHMP noted that the two-arm design cannot distinguish the contribution of durvalumab as neoadjuvant versus adjuvant therapy. During the SA, the MAH proposed a double-blinded, placebo-controlled study, but subsequently changed it to an open-label design, reportedly in agreement with the FDA. From a regulatory perspective, this change increases the relevance of the inability to separate the contribution of the adjuvant phase, particularly as blinding was feasible. The absence of a placebo in the control arm's adjuvant phase further increases the risk of bias. The CHMP further highlighted that the relationship between EFS and OS in this population was not established and that pCR was not a validated prognostic marker. The CHMP recommended to stratify according to PD-L1 status and endorsed stratification by tumour stage and renal function.

Endpoints

The secondary endpoint OS and the co-primary endpoint EFS are considered to be the clinically most relevant endpoints in the NIAGARA study. The MAH chose to maintain pCR as a dual primary endpoint, justified by the need of an early clinical endpoint. The Society for Immunotherapy of Cancer and the International Bladder Cancer Group (A.M. Kamat et. al., 2023 doi.org/10.1200/JCO.23.00307) support the use of pCR as a co-primary endpoint based on data from a retrospective study suggesting pCR as a surrogate endpoint for OS. However, the absence of supportive prospective data available validating pCR in MIBC, particularly in the setting of neoadjuvant immunotherapy, limits the use of pCR for regulatory decision making. Other secondary endpoints were DFS and MFS. Patient reported outcomes (PROs) were exploratory endpoints.

PD-L1 expression classification

An exploratory endpoint of the trial was to investigate the predictive value of biomarkers, including PD-L1 expression. In the NIAGARA Study, the CE-marked Ventana PD-L1 (SP263) Assay was used. Although the SP263 Assays ability to detect PD-L1 expression in urothelial carcinoma has been validated and is in concordance with other approved PD-L1 assays, the chosen clinical scoring algorithm for patient classification according to PD-L1 expression is different from those used in other trials. In the NIAGARA Study, PD-L1 status was classified as high if ≥25% of tumour cells (TC) exhibited membrane staining or if the Immune Cells Present (ICP) were > 1% and ≥ 25% of these had membrane staining or if ICP = 1% and 100% had membrane staining. This composite scoring algorithm differs from established PD-L1 classification methods for other approved PD-L1 inhibitors in muscle-invasive bladder cancer, i.e. algorithms classifying PD-L1 expression according to CPS or percentage of TC. It would have been preferable to use a classification algorithm for PD-L1 expression validated to predict response and also to ensure consistency with other trials. However, this limitation did not impact the assessment of the efficacy results, which seem independent of PD-L1 status.

Study conduct

Protocol Amendments and SAP Revisions

Several protocol amendments were implemented in the course of the study. These included an expansion of the study population to include patients with cN1 disease, the permission of patients with a clinical complete response to enter a non-cystectomy extension phase with durvalumab treatment as well as a

restriction of patients with T2 disease to 40%. These amendments are not considered to have had a significant impact on the study results

For what concerns the statistical method, the planned number of EFS events was revised across multiple protocols and SAPs. In the fifth amendment (22/06/2023), the planned number of EFS events was reduced to 451, ensuring at least 90% power. According to the MAH, this change was motivated by a review of the literature (Bajorin et al., 2022; Bellmunt et al., 2021; Cathomas et al., 2022) from studies performed with different immune-checkpoint inhibitors in this setting, which highlighted a slowdown in EFS events after two years in patients treated for MIBC. Although these changes might not directly impact on the inflation of type I error if this change was based exclusively on external evidence, the open-label nature of the study raises concerns regarding the motivation for this amendment. Given that the results presented include 433 EFS events at IA2 (DCO: 29/04/2024) and the fifth amendment was implemented less than a year earlier (22/06/2023), it seems that the collection of the required EFS events may not have been as challenging as implied in the rationale for the amendment. However, the MAH has later provided event predictions for IA2, the final analysis per Amendment 5, and the original assumptions, to illustrate differences in timeline had the accrual model not been adjusted. Additionally, p-value boundaries for both the original (509 EFS events) and revised (451 EFS events) assumptions have been presented. Based on this information, the concern is considered resolved.

Interim analyses

Throughout the protocol amendments, the number and timing of interim analyses (IAs) were significantly modified. In the original protocol, only one IA was planned for EFS, which was to be conducted in the ITT population only if the primary EFS endpoint was significant, with an estimated 410 EFS events (80% of the target events). No IAs were planned for OS at that time.

The MAH has confirmed that blinding was maintained until IA2 despite the open-label design. In the amendment, although an amendment, which introduced changes to the ITT and added OS as a key secondary endpoint, was implemented late, thisis considered acceptable, as consistent results were observed and the majority of patients already belonged to the ITT population. Consistent efficacy outcomes were observed across amendments for both ITT and the "adequate renal function" subgroup, and the lack of subgroup analyses after Amendment 4 is accepted due to the low number of patients enrolled thereafter

Patient disposition and flow

The patient disposition and flow did not differ substantially between the two treatment arms. Of note, 72.3% (383/533) patients received neoadjuvant durvalumab and proceeded to adjuvant therapy and 27.7% did not initiate adjuvant durvalumab. The reasons for not receiving adjuvant treatment were not collected in the NIAGARA trial, which is considered a flaw of the study design. In the D+C+G arm there were 86 patients (out of 469) who underwent radical cystectomy, but did not receive adjuvant treatment. The MAH has retrospectively identified potential reasons for 38 patients. The reasons were not mutually exclusive, adding to the uncertainty of their validity. A quarter of the patients who initiated adjuvant durvalumab (95/383 or ~18% of the ITT population in the durvalumab arm (N=533), did not complete the planned adjuvant therapy and in total approximately 46% did not complete the full perioperative durvalumab treatment. This is noteworthy, but in an oncological adjuvant setting, a near 100% completion rate would not be expected. The relatively high proportion of patients not completing the planned adjuvant durvalumab treatment in the study, could translate into an even lower completion rate of the perioperative regimen in an older, frailer real-world population.However, this limitation did not impact the robustness of the EFS and OS results in the ITT population.

The overall proportion of patients in the NIAGARA study who did not undergo the planned radical cystectomy was 13.8%. A higher proportion underwent radical cystectomy in the durvalumab arm:

88.2% versus 84.2%. The reasons for not undergoing radical cystectomy were overall balanced with regards to disease progression, AEs, investigator decision and patient decision (main reason). Three times as many patients (12 versus 3) in the comparator arm did not have radical cystectomy performed due to study discontinuation. It is expected that a proportion of patients will not opt for radical cystectomy after neoadjuvant treatment, as the neoadjuvant approach implies a risk of losing some patients who were upfront candidates for radical cystectomy. The data presented show no apparent detriment in the durvalumab-arm with regards to the proportion of patients who undergo cystectomy.

The number of patients who had important protocol deviations were fairly balanced between the treatment arms (8.8% versus 7.0%) and are not considered to have had any major impact on the study results.

Efficacy data and additional analyses

Overall, the baseline characteristics in the NIAGARA study were balanced between the two treatment arms for all categories. The median age of the study population is 64.4. years, which is approximately 10 years younger than the median age at bladder cancer diagnosis in a real-world setting. The majority of the population studied consisted of males (81.8% versus 18.2% females), which is close to the actual difference in gender related incidence. There were 67.0% Whites, 27.9% Asian and 10% Blacks, roughly reflecting the demography in the geographic regions in which the study was conducted. Most patients were Performance Status 0 (78.0%). Renal function was described as adequate in 81.1% and borderline in 18.9% (stratification factor at randomization). The proportion of clinical stage T2N0 was 40.3%, and stage > T2N0 was 59.7%. The majority of patients included had stage T3 (43.6%), slightly higher in the durvalumab arm (241; 45.2%) and lower in the SOC arm (222; 41.9%). Only 11.8% had stage T4, and here the distribution was slightly higher in the SOC arm (68; 12.8% versus 57; 10.7%). The prognosis for T2, T3 and T4 differs. The differences in the distribution of high-risk stages in the two arms are relatively small and not likely to have significantly impacted the EFS and OS results, however, if efficacy of adding durvalumab is highest in the T3 group, and less pronounced in the T4 group, the uneven distribution would favour the magnitude of the effect in the experimental arm. Only 5.5% had N1 disease.

Endpoint Results

Data on EFS in the ITT population from the second planned interim analysis at DCO 29 April 2024 were presented with a maturity of 40.7% (433/1063 EFS events). The durvalumab arm showed superiority with events having occurred in 35.1% versus 46.4% in the comparator arm (HR 0.68, 95% CI 0.558-0.817), corresponding to a 32% reduction in the risk of an EFS event. At 36 months there is an approximately 10% difference in EFS rate in favour of durvalumab (63.7% versus 53.6%). The median EFS was not reached in the durvalumab arm and was 46.1 months in the comparator arm. As shown in the pre-planned subgroups analysis (ancillary analysis), the benefit of durvalumab appears to be mainly driven by the prognostically worse subgroup of patients with clinical stage >T2N0 (n=635 patients), in which the HR for EFS was 0.61 (95% CI 0.477-0.778, p-value = 0.0001) in favour of durvalumab. The same magnitude of effect is not seen for the lower-risk subgroup of patients with clinical stage T2N0 group (n=428 patients), with an HR of 0.81, 95% CI 0.595 – 1.096, p-value = 0.1694. The EFS KM Plot for the T2N0 group shows a sustained separation of the curves at 6 months in favour of durvalumab. The EFS KM Plot for the subgroup of patients with stage >T2N0 shows a clear and sustained separation from the time of randomisation. The small number of patients in the N1 subgroup precludes statistically significant conclusions on EFS benefit in this subgroup. However, the overall ITT population's EFS and OS benefits include N1 patients and therefore no further regulatory actions are warranted. Pre-specified EFS sensitivity analyses were conducted and overall showed consistent results with the primary analysis, which is reassuring.

The OS data from the second interim analysis are presented with a maturity of 28.7% (305/1063 events) and shows superiority of the durvalumab arm (HR 0.75, 95% CI 0.594-0.934). Median OS is not reached for the two treatment arms. The Kaplan-Meier curves separate at 6 months and this separation is sustained. The median duration of follow-up for OS was 42.3 months and 39.6 months in the durvalumab and control arm respectively. While OS data might be considered immature at 28.7%, OS was statistically significant at the IA analysis submitted, therefore any later OS data would be descriptive in nature. Although subgroup analyses were not pre-planned for OS, data were presented showing that the positive effect of durvalumab on OS again appears to be primarily driven by the subgroup of patients with clinical stage >T2N0 (HR 0.67; 95%CI 0.501-0.894). For the subgroup of patients with clinical stage T2N0, the HR was 0.89 (95% CI 0.612–1.275). The OS KM Plots, although presenting immature survival data, show a clear and sustained curve separation in both stage groups. It is reassuring, that the positive results for the primary endpoint EFS are supported by an apparently also positive effect of durvalumab on OS.

The benefit of durvalumab on EFS appears to be primarily driven by the prognostically worse subgroup of patients with clinical stage >T2N0 (n=635 patients), with an EFS HR of 0.61 (95% CI 0.477-0.778, p-value = 0.0001) in favour of durvalumab. In contrast, EFS superiority of durvalumab was not formally demonstrated in T2N0 (n=428 patients) subgroup, with an EFS HR of 0.81, (95% CI 0.595 – 1.096, p-value = 0.1694). The lower risk subgroup of patients have a better prognosis than the higher-risk subgroup and this is most likely the reason for the difference in magnitude of treatment benefit in the two subgroups. While the benefit-risk is considered positive in both subgroups, the differential effects in EFS and OS between Stage T2N0 and >T2N0 are clinically relevant for prescribers. Therefore, data for these two subgroups is reflected in section 5.1 of the SmPC. Further, the MAH will present OS results for the ITT population and for both stage subgroups separately at 5 years (**REC**).

Pathological complete response (pCR) showed no statistically significant difference in pCR rate (per central pathology review) between the two treatment arms, where a numerical difference in favour of the durvalumab-arm was observed (37.3% versus 27.5%). The results of the secondary endpoints disease free survival (DFS) and metastasis free survival (MFS) are supportive of the beneficial effect of durvalumab on EFS and OS.

Results on PD-L1 expression

Patient classification according to the predefined categories of PD-L1 expression was hampered due to inconsistency in measuring outcomes of the immune cell (IC) component between the two central laboratories used in the trial. Due to this inconsistency, the originally planned PD-L1 expression algorithm could not be applied. There was, though, consistency when determining PD-L1 expression in tumour cells (TC) and therefore additional subgroup analyses of EFS and OS were instead performed using the TC 25% and TC 1% cutoffs. PD-L1 expression was balanced between the two arms. A sensitivity analysis of EFS by BICR was performed, that excluded the PD-L1 stratification factor (i.e. PD-L1 by TC/IC 25%) from the primary EFS analysis, or applied TC 1% or TC 25% as a categorical covariate. The statistical method used is endorsed. The percentage of PD-L1 expression on TC was not shown to be predictive of treatment benefit of durvalumab. Whether the application of the originally planned algorithm would have given another result cannot be definitively ruled out, but it is acknowledged that PD-L1 expression is a dynamic biomarker with less consistent predictive results in bladder cancer compared to other cancer types (Maiorano et al. 2024 doi:10.1001/jamanetworkopen.2024.1215).

Adequate/borderline renal function

In the subgroup with borderline renal function (n=201 patients) stratified at randomization, the HR for EFS of 0.69 is consistent with the HR of the group with adequate renal function, but its broader 95% confidence interval crossed 1 (95% CI 0.464-1.012), indicating lack of statistical significance. The broad CI interval may reflect the relatively small number of patients with borderline renal function (18.9% of the ITT), but introduces uncertainty about the consistency of durvalumab efficacy when added to SOC in

this subgroup. However, given the overall ITT population efficacy results in EFS and OS, no further regulatory actions are warranted.

Other subgroups

There was consistency in EFS benefit with regards to age, gender and histology. No pivotal differences regarding race or geographical regions were observed.

Wording of the indication

Considering that all patients in NIAGARA trial received cisplatin and gemcitabine, and no alternative chemotherapy regimens were allowed, the indication was amended to specify the regimen that was given during the clinical trial. A supportive argument to this is that 2021 ESMO Clinical Practice Guideline on bladder cancer recommends two cisplatin-based regimens for this setting, and there is no evidence for efficacy of durvalumab with MVAC. In addition, although the term "neoadjuvant" in theory implies that the treatment is intended for patients who are considered resectable, in practice the term may also be used with the intention of downsizing an a priori unresectable or borderline resectable tumour. To adequately describe the intended target population and to underscore that patients must be found resectable before initiation of neoadjuvant therapy, the word "resectable" was added to the proposed indication.

The following wording of indication is accepted:

IMFINZI in combination with gemcitabine and cisplatin as neoadjuvant treatment, followed by IMFINZI as monotherapy adjuvant treatment after radical cystectomy, is indicated for the treatment of patients with resectable muscle invasive bladder cancer (MIBC)."

2.4.4. Conclusions on the clinical efficacy

The addition of neoadjuvant durvalumab to gemcitabine and cisplatin in adult patients with resectable MIBC, followed by adjuvant durvalumab monotherapy after radical cystectomy, led to a statistically significant improvement in EFS of 11.3% (EFS maturity of 40.7%) with an HR 0.68 (95% CI 0.558-0.817, p<0.001). The second interim analysis of OS supports this finding, with an HR of 0.75 (95% CI 0.594-0.934) and OS maturity of 28.7%. Several protocol amendments were implemented during the trial and the MAH was requested to provide sensitivity analyses to assess any impact these amendments may have had on the trial results. The sensitivity analyses confirm the robustness of the treatment effect and suggest that the observed efficacy outcomes were not driven by the protocol amendments or early emerging trends. The beneficial effect of durvalumab on EFS is seen in both tumour stage subgroups (T2N0 and > T2N0), but the effect in the ITT population appears to be primarily driven by the higher stage subgroup (>T2N0). While the benefit-risk is considered positive in both subgroups, the differential effects in EFS and OS between Stage T2N0 and >T2N0 are clinically relevant for prescribers. Therefore, efficacy data for these two subgroups is reflected in section 5.1 of the SmPC. Although the planned classification algorithm for PD-L1 expression could not be applied, PD-L1 expression may not be predictive of the efficacy of durvalumab. The study design does not allow for distinguishing the contributions of neoadjuvant versus adjuvant durvalumab to the treatment effect.

2.5. Clinical safety

Introduction

Assessment of the safety profile of durvalumab in combination with G+C as neoadjuvant treatment, followed by (adjuvant) durvalumab as monotherapy after radical cystectomy, in adults with resectable MIBC is based on safety data from the pivotal, phase III trial, NIAGARA (IA2 DCO 29 April 2024).

Supportive safety data are provided in the form of pooled safety data ("D Pan-Tumor Pool") from 13 completed clinical studies on durvalumab monotherapy performed in a variety of solid tumor types.

Selected supportive safety data are also provided from three trials investigating durvalumab in combination with chemotherapy in SCLC (CASPIAN trial), biliary tract cancers (TOPAZ-1 trial) and endometrial cancer (DUO-E) with the aim to characterize ADRs and imAEs presented in the proposed SmPC.

The list of studies contributing to the safety pool is described in Table 45.

Table 45 Study Numbers, Names and Location of CSRs in Module 5

Study number and name	Study title	Number of patients	Data cutoff	Location in Module 5
Pivotal study				
D933RC00001 **NIAGARA**	A Phase III, Randomized, Open-Label, Multi-Center, Global Study to Determine the Efficacy and Safety of Durvalumab in Combination with Gemcitabine+Cisplatin for Neoadjuvant Treatment Followed by Durvalumab Alone for Adjuvant Treatment in Patients with Muscle-Invasive Bladder Cancer	1056	Interim analysis 2, 29 Apr 2024	5.3.5.1
Supportive studies included in the D pan-tumor pool				
D419CC00002 **HIMALAYA**	A randomized, open-label, multicenter Phase III study of durvalumab and tremelimumab as first-line treatment in patients with advanced hepatocellular carcinoma	388	27 Aug 2021	5.3.5.1
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 subjects with advanced unresectable hepatocellular carcinoma	104	06 Nov 2020	5.3.5.2
CD-ON-MEDI4736-1108 **Study 1108**	A Phase I/II study to evaluate the safety, tolerability, and pharmacokinetics of MEDI4736 in subjects with advanced solid tumors	1001	16 Oct 2017	5.3.5.2
D4190C00002 **Japan Study 02**	A Phase I, open-label, multicenter study to evaluate the safety, tolerability and pharmacokinetics of MEDI4736 in patients with advanced solid tumors	124	31 Mar 2018	5.3.5.2

Table 45 Study Numbers, Names and Location of CSRs in Module 5

Study number and name	Study title	Number of patients	Data cutoff	Location in Module 5
D4191C00004 **ARCTIC**	A Phase III, open-label, randomized, multi-center, international study of MEDI4736, given as monotherapy or in combination with tremelimumab, determined by PD-L1 expression, versus standard-of-care in patients with locally advanced or metastatic non-small cell lung cancer (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	179	09 Feb 2018	5.3.5.1
D419AC00001 **MYSTIC**	A Phase III randomized, open-label, multi-center, global study of MEDI4736 in combination with tremelimumab therapy or MEDI4736 monotherapy versus standard of care platinum-based chemotherapy in first-line treatment of patients with advanced or metastatic non-small-cell lung cancer (NSCLC)	369	04 Oct 2018	5.3.5.1
D4193C00003 **CONDOR**	A Phase II, randomized, open-label, multi-center, global study of MEDI4736 monotherapy, tremelimumab monotherapy, and MEDI4736 in combination with tremelimumab in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN)	65	27 Aug 2018	5.3.5.2
D4193C00002 **EAGLE**	A Phase III randomized, open-label, multicenter, global study of MEDI4736 monotherapy and MEDI4736 in combination with tremelimumab versus standard-of-care therapy in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN)	237	10 Sep 2018	5.3.5.1
D4193C00001 **HAWK**	A Phase II, multi-center, single-arm, global study of MEDI4736 monotherapy in patients with recurrent or metastatic squamous cell carcinoma of the head and neck	112	05 Oct 2018	5.3.5.2
D4191C00001 **PACIFIC**	A Phase III, randomized, double-blind, placebo-controlled, multi-center, international study of MEDI4736 as sequential therapy in patients with locally advanced, unresectable non-small cell lung cancer (Stage III) who have not progressed following definitive, platinum-based, concurrent chemoradiation therapy	475	22 Mar 2018	5.3.5.1

Table 45 Study Numbers, Names and Location of CSRs in Module 5

Study number and name	Study title	Number of patients	Data cutoff	Location in Module 5
D4191C00003 **ATLANTIC**	A Phase II, non-comparative, open-label, multi-center, international study of MEDI4736, in patients with locally advanced or metastatic non-small cell lung cancer (Stage IIIB-IV) who have received at least 2 prior systemic treatment regimens including one platinum-based chemotherapy regimen	444	03 Jun 2016	5.3.5.2
D419BC00001 **DANUBE**	A Phase III randomized, open-label, controlled, multi-center, global study of first-line MEDI4736 monotherapy and MEDI4736 in combination with tremelimumab versus standard of care chemotherapy in patients with unresectable stage IV urothelial cancer	345	27 Jan 2020	5.3.5.1
D419LC00001 **KESTREL**	A Phase III randomized, open-label, multi-center, global study of durvalumab alone or in combination with tremelimumab versus standard of care in the treatment of first-line recurrent or metastatic squamous cell head and neck cancer patients	202	06 Jul 2020	5.3.5.1
Studies included in additional chemotherapy pools (the D + CTx and CTx pools)				
NIAGARA	A Phase III, Randomized, Open-Label, Multi-Center, Global Study to Determine the Efficacy and Safety of Durvalumab in Combination with Gemcitabine+Cisplatin for Neoadjuvant Treatment Followed by Durvalumab Alone for Adjuvant Treatment in Patients with Muscle-Invasive Bladder Cancer	1056	Interim analysis 2, 29 Apr 2024	5.3.5.1
D419QC00001 **CASPIAN** [a]	A Phase III, randomized, multicenter, 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 small-cell lung cancer	531	27 Jan 2020	5.3.5.1
D933AC00001 **TOPAZ-1** [a]	A Phase III, randomized, multicenter, double-blind placebo controlled study evaluating D + Gemcitabine+Cisplatin versus placebo + Gemcitabine+Cisplatin for the treatment of patients with first-line, unresectable locally advanced or metastatic BTC.	680	25 Feb 2022	5.3.5.1

Table 45 Study Numbers, Names and Location of CSRs in Module 5

Study number and name	Study title	Number of patients	Data cutoff	Location in Module 5
D9311C00001 **DUO-E** [a]	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)	471	12 Apr 2023	5.3.5.1

Source: SCS

Demographics of the enrolled population in NIAGARA:

Table 46 Key Demographic and Patient Characteristics in the NIAGARA Study and D Pan-tumor pool (Safety Analysis Set)

Characteristic	Number (%) of patients		
	NIAGARA study (Overall period)		D Pan-tumor pool (N = 4045)
	D + G+C (N = 530)	G+C (N = 526)	
Age (years)			
Mean (StD)	64.0 (8.91)	64.6 (8.96)	61.9 (10.87)
Median (Min, Max)	65.0 (34, 84)	66.0 (32, 83)	63.0 (19, 96)
Age group (years) (n%)			
< 50	33 (6.2)	35 (6.7)	482 (11.9)
≥ 50 - < 65	225 (42.5)	203 (38.6)	1768 (43.7)
≥ 65 - < 75	215 (40.6)	225 (42.8)	1356 (33.5)
≥ 75	57 (10.8)	63 (12.0)	439 (10.9)
Sex, n (%)			
Male	434 (81.9)	430 (81.7)	2783 (68.8)
Female	96 (18.1)	96 (18.3)	1262 (31.2)
Race, n (%)			
White	353 (66.6)	355 (67.5)	2691 (66.5)
Black or African American	6 (1.1)	4 (0.8)	84 (2.1)
Asian	150 (28.3)	144 (27.4)	1121 (27.7)
Other	7 (1.3)	1 (0.2)	72 (1.8)
Missing	14 (2.6)	22 (4.2)	77 (1.9)
Geographic region			
Asia	149 (28.1)	142 (27.0)	1032 (25.5)

Europe	275 (51.9)	299 (56.8)	1756 (43.4)
North America	55 (10.4)	47 (8.9)	1209 (29.9)
South America	51 (9.6)	38 (7.2)	48 (1.2)
Non-Asia Regions	381 (71.9)	384 (73.0)	3013 (74.5)
Baseline ECOG/WHO Performance Status, n (%) [a]			
0	416 (78.5)	412 (78.3)	1646 (40.7)
≥ 1	114 (21.5)	114 (21.7)	2394 (59.2)
Missing	0	0	5 (0.1)

[a] Study 1108, Japan Study 2, Danube, Study 22 and Himalaya collected ECOG. Arctic, Atlantic, Mystic and Pacific collected WHO. NIAGARA, Eagle, Condor, Hawk and Kestrel collected both ECOG and WHO with the latest test being used for analysis.

ECOG/WHO PS (0) = Normal activity; (1) = Restricted activity; (2) = In bed ≤ 50% of the time; (3) = In bed > 50% of the time; (4) = 100% bedridden; (5) = Death.

Source: see Table 2.7.4.1.2, Pooled Safety Outputs, Module 5.3.5.3.

Patient exposure

The median duration of follow-up in all patients in the D + G+C arm was 42.3 months (range: 0.26 to 64.62) and 39.6 months (range: 0.03 to 64.66) in the G+C arm. Each patient was followed up for safety until their protocol-defined safety follow-up period of 90 days was completed. In the D + G+C arm, this was 90 days after the last dose of study treatment, or date of surgery (whichever occurred later), date of first dose of subsequent anticancer therapy, or date of DCO. In the G+C arm, this was 90 days after the last neoadjuvant treatment, date of surgery, or adjuvant study visit (whichever occurred later), date of first dose of subsequent anticancer therapy, or date of DCO. Beyond the 90-day follow-up period, the only safety data collected was if an AE/SAE was considered to be due to late-onset toxicity to study drug. At the time of IA2 DCO, all patients had completed the safety follow-up period and all scheduled safety data collection for the NIAGARA study was considered complete.

The safety follow-up is distinct from survival follow-up, which is ongoing but for which the data cut-off was applied for the interim CSR.

The total number of years at risk for an AE (which includes the 90-day follow-up for patients) was 540.3 years in the D + G+C arm and 551.7 years in the G+C arm.

Table 47 Duration of Durvalumab Exposure in the NIAGARA Study and D Pan-tumor Pool (Safety Analysis Set)

Parameter	Number (%) of patients			
	NIAGARA			D Pan-tumor pool (N = 4045)
	Neoadjuvant period	Adjuvant period	Overall period	
	D + G+C (N = 530)	D + G+C (N = 383)	D + G+C (N = 530)	
Total number of infusions				
Number of patients	530	383	530	4045
Mean (StD)	3.85 (1.081)	6.90 (2.150)	8.84 (3.835)	10.73 (10.307)
Median (Min, Max)	4.00 (1.0, 12.0)	8.00 (1.0, 8.0)	12.00 (1.0, 12.0)	6.00 (1.0, 70.0)
Total treatment duration (weeks) [a]				
Number of patients	530	383	530	4045
Mean (StD)	12.58 (6.182)	28.90 (9.303)	33.47 (16.329)	28.90 (32.179)

Table 47 Duration of Durvalumab Exposure in the NIAGARA Study and D Pan-tumor Pool (Safety Analysis Set)

Parameter	Number (%) of patients			
	NIAGARA			D Pan-tumor pool (N = 4045)
	Neoadjuvant period	Adjuvant period	Overall period	
	D + G+C (N = 530)	D + G+C (N = 383)	D + G+C (N = 530)	
Median (Min, Max)	12.14 (1.1, 83.6)	32.00 (2.4, 50.1)	44.00 (1.1, 83.6)	16.14 (0.4, 220.0)
Patient-years exposure [b]	127.8	212.1	340.0	2240.4

a Total treatment duration of D in neoadjuvant = (earliest (last dose date where dose > 0 + XX, death date, DCO) - first dose date + 1) /7. XX = 20 if last dose is in neoadjuvant phase, XX = 27 if last dose is in non-cystectomy extension phase. Total treatment duration of D in adjuvant = (earliest (last dose date where dose > 0 + 27, death date, DCO) - first dose date + 1) /7.

b Patient-years exposure = Total treatment duration (years) summed across all patients within a group, where treatment duration (years) = (last dose date + X days or death date or DCO whichever occurs earlier - first dose date +1)/365.25.

X is defined as the planned frequency in dosing (in days) - 1. For Q4W, X = 27. For Q3W, X = 20. For Q2W, X = 13.

Table 48 Patients discontinued neoadjuvant treatment by cycle (Safety Analysis Set)

	Number (%) of patients		
	D+G+C (N=530)	G+C (N=526)	Total (N=1056)
Patients ongoing neoadjuvant treatment [a]	0	0	0
Patients discontinued neoadjuvant treatment [b]	113 (21.3)	137 (26.0)	250 (23.7)
At cycle 1	19 (3.6)	36 (6.8)	55 (5.2)
At cycle 2	20 (3.8)	30 (5.7)	50 (4.7)
At cycle 3	41 (7.7)	37 (7.0)	78 (7.4)
At cycle 4	33 (6.2)	34 (6.5)	67 (6.3)
Patients completed neoadjuvant treatment [c]	417 (78.7)	389 (74.0)	806 (76.3)

C = Cisplatin, D = Durvalumab, G = Gemcitabine

[a] Patients who had not discontinued all their dosed IPs are considered ongoing treatment.

[b] Patients are considered discontinued at a particular cycle if dosed at least one drug in this cycle.The smallest cycle among the drugs was chosen. Patients are considered discontinued neoadjuvant treatment if discontinued all dosed IPs and at least one was not due to 'Maximum cycle reached'.

[c] Patients who discontinued all their dosed IPs with reasons 'Maximum cycle reached' are considered completed treatment.

Source: CSR

Table 49 Subjects Discontinued Adjuvant Treatment by Cycle Reached (Safety Analysis Set)

	Number (%) of subjects	
	D + G+C (N = 530)	**G+C (N = 526)**
Started adjuvant treatment	383 (72.3)	NA
Completed adjuvant treatment	288 (54.3)	NA
Subjects discontinued adjuvant treatment [a]	95 (17.9)	NA
At cycle 1	17 (3.2)	NA
At cycle 2	18 (3.4)	NA
At cycle 3	19 (3.6)	NA
At cycle 4	6 (1.1)	NA
At cycle 5	13 (2.5)	NA
At cycle 6	11 (2.1)	NA
At cycle 7	10 (1.9)	NA
At cycle 8	1 (0.2)	NA

[a] Subjects are considered to have discontinued adjuvant treatment if they discontinued and it was not due to 'Maximum cycle reached'.

Adverse events

AEs are provided for the following study periods:

Overall period:

Date of first dose of study treatment until the earliest of:

• D + G+C arm: 90 days after the last dose of study treatment, or date of surgery (whichever occurs later), date of first dose of subsequent anticancer therapy, or date of DCO.

• G+C arm: 90 days after the last neoadjuvant treatment, date of surgery, or adjuvant study visit (whichever occurs later), date of first dose of subsequent anticancer therapy, or date of DCO.

Neoadjuvant period:

• Date of first dose of neoadjuvant study treatment until the date of surgery or, for patients without surgery, up to the earliest of: date of last dose of last neoadjuvant treatment + 90 days, date of first dose of subsequent anticancer therapy, or the DCO date. Note, for assessments recorded on the day of surgery, time of event was used to determine if it was pre- or post-surgery, if time was not available it was assumed to occur post-surgery.

Post-surgery period:

• Date of the day of surgery until the earliest of: date of surgery + 90 days, date of first dose of subsequent anticancer therapy, or the DCO date. Note, some patients may have had an overlap between their post-surgery period and adjuvant period.

Adjuvant period:

• Date of first dose of adjuvant study treatment (D + G+C arm), or date of first adjuvant study visit (G+C arm), until the earliest of: 90 days after the last dose of adjuvant study treatment (D + G+C arm) or last adjuvant study visit (G+C arm), date of first dose of subsequent anticancer therapy, or the DCO date.

Table 50 List of summaries for AESI or AEPI and imAE

Category	Table, Figure or Listing
AESI or AEPI and imAE at grouped term level	• AESI or AEPI, and imAE in any category • AESI or AEPI, and imAE by category and PT with number of patients and incidence in any grade, grade 3-4, serious, fatal outcome, systemic corticosteroids, high dose systemic corticosteroids, other immunosuppressants, endocrine therapy, discontinuation, outcome of resolved, unresolved) for the following categories by treatment groups and pools: o Pneumonitis o Hepatic Events o Diarrhoea/Colitis o Intestinal Perforations o Infusion/hypersensitivity reactions (not potential imAEs, so excluded from imAEs) o Adrenal Insufficiency o Type I Diabetes Mellitus o Hyperthyroid Events o Hypophysitis o Hypothyroid Events o Thyroiditis o Renal Events o Dermatitis/Rash o Pancreatic events o Myocarditis o Myasthenia Gravis o Guillain-Barre Syndrome o Myositis o Other rare/miscellaneous • AESI, AEPI and imAE by Grouped Term
AESI or AEPI, and imAE at PT level	• AESI or AEPI, and imAE by Grouped Term and PT
Time to event	• AESI or AEPI, and imAE Time to Event
Listings	• Listing of AESI or AEPI

Source: SAP

Table 51 Number (%) of Patients in the NIAGARA Study and D Pan-tumor Pool With at Least One Adverse Event in any Category (Safety Analysis Set)

AE category	Number (%) of patients [a]						
	NIAGARA study						D Pan-tumor pool (N = 4045)
	Neoadjuvant period		Adjuvant		Overall period		
	D + G+C (N = 530)	G+C (N = 526)	D + G+C (N = 383)	G+C (N = 383)	D + G+C (N = 530)	G+C (N = 526)	
Any AE	520 (98.1)	515 (97.9)	331 (86.4)	273 (71.3)	527 (99.4)	525 (99.8)	3825 (94.6)
Any AE possibly related to any study treatment [b]	493 (93.0)	487 (92.6)	156 (40.7)	23 (6.0)	502 (94.7)	487 (92.6)	2340 (57.8)
Any AE possibly related to D [b]	248 (46.8)	NA	148 (38.6)	NA	328 (61.9)	NA	2340 (57.8)
Any AE of CTCAE Grade 3 or 4 [c]	249 (47.0)	271 (51.5)	119 (31.1)	91 (23.8)	368 (69.4)	355 (67.5)	1754 (43.4)
Any AE of CTCAE Grade 3 or 4, possibly related to any study treatment [b, c]	201 (37.9)	213 (40.5)	21 (5.5)	3 (0.8)	215 (40.6)	215 (40.9)	475 (11.7)
Any AE of CTCAE Grade 3 or 4, possibly related to D [b, c]	41 (7.7)	NA	17 (4.4)	NA	61 (11.5)	NA	475 (11.7)
Any AE of maximum CTCAE Grade 3 or 4 [d]	248 (46.8)	267 (50.8)	117 (30.5)	90 (23.5)	353 (66.6)	336 (63.9)	1600 (39.6)
Any AE of maximum CTCAE Grade 3 or 4, possibly related to any study treatment [b, d]	201 (37.9)	212 (40.3)	21 (5.5)	3 (0.8)	215 (40.6)	213 (40.5)	465 (11.5)
Any AE of maximum CTCAE Grade 3 or 4, possibly related to D [b, d]	41 (7.7)	NA	17 (4.4)	NA	61 (11.5)	NA	465 (11.5)
Any AE with outcome of death	6 (1.1)	10 (1.9)	7 (1.8)	6 (1.6)	27 (5.1)	29 (5.5)	231 (5.7)
Any AE with outcome of death, possibly related to any study treatment [b]	3 (0.6)	2 (0.4)	0	0	3 (0.6)	3 (0.6)	27 (0.7)
Any AE with outcome of death, possibly related to D [b]	1 (0.2)	NA	0	NA	1 (0.2)	NA	27 (0.7)
Any SAE (including events with outcome of death) [e]	125 (23.6)	118 (22.4)	101 (26.4)	85 (22.2)	326 (61.5)	287 (54.6)	1447 (35.8)
Any SAE (including events with outcome of death), possibly related to any study treatment [b, e]	70 (13.2)	61 (11.6)	14 (3.7)	1 (0.3)	86 (16.2)	63 (12.0)	288 (7.1)

AE category	Number (%) of patients [a]						
	NIAGARA study						D Pan-tumor pool (N = 4045)
	Neoadjuvant period		Adjuvant		Overall period		
	D + G+C (N = 530)	G+C (N = 526)	D + G+C (N = 383)	G+C (N = 383)	D + G+C (N = 530)	G+C (N = 526)	
Any SAE (including events with outcome of death), possibly related to D [b, e]	19 (3.6)	NA	12 (3.1)	NA	35 (6.6)	NA	288 (7.1)
Any AE leading to discontinuation of any study treatment	79 (14.9)	80 (15.2)	30 (7.8)	0	112 (21.1)	80 (15.2)	397 (9.8)
Any AE leading to discontinuation of D	50 (9.4)	NA	30 (7.8)	NA	86 (16.2)	NA	397 (9.8)
Any AE leading to discontinuation of any study treatment possibly related to any study treatment [b]	64 (12.1)	64 (12.2)	21 (5.5)	0	85 (16.0)	64 (12.2)	183 (4.5)
Any AE leading to discontinuation of D, possibly related to D [b]	19 (3.6)	NA	19 (5.0)	NA	42 (7.9)	NA	183 (4.5)
Any AE leading to dose modification of any study treatment [f]	269 (50.8)	248 (47.1)	75 (19.6)	0	306 (57.7)	248 (47.1)	1129 (27.9)
Any AE leading to dose delay or interruption of any study treatment [g]	219 (41.3)	212 (40.3)	75 (19.6)	0	264 (49.8)	212 (40.3)	1120 (27.7)
Any AE leading to dose delay or interruption of D [g]	132 (24.9)	NA	75 (19.6)	NA	192 (36.2)	NA	1120 (27.7)

[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] As assessed by the Investigator. Missing responses are counted as related. Study treatment includes durvalumab, cisplatin, and gemcitabine, in this context surgery is not included as a study treatment.
[c] All CTCAE Grades per patient/treatment period, not just the maximum, are considered when identifying whether there is a Grade 3 or 4.
[d] Maximum CTCAE Grade per patient/treatment period/event is considered.
[e] Seriousness, as assessed by the Investigator. An AE with missing seriousness is considered serious.
[f] 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.
[g] 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.
Percentages are based on the total number of patients in the treatment group (N).
Definitions of the NIAGARA neoadjuvant, adjuvant, and overall periods are provided in Section 2.1.
Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.
Disease progression AEs reported in Study 1108 are not included in this summary.
All studies use CTCAE version 4.03 except for NIAGARA which uses version 5.0. MedDRA version 26.1.
DCO for NIAGARA study: 29 April 2024.

Table 52 AEs in Any Category – Patient level (Safety Analysis Set)

AE category	Number (%) of patients [a]					
	Neoadjuvant period		Adjuvant period		Overall period	
	D + G+C (N = 530)	G+C (N = 526)	D + G+C (N = 383)	G+C (N = 383)	D + G+C (N = 530)	G+C (N = 526)
Any AE	520 (98.1)	515 (97.9)	331 (86.4)	273 (71.3)	527 (99.4)	525 (99.8)
Any AE possibly related to study treatment [b c]	493 (93.0)	487 (92.6)	156 (40.7)	23 (6.0)	502 (94.7)	487 (92.6)
Any AE possibly related to D [b]	248 (46.8)	NA	148 (38.6)	NA	328 (61.9)	NA
Any AE possibly related to G or C [b]	484 (91.3)	487 (92.6)	21 (5.5)	23 (6.0)	484 (91.3)	487 (92.6)
Any AE of CTCAE Grade 3 or 4	249 (47.0)	271 (51.5)	119 (31.1)	91 (23.8)	368 (69.4)	355 (67.5)
Any AE of CTCAE Grade 3 or 4, possibly related to study treatment [b c]	201 (37.9)	213 (40.5)	21 (5.5)	3 (0.8)	215 (40.6)	215 (40.9)
Any AE of CTCAE Grade 3 or 4, possibly related to D [b]	41 (7.7)	NA	17 (4.4)	NA	61 (11.5)	NA
Any AE of CTCAE Grade 3 or 4, possibly related to G or C [b]	195 (36.8)	213 (40.5)	5 (1.3)	3 (0.8)	200 (37.7)	215 (40.9)
Any AE with outcome of death	6 (1.1)	10 (1.9)	7 (1.8)	6 (1.6)	27 (5.1)	29 (5.5)
Any AE with outcome of death, possibly related to study treatment [b c]	3 (0.6)	2 (0.4)	0	0	3 (0.6)	3 (0.6)
Any AE with outcome of death, possibly related to D [b]	1 (0.2)	NA	0	NA	1 (0.2)	NA
Any AE with outcome of death, possibly related to G or C [b]	3 (0.6)	2 (0.4)	0	0	3 (0.6)	3 (0.6)
Any AE leading to discontinuation of study treatment [c]	79 (14.9)	80 (15.2)	30 (7.8)	0	112 (21.1)	80 (15.2)
Any AE leading to discontinuation of D	50 (9.4)	NA	30 (7.8)	NA	86 (16.2)	NA
Any AE leading to discontinuation of D, possibly related to D [b]	19 (3.6)	NA	19 (5.0)	NA	42 (7.9)	NA
Any AE leading to discontinuation of G or C	72 (13.6)	80 (15.2)	NA	NA	72 (13.6)	80 (15.2)
Any AE leading to discontinuation of G or C (at least one component), possibly related to G or C [b]	55 (10.4)	64 (12.2)	NA	NA	55 (10.4)	64 (12.2)
Any AE leading to dose interruption or reduction of study treatment [c]	269 (50.8)	247 (47.0)	75 (19.6)	0	305 (57.5)	247 (47.0)
Any AE leading to dose interruption of D	132 (24.9)	NA	75 (19.6)	NA	192 (36.2)	NA
Any AE leading to dose interruption or reduction of G or C (at least one component)	260 (49.1)	247 (47.0)	NA	NA	260 (49.1)	247 (47.0)
Any AE leading to surgery not done [d]	6 (1.1)	7 (1.3)	NA	NA	6 (1.1)	7 (1.3)
Any AE leading to a delay in surgery (> 56 days after last dose of study treatment in neoadjuvant period) [d]	9 (1.7)	6 (1.1)	NA	NA	9 (1.7)	6 (1.1)
Any SAE (including events with outcome of death)	125 (23.6)	118 (22.4)	101 (26.4)	85 (22.2)	326 (61.5)	287 (54.6)
Any SAE (including events with outcome of death), possibly related to study treatment [b,c]	70 (13.2)	61 (11.6)	14 (3.7)	1 (0.3)	86 (16.2)	63 (12.0)
Any SAE (including events with outcome of death), possibly related to D [b]	19 (3.6)	NA	12 (3.1)	NA	35 (6.6)	NA
Any SAE (including events with outcome of death), possibly related to G or C [b]	65 (12.3)	61 (11.6)	2 (0.5)	1 (0.3)	68 (12.8)	63 (12.0)
Any AESI/AEPI [e]	262 (49.4)	222 (42.2)	208 (54.3)	84 (21.9)	377 (71.1)	284 (54.0)
Any AESI/AEPI, possibly related to D [c,e]	148 (27.9)	NA	124 (32.4)	NA	242 (45.7)	NA
Any AESI/AEPI leading to a delay in surgery (> 56 days after last dose of study treatment in neoadjuvant period) [e]	1 (0.2)	0	NA	NA	1 (0.2)	0
Any AESI/AEPI leading to discontinuation of D [e]	18 (3.4)	NA	17 (4.4)	NA	35 (6.6)	NA
Immune-mediated AEs [b]	161 (30.4)	0	127 (33.2)	0	248 (46.8)	0

Infusion reaction AEs [b]	45 (8.5)	43 (8.2)	2 (0.5)	1 (0.3)	48 (9.1)	44 (8.4)

[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] As assessed by the Investigator. Missing responses are counted as related.

[c] Study treatment refers to durvalumab/gemcitabine/cisplatin and does not include surgery.

[d] Taken from SURG module.

[e] An AESI/AEPI is of scientific and medical interest to the study treatment. An AESI/AEPI may be serious or nonserious.

Definitions of the neoadjuvant, adjuvant, and overall periods are provided in Section 12.2.1.

CTCAE version 5.0.

DCO: 29 April 2024

Table 53 Most Common Adverse Events (Frequency of ≥ 5%) by System Organ Class and Preferred Term (Safety Analysis Set)

	Number (%) of subjects [a]						
	NIAGARA						D Pan-tumor pool
	Neoadjuvant period		Adjuvant period		Overall period		
System organ class/Preferred term	D + G+C (N = 530)	G+C (N = 526)	D + G+C (N = 383)	G+C (N = 383)	D + G+C (N = 530)	G+C (N = 526)	(N = 4045)
Subjects with any AE	509 (96.0)	503 (95.6)	272 (71.0)	207 (54.0)	522 (98.5)	515 (97.9)	3485 (86.2)
Gastrointestinal disorders	378 (71.3)	342 (65.0)	88 (23.0)	56 (14.6)	405 (76.4)	372 (70.7)	1827 (45.2)
Abdominal distension	9 (1.7)	8 (1.5)	4 (1.0)	2 (0.5)	29 (5.5)	23 (4.4)	83 (2.1)
Abdominal pain	28 (5.3)	16 (3.0)	18 (4.7)	13 (3.4)	66 (12.5)	41 (7.8)	314 (7.8)
Abdominal pain upper	20 (3.8)	16 (3.0)	9 (2.3)	4 (1.0)	31 (5.8)	23 (4.4)	160 (4.0)
Constipation	163 (30.8)	166 (31.6)	28 (7.3)	25 (6.5)	205 (38.7)	203 (38.6)	651 (16.1)
Diarrhea	63 (11.9)	52 (9.9)	32 (8.4)	9 (2.3)	109 (20.6)	74 (14.1)	649 (16.0)
Dyspepsia	38 (7.2)	40 (7.6)	6 (1.6)	3 (0.8)	49 (9.2)	47 (8.9)	122 (3.0)
Nausea	268 (50.6)	240 (45.6)	18 (4.7)	10 (2.6)	284 (53.6)	255 (48.5)	678 (16.8)
Vomiting	81 (15.3)	75 (14.3)	12 (3.1)	7 (1.8)	102 (19.2)	97 (18.4)	422 (10.4)
General disorders and administration site conditions	303 (57.2)	286 (54.4)	70 (18.3)	47 (12.3)	354 (66.8)	327 (62.2)	1879 (46.5)
Asthenia	77 (14.5)	80 (15.2)	16 (4.2)	12 (3.1)	93 (17.5)	96 (18.3)	466 (11.5)
Fatigue	177 (33.4)	158 (30.0)	28 (7.3)	10 (2.6)	191 (36.0)	169 (32.1)	998 (24.7)
Malaise	31 (5.8)	25 (4.8)	2 (0.5)	0	34 (6.4)	27 (5.1)	75 (1.9)
Oedema peripheral	29 (5.5)	27 (5.1)	8 (2.1)	10 (2.6)	46 (8.7)	45 (8.6)	347 (8.6)
Pyrexia	40 (7.5)	42 (8.0)	26 (6.8)	19 (5.0)	110 (20.8)	87 (16.5)	520 (12.9)
Blood and lymphatic system disorders	246 (46.4)	279 (53.0)	28 (7.3)	24 (6.3)	291 (54.9)	307 (58.4)	580 (14.3)
Anaemia	145 (27.4)	167 (31.7)	25 (6.5)	24 (6.3)	205 (38.7)	213 (40.5)	521 (12.9)
Leukopenia	31 (5.8)	37 (7.0)	0	0	31 (5.8)	37 (7.0)	22 (0.5)
Neutropenia	136 (25.7)	164 (31.2)	1 (0.3)	0	137 (25.8)	165 (31.4)	32 (0.8)
Thrombocytopenia	54 (10.2)	55 (10.5)	2 (0.5)	1 (0.3)	57 (10.8)	57 (10.8)	69 (1.7)
Investigations	193 (36.4)	186 (35.4)	69 (18.0)	35 (9.1)	244 (46.0)	204 (38.8)	751 (18.6)
Alanine aminotransferase increased	37 (7.0)	34 (6.5)	8 (2.1)	3 (0.8)	46 (8.7)	38 (7.2)	256 (6.3)
Amylase increased	22 (4.2)	19 (3.6)	13 (3.4)	1 (0.3)	34 (6.4)	19 (3.6)	70 (1.7)
Blood creatinine increased	54 (10.2)	56 (10.6)	38 (9.9)	18 (4.7)	98 (18.5)	77 (14.6)	145 (3.6)
Lipase increased	26 (4.9)	23 (4.4)	14 (3.7)	4 (1.0)	39 (7.4)	27 (5.1)	88 (2.2)
Neutrophil count decreased	81 (15.3)	73 (13.9)	0	1 (0.3)	81 (15.3)	74 (14.1)	24 (0.6)

Table 53 Most Common Adverse Events (Frequency of ≥ 5%) by System Organ Class and Preferred Term (Safety Analysis Set)

System organ class/Preferred term	Number (%) of subjects [a]						
	NIAGARA						D Pan-tumor pool
	Neoadjuvant period		Adjuvant period		Overall period		
	D + G+C (N = 530)	G+C (N = 526)	D + G+C (N = 383)	G+C (N = 383)	D + G+C (N = 530)	G+C (N = 526)	(N = 4045)
Platelet count decreased	35 (6.6)	34 (6.5)	2 (0.5)	1 (0.3)	37 (7.0)	35 (6.7)	41 (1.0)
Weight decreased	19 (3.6)	15 (2.9)	8 (2.1)	12 (3.1)	41 (7.7)	27 (5.1)	285 (7.0)
White blood cell count decreased	28 (5.3)	35 (6.7)	1 (0.3)	0	28 (5.3)	35 (6.7)	23 (0.6)
Metabolism and nutrition disorders	185 (34.9)	174 (33.1)	41 (10.7)	27 (7.0)	227 (42.8)	200 (38.0)	1104 (27.3)
Decreased appetite	116 (21.9)	119 (22.6)	16 (4.2)	8 (2.1)	141 (26.6)	131 (24.9)	769 (19.0)
Hyperglycaemia	20 (3.8)	14 (2.7)	9 (2.3)	4 (1.0)	32 (6.0)	23 (4.4)	128 (3.2)
Hyperkalaemia	22 (4.2)	15 (2.9)	15 (3.9)	9 (2.3)	45 (8.5)	27 (5.1)	125 (3.1)
Hypokalaemia	17 (3.2)	10 (1.9)	3 (0.8)	4 (1.0)	33 (6.2)	24 (4.6)	174 (4.3)
Hypomagnesaemia	44 (8.3)	44 (8.4)	6 (1.6)	7 (1.8)	56 (10.6)	55 (10.5)	119 (2.9)
Infections and infestations	69 (13.0)	70 (13.3)	85 (22.2)	84 (21.9)	199 (37.5)	192 (36.5)	280 (6.9)
COVID-19	8 (1.5)	13 (2.5)	12 (3.1)	17 (4.4)	30 (5.7)	35 (6.7)	1 (< 0.1)
Pyelonephritis	4 (0.8)	5 (1.0)	13 (3.4)	12 (3.1)	29 (5.5)	32 (6.1)	12 (0.3)
Urinary tract infection	58 (10.9)	56 (10.6)	69 (18.0)	65 (17.0)	159 (30.0)	153 (29.1)	272 (6.7)
Skin and subcutaneous tissue disorders	106 (20.0)	90 (17.1)	70 (18.3)	11 (2.9)	166 (31.3)	110 (20.9)	767 (19.0)
Alopecia	48 (9.1)	57 (10.8)	0	0	49 (9.2)	57 (10.8)	36 (0.9)
Pruritus	29 (5.5)	18 (3.4)	49 (12.8)	10 (2.6)	80 (15.1)	38 (7.2)	462 (11.4)
Rash	39 (7.4)	25 (4.8)	24 (6.3)	1 (0.3)	67 (12.6)	30 (5.7)	394 (9.7)
Nervous system disorders	125 (23.6)	108 (20.5)	17 (4.4)	21 (5.5)	144 (27.2)	130 (24.7)	629 (15.6)
Dizziness	37 (7.0)	34 (6.5)	7 (1.8)	6 (1.6)	43 (8.1)	39 (7.4)	236 (5.8)
Dysgeusia	37 (7.0)	32 (6.1)	1 (0.3)	1 (0.3)	40 (7.5)	33 (6.3)	71 (1.8)
Headache	53 (10.0)	48 (9.1)	2 (0.5)	7 (1.8)	59 (11.1)	59 (11.2)	323 (8.0)
Neuropathy peripheral	19 (3.6)	19 (3.6)	8 (2.1)	7 (1.8)	32 (6.0)	29 (5.5)	78 (1.9)
Respiratory, thoracic and mediastinal disorders	105 (19.8)	84 (16.0)	29 (7.6)	11 (2.9)	144 (27.2)	99 (18.8)	1095 (27.1)
Cough	24 (4.5)	18 (3.4)	8 (2.1)	5 (1.3)	36 (6.8)	24 (4.6)	643 (15.9)
Dyspnoea	35 (6.6)	14 (2.7)	13 (3.4)	3 (0.8)	51 (9.6)	20 (3.8)	596 (14.7)
Hiccups	38 (7.2)	49 (9.3)	1 (0.3)	0	41 (7.7)	50 (9.5)	30 (0.7)
Pulmonary embolism	17 (3.2)	10 (1.9)	10 (2.6)	4 (1.0)	39 (7.4)	18 (3.4)	54 (1.3)
Musculoskeletal and connective tissue disorders	75 (14.2)	64 (12.2)	57 (14.9)	41 (10.7)	137 (25.8)	105 (20.0)	1063 (26.3)
Arthralgia	25 (4.7)	18 (3.4)	29 (7.6)	14 (3.7)	55 (10.4)	35 (6.7)	540 (13.3)
Back pain	26 (4.9)	23 (4.4)	18 (4.7)	19 (5.0)	51 (9.6)	47 (8.9)	441 (10.9)
Myalgia	18 (3.4)	10 (1.9)	9 (2.3)	3 (0.8)	32 (6.0)	13 (2.5)	196 (4.8)
Pain in extremity	15 (2.8)	15 (2.9)	6 (1.6)	9 (2.3)	27 (5.1)	28 (5.3)	193 (4.8)
Renal and urinary disorders	46 (8.7)	34 (6.5)	29 (7.6)	30 (7.8)	95 (17.9)	83 (15.8)	154 (3.8)
Acute kidney injury	18 (3.4)	11 (2.1)	14 (3.7)	9 (2.3)	45 (8.5)	33 (6.3)	74 (1.8)

Table 53 Most Common Adverse Events (Frequency of ≥ 5%) by System Organ Class and Preferred Term (Safety Analysis Set)

System organ class/Preferred term	Number (%) of subjects [a]						
	NIAGARA						D Pan-tumor pool
	Neoadjuvant period		Adjuvant period		Overall period		
	D + G+C (N = 530)	G+C (N = 526)	D + G+C (N = 383)	G+C (N = 383)	D + G+C (N = 530)	G+C (N = 526)	(N = 4045)
Dysuria	24 (4.5)	19 (3.6)	1 (0.3)	0	28 (5.3)	19 (3.6)	60 (1.5)
Hydronephrosis	5 (0.9)	6 (1.1)	15 (3.9)	21 (5.5)	28 (5.3)	37 (7.0)	25 (0.6)
Endocrine disorders	28 (5.3)	7 (1.3)	39 (10.2)	13 (3.4)	79 (14.9)	19 (3.6)	472 (11.7)
Hyperthyroidism	20 (3.8)	4 (0.8)	9 (2.3)	6 (1.6)	31 (5.8)	9 (1.7)	163 (4.0)
Hypothyroidism	16 (3.0)	3 (0.6)	31 (8.1)	8 (2.1)	61 (11.5)	11 (2.1)	379 (9.4)
Vascular disorders	41 (7.7)	30 (5.7)	13 (3.4)	5 (1.3)	61 (11.5)	43 (8.2)	170 (4.2)
Hypertension	41 (7.7)	30 (5.7)	13 (3.4)	5 (1.3)	61 (11.5)	43 (8.2)	170 (4.2)
Injury, poisoning and procedural complications	1 (0.2)	2 (0.4)	4 (1.0)	1 (0.3)	46 (8.7)	38 (7.2)	34 (0.8)
Procedural pain	1 (0.2)	2 (0.4)	4 (1.0)	1 (0.3)	46 (8.7)	38 (7.2)	34 (0.8)
Psychiatric disorders	21 (4.0)	29 (5.5)	7 (1.8)	5 (1.3)	43 (8.1)	45 (8.6)	300 (7.4)
Insomnia	21 (4.0)	29 (5.5)	7 (1.8)	5 (1.3)	43 (8.1)	45 (8.6)	300 (7.4)
Ear and labyrinth disorders	34 (6.4)	41 (7.8)	5 (1.3)	3 (0.8)	36 (6.8)	43 (8.2)	23 (0.6)
Tinnitus	34 (6.4)	41 (7.8)	5 (1.3)	3 (0.8)	36 (6.8)	43 (8.2)	23 (0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (0.3)	0	35 (6.6)	31 (5.9)	3 (0.1)
Prostate cancer	0	0	1 (0.3)	0	35 (6.6)	31 (5.9)	3 (0.1)

a Number (%) of subjects with most common AEs, sorted by descending frequency of system organ class in the NIAGARA overall D + G+C treatment group, then sorted alphabetically for preferred term.

Subjects with multiple AEs are counted once for each system organ class/preferred term.

Note: Neoadjuvant Period includes AEs between date of first neoadjuvant dose and the day before surgery, or for subjects without surgery up to the earliest of: 90 days after date of last dose of neoadjuvant treatment; first dose of subsequent anticancer therapy, date of DCO.

Note: Adjuvant Period includes AEs between date of first dose of adjuvant study treatment (Arm 1) or date of first adjuvant study visit (Arm 2) and the earliest of: 90 days after the last dose of adjuvant study treatment (Arm 1) or last adjuvant study visit (Arm 2), date of first dose of subsequent anticancer therapy, date of DCO.

Overall Period includes AEs between date of first dose of study treatment and the earliest of: 90 days after the last dose of treatment or surgery (Arm 1) or last adjuvant study visit (Arm 2) or date of first dose of subsequent anticancer therapy or date of DCO.

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

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

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Table 54 Most Common Adverse Events (Frequency of ≥ 5%) of CTCAE Grade 3 or 4 by System Organ Class and Preferred Term (Safety Analysis Set)

System organ class/Preferred term	Number (%) of subjects [a]						
	NIAGARA						D Pan-tumor pool
	Neoadjuvant period		Adjuvant period		Overall period		
	D + G+C (N = 530)	G+C (N = 526)	D + G+C (N = 383)	G+C (N = 383)	D + G+C (N = 530)	G+C (N = 526)	(N = 4045)
Subjects with any CTCAE Grade 3 or 4 AE	150 (28.3)	173 (32.9)	34 (8.9)	31 (8.1)	211 (39.8)	213 (40.5)	223 (5.5)
Blood and lymphatic system disorders	109 (20.6)	140 (26.6)	8 (2.1)	8 (2.1)	138 (26.0)	155 (29.5)	189 (4.7)
Anaemia	37 (7.0)	61 (11.6)	8 (2.1)	8 (2.1)	73 (13.8)	79 (15.0)	180 (4.4)

Table 54 Most Common Adverse Events (Frequency of ≥ 5%) of CTCAE Grade 3 or 4 by System Organ Class and Preferred Term (Safety Analysis Set)

System organ class/Preferred term	Number (%) of subjects [a]						
	NIAGARA						D Pan-tumor pool
	Neoadjuvant period		Adjuvant period		Overall period		
	D + G+C (N = 530)	G+C (N = 526)	D + G+C (N = 383)	G+C (N = 383)	D + G+C (N = 530)	G+C (N = 526)	(N = 4045)
Neutropenia	76 (14.3)	88 (16.7)	0	0	76 (14.3)	89 (16.9)	9 (0.2)
Infections and infestations	11 (2.1)	17 (3.2)	29 (7.6)	26 (6.8)	75 (14.2)	70 (13.3)	41 (1.0)
Urinary tract infection	11 (2.1)	17 (3.2)	29 (7.6)	26 (6.8)	75 (14.2)	70 (13.3)	41 (1.0)
Investigations	37 (7.0)	35 (6.7)	0	0	37 (7.0)	35 (6.7)	6 (0.1)
Neutrophil count decreased	37 (7.0)	35 (6.7)	0	0	37 (7.0)	35 (6.7)	6 (0.1)

a Number (%) of subjects with most common Grade 3 or 4 AEs, sorted by descending frequency of system organ class in the NIAGARA overall D + G+C treatment group, then sorted alphabetically for preferred term.

Subjects with multiple AEs are counted once for each system organ class/preferred term.

Note: Neoadjuvant Period includes AEs between date of first neoadjuvant dose and the day before surgery, or for subjects without surgery up to the earliest of: 90 days after date of last dose of neoadjuvant treatment; first dose of subsequent anticancer therapy, date of DCO.

Note: Adjuvant Period includes AEs between date of first dose of adjuvant study treatment (Arm 1) or date of first adjuvant study visit (Arm 2) and the earliest of: 90 days after the last dose of adjuvant study treatment (Arm 1) or last adjuvant study visit (Arm 2), date of first dose of subsequent anticancer therapy, date of DCO.

Overall Period includes AEs between date of first dose of study treatment and the earliest of: 90 days after the last dose of treatment or surgery (Arm 1) or last adjuvant study visit (Arm 2) or date of first dose of subsequent anticancer therapy or date of DCO.

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

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

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Table 55 Urinary Tract Infection Events in NIAGARA Study (Safety Analysis Set; IA2)

	Number (%) of subjects					
	Neoadjuvant period		Adjuvant period		Overall period	
	D + G+C (N = 530)	G+C (N = 526)	D + G+C (N = 383)	G+C (N = 383)	D + G+C (N = 530)	G+C (N = 526)
Urinary tract infection events						
All AEs	58 (10.9)	56 (10.6)	69 (18.0)	65 (17.0)	159 (30.0)	153 (29.1)
Grade 3-4 AEs	11 (2.1)	17 (3.2)	29 (7.6)	26 (6.8)	75 (14.2)	70 (13.3)
SAEs	7 (1.3)	14 (2.7)	23 (6.0)	27 (7.0)	59 (11.1)	69 (13.1)

Subjects with multiple events in a study period are counted once.

Neoadjuvant Period includes AEs between date of first neoadjuvant dose and the day before surgery, or for subjects without surgery up to the earliest of: 90 days after date of last dose of neoadjuvant treatment; first dose of subsequent anticancer therapy, date of DCO.

Adjuvant Period includes AEs between date of first dose of adjuvant study treatment (Arm 1) or date of first adjuvant study visit (Arm 2) and the earliest of: 90 days after the last dose of adjuvant study treatment (Arm 1) or last adjuvant study visit (Arm 2), date of first dose of subsequent anticancer therapy, date of DCO.

Overall Period includes AEs between date of first dose of study treatment and the earliest of: 90 days after the last dose of treatment or surgery (Arm 1) or last adjuvant study visit (Arm 2) or date of first dose of subsequent anticancer therapy or date of DCO.

Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.

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Table 56 Adverse Events by Maximum Reported CTCAE Grade in the NIAGARA Study and D Pan-tumor Pool (Safety Analysis Set)

Maximum reported CTCAE Grade	Number (%) of patients						
	NIAGARA study						D Pan-tumor pool (N = 4045)
	Neoadjuvant period		Adjuvant period		Overall period		
	D + G+C (N = 530)	G+C (N = 526)	D + G+C (N = 383)	G+C (N = 383)	D + G+C (N = 530)	G+C (N = 526)	
Total	520 (98.1)	515 (97.9)	331 (86.4)	273 (71.3)	527 (99.4)	525 (99.8)	3825 (94.6)
Grade 1	60 (11.3)	58 (11.0)	82 (21.4)	87 (22.7)	15 (2.8)	28 (5.3)	564 (13.9)
Grade 2	206 (38.9)	180 (34.2)	125 (32.6)	90 (23.5)	132 (24.9)	132 (25.1)	1432 (35.4)
Grade 3	204 (38.5)	231 (43.9)	106 (27.7)	84 (21.9)	281 (53.0)	278 (52.9)	1412 (34.9)
Grade 4	44 (8.3)	36 (6.8)	11 (2.9)	6 (1.6)	72 (13.6)	58 (11.0)	188 (4.6)
Grade 5	6 (1.1)	10 (1.9)	7 (1.8)	6 (1.6)	27 (5.1)	29 (5.5)	229 (5.7)

Percentages are based on the total number of patients in the treatment group (N).
Patients with multiple AEs are counted once at the maximum reported CTCAE grade for each system organ class/preferred term.
Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.
Disease progression AEs reported in Study 1108 are not included in this summary.
Definitions of the NIAGARA Neoadjuvant, Adjuvant, and Overall periods are provided in Section 2.1.
All studies use CTCAE version 4.03 except for NIAGARA which uses version 5.0.

Table 57 Adverse Events of Maximum CTCAE Grade 3 or 4 in the NIAGARA Study and D Pan-tumor Pool (frequency >5% in either NIAGARA treatment Arm [Overall Period] (Safety Analysis Set)

MedDRA Preferred term	Number (%) of patients [a]						
	NIAGARA study						D Pan-tumor pool (N = 4045)
	Neoadjuvant period		Adjuvant period		Overall period		
	D + G+C (N = 530)	G+C (N = 526)	D + G+C (N = 383)	G+C (N = 383)	D + G+C (N = 530)	G+C (N = 526)	
Patients with any AE of maximum CTCAE grade 3 or 4	248 (46.8)	267 (50.8)	117 (30.5)	90 (23.5)	353 (66.6)	336 (63.9)	1600 (39.6)
Neutropenia	76 (14.3)	88 (16.7)	0	0	76 (14.3)	89 (16.9)	9 (0.2)
Urinary tract infection	11 (2.1)	17 (3.2)	29 (7.6)	26 (6.8)	75 (14.2)	70 (13.3)	41 (1.0)
Anaemia	37 (7.0)	61 (11.6)	8 (2.1)	8 (2.1)	73 (13.8)	79 (15.0)	180 (4.4)
Neutrophil count decreased	37 (7.0)	35 (6.7)	0	0	37 (7.0)	35 (6.7)	6 (0.1)

[a] Number (%) of patients with AEs of maximum CTCAE Grade 3 or 4, sorted in decreasing frequency of PT in the NIAGARA Overall Period D + G+C arm.
Maximum CTCAE grade per patient/event is considered. Patients with multiple AEs of CTCAE grade 3 or 4 are counted once for each preferred term.
Percentages are based on the total number of patients in the treatment group (N).
Definitions of the NIAGARA Neoadjuvant, Adjuvant, and Overall periods are provided in Section 2.1.
Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.
Disease progression AEs reported in Study 1108 are not included in this summary.
All studies use CTCAE version 4.03 except for NIAGARA which uses version 5.0. MedDRA version 26.1.

Adverse drug reactions

ADR methodology

MedDRA version 26.1 was used for coding of AE data in NIAGARA. Data from studies in the D pan-tumor pool originally reported in earlier versions of MedDRA were up-versioned and coded to MedDRA version 26.1 for the integrated safety database. All AEs were summarized descriptively by patient count (n) and percentage (%) in terms of MedDRA Preferred Term (PT) and/or CTCAE grade.

Severity assessments of AEs were based on CTCAE version 5.0 for NIAGARA and CTCAE version 4.03 in the D pan-tumor pool studies. Up-versioning of studies in the D pan-tumor pool from version 4.03 to version 5.0 was not performed given no detrimental impact on interpretation of results was expected and it was therefore not deemed appropriate to retrospectively change Investigators' assessments of AEs and laboratory parameters.

The MAH has a process for identifying ADRs that does not fundamentally rely on the Investigator's assessment of an individual case. ADR safety signals are continuously monitored and evaluated, based on biological plausibility consistent with the mechanism of action of durvalumab, temporal association and re-challenge responses, known risks associated with the anti-PD-1/PD-L1 drug class, totality of the data, and context of background rates in target populations. Those events not already on the known ADR list are medically reviewed further for alternative causes (medical history, concomitant medications, comorbidities or other risk factors), biological plausibility, and rechallenge response, which are considered to determine whether an AE is an additional ADR.

Table 58 Adverse Drug Reactions by Category in the NIAGARA Study and D Pan-tumor Pool, D+ CTx and CTx Pools (Safety Analysis Set)

ADR category	NIAGARA overall period		D Pan-tumor pool (N = 4045)	D + CTx pool (N = 1368) [a]	CTx pool (N = 1370) [a]
	D + G+C (N = 530)	G+C (N = 526)			
	n (%) patients	n (%) patients	n (%) patients	n (%) patients	n (%) patients
Patients with any ADR	516 (97.4)	505 (96.0)	2959 (73.2)	1318 (96.3)	1317 (96.1)
ADRs of maximum CTCAE grade 3 or 4 [b]	221 (41.7)	227 (43.2)	497 (12.3)	667 (48.8)	687 (50.1)
ADRs of any CTCAE grade 3 or 4 [c]	222 (41.9)	229 (43.5)	506 (12.5)	669 (48.9)	692 (50.5)
ADRs of maximum CTCAE grade ≥ 3 [b]	222 (41.9)	229 (43.5)	525 (13.0)	671 (49.0)	696 (50.8)
Serious ADRs [d]	70 (13.2)	60 (11.4)	437 (10.8)	205 (15.0)	206 (15.0)
ADRs with an outcome of death	1 (0.2)	2 (0.4)	28 (0.7)	4 (0.3)	9 (0.7)
ADRs leading to discontinuation of durvalumab treatment	48 (9.1)	NA	146 (3.6)	78 (5.7)	18 (1.3)
ADRs leading to dose delay or interruption of durvalumab [e]	134 (25.3)	NA	527 (13.0)	394 (28.8)	163 (11.9)

[a] D + CTx and CTx pools include CASPIAN, TOPAZ-1, DUO-E and NIAGARA data.

[b] Maximum CTCAE grade per patient/treatment period/event is considered.

[c] All CTCAE grades per patient, not just the maximum, are considered when identifying whether there is a Grade 3 or 4.

[d] Seriousness, as assessed by the investigator. An AE with missing seriousness is considered serious.

[e] 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.

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.

Definition of the NIAGARA overall period is provided in Section 1.1.4.1.

Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.

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

ADR terms are grouped Preferred Terms.

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

All studies use CTCAE version 4.03 except for NIAGARA which uses version 5.0.

MedDRA version 26.1.

Table 59 Adverse Drug Reactions by ADR Term and CIOMS Category in the NIAGARA Study and D Pan-tumor Pool, D+ CTx Pools (Safety Analysis Set)

ADR SOC/ ADR term	NIAGARA Overall Period				D Pan-tumor pool (N=4045)		D + CTx pool (N = 1368)		CTx pool (N = 1370)	
	D + G+C (N = 530)		G+C (N = 526)							
	n (%) [a]	CIOMS cat [b]	n (%)	CIOMS cat [b]	n (%)	CIOMS cat [b]	n (%)	CIOMS cat [c]	n (%)	CIOMS cat [c]
Patients with any ADR	516 (97.4)	-	505 (96.0)	-	2959 (73.2)	-	1318 (96.3)	-	1317 (96.1)	-
Blood and lymphatic system disorders										
Anaemia	205 (38.7)	Very common	213 (40.5)	Very common	NA		581 (42.5)	Very common	620 (45.3)	Very common
Febrile neutropenia	11 (2.1)	Common	11 (2.1)	Common	NA		39 (2.9)	Common	44 (3.2)	Common
Immune Thrombocytopenia	0	NR	0	NR	3 (0.1)	Rare	1 (0.1)	Rare	0	NR
Leukopenia	58 (10.9)	Very common	71 (13.5)	Very common	NA		202 (14.8)	Very common	226 (16.5)	Very common
Neutropenia	214 (40.4)	Very common	237 (45.1)	Very common	NA		610 (44.6)	Very common	675 (49.3)	Very common
Pancytopenia	3 (0.6)	Uncommon	2 (0.4)	Uncommon	NA		13 (1.0)	Uncommon	7 (0.5)	Uncommon
Thrombocytopenia	91 (17.2)	Very common	91 (17.3)	Very common	NA		326 (23.8)	Very common	328 (23.9)	Very common
Cardiac disorders										
Myocarditis	1 (0.2)	Uncommon	0	NR	5 (0.1)	Uncommon	1 (0.1)	Rare	0	NR
Endocrine disorders										
Adrenal insufficiency	2 (0.4)	Uncommon	0	NR	24 (0.6)	Uncommon	10 (0.7)	Uncommon	1 (0.1)	Rare
Diabetes insipidus	0	NR	0	NR	1 (<0.1)	Rare	0	NR	0	NR
Hyperthyroidism	33 (6.2)	Common	12 (2.3)	Common	199 (4.9)	Common	88 (6.4)	Common	21 (1.5)	Common
Hypopituitarism/Hypophysitis	3 (0.6)	Uncommon	0	NR	3 (0.1)	Rare	3 (0.2)	Uncommon	0	NR
Hypothyroidism	67 (12.6)	Very common	12 (2.3)	Common	439 (10.9)	Very common	160 (11.7)	Very common	38 (2.8)	Common
Thyroiditis	2 (0.4)	Uncommon	0	NR	30 (0.7)	Uncommon	11 (0.8)	Uncommon	0	NR
Type 1 diabetes mellitus	0	NR	0	NR	3 (0.1)	Rare	4 (0.3)	Uncommon	0	NR
Eye Disorders										
Uveitis	0	NR	0	NR	1 (<0.1)	Rare	2 (0.1)	Uncommon	0	NR
Gastrointestinal disorders										
Abdominal pain	107 (20.2)	Very common	71 (13.5)	Very common	522 (12.9)	Very common	277 (20.2)	Very common	224 (16.4)	Very common
Colitis	7 (1.3)	Common	1 (0.2)	Uncommon	37 (0.9)	Uncommon	15 (1.1)	Common	5 (0.4)	Uncommon
Constipation	205 (38.7)	Very common	203 (38.6)	Very common	NA		422 (30.8)	Very common	434 (31.7)	Very common
Diarrhoea	109 (20.6)	Very common	74 (14.1)	Very common	649 (16.0)	Very common	269 (19.7)	Very common	223 (16.3)	Very common
Nausea	284 (53.6)	Very common	255 (48.5)	Very common	NA		607 (44.4)	Very common	568 (41.5)	Very common
Pancreatitis	2 (0.4)	Uncommon	1 (0.2)	Uncommon	8 (0.2)	Uncommon	7 (0.5)	Uncommon	3 (0.2)	Uncommon
Stomatitis	34 (6.4)	Common	30 (5.7)	Common	NA		95 (6.9)	Common	87 (6.4)	Common
Vomiting	102 (19.2)	Very common	97 (18.4)	Very common	NA		253 (18.5)	Very common	248 (18.1)	Very common
General disorders and administration site conditions										

ADR SOC/ ADR term	NIAGARA Overall Period				D Pan-tumor pool (N=4045)		D + CTx pool (N = 1368)		CTx pool (N = 1370)	
	D + G+C (N = 530)		G+C (N = 526)							
	n (%) [a]	CIOMS cat [b]	n (%)	CIOMS cat [b]	n (%)	CIOMS cat [b]	n (%)	CIOMS cat [c]	n (%)	CIOMS cat [c]
Fatigue	273 (51.5)	Very common	257 (48.9)	Very common	NA		598 (43.7)	Very common	582 (42.5)	Very common
Oedema peripheral	47 (8.9)	Common	52 (9.9)	Common	380 (9.4)	Common	131 (9.6)	Common	109 (8.0)	Common
Pyrexia	110 (20.8)	Very common	87 (16.5)	Very common	520 (12.9)	Very common	221 (16.2)	Very common	181 (13.2)	Very common
Hepatobiliary disorders										
Aspartate aminotransferase increased /Alanine aminotransferase increased	55 (10.4)	Very common	48 (9.1)	Common	369 (9.1)	Common	143 (10.5)	Very common	128 (9.3)	Common
Hepatitis	4 (0.8)	Uncommon	4 (0.8)	Uncommon	45 (1.1)	Common	21 (1.5)	Common	9 (0.7)	Uncommon
Infections and infestations										
Dental and oral soft tissue infections	6 (1.1)	Common	3 (0.6)	Uncommon	56 (1.4)	Common	22 (1.6)	Common	15 (1.1)	Common
Influenza	4 (0.8)	Uncommon	4 (0.8)	Uncommon	57 (1.4)	Common	9 (0.7)	Uncommon	6 (0.4)	Uncommon
Oral candidiasis	2 (0.4)	Uncommon	2 (0.4)	Uncommon	76 (1.9)	Common	9 (0.7)	Uncommon	7 (0.5)	Uncommon
Pneumonia	22 (4.2)	Common	13 (2.5)	Common	319 (7.9)	Common	54 (3.9)	Common	48 (3.5)	Common
Upper respiratory tract infections	28 (5.3)	Common	27 (5.1)	Common	489 (12.1)	Very common	97 (7.1)	Common	87 (6.4)	Common
Injury, poisoning and procedural complications										
Infusion related reaction	7 (1.3)	Common	2 (0.4)	Uncommon	65 (1.6)	Common	36 (2.6)	Common	34 (2.5)	Common
Metabolism and nutrition disorders										
Decreased appetite	141 (26.6)	Very common	131 (24.9)	Very common	NA		319 (23.3)	Very common	303 (22.1)	Very common
Musculoskeletal and connective tissue disorders										
Arthralgia	55 (10.4)	Very common	35 (6.7)	Common	540 (13.3)	Very common	160 (11.7)	Very common	121 (8.8)	Common
Immune-Mediated Arthritis	1 (0.2)	Uncommon	0	NR	3 (0.1)	Rare	4 (0.3)	Uncommon	0	NR
Myalgia	32 (6.0)	Common	13 (2.5)	Common	196 (4.8)	Common	88 (6.4)	Common	84 (6.1)	Common
Myositis	5 (0.9)	Uncommon	0	NR	10 (0.2)	Uncommon	11 (0.8)	Uncommon	0	NR
Polymyositis	0	NR	0	NR	0	NR	0	NR	1 (0.1)	Rare
Nervous system disorders										
Meningitis	0	NR	0	NR	1 (<0.1)	Rare	0	NR	0	NR
Myasthenia Gravis	1 (0.2)	Uncommon	0	NR	3 (0.1)	Rare	3 (0.2)	Uncommon	0	NR
Neuropathy peripheral	66 (12.5)	Very common	59 (11.2)	Very common	NA		243 (17.8)	Very common	254 (18.5)	Very common
Renal and urinary disorders										
Blood creatinine increased	98 (18.5)	Very common	77 (14.6)	Very common	145 (3.6)	Common	123 (9.0)	Common	130 (9.5)	Common
Cystitis noninfective	3 (0.6)	Uncommon	1 (0.2)	Uncommon	4 (0.1)	Rare	5 (0.4)	Uncommon	3 (0.2)	Uncommon

ADR SOC/ ADR term	NIAGARA Overall Period				D Pan-tumor pool (N=4045)		D + CTx pool (N = 1368)		CTx pool (N = 1370)	
	D + G+C (N = 530)		G+C (N = 526)							
	n (%) [a]	CIOMS cat [b]	n (%)	CIOMS cat [b]	n (%)	CIOMS cat [b]	n (%)	CIOMS cat [c]	n (%)	CIOMS cat [c]
Dysuria	28 (5.3)	Common	19 (3.6)	Common	60 (1.5)	Common	47 (3.4)	Common	43 (3.1)	Common
Nephritis	6 (1.1)	Common	2 (0.4)	Uncommon	12 (0.3)	Uncommon	6 (0.4)	Uncommon	6 (0.4)	Uncommon
Respiratory, thoracic and mediastinal disorders										
Cough/ Productive cough	43 (8.1)	Common	30 (5.7)	Common	754 (18.6)	Very common	147 (10.7)	Very common	105 (7.7)	Common
Dysphonia	8 (1.5)	Common	8 (1.5)	Common	103 (2.5)	Common	15 (1.1)	Common	15 (1.1)	Common
Interstitial lung disease	1 (0.2)	Uncommon	0	NR	21 (0.5)	Uncommon	5 (0.4)	Uncommon	1 (0.1)	Rare
Pneumonitis	9 (1.7)	Common	3 (0.6)	Uncommon	137 (3.4)	Common	22 (1.6)	Common	14 (1.0)	Common
Skin and subcutaneous tissue disorders										
Alopecia	49 (9.2)	Common	57 (10.8)	Very common	NA		279 (20.4)	Very common	281 (20.5)	Very common
Dermatitis	5 (0.9)	Uncommon	3 (0.6)	Uncommon	28 (0.7)	Uncommon	23 (1.7)	Common	5 (0.4)	Uncommon
Night sweats	3 (0.6)	Uncommon	4 (0.8)	Uncommon	60 (1.5)	Common	7 (0.5)	Uncommon	6 (0.4)	Uncommon
Pemphigoid	1 (0.2)	Uncommon	1 (0.2)	Uncommon	6 (0.1)	Uncommon	3 (0.2)	Uncommon	2 (0.1)	Uncommon
Pruritus	80 (15.1)	Very common	38 (7.2)	Common	462 (11.4)	Very common	179 (13.1)	Very common	106 (7.7)	Common
Psoriasis	2 (0.4)	Uncommon	1 (0.2)	Uncommon	30 (0.7)	Uncommon	5 (0.4)	Uncommon	4 (0.3)	Uncommon
Rash	111 (20.9)	Very common	51 (9.7)	Common	619 (15.3)	Very common	266 (19.4)	Very common	157 (11.5)	Very common

[a] Number (%) of patients with ADRs, sorted in alphabetical order by ADR system organ class and ADR preferred term.

[b] 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 (no result - cannot be estimated from available data).

[c] D + CTx and CTx pools include CASPIAN, TOPAZ-1, DUO-E and NIAGARA data.

Definition of the NIAGARA overall period is provided in Section 1.1.4.1.

A patient can have one or more preferred terms reported under a given system organ class.

ADR terms are grouped Preferred Terms.

n (%) = number (%) of patients with ADRs.

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 1 day after latest dose.

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Updated Imfinzi in combination with chemotherapy pool leading to updated information in section 4.8 of the SmPC:

The safety pool of IMFINZI in combination with chemotherapy was updated based on pooled data in 1769 patients from 5 studies (TOPAZ-1, CASPIAN, DUO-E, AEGEAN, and NIAGARA).

Table 60 Most commong (>10%) ADRs based on the updated safety pool of Imfinzi in combination with durvalumab

The most common (>10%) adverse reactions			
ADR	**Number of Patients (N=1769)**	**%**	**CIOMS III category**
Neutropenia	738	41.7	Very common
Anaemia	721	40.8	Very common
Fatigue	701	39.6	Very common
Constipation	526	29.7	Very common
Decreased appetite	393	22.2	Very common
Thrombocytopenia	381	21.5	Very common
Alopecia	348	19.7	Very common
Rash	349	19.7	Very common
Diarrhoea	322	18.2	Very common

Vomiting	298	16.8	Very common
Abdominal pain	295	16.7	Very common
Neuropathy peripheral	289	16.3	Very common
Leukopenia	262	14.8	Very common
Pyrexia	247	14.0	Very common
Pruritus	230	13.0	Very common
Hypothyroidism	210	11.9	Very common
Cough/productive cough	194	11.0	Very common
Aspartate aminotransferase increased/Alanine aminotransferase increased	190	10.7	Very common
Myocarditis	2	0.1	Uncommon
Nausea	710	40.1	Very common

Table 61 Most common (>2%) ADRs based on the updated safety pool of Imfinzi in combination with durvalumab

The most common (>2%) CTCAE Grade >=3 adverse reactions			
ADR	**Number of Patients (N=1769)**	**%**	**CIOMS III category**
Neutropenia	446	25.2	Very common
Anaemia	242	13.7	Very common
Thrombocytopenia	122	6.9	Common
Leukopenia	79	4.5	Common
Fatigue	50	2.8	Common
Pneumonia	42	2.4	Common
Febrile neutropenia	37	2.1	Common

Imfinzi was discontinued due to ADRs in 110 patients (6.2%).

Table 62 Most common ADRs leading to treatment discontinuation based on the updated safety pool of Imfinzi in combination with durvalumab

The most common adverse reactions leading to treatment discontinuation			
ADR	**Number of Patients (N=1769)**	**%**	**CIOMS III category**
Rash	12	0.7	Uncommon
Pneumonitis	13	0.7	Uncommon
Fatigue	10	0.6	Uncommon

Imfinzi was delayed or interrumped in 516 patients (29.2%).

Table 63 Most common ADRs leading to dose delay or interruption based on the updated safety pool of Imfinzi in combination with durvalumab

The most common adverse reactions leading to dose delay or interruption			
ADR	**Number of Patients (N=1769)**	**%**	**CIOMS III category**
Neutropenia	223	12.6	Very common
Thrombocytopenia	79	4.5	Common
Anaemia	69	3.9	Common
Leukopenia	38	2.1	Common

Table 64 Laboratory abnormalities ADRs based on the updated safety pool of Imfinzi in combination with durvalumab

Laboratory abnormalities; a shift from baseline to a Grade 3 or 4		
ADR	**Number of Patients (N=1769)**	**%**
Alanine transferase increased	81/1755	4.6
Aspartate aminotransferase increased	68/1754	3.9
Blood creatinine increased	81/1755	4.6
Amylase increased	96/1685	5.7
Lipase increased	161/1584	10.2
Bilirubin increased	53/1753	3.0
TSH shift from baseline from within ULN to greater than ULN	408/1769	23.1
TSH shift from baseline that was greater than LLN to less than LLN	382/1769	21.6

Serious adverse event/deaths/other significant events

Table 65 Serious Adverse Events and Event Rates in the NIAGARA Study and D Pan-Tumor Pool (Frequency >2% in either NIAGARA Treatment Arm [Overall Period] by Preferred Term (Safety Analysis Set) DCO: 29 APR 2024

	Number (%) of patients													
	NIAGARA neoadjuvant period				NIAGARA adjuvant period				NIAGARA overall period				D Pan-tumor pool (N = 4045, Dur = 2240.4)	
	D + G+C (N = 530, Dur = 131.1)		G+C (N = 526, Dur = 116.9)		D + G+C (N = 383, Dur = 212.1)		G+C (N = 383, Dur = 311.9)		D + G+C (N = 530, Dur = 540.3)		G+C (N = 526, Dur = 551.7)			
MedDRA Preferred term	n (%) [a]	Event rate (per 100 PY)	n (%)	Event rate (per 100 PY)	n (%)	Event rate (per 100 PY)	n (%)	Event rate (per 100 PY)	n (%)	Event rate (per 100 PY)	n (%)	Event rate (per 100 PY)	n (%)	Event rate (per 100 PY)
Patients with any SAE	125 (23.6)	95.3	118 (22.4)	101.0	101 (26.4)	47.6	85 (22.2)	27.3	326 (61.5)	60.3	287 (54.6)	52.0	1447 (35.8)	64.6
Urinary tract infection	7 (1.3)	5.3	14 (2.7)	12.0	23 (6.0)	10.8	27 (7.0)	8.7	59 (11.1)	10.9	69 (13.1)	12.5	37 (0.9)	1.7
Prostate cancer	0		0		1 (0.3)	0.5	0		35 (6.6)	6.5	27 (5.1)	4.9	3 (0.1)	0.1
Acute kidney injury	7 (1.3)	5.3	6 (1.1)	5.1	11 (2.9)	5.2	8 (2.1)	2.6	25 (4.7)	4.6	24 (4.6)	4.4	30 (0.7)	1.3
Prostate cancer stage II	0	0	0	0	0	0	0	0	21 (4.0)	3.9	10 (1.9)	1.8	0	0
Urosepsis	5 (0.9)	3.8	1 (0.2)	0.9	7 (1.8)	3.3	2 (0.5)	0.6	20 (3.8)	3.7	10 (1.9)	1.8	11 (0.3)	0.5
Pyelonephritis	3 (0.6)	2.3	4 (0.8)	3.4	8 (2.1)	3.8	8 (2.1)	2.6	19 (3.6)	3.5	23 (4.4)	4.2	8 (0.2)	0.4
Sepsis	3 (0.6)	2.3	2 (0.4)	1.7	6 (1.6)	2.8	4 (1.0)	1.3	19 (3.6)	3.5	14 (2.7)	2.5	54 (1.3)	2.4
Pulmonary embolism	10 (1.9)	7.6	3 (0.6)	2.6	3 (0.8)	1.4	1 (0.3)	0.3	18 (3.4)	3.3	5 (1.0)	0.9	31 (0.8)	1.4
Hydronephrosis	2 (0.4)	1.5	0	0	8 (2.1)	3.8	6 (1.6)	1.9	15 (2.8)	2.8	8 (1.5)	1.5	6 (0.1)	0.3
Pneumonia	7 (1.3)	5.3	4 (0.8)	3.4	0	0	0	0	12 (2.3)	2.2	5 (1.0)	0.9	152 (3.8)	6.8
Anaemia	4 (0.8)	3.1	15 (2.9)	12.8	0	0	1 (0.3)	0.3	5 (0.9)	0.9	17 (3.2)	3.1	27 (0.7)	1.2

[a] Number (%) of patients with AEs, sorted by international order for system organ class and alphabetically for preferred term.
[b] Number of patients with AEs divided by the total number of years at risk for AEs across all patients within a group, multiplied by 100.
Patients with multiple AEs are counted once for each system organ class / preferred term.
Definitions of the NIAGARA Neoadjuvant, Adjuvant, and Overall periods are provided in Section 1.1.4.1.
Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.
Disease progression AEs reported in Study 1108 are not included in this summary.
Percentages are based on the total numbers of patients in the treatment group (N).
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Table 66 Serious Adverse events by System Organ Class with frequency ≥2%, Overall Period (Safety analysis set) DCO: 29 APR 2024

D+G+C arm (N=530)				G+C arm (N=526)		
SOC/MedDRA PT	N (%)	Outcome		N (%)	Outcome	
		Not resolved N (%)	Fatal N (%)		Not resolved N (%)	Fatal N (%)
Infections and Infestations	153(28.9)	4(2.6)	10(6.5)	136(25.9)	6(4.4)	7(5.1)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	67(12.6)	6(9)	0	44(8.4)	2(4.5)	2(4.5)
Renal and urinary disorders	66(12.5)	24(36.4)	0	58(11)	11(19)	2(3.4)
Gastrointestinal disorders	53(10)	5(9.4)	1(1.9)	35(6.7)	0	1(2.9)
Respiratory, thoracic and mediastinal disorders	30(5.7)	9(30)	2(6.7)	14(2.7)	1(7.1)	3(21.4)
Injury, poisoning and procedural complications	28(5.3)	1(3.6)	0	23 (4.4)	5(21.7)	0
Cardiac disorders	23(4.3)	4(17.4)	6(26.1)	10(1.9)	0	4(40)
Vascular disorders	21(4)	3(14.3)	2(9.5)	21(4)	5(23.8)	1(4.8)
Investigations	19(3.6)	4(21.1)	0	11(2.1)	0	0
Metabolism and nutrition disorders	18(3.4)	3(16.7)	0	12(2.3)	4(33.3)	0
Nervous system disorders	17(3.2)	3(17.6)	0	13(2.5)	4(30.8)	2(15.4)
Blood and lymphatic system disorders	15(2.8)	2(13.3)	0	32(6.1)	6(18.8)	0
General disorders and administration site conditions	14(2.6)	1(7.1)	4(28.6)	18(3.4)	2(11.1)	7(38.9)

SAE = Serious Adverse Event ,C = Cisplatin, D = Durvalumab, G = Gemcitabine

[a] Number (%) of patients with SAEs, sorted by international order for system organ class and alphabetical order for preferred term.

Patients with multiple SAEs are counted once for each system organ class / preferred term.

[b] Represents the number (percent) of patients with an outcome for the event.

If a patient has the same event more than once then the outcome from the last event is counted.

If a subject has multiple events within a specific group then the outcome of the event with the worst outcome is counted. Outcomes from worst to best are fatal, not resolved, resolved.

[c] Not resolved includes outcomes of: not recovered/not resolved; recovering/resolving; unknown. Resolved includes outcomes of: recovered/resolved, recovered/resolved with sequelae.

[d] Outcome of death as recorded on the AE form.

Includes SAEs between date of first dose of study treatment and the earliest of: 90 days after the last dose of treatment or surgery (Arm 1) (dose of study treatment or date of surgery, whichever occurs later) or 90 days after the last neoadjuvant treatment, surgery or last adjuvant study visit (neoadjuvant treatment, date of surgery, or adjuvant study visit, whichever occurs later) (Arm 2), date of first dose of subsequent anti-cancer therapy, date of DCO.

Includes SAEs with an onset date during this period and SAEs with an onset date prior to dosing which worsen during this period.

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Deaths

Table 67 All deaths – overall period (Full Analysis Set) DCO: 29 APR 2024

Category	Number (%) of patients D+G+C (N=533)	G+C (N=530)
Total number of deaths	136 (25.5)	169 (31.9)
Death related to disease under investigation only [a]	83 (15.6)	112 (21.1)
Death related to disease under investigation [a] and AE with outcome of death	2 (0.4)	2 (0.4)
AE onset prior or up to subsequent therapy [b]	2 (0.4)	2 (0.4)
AE onset after start of subsequent therapy [c]	0	0
AE with outcome of death only	22 (4.1)	19 (3.6)
AE onset prior or up to subsequent therapy [b]	22 (4.1)	19 (3.6)
AE onset after start of subsequent therapy [c]	0	0
Death after end of safety follow up period and not due to disease under investigation [d]	26 (4.9)	30 (5.7)
Unknown reason for death	2 (0.4)	6 (1.1)
Other deaths [e]	1 (0.2)	0

C = Cisplatin, D = Durvalumab, G = Gemcitabine, TEAE = Treatment emergent adverse event
[a] Death related to disease under investigation is determined by the investigator.
[b] Includes AEs between date of first dose of study treatment and the earliest of: 90 days after the last dose of treatment or surgery (Arm 1) (dose of study treatment or date of surgery, whichever occurs later) or 90 days after the last neoadjuvant treatment, surgery or last adjuvant study visit (neoadjuvant treatment, date of surgery, or adjuvant study visit, whichever occurs later) (Arm 2), date of first dose of subsequent anti-cancer therapy, date of DCO. Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.
[c] AE start date <= 90 days following the last dose of the study treatment and AE start date > the date of initiation of the first subsequent therapy.
[d] Death not due to disease progression or a TEAE.
[e] Patients who died and are not captured in the earlier categories.
Rows are mutually exclusive, patients are only reported in one category.

Table 68 All Deaths – by Study Period (Safety Analysis Set) DCO: 29 APR 2024

Category	Number (%) of subjects							
	Neoadjuvant period		Post-surgery period		Adjuvant period		Overall period	
	D + G+C (N = 530)	G+C (N = 526)	D + G+C (N = 470)	G+C (N = 446)	D + G+C (N = 383)	G+C (N = 383)	D + G+C (N = 530)	G+C (N = 526)
Total number of deaths	7 (1.3)	8 (1.5)	14 (3.0)	13 (2.9)	15 (3.9)	14 (3.7)	135 (25.5)	168 (31.9)
Death related to disease under investigation only [a]	1 (0.2)	1 (0.2)	0	1 (0.2)	10 (2.6)	5 (1.3)	82 (15.5)	110 (20.9)
Death related to disease under investigation [a] and AE with outcome of death	0	1 (0.2)	0	1 (0.2)	2 (0.5)	1 (0.3)	2 (0.4)	3 (0.6)
AE onset prior or up to subsequent therapy [b]	0	1 (0.2)	0	1 (0.2)	2 (0.5)	1 (0.3)	2 (0.4)	3 (0.6)
AE onset after start of subsequent therapy [c]	0	0	0	0	0	0	0	0
AE with outcome of death only	6 (1.1)	5 (1.0)	14 (3.0)	10 (2.2)	3 (0.8)	6 (1.6)	25 (4.7)	25 (4.8)
AE onset prior or up to subsequent therapy [b]	6 (1.1)	5 (1.0)	14 (3.0)	10 (2.2)	3 (0.8)	6 (1.6)	25 (4.7)	25 (4.8)
AE onset after start of subsequent therapy [c]	0	0	0	0	0	0	0	0
Death after end of safety follow-up period and not due to disease under investigation [d]	NA	NA	NA	NA	NA	NA	23 (4.3)	22 (4.2)
Unknown reason for death	0	1 (0.2)	0	1 (0.2)	0	0	2 (0.4)	6 (1.1)
Other deaths [e]	0	0	0	0	0	2 (0.5)	1 (0.2)	2 (0.4)

a Death related to disease under investigation is determined by the investigator.

b AEs in neoadjuvant period includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period between date of first dose of neoadjuvant study treatment until the date of surgery, or for subjects without surgery up to min (date of last dose of neoadjuvant treatment + 90 days, date of first dose of subsequent anticancer therapy, date of DCO).

AEs in post-surgery period includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period between date of surgery and the earliest of: 90 days after radical cystectomy; date of first dose of subsequent anticancer therapy; date of DCO.

AEs in adjuvant period includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period between the date of first dose of adjuvant study treatment (Arm 1) or date of first adjuvant study visit (Arm 2) until min (90 days after the last dose of adjuvant study treatment (Arm 1) or last adjuvant study visit (Arm 2), date of first dose of subsequent anticancer therapy, date of DCO).

Table 69 All deaths on treatment or within 90 days of last dose (Full Analysis Set) – DCO 29 Apr 2024

Category	Number (%) of patients D+G+C (N=530)	Number (%) of patients G+C (N=526)
Total number of deaths	31 (5.8)	19 (3.6)
Death related to disease under investigation only [a]	11 (2.1)	1 (0.2)
Death related to disease under investigation [a] and AE with outcome of death	2 (0.4)	2 (0.4)
AE onset prior or up to subsequent therapy [b]	2 (0.4)	2 (0.4)
AE onset after start of subsequent therapy [c]	0	0
AE with outcome of death only	18 (3.4)	14 (2.7)
AE onset prior or up to subsequent therapy [b]	18 (3.4)	14 (2.7)
AE onset after start of subsequent therapy [c]	0	0
Unknown reason for death	0	2 (0.4)
Other deaths [d]	0	0

C = Cisplatin, D = Durvalumab, G = Gemcitabine
[a] Death related to disease under investigation is determined by the investigator.
[b] 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 up to and including the date of initiation of the first subsequent therapy (whichever occurs first).
[c] AE start date <= 90 days following the last dose of the study treatment and AE start date > the date of initiation of the first subsequent therapy.
[d] Patients who died and are not captured in the earlier categories.
Rows are mutually exclusive, patients are only reported in one category.

Source: CSR

Table 70 Adverse Events with Outcome of Death, possibly related to study treatment, by PT (Neoadjuvant, Adjuvant and Overall Periods) (Full Analysis Set; IA-2, 29-Apr-2024)

MedDRA preferred term	Number (%) of patients [a] Neoadjuvant period D + G+C (N = 530)	Neoadjuvant period G+C (N = 526)	Adjuvant period D + G+C (N = 383)	Adjuvant period G+C (N = 383)	Overall period D + G+C (N = 530)	Overall period G+C (N = 526)
Patients with any AE with outcome of death, possibly related to study treatment [b]	3 (0.6)	2 (0.4)	0	0	3 (0.6)	3 (0.6)
CARDIAC DISORDERS	2 (0.4)	1 (0.2)	0	0	2 (0.4)	1 (0.2)
Cardio-respiratory arrest	1 (0.2)	1 (0.2)	0	0	1 (0.2)	1 (0.2)
Myocardial infarction	1 (0.2)	0	0	0	1 (0.2)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.2)	1 (0.2)	0	0	1 (0.2)	1 (0.2)
Pulmonary embolism	1 (0.2)	0	0	0	1 (0.2)	0
Pneumonitis	0	1 (0.2)	0	0	0	1 (0.2)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	0	0	0	0	1 (0.2)
Death	0	0	0	0	0	1 (0.2)

[a] Number (%) of patients with AEs with outcome of death, possibly related to study treatment, sorted in decreasing frequency by PT in the D + G+C arm.
[b] Possibly related to treatment, as assessed by the Investigator. Missing responses are counted as related. Adverse events are counted as related if related or missing response for any treatment.

Definitions of the neoadjuvant, adjuvant, and overall periods are provided in Section 12.2.1.
MedDRA version 26.1.

Table 71 Adverse Events and Event Rates with Outcome of Death in the NIAGARA Study (Overall Period) and D Pan-tumor Pool by System Organ Class and Preferred Term (Safety Analysis Set) DCO: 29 APR 2024

SOC / MedDRA Preferred term	NIAGARA overall period				D Pan-tumor pool (N = 4045, Dur = 2240.4)	
	D + G+C (N = 530, Dur = 540.3)		G+C (N = 526, Dur = 551.7)			
	n (%) [a]	Event rate (per 100 PY) [b]	n (%) [a]	Event rate (per 100 PY) [b]	n (%) [a]	Event rate (per 100 PY) [b]
Patients with any AE with outcome of death	27 (5.1)	5.0	29 (5.5)	5.3	231 (5.7)	10.3
Infections and infestations	10 (1.9)	1.9	7 (1.3)	1.3	46 (1.1)	2.1
Bacterial sepsis	1 (0.2)	0.2	0	0	1 (<0.1)	<0.1
COVID-19	2 (0.4)	0.4	1 (0.2)	0.2	0	0
Pneumonia	1 (0.2)	0.2	0	0	15 (0.4)	0.7
Sepsis	4 (0.8)	0.7	2 (0.4)	0.4	13 (0.3)	0.6
Septic shock	1 (0.2)	0.2	3 (0.6)	0.5	6 (0.1)	0.3
Severe acute respiratory syndrome	1 (0.2)	0.2	0	0	0	0
Suspected COVID-19	0	0	1 (0.2)	0.2	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	2 (0.4)	0.4	2 (<0.1)	0.1
Gastric cancer	0	0	1 (0.2)	0.2	0	0
Prostate cancer stage IV	0	0	1 (0.2)	0.2	0	0
Psychiatric disorders	1 (0.2)	0.2	0	0	5 (0.1)	0.2
Completed suicide	1 (0.2)	0.2	0	0	3 (0.1)	0.1
Nervous system disorders	0	0	2 (0.4)	0.4	7 (0.2)	0.3
Cerebrovascular accident	0	0	1 (0.2)	0.2	4 (0.1)	0.2
Ischaemic stroke	0	0	1 (0.2)	0.2	1 (<0.1)	<0.1
Cardiac disorders	6 (1.1)	1.1	4 (0.8)	0.7	28 (0.7)	1.2
Acute myocardial infarction	0	0	1 (0.2)	0.2	0	0
Cardiac arrest	1 (0.2)	0.2	1 (0.2)	0.2	7 (0.2)	0.3
Cardio-respiratory arrest	3 (0.6)	0.6	1 (0.2)	0.2	6 (0.1)	0.3
Cardiopulmonary failure	1 (0.2)	0.2	0	0	2 (<0.1)	0.1
Myocardial infarction	1 (0.2)	0.2	1 (0.2)	0.2	7 (0.2)	0.3
Vascular disorders	2 (0.4)	0.4	1 (0.2)	0.2	10 (0.2)	0.4
Arterioenteric fistula	0	0	1 (0.2)	0.2	0	0
Embolism	1 (0.2)	0.2	0	0	1 (<0.1)	<0.1
Shock haemorrhagic	1 (0.2)	0.2	0	0	1 (<0.1)	<0.1
Respiratory, thoracic and mediastinal disorders	2 (0.4)	0.4	3 (0.6)	0.5	51 (1.3)	2.3
Aspiration	0	0	1 (0.2)	0.2	0	0
Pneumonitis	0	0	1 (0.2)	0.2	7 (0.2)	0.3
Pulmonary embolism	2 (0.4)	0.4	1 (0.2)	0.2	6 (0.1)	0.3

Table 71 Adverse Events and Event Rates with Outcome of Death in the NIAGARA Study (Overall Period) and D Pan-tumor Pool by System Organ Class and Preferred Term (Safety Analysis Set) DCO: 29 APR 2024

SOC / MedDRA Preferred term	NIAGARA overall period				D Pan-tumor pool (N = 4045, Dur = 2240.4)	
	D + G+C (N = 530, Dur = 540.3)		G+C (N = 526, Dur = 551.7)			
	n (%) [a]	Event rate (per 100 PY) [b]	n (%) [a]	Event rate (per 100 PY) [b]	n (%) [a]	Event rate (per 100 PY) [b]
Gastrointestinal disorders	1 (0.2)	0.2	1 (0.2)	0.2	15 (0.4)	0.7
Gastrointestinal haemorrhage	1 (0.2)	0.2	1 (0.2)	0.2	5 (0.1)	0.2
Hepatobiliary disorders	1 (0.2)	0.2	0	0	14 (0.3)	0.6
Chronic hepatic failure	1 (0.2)	0.2	0	0	1 (<0.1)	<0.1
Renal and urinary disorders	0	0	2 (0.4)	0.4	4 (0.1)	0.2
Chronic kidney disease	0	0	1 (0.2)	0.2	0	0
Nephritis	0	0	1 (0.2)	0.2	0	0
Renal failure	0	0	0	0	1 (<0.1)	<0.1
General disorders and administration site conditions	4 (0.8)	0.7	7 (1.3)	1.3	45 (1.1)	2.0
Death	3 (0.6)	0.6	5 (1.0)	0.9	21 (0.5)	0.9
Multiple organ dysfunction syndrome	0	0	2 (0.4)	0.4	0	0
Sudden cardiac death	1 (0.2)	0.2	0	0	2 (<0.1)	0.1

Source: CSR

Adverse events of special interest

Table 72 Adverse events of special interest by event type in NIAGARA with frequency ≥5% and in the D Pan-tumor Pool (Safety Analysis Set) DCO: 29 APR 2024

						Received intervention				Event outcome[b]			
AESI group Treatment group	Any AE	Any SAE	Maximum CTCAE grade 3 or 4[a]	Maximum CTCAE grade 3 [a]	Maximum CTCAE grade 4[a]	Systemic cortico-steroids	≥40 mg prednisone or equiv steroid[d]	Other immuno-suppress-ants	Endocrine therapy	Discontin-uation of treatment	Resulted in death	Not resolved[c]	Resolved [c]
Hepatic events													
NIAGARA (D+G+C) (N=530)	68 (12.8)	3 (0.6)	16 (3.0)	14 (2.6)	2 (0.4)	7 (1.3)	7 (1.3)	0	0	4 (0.8)	0	5 (0.9)	63 (11.9)
NIAGARA (G+C) (N=526)	58 (11.0)	1 (0.2)	6 (1.1)	4 (0.8)	2 (0.4)	1 (0.2)	0	0	0	3 (0.6)	0	9 (1.7)	49 (9.3)
D Pan-Tumor Pool (N=4045)	516 (12.8)	75 (1.9)	183 (4.5)	168 (4.2)	15 (0.4)	116 (2.9)	89 (2.2)	7 (0.2)	0	38 (0.9)	11 (0.3)	255 (6.3)	250 (6.2)
Diarrhoea or Colitis													
NIAGARA (D+G+C) (N=530)	114 (21.5)	11 (2.1)	9 (1.7)	9 (1.7)	0	8 (1.5)	6 (1.1)	1 (0.2)	0	4 (0.8)	0	9 (1.7)	105 (19.8)
NIAGARA (G+C) (N=526)	77 (14.6)	2 (0.4)	3 (0.6)	3 (0.6)	0	0	0	0	0	0	0	5 (1.0)	72 (13.7)
D Pan-Tumor Pool (N=4045)	687 (17.0)	38 (0.9)	43 (1.1)	41 (1.0)	2 (<0.1)	76 (1.9)	52 (1.3)	3 (0.1)	0	14 (0.3)	0	124 (3.1)	563 (13.9)
Hyperthyroid events													
NIAGARA (D+G+C) (N=530)	33 (6.2)	1 (0.2)	0	0	0	2 (0.4)	1 (0.2)	0	12 (2.3)	0	0	9 (1.7)	24 (4.5)
NIAGARA (G+C) (N=526)	12 (2.3)	0	0	0	0	0	0	0	4 (0.8)	0	0	5 (1.0)	7 (1.3)
D Pan-Tumor Pool (N=4045)	206 (5.1)	2 (<0.1)	0	0	0	11 (0.3)	4 (0.1)	0	59 (1.5)	2 (<0.1)	0	48 (1.2)	158 (3.9)
Hypothyroid events													
NIAGARA (D+G+C) (N=530)	68 (12.8)	1 (0.2)	2 (0.4)	2 (0.4)	0	1 (0.2)	0	0	55 (10.4)	1 (0.2)	0	52 (9.8)	16 (3.0)
NIAGARA (G+C) (N=526)	13 (2.5)	0	0	0	0	0	0	0	5 (1.0)	0	0	7 (1.3)	6 (1.1)
D Pan-Tumor Pool (N=4045)	451 (11.1)	5 (0.1)	5 (0.1)	5 (0.1)	0	17 (0.4)	6 (0.1)	0	307 (7.6)	0	0	331 (8.2)	120 (3.0)
Renal events													
NIAGARA (D+G+C) (N=530)	109 (20.6)	10 (1.9)	13 (2.5)	12 (2.3)	1 (0.2)	12 (2.3)	11 (2.1)	0	0	12 (2.3)	0	49 (9.2)	60 (11.3)
NIAGARA (G+C) (N=526)	86 (16.3)	2 (0.4)	4 (0.8)	2 (0.4)	2 (0.4)	0	0	0	0	8 (1.5)	1 (0.2)	40 (7.6)	45 (8.6)
D Pan-Tumor Pool (N=4045)	167 (4.1)	9 (0.2)	10 (0.2)	8 (0.2)	2 (<0.1)	19 (0.5)	14 (0.3)	1 (<0.1)	0	11 (0.3)	0	73 (1.8)	94 (2.3)
Dermatitis or Rash													
NIAGARA (D+G+C) (N=530)	181 (34.2)	1 (0.2)	6 (1.1)	6 (1.1)	0	12 (2.3)	2 (0.4)	0	0	4 (0.8)	0	44 (8.3)	137 (25.8)
NIAGARA (G+C) (N=526)	89 (16.9)	1 (0.2)	3 (0.6)	3 (0.6)	0	4 (0.8)	1 (0.2)	0	0	0	0	18 (3.4)	71 (13.5)
D Pan-Tumor Pool (N=4045)	988 (24.4)	9 (0.2)	31 (0.8)	31 (0.8)	0	68 (1.7)	34 (0.8)	0	0	8 (0.2)	0	381 (9.4)	607 (15.0)
Pancreatic events													
NIAGARA (D+G+C) (N=530)	53 (10.0)	0	12 (2.3)	11 (2.1)	1 (0.2)	2 (0.4)	2 (0.4)	0	0	1 (0.2)	0	19 (3.6)	34 (6.4)

						Received intervention				Event outcome[b]			
AESI group Treatment group	Any AE	Any SAE	Maximum CTCAE grade 3 or 4[a]	Maximum CTCAE grade 3 [a]	Maximum CTCAE grade 4[a]	Systemic cortico-steroids	≥40 mg prednisone or equiv steroid[d]	Other immuno-suppress-ants	Endocrine therapy	Discontin-uation of treatment	Resulted in death	Not resolved[c]	Resolved [c]
NIAGARA (G+C) (N=526)	35 (6.7)	1 (0.2)	8 (1.5)	8 (1.5)	0	0	0	0	0	0	0	3 (0.6)	32 (6.1)
D Pan-Tumor Pool (N=4045)	132 (3.3)	7 (0.2)	76 (1.9)	62 (1.5)	14 (0.3)	9 (0.2)	5 (0.1)	0	0	4 (0.1)	0	46 (1.1)	86 (2.1)
Other rare/miscellaneous													
NIAGARA (D+G+C) (N=530)	68 (12.8)	2 (0.4)	2 (0.4)	2 (0.4)	0	10 (1.9)	4 (0.8)	1 (0.2)	0	3 (0.6)	0	33 (6.2)	35 (6.6)
NIAGARA, (G+C) (N=526)	43 (8.2)	0	2 (0.4)	2 (0.4)	0	0	0	0	0	0	0	16 (3.0)	27 (5.1)
D Pan-Tumor Pool (N=4045)	614 (15.2)	19 (0.5)	34 (0.8)	33 (0.8)	1 (<0.1)	67 (1.7)	22 (0.5)	1 (<0.1)	0	8 (0.2)	1 (<0.1)	385 (9.5)	228 (5.6)

Includes AESI groups with frequency ≥5% in either NIAGARA group in the overall study period.
AE: Adverse event, C: Cisplatin, CTCAE Common Terminology Criteria for Adverse Events; D: Durvalumab, G: Gemcitabine, SAE: Serious adverse event.
[a] Grade 3: severe, Grade 4: life-threatening.
[b] If a subject has multiple events within a specific group then the outcome of the event with the worst outcome is counted. Outcomes from worst to best are death, not resolved, resolved.
[c] Not resolved includes outcomes of not recovered/not resolved; recovering/resolving; unknown. Resolved includes outcomes of recovered/resolved, recovered
[d] Other dose frequency has been used as well in the derivation.
Note: Overall Period includes AEs between date of first dose of study treatment and the earliest of 90 days after the last dose of treatment or surgery (Arm 1) or last adjuvant study visit (Arm 2) or date of first dose of subsequent anti-cancer therapy or date of data cut off.
Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.
Subjects with multiple occurrences in the same category are counted once per category regardless of the number of occurrences.
AESI Version 19.1; MedDRA Medical Dictionary for Regulatory Activities Version 26.1.
All studies used CTCAE version 4.03 except for NIAGARA which uses version 5.0.

Immune-mediated AEs

Immune-mediated AEs were assessed using the programmatic adjudication process.

Table 73 Immune-mediated Adverse Events in any Category in the NIAGARA Study and D Pan-tumor Pool (Safety Analysis Set) DCO: 29 APR 2024

AE category	n (%) of patients [a]						
	NIAGARA study						D Pan-tumor pool (N = 4045)
	Neoadjuvant period		Adjuvant period		Overall period		
	D + G+C (N = 530)	G+C (N = 526)	D + G+C (N = 383)	G+C (N = 383)	D + G+C (N = 530)	G+C (N = 526)	
Any imAE	**44 (8.3)**	**8 (1.5)**	**50 (13.1)**	**8 (2.1)**	**111 (20.9)**	**16 (3.0)**	**717 (17.7)**
Any imAE of maximum CTCAE Grade 3 or 4 [b]	11 (2.1)	1 (0.2)	4 (1.0)	0	16 (3.0)	1 (0.2)	175 (4.3)
Any serious imAE (including events with outcome of death)	8 (1.5)	1 (0.2)	7 (1.8)	0	18 (3.4)	1 (0.2)	159 (3.9)
Any imAE with outcome of death	0	1 (0.2)	0	0	0	1 (0.2)	15 (0.4)
Any imAE, possibly related to study treatment [c]	39 (7.4)	5 (1.0)	42 (11.0)	1 (0.3)	96 (18.1)	6 (1.1)	593 (14.7)
Any imAE of maximum CTCAE Grade 3 or 4, possibly related to study treatment [b]	11 (2.1)	1 (0.2)	4 (1.0)	0	16 (3.0)	1 (0.2)	147 (3.6)

Table 73 Immune-mediated Adverse Events in any Category in the NIAGARA Study and D Pan-tumor Pool (Safety Analysis Set) DCO: 29 APR 2024

AE category	n (%) of patients [a]						
	NIAGARA study						D Pan-tumor pool (N = 4045)
	Neoadjuvant period		Adjuvant period		Overall period		
	D + G+C (N = 530)	G+C (N = 526)	D + G+C (N = 383)	G+C (N = 383)	D + G+C (N = 530)	G+C (N = 526)	
Any serious imAE, possibly related to study treatment [c]	8 (1.5)	1 (0.2)	6 (1.6)	0	17 (3.2)	1 (0.2)	141 (3.5)
Any imAE with outcome of death, causally related to study treatment [c]	0	1 (0.2)	0	0	0	1 (0.2)	13 (0.3)
Received systemic corticosteroids	26 (4.9)	5 (1.0)	24 (6.3)	2 (0.5)	57 (10.8)	7 (1.3)	433 (10.7)
Received high dose steroids [d]	16 (3.0)	2 (0.4)	16 (4.2)	0	35 (6.6)	2 (0.4)	285 (7.0)
Received endocrine therapy	21 (4.0)	3 (0.6)	32 (8.4)	6 (1.6)	65 (12.3)	9 (1.7)	359 (8.9)
Received other immunosuppressants	2 (0.4)	0	1 (0.3)	0	3 (0.6)	0	15 (0.4)
Any imAE leading to discontinuation of study treatment	12 (2.3)	0	11 (2.9)	0	23 (4.3)	0	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 Grade 3: severe, Grade 4: life-threatening.
c Possibly related is defined as reasonable possibility that the AE was caused by treatment, as assessed by investigator. Missing responses are counted as possibly related.
d A dose of ≥ 40 mg prednisone or equivalent per day (oral) was considered to be a high dose. Other dose frequency has been used as well in the derivation.
Definitions of the NIAGARA neoadjuvant, adjuvant, and overall periods are provided in Section 1.1.4.1.
Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.
AESI category of Infusion/Hypersensitivity reactions is not included in this table.
All studies use CTCAE version 4.03 except for NIAGARA which uses version 5.0.
AESI or AEPI Version 19.1; MedDRA Version 26.1.
n Number of patients per category; N Number of patients per treatment group.

Table 74 Immune-mediated Adverse Events by Event Type occurring in ≥2 patients in in the NIAGARA Study and in the D Pan-tumor Pool (Safety Analysis Set) DCO: 29 APR 2024

						Received intervention				Event outcome[b]			
AESI group/ Treatment group	Any AE	Any SAE	Maximum CTCAE grade 3 or 4[a]	Maximum CTCAE grade 3 [a]	Maximum CTCAE grade 4[a]	Systemic cortico-steroids	≥40 mg prednisone equiv steroid[d]	Other immuno-suppress-ants	Endocrine therapy	Discontin-uation of treatment	Death	Not resolved[c]	Resolved [c]
Pneumonitis													
NIAGARA (D+G+C) (N=530)	7 (1.3)	3 (0.6)	1 (0.2)	1 (0.2)	0	7 (1.3)	5 (0.9)	1 (0.2)	0	3 (0.6)	0	2 (0.4)	5 (0.9)
NIAGARA (G+C) (N=526)	3 (0.6)	1 (0.2)	0	0	0	3 (0.6)	1 (0.2)	0	0	0	1 (0.2)	1 (0.2)	1 (0.2)
D Pan-Tumor Pool (N=4045)	105 (2.6)	51 (1.3)	29 (0.7)	27 (0.7)	2 (<0.1)	105 (2.6)	78 (1.9)	3 (0.1)	0	41 (1.0)	7 (0.2)	36 (0.9)	62 (1.5)
Hepatic events													
NIAGARA (D+G+C) (N=530)	5 (0.9)	1 (0.2)	4 (0.8)	3 (0.6)	1 (0.2)	5 (0.9)	5 (0.9)	0	0	3 (0.6)	0	1 (0.2)	4 (0.8)
NIAGARA (G+C) (N=526)	0	0	0	0	0	0	0	0	0	0	0	0	0
D Pan-Tumor Pool (N=4045)	112 (2.8)	39 (1.0)	73 (1.8)	65 (1.6)	8 (0.2)	112 (2.8)	86 (2.1)	7 (0.2)	0	26 (0.6)	6 (0.1)	56 (1.4)	50 (1.2)
Diarrhoea or Colitis													
NIAGARA (D+G+C) (N=530)	8 (1.5)	4 (0.8)	1 (0.2)	1 (0.2)	0	8 (1.5)	6 (1.1)	1 (0.2)	0	4 (0.8)	0	1 (0.2)	7 (1.3)
NIAGARA (G+C) (N=526)	0	0	0	0	0	0	0	0	0	0	0	0	0
D Pan-Tumor Pool (N=4045)	76 (1.9)	20 (0.5)	15 (0.4)	13 (0.3)	2 (<0.1)	76 (1.9)	52 (1.3)	3 (0.1)	0	12 (0.3)	0	22 (0.5)	54 (1.3)
Adrenal insufficiency													
NIAGARA (D+G+C) (N=530)	2 (0.4)	0	0	0	0	2 (0.4)	0	0	0	1 (0.2)	0	2 (0.4)	0
NIAGARA (G+C) (N=526)	0	0	0	0	0	0	0	0	0	0	0	0	0
D Pan-Tumor Pool (N=4045)	20 (0.5)	7 (0.2)	6 (0.1)	6 (0.1)	0	20 (0.5)	7 (0.2)	0	7 (0.2)	0	0	15 (0.4)	5 (0.1)
Hyperthyroid events													
NIAGARA (D+G+C) (N=530)	13 (2.5)	1 (0.2)	0	0	0	2 (0.4)	1 (0.2)	0	12 (2.3)	0	0	5 (0.9)	8 (1.5)
NIAGARA (G+C) (N=526)	4 (0.8)	0	0	0	0	0	0	0	4 (0.8)	0	0	2 (0.4)	2 (0.4)
D Pan-Tumor Pool (N=4045)	62 (1.5)	2 (<0.1)	0	0	0	11 (0.3)	4 (0.1)	0	58 (1.4)	1 (<0.1)	0	15 (0.4)	47 (1.2)
Hypophysitis													
NIAGARA (D+G+C) (N=530)	3 (0.6)	1 (0.2)	0	0	0	3 (0.6)	1 (0.2)	0	1 (0.2)	0	0	2 (0.4)	1 (0.2)
NIAGARA (G+C) (N=526)	0	0	0	0	0	0	0	0	0	0	0	0	0
D Pan-Tumor Pool (N=4045)	4 (0.1)	4 (0.1)	3 (0.1)	3 (0.1)	0	4 (0.1)	2 (<0.1)	0	1 (<0.1)	2 (<0.1)	0	3 (0.1)	1 (<0.1)
Hypothyroid events													
NIAGARA (D+G+C) (N=530)	55 (10.4)	1 (0.2)	1 (0.2)	1 (0.2)	0	1 (0.2)	0	0	55 (10.4)	1 (0.2)	0	46 (8.7)	9 (1.7)

NIAGARA (G+C) (N=526)	5 (1.0)	0	0	0	0	0	0	0	5 (1.0)	0	0	5 (1.0)	0
D Pan-Tumor Pool (N=4045)	309 (7.6)	5 (0.1)	4 (0.1)	4 (0.1)	0	17 (0.4)	6 (0.1)	0	304 (7.5)	0	0	248 (6.1)	61 (1.5)
Thyroiditis													
NIAGARA (D+G+C) (N=530)	2 (0.4)	1 (0.2)	0	0	0	0	0	0	2 (0.4)	2 (0.4)	0	2 (0.4)	0
NIAGARA, (G+C) (N=526)	0	0	0	0	0	0	0	0	0	0	0	0	0
D Pan-Tumor Pool (N=4045)	16 (0.4)	1 (<0.1)	2 (<0.1)	2 (<0.1)	0	5 (0.1)	3 (0.1)	0	13 (0.3)	1 (<0.1)	0	11 (0.3)	5 (0.1)
Renal events													
NIAGARA (D+G+C) (N=530)	9 (1.7)	5 (0.9)	2 (0.4)	2 (0.4)	0	9 (1.7)	9 (1.7)	0	0	6 (1.1)	0	3 (0.6)	6 (1.1)
NIAGARA, (G+C) (N=526)	0	0	0	0	0	0	0	0	0	0	0	0	0
D Pan-Tumor Pool (N=4045)	17 (0.4)	5 (0.1)	5 (0.1)	4 (0.1)	1 (<0.1)	17 (0.4)	12 (0.3)	1 (<0.1)	0	7 (0.2)	0	9 (0.2)	8 (0.2)
Dermatitis or Rash													
NIAGARA (D+G+C) (N=530)	12 (2.3)	0	4 (0.8)	4 (0.8)	0	12 (2.3)	2 (0.4)	0	0	1 (0.2)	0	0	12 (2.3)
NIAGARA, (G+C) (N=526)	4 (0.8)	0	1 (0.2)	1 (0.2)	0	4 (0.8)	1 (0.2)	0	0	0	0	0	4 (0.8)

AESI group/ Treatment group	**Any AE**	**Any SAE**	**Maximum CTCAE grade 3 or 4[a]**	**Maximum CTCAE grade 3 [a]**	**Maximum CTCAE grade 4[a]**	**Systemic cortico-steroids**	**≥40 mg prednisone equiv steroid[d]**	**Other immuno-suppress-ants**	**Endocrine therapy**	**Discontin-uation of treatment**	**Death**	**Not resolved[c]**	**Resolved [c]**
D Pan-Tumor Pool (N=4045)	65 (1.6)	5 (0.1)	17 (0.4)	17 (0.4)	0	65 (1.6)	34 (0.8)	0	0	5 (0.1)	0	24 (0.6)	41 (1.0)
Pancreatic events													
NIAGARA (D+G+C) (N=530)	2 (0.4)	0	1 (0.2)	1 (0.2)	0	2 (0.4)	2 (0.4)	0	0	0	0	1 (0.2)	1 (0.2)
NIAGARA, (G+C) (N=526)	0	0	0	0	0	0	0	0	0	0	0	0	0
D Pan-Tumor Pool (N=4045)	9 (0.2)	2 (<0.1)	4 (0.1)	3 (0.1)	1 (<0.1)	9 (0.2)	5 (0.1)	0	0	1 (<0.1)	0	3 (0.1)	6 (0.1)
Myositis													
NIAGARA (D+G+C) (N=530)	2 (0.4)	1 (0.2)	1 (0.2)	1 (0.2)	0	2 (0.4)	2 (0.4)	0	0	1 (0.2)	0	1 (0.2)	1 (0.2)
NIAGARA, (G+C) (N=526)	0	0	0	0	0	0	0	0	0	0	0	0	0
D Pan-Tumor Pool (N=4045)	4 (0.1)	3 (0.1)	3 (0.1)	2 (<0.1)	1 (<0.1)	4 (0.1)	4 (0.1)	0	0	2 (<0.1)	0	2 (<0.1)	2 (<0.1)
Other rare/miscellaneous													
NIAGARA (D+G+C) (N=530)	8 (1.5)	1 (0.2)	1 (0.2)	1 (0.2)	0	7 (1.3)	3 (0.6)	1 (0.2)	0	2 (0.4)	0	5 (0.9)	3 (0.6)
NIAGARA, (G+C) (N=526)	0	0	0	0	0	0	0	0	0	0	0	0	0
D Pan-Tumor Pool (N=4045)	54 (1.3)	9 (0.2)	11 (0.3)	10 (0.2)	1 (<0.1)	54 (1.3)	18 (0.4)	0	0	7 (0.2)	1 (<0.1)	34 (0.8)	19 (0.5)

Includes imAE grouped terms that occurred in 2 or more patients in either NIAGARA Overall period group.

AE: Adverse event, C: Cisplatin; CTCAE: Common Terminology Criteria for Adverse Events; D: Durvalumab, G: Gemcitabine, SAE: Serious adverse event.

[a] Grade 3: severe, Grade 4: life-threatening.

[b] If a subject has multiple events within a specific group then the outcome of the event with the worst outcome is counted. Outcomes from worst to best are death, not resolved, resolved.

[c] Not resolved includes outcomes of not recovered/not resolved; recovering/resolving; unknown. Resolved includes outcomes of recovered/resolved, recovered/resolved with sequelae.

[d] Other dose frequency has been used as well in the derivation.

Note: Overall Period includes AEs between date of first dose of study treatment and the earliest of 90 days after the last dose of treatment or surgery (Arm 1) or last adjuvant study visit (Arm 2) or date of first dose of subsequent anti-cancer therapy or date of DCO.

Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.

Subjects with multiple occurrences in the same category are counted once per category regardless of the number of occurrences.

AESI Version 19.1; MedDRA Medical Dictionary for Regulatory Activities Version 26.1.

All studies use CTCAE version 4.03 except for NIAGARA which uses version 5.0.

Infusion/Hypersensitivity Reactions

Table 75 Adverse events of infusion/hypersensitivity reactions by frequency by PT. DCO: 29 APR 2024

	Infusion/hypersensitivity reactions in total in the overall period n (%)	Frequency by PT n (%)	Notes for SOC
D+G+C arm	17 (3.2)	Infusion related reaction 5 (0.9) Drug eruption 4 (0.8) Drug hypersensitivity 4(0.8) Anaphylactic reaction 2 (0.4) Urticaria 2 (0.4) Anaphylactic shock 1(0.2)	Resolved events 17 (3.2) SAE 3 (0.6) AEs with death 0 Leading to discontinuation 2 (0.4)
G+C arm	14 (2.7)	Drug hypersensitivity 6 (1.1) Drug eruption 4 (0.8) Infusion related reaction 2 (0.4) Anaphylactic reaction 1 (0.2) Anaphylactic shock 1 (0.2)	Resolved events 13 (2.5) SAE 2 (0.4) AEs with death 0 Leading to discontinuation 1 (0.2)
D Pan-tumor pool	94 (2.3)	Infusion related reaction 55 (1.4) Drug hypersensitivity 21 (0.5) Urticaria 10 (0.2) Drug eruption 5 (0.1) Hypersensitivity 4 (0.1) Anaphylactic reaction 3 (0.1) Infusion related hypersensitivity 1 (<0.1) Anaphylactic shock 1 (<0.1)	Resolved events 83 (2.1) SAE 12 (0.3) AEs with death 0 Leading to discontinuation 4 (0.1)

Laboratory findings

Table 76 Clinically Important Changes in haematolgy parameters (Full Analysis Set) DCO: 29 APR 2024

	Number (%) patients								
	NIAGARA overall period						D Pan-tumor pool		
	D + G+C (N = 530)			G+C (N = 526)			(N=4045)		
Parameters	≥1 CTCAE grade changes	≥2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥1 CTCAE grade changes	≥2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥1 CTCAE grade changes	≥2 CTCAE grade changes	CTCAE grade changes to 3 or 4
Hemoglobin	466/528 (88.3)	172/528 (32.6)	71/528 (13.4)	455/521 (87.3)	170/521 (32.6)	71/521 (13.6)	1489/3868 (38.5)	209/3868 (5.4)	193/3868 (5.0)
Leukocytes	432/528 (81.8)	205/528 (38.8)	57/528 (10.8)	428/521 (82.1)	211/521 (40.5)	64/521 (12.3)	640/3868 (16.5)	75/3868 (1.9)	22/3868 (0.6)
Lymphocytes	256/527 (48.6)	166/527 (31.5)	54/527 (10.2)	240/520 (46.2)	155/520 (29.8)	40/520 (7.7)	1706/3828 (44.6)	748/3828 (19.5)	507/3828 (13.2)
Neutrophils	401/528 (75.9)	334/528 (63.3)	165/528 (31.3)	385/520 (74.0)	335/520 (64.4)	176/520 (33.8)	269/3833 (7.0)	119/3833 (3.1)	37/3833 (1.0)
Platelets	275/528 (52.1)	56/528 (10.6)	32/528 (6.1)	258/521 (49.5)	63/521 (12.1)	35/521 (6.7)	558/3865 (14.4)	64/3865 (1.7)	44/3865 (1.1)

Overall period and D pan-tumor pool is 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).

Patient's worst (highest CTCAE grade; highest CTC grade in the direction of high corrected calcium) changes from baseline are used.

All studies use CTCAE version 4.03, except for NIAGARA which uses version 5.0.

Version 4.03 of the CTCAE grading criteria only assessed hemoglobin in the low direction, in version 5.0 hemoglobin is a bi-directional lab parameter.

Table 77 Clinically Important Changes in Clinical chemistry parameters (Full Analysis Set) DCO: 29 APR 2024

Parameters	Number (%) patients								
	NIAGARA overall period						D Pan-tumor pool		
	D + G+C (N = 530)			G+C (N = 526)			(N = 4045)		
	≥ 1 CTCAE grade changes	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 1 CTCAE grade changes	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 1 CTCAE grade changes	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4
Alanine aminotransferase	282/528 (53.4)	36/528 (6.8)	12/528 (2.3)	281/520 (54.0)	37/520 (7.1)	21/520 (4.0)	1219/3860 (31.6)	224/3860 (5.8)	145/3860 (3.8)
Albumin	101/527 (19.2)	63/527 (12.0)	2/527 (0.4)	82/520 (15.8)	57/520 (11.0)	6/520 (1.2)	1144/3821 (29.9)	475/3821 (12.4)	60/3821 (1.6)
Alkaline phosphatase	135/526 (25.7)	16/526 (3.0)	4/526 (0.8)	129/519 (24.9)	16/519 (3.1)	2/519 (0.4)	1166/3840 (30.4)	192/3840 (5.0)	168/3840 (4.4)
Amylase	181/504 (35.9)	52/504 (10.3)	38/504 (7.5)	168/503 (33.4)	46/503 (9.1)	17/503 (3.4)	292/1225 (23.8)	83/1225 (6.8)	66/1225 (5.4)
Aspartate aminotransferase	222/528 (42.0)	27/528 (5.1)	8/528 (1.5)	202/520 (38.8)	22/520 (4.2)	11/520 (2.1)	1324/3850 (34.4)	259/3850 (6.7)	235/3850 (6.1)
Total bilirubin	46/528 (8.7)	16/528 (3.0)	7/528 (1.3)	48/520 (9.2)	14/520 (2.7)	2/520 (0.4)	505/3853 (13.1)	202/3853 (5.2)	103/3853 (2.7)
Calcium, corrected	275/519 (53.0)	23/519 (4.4)	11/519 (2.1)	221/506 (43.7)	15/506 (3.0)	9/506 (1.8)	1370/3696 (37.1)	196/3696 (5.3)	111/3696 (3.0)
Creatinine	334/528 (63.3)	212/528 (40.2)	50/528 (9.5)	302/521 (58.0)	166/521 (31.9)	35/521 (6.7)	1139/3796 (30.0)	154/3796 (4.1)	33/3796 (0.9)
Gamma glutamyltransferase	227/486 (46.7)	50/486 (10.3)	20/486 (4.1)	207/473 (43.8)	49/473 (10.4)	18/473 (3.8)	648/1765 (36.7)	187/1765 (10.6)	170/1765 (9.6)
Glucose [a]	13/525 (2.5)	10/525 (1.9)	4/525 (0.8)	12/518 (2.3)	6/518 (1.2)	1/518 (0.2)	1694/3826 (44.3)	546/3826 (14.3)	227/3826 (5.9)
Lipase	192/482 (39.8)	96/482 (19.9)	67/482 (13.9)	187/467 (40.0)	93/467 (19.9)	61/467 (13.1)	286/1225 (23.3)	130/1225 (10.6)	103/1225 (8.4)
Magnesium	195/486 (40.1)	59/486 (12.1)	15/486 (3.1)	183/476 (38.4)	69/476 (14.5)	16/476 (3.4)	569/3297 (17.3)	58/3297 (1.8)	54/3297 (1.6)
Potassium	328/528 (62.1)	84/528 (15.9)	45/528 (8.5)	307/520 (59.0)	80/520 (15.4)	38/520 (7.3)	1363/3853 (35.4)	295/3853 (7.7)	157/3853 (4.1)
Sodium	314/527 (59.6)	52/527 (9.9)	50/527 (9.5)	315/521 (60.5)	54/521 (10.4)	55/521 (10.6)	1671/3861 (43.3)	328/3861 (8.5)	325/3861 (8.4)

[a] For NIAGARA random glucose is presented and the D pan-tumor pool column contains a mix of random, fasting and non-fasting glucose.

Overall period and D pan-tumor pool is 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).

Patient's worst (highest CTCAE grade; highest CTC grade in the direction of high corrected calcium) changes from baseline are used.

All studies use CTCAE version 4.03, except for NIAGARA which uses version 5.0.

Table 78 Liver Biochemistry Test Abnormalities on-treatment (Full Analysis Set) DCO: 29 APR 2024

	Number (%) patients		
	NIAGARA overall period		D Pan-tumor pool
	D + G+C (N = 530)	G+C (N = 526)	(N=4045)
Number of patients with measurements	528 (100.0)	521 (100.0)	
Elevated ALT			
≥ 3 × to ≤ 5 × ULN	37 (7.0)	34 (6.5)	194 (4.8)
> 5 × to ≤ 8 × ULN	8 (1.5)	14 (2.7)	67 (1.7)
> 8 × to ≤ 10 × ULN	1 (0.2)	4 (0.8)	33 (0.8)
> 10 × to ≤ 20 × ULN	2 (0.4)	1 (0.2)	34 (0.8)
> 20 × ULN	3 (0.6)	2 (0.4)	14 (0.3)
Elevated AST			
≥ 3 × to ≤ 5 × ULN	17 (3.2)	12 (2.3)	202 (5.0)
> 5 × to ≤ 8 × ULN	0	5 (1.0)	126 (3.1)
> 8 × to ≤ 10 × ULN	2 (0.4)	0	44 (1.1)
> 10 × to ≤ 20 × ULN	4 (0.8)	3 (0.6)	52 (1.3)
> 20 × ULN	2 (0.4)	2 (0.4)	25 (0.6)
Total bilirubin			
≥ 2 × to ≤ 3 × ULN	4 (0.8)	5 (1.0)	67 (1.7)
> 3 × to ≤ 5 × ULN	3 (0.6)	0	48 (1.2)
> 5 × ULN	1 (0.2)	1 (0.2)	56 (1.4)
ALT or AST			
≥ 3 × to ≤ 5 × ULN	44 (8.3)	37 (7.0)	242 (6.0)
> 5 × to ≤ 8 × ULN	6 (1.1)	15 (2.9)	127 (3.1)
> 8 × to ≤ 10 × ULN	2 (0.4)	3 (0.6)	57 (1.4)
> 10 × to ≤ 20 × ULN	4 (0.8)	3 (0.6)	67 (1.7)
> 20 × ULN	3 (0.6)	2 (0.4)	29 (0.7)
Potential Hy's Law [a]			
(ALT or AST ≥ 3 × ULN) and total bilirubin ≥ 2 × ULN	7 (1.3)	5 (1.0)	131 (3.2)

[a] The onset date of ALT or AST elevation should be prior to or on the date of total bilirubin evaluation.
Overall period and D pan-tumor pool is 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).
Patients are counted only once in the worst reported sub-category.
Percentages are based on the total number of patients in the treatment group (N).

Seven patients (1.3%) in the D+G+C arm vs. five (1%) of those in the G+C arm met the criteria for a potential Hy's Laws cases. Of these three cases in the D+G+C arm were considered to be true ones.

Table 79 Abnormal Thyroid Tests (Safety Analysis Set) DCO: 29 APR 2024

	Number (%) of patients		
	NIAGARA		D Pan-tumor pool
Thyroid Function Tests	D + G+C (N = 530)	G+C (N = 526)	(N=4045)
On-treatment elevated TSH > ULN	142 (26.8)	90 (17.1)	1269 (31.4)

	Number (%) of patients		
	NIAGARA		D Pan-tumor pool
Thyroid Function Tests	**D + G+C (N = 530)**	**G+C (N = 526)**	**(N=4045)**
On-treatment elevated TSH > ULN with TSH ≤ ULN at baseline	112 (21.1)	58 (11.0)	780 (19.3)
With at least one T3 free/T4 free < LLN [a]	62 (55.4)	18 (31.0)	456 (58.5)
With all other T3 free/T4 free ≥ LLN [a]	33 (29.5)	30 (51.7)	270 (34.6)
With all T3 free/T4 free missing [a]	17 (15.2)	10 (17.2)	54 (6.9)
On-treatment low TSH < LLN	121 (22.8)	83 (15.8)	880 (21.8)
On-treatment low TSH < LLN with TSH ≥ LLN at baseline *	101 (19.1)	60 (11.4)	709 (17.5)
With at least one T3 free/T4 free > ULN [a]	46 (45.5)	11 (18.3)	310 (43.7)
With all other T3 free/T4 free ≤ ULN [a]	43 (42.6)	37 (61.7)	348 (49.1)
With all T3 free/T4 free missing [a]	12 (11.9)	12 (20.0)	51 (7.2)
Number of subjects with at least one baseline and post-baseline TSH result *	523 (98.7)	500 (95.1)	3679 (91.0)
On-treatment elevated TSH > ULN and above baseline [a]	139 (26.6)	81 (16.2)	1108 (30.1)
On-treatment decreased TSH < LLN and below baseline [a]	116 (22.2)	77 (15.4)	816 (22.2)

Percentages are based on the total number of patients in the treatment group (N).
a Percentages are 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.
Overall period and D pan-tumor pool is derived from laboratory assessments between the start of treatment and up to and including X days following the date of last dose of study medication or until the initiation of the first subsequent therapy (whichever occurs first). X = 90 for NIAGARA; X = 30 for studies in Durvalumab pan-tumor pool.

Table 80 Creatinine Clearance (Nephrotoxicity), Baseline vs Minimum Value On Treatment (Safety Analysis Set) DCO: 29 APR 2024

			Number (%) of patients					
			Minimum value during treatment [b]					
	Group	**Baseline assessment [a]**	**Normal**	**Mild impairment**	**Moderate impairment**	**Severe impairment**	**Kidney failure**	**Total**
NIAGARA	D + G+C (N = 530)	Normal	36 (7.2)	80 (16.0)	52 (10.4)	4 (0.8)	2 (0.4)	174 (34.7)
		Mild impairment	4 (0.8)	66 (13.2)	141 (28.1)	15 (3.0)	1 (0.2)	227 (45.3)
		Moderate impairment	0	3 (0.6)	79 (15.8)	14 (2.8)	3 (0.6)	99 (19.8)
		Severe impairment	0	0	0	1 (0.2)	0	1 (0.2)
		Kidney failure	0	0	0	0	0	0

	Group	Baseline assessment [a]	Number (%) of patients					
			Minimum value during treatment [b]					
			Normal	Mild impairment	Moderate impairment	Severe impairment	Kidney failure	Total
		Total	40 (8.0)	149 (29.7)	272 (54.3)	34 (6.8)	6 (1.2)	501 (100.0)
	G+C (N = 526)	Normal	37 (7.4)	78 (15.6)	49 (9.8)	6 (1.2)	1 (0.2)	171 (34.2)
		Mild impairment	5 (1.0)	68 (13.6)	139 (27.8)	17 (3.4)	1 (0.2)	230 (46.0)
		Moderate impairment	0	1 (0.2)	76 (15.2)	20 (4.0)	1 (0.2)	98 (19.6)
		Severe impairment	0	0	0	0	0	0
		Kidney failure	0	1 (0.2)	0	0	0	1 (0.2)
		Total	42 (8.4)	148 (29.6)	264 (52.8)	43 (8.6)	3 (0.6)	500 (100.0)
D Pan-tumor pool	(N=4045)	Normal	846 (58.7)	529 (36.7)	62 (4.3)	2 (0.1)	2 (0.1)	1441 (40.5)
		Mild impairment	62 (4.2)	909 (62.0)	476 (32.4)	14 (1.0)	6 (0.4)	1467 (41.3)
		Moderate impairment	1 (0.2)	43 (6.7)	532 (83.0)	53 (8.3)	12 (1.9)	641 (18.0)
		Severe impairment	0	0	1 (25.0)	3 (75.0)	0	4 (0.1)
		Kidney failure	0	1 (100)	0	0	0	1 (<0.1)
		Total	909 (25.6)	1482 (41.7)	1071 (30.1)	72 (2.0)	20 (0.6)	3554 (100)

[a] Baseline is defined as the last result obtained prior to the start of study treatment

[b] Percentages have been calculated using the number of patients with a baseline value and a post baseline value.

Overall period and D pan-tumor pool is 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).

Creatinine clearance is calculated using serum creatinine and the Cockcroft-Gault formula.

Normal: creatinine clearance (CrCl) ≥ 90 mL/min; Mild Impairment: CrCl ≥ 60 - < 90 mL/min; Moderate Impairment: CrCl ≥ 30 - < 60 mL/min; Severe Impairment: CrCl ≥ 15 - < 30 mL/min; Kidney Failure: CrCl < 15 mL/min.

Table 81 Reversibility of Creatinine Clearance (Full Analysis Set)

	Number (%) of patients	
	D + G+C C (N = 530) n/N (%)	G+C (N = 526) n/N (%)
Patient with baseline and on treatment CrCl assessment	501 / 530 (94.5)	500 / 526 (95.1)
Shift to worse renal impairment category from baseline	312 / 501 (62.3)	312 / 500 (62.4)
Patients with subsequent CrCl assessment after worsening from baseline	297 / 312 (95.2)	289 / 312 (92.6)
Worsened renal impairment reversible and transient	178 / 297 (59.9)	159 / 289 (55.0)

Reversible and transient is defined as a subsequent CrCl value that is higher than the worst CrCl value and in a better impairment category.

Normal: GFR ≥ 90 mL/min; Mild impairment: GFR ≥ 60 to < 90 mL/min; Moderate impairment: GFR ≥ 30 to < 60 mL/min; Severe impairment: GFR ≥ 15 to < 30 mL/min; Kidney failure: GFR < 15 mL/min.

n = number of patients included in analysis; N = Number of patients in treatment group.

DCO: 29 April 2024

Safety in special populations

Sex

Table 82 Adverse Events in any Category - Patient Level by Sex (Safety Analysis Set)

		Number (%) of patients [a]				
		NIAGARA				
		Neoadjuvant period		Overall period		D Pan-tumor Pool
AE Category	Sex group	D + G+C (N1 = 434) (N2 = 96)	G+C (N1 = 430) (N2 = 96)	D + G+C (N1 = 434) (N2 = 96)	G+C (N1 = 430) (N2 = 96)	(N1 = 2783) (N2 = 1262)
Any AE possibly related to Durvalumab [b]	Male	198 (45.6)	NA	264 (60.8)	NA	1605 (57.7)
	Female	50 (52.1)	NA	64 (66.7)	NA	735 (58.2)
Any AE possibly related to any study treatment [b]	Male	403 (92.9)	393 (91.4)	410 (94.5)	393 (91.4)	1605 (57.7)
	Female	90 (93.8)	94 (97.9)	92 (95.8)	94 (97.9)	735 (58.2)
Any AE of maximum CTCAE grade 3 or grade 4, possibly related to Durvalumab [b,c]	Male	31 (7.1)	NA	47 (10.8)	NA	324 (11.6)
	Female	10 (10.4)	NA	14 (14.6)	NA	141 (11.2)
Any AE of maximum CTCAE grade 3 or grade 4, possibly related to any study treatment [b,c]	Male	157 (36.2)	167 (38.8)	170 (39.2)	168 (39.1)	324 (11.6)
	Female	44 (45.8)	45 (46.9)	45 (46.9)	45 (46.9)	141 (11.2)
Any AE with outcome = death	Male	6 (1.4)	9 (2.1)	24 (5.5)	24 (5.6)	167 (6.0)
	Female	0	1 (1.0)	3 (3.1)	5 (5.2)	64 (5.1)
Any SAE (including events with outcome = death) [d]	Male	101 (23.3)	103 (24.0)	274 (63.1)	240 (55.8)	989 (35.5)
	Female	24 (25.0)	15 (15.6)	52 (54.2)	47 (49.0)	458 (36.3)
Any AE leading to discontinuation of Durvalumab	Male	41 (9.4)	NA	71 (16.4)	NA	289 (10.4)
	Female	9 (9.4)	NA	15 (15.6)	NA	108 (8.6)
	Male	62 (14.3)	64 (14.9)	89 (20.5)	64 (14.9)	289 (10.4)

Table 82 Adverse Events in any Category - Patient Level by Sex (Safety Analysis Set)

		Number (%) of patients [a]				
		NIAGARA				
		Neoadjuvant period		Overall period		D Pan-tumor Pool
AE Category	Sex group	D + G+C (N1 = 434) (N2 = 96)	G+C (N1 = 430) (N2 = 96)	D + G+C (N1 = 434) (N2 = 96)	G+C (N1 = 430) (N2 = 96)	(N1 = 2783) (N2 = 1262)
Any AE leading to discontinuation of any study treatment	Female	17 (17.7)	16 (16.7)	23 (24.0)	16 (16.7)	108 (8.6)

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 As assessed by the investigator. Missing responses are counted as related. Study treatment includes durvalumab, cisplatin, and gemcitabine, in this context surgery is not included as a study treatment.
c Maximum CTCAE grade per patient/treatment period/event is considered.
d Seriousness, as assessed by the investigator. An AE with missing seriousness is considered serious.
N1 = Total number of male patients, N2 = Total number of female patients. Percentages are calculated from N1 and N2 for male and female respectively.
Definitions of the NIAGARA Neoadjuvant and Overall periods are provided in Section 1.1.4.1.
Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.
Disease progression AEs reported in Study 1108 are not included in this summary.
All studies use version CTCAE 4.03, except for NIAGARA which uses version 5.0. MedDRA version 26.1.

Age

Table 83 Adverse Events in any Category - Patient Level by Age Group (Safety Analysis Set)

		Number (%) of patients [a]				
		NIAGARA				
		Neoadjuvant period		Overall period		D Pan-tumor Pool
AE Category	Age group	D + G+C (N1 = 33) (N2 = 225) (N3 = 215) (N4 = 57)	G+C (N1 = 35) (N2 = 203) (N3 = 225) (N4 = 63)	D + G+C (N1 = 33) (N2 = 225) (N3 = 215) (N4 = 57)	G+C (N1 = 35) (N2 = 203) (N3 = 225) (N4 = 63)	(N1 = 482) (N2 = 1768) (N3 = 1356) (N4 = 439)
Any AE possibly related to Durvalumab [b]	< 50	19 (57.6)	NA	21 (63.6)	NA	255 (52.9)
	≥ 50 - < 65	106 (47.1)	NA	144 (64.0)	NA	1033 (58.4)
	≥ 65 - < 75	88 (40.9)	NA	123 (57.2)	NA	804 (59.3)
	≥ 75	35 (61.4)	NA	40 (70.2)	NA	248 (56.5)
Any AE possibly related to any study treatment [b]	< 50	31 (93.9)	32 (91.4)	31 (93.9)	32 (91.4)	255 (52.9)
	≥ 50 - < 65	203 (90.2)	184 (90.6)	209 (92.9)	184 (90.6)	1033 (58.4)
	≥ 65 - < 75	203 (94.4)	215 (95.6)	206 (95.8)	215 (95.6)	804 (59.3)
	≥ 75	56 (98.2)	56 (88.9)	56 (98.2)	56 (88.9)	248 (56.5)
Any AE of maximum CTCAE grade 3 or grade 4, possibly related to Durvalumab [b,c]	< 50	4 (12.1)	NA	5 (15.2)	NA	40 (8.3)
	≥ 50 - < 65	19 (8.4)	NA	29 (12.9)	NA	204 (11.5)
	≥ 65 - < 75	13 (6.0)	NA	20 (9.3)	NA	165 (12.2)
	≥ 75	5 (8.8)	NA	7 (12.3)	NA	56 (12.8)
Any AE of maximum CTCAE grade 3 or grade 4, possibly related to any study treatment [b,c]	< 50	8 (24.2)	9 (25.7)	9 (27.3)	9 (25.7)	40 (8.3)
	≥ 50 - < 65	82 (36.4)	77 (37.9)	89 (39.6)	77 (37.9)	204 (11.5)
	≥ 65 - < 75	92 (42.8)	100 (44.4)	97 (45.1)	102 (45.3)	165 (12.2)
	≥ 75	19 (33.3)	26 (41.3)	20 (35.1)	25 (39.7)	56 (12.8)
Any AE with outcome = death	< 50	0	0	1 (3.0)	0	23 (4.8)
	≥ 50 - < 65	1 (0.4)	2 (1.0)	6 (2.7)	6 (3.0)	89 (5.0)

Table 83 Adverse Events in any Category - Patient Level by Age Group (Safety Analysis Set)

		Number (%) of patients [a]				
		NIAGARA				
		Neoadjuvant period		Overall period		D Pan-tumor Pool
AE Category	Age group	D + G+C (N1 = 33) (N2 = 225) (N3 = 215) (N4 = 57)	G+C (N1 = 35) (N2 = 203) (N3 = 225) (N4 = 63)	D + G+C (N1 = 33) (N2 = 225) (N3 = 215) (N4 = 57)	G+C (N1 = 35) (N2 = 203) (N3 = 225) (N4 = 63)	(N1 = 482) (N2 = 1768) (N3 = 1356) (N4 = 439)
	≥ 65 - < 75	4 (1.9)	6 (2.7)	16 (7.4)	17 (7.6)	90 (6.6)
	≥ 75	1 (1.8)	2 (3.2)	4 (7.0)	6 (9.5)	29 (6.6)
Any SAE (including events with outcome = death) [d]	< 50	5 (15.2)	7 (20.0)	16 (48.5)	13 (37.1)	165 (34.2)
	≥ 50 - < 65	48 (21.3)	36 (17.7)	129 (57.3)	105 (51.7)	596 (33.7)
	≥ 65 - < 75	55 (25.6)	58 (25.8)	147 (68.4)	129 (57.3)	482 (35.5)
	≥ 75	17 (29.8)	17 (27.0)	34 (59.6)	40 (63.5)	204 (46.5)
Any AE leading to discontinuation of Durvalumab	< 50	2 (6.1)	NA	3 (9.1)	NA	35 (7.3)
	≥ 50 - < 65	12 (5.3)	NA	31 (13.8)	NA	153 (8.7)
	≥ 65 - < 75	28 (13.0)	NA	43 (20.0)	NA	156 (11.5)
	≥ 75	8 (14.0)	NA	9 (15.8)	NA	53 (12.1)
Any AE leading to discontinuation of any study treatment	< 50	2 (6.1)	8 (22.9)	3 (9.1)	8 (22.9)	35 (7.3)
	≥ 50 - < 65	27 (12.0)	21 (10.3)	43 (19.1)	21 (10.3)	153 (8.7)
	≥ 65 - < 75	40 (18.6)	42 (18.7)	55 (25.6)	42 (18.7)	156 (11.5)
	≥ 75	10 (17.5)	9 (14.3)	11 (19.3)	9 (14.3)	53 (12.1)

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 As assessed by the investigator. Missing responses are counted as related. Study treatment includes durvalumab, cisplatin, and gemcitabine, in this context surgery is not included as a study treatment.
c Maximum CTCAE grade per patient/treatment period/event is considered.
d Seriousness, as assessed by the investigator. An AE with missing seriousness is considered serious.
N1 = Total number of patients < 50 years old, N2 = Total number of patients ≥ 50 to < 65 years old, N3 = Total number of patients ≥ 65 to < 75 years old, N4 = Total number of patients ≥ 75 years old. Percentages are calculated from N1, N2, N3, and N4 for patients who are < 50, ≥ 50 to < 65, ≥ 65 to < 75, and ≥ 75 years old respectively.Definitions of the NIAGARA Neoadjuvant and Overall periods are provided in Section 1.1.4.1.
Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.
Disease progression AEs reported in Study 1108 are not included in this summary. All studies use CTCAE version 4.03, except for NIAGARA which uses version 5.0. MedDRA version 26.1.

Table 84 Adverse Events in any Category by Age Group - Subject Level (Safety Analysis Set)

	Number (%) of subjects [a]		
	NIAGARA		D Pan-tumor pool
	Overall period		
AE category	D + G+C (N1=258) (N2=272)	G+C (N1=238) (N2=288)	Durvalumab (N1=2250) (N2=1795)
Any AE			
< 65	256 (99.2)	237 (99.6)	2111 (93.8)
≥ 65	271 (99.6)	288 (100)	1714 (95.5)
Any AE of maximum Grade 3 or 4 [b]			

Table 84 Adverse Events in any Category by Age Group - Subject Level (Safety Analysis Set)

	Number (%) of subjects [a]		
	NIAGARA		D Pan-tumor pool
	Overall period		
AE category	**D + G+C (N1=258) (N2=272)**	**G+C (N1=238) (N2=288)**	**Durvalumab (N1=2250) (N2=1795)**
< 65	171 (66.3)	157 (66.0)	882 (39.2)
≥ 65	182 (66.9)	179 (62.2)	718 (40.0)
SAEs (including events with outcome = death)			
< 65	145 (56.2)	118 (49.6)	761 (33.8)
≥ 65	181 (66.5)	169 (58.7)	686 (38.2)
AEs with outcome of death			
< 65	7 (2.7)	6 (2.5)	112 (5.0)
≥ 65	20 (7.4)	23 (8.0)	119 (6.6)
AEs with outcome of death, causally related to any study treatment [c]			
< 65	1 (0.4)	0	10 (0.4)
≥ 65	2 (0.7)	3 (1.0)	17 (0.9)
AEs leading to discontinuation of any study treatment			
< 65	46 (17.8)	29 (12.2)	188 (8.4)
≥ 65	66 (24.3)	51 (17.7)	209 (11.6)

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

[b] Maximum CTCAE Grade per subject/treatment period/event is considered.

[c] As assessed by the investigator. Missing responses are counted as related. Study treatment includes durvalumab, cisplatin, and gemcitabine, in this context surgery is not included as a study treatment.

N1 = Total number of < 65 years subjects, N2 = Total number of ≥ 65 years subjects; Percentages are calculated from N1 and N2 for < 65 years and ≥ 65 years, respectively.

Overall Period includes AEs between date of first dose of study treatment and the earliest of: 90 days after the last dose of treatment or surgery (Arm 1) or last adjuvant study visit (Arm 2) or date of first dose of subsequent anticancer therapy or date of DCO.

Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.

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

All studies use CTCAE version 4.03, except for NIAGARA which uses version 5.0. MedDRA version 26.1.

Race

Table 85 Adverse Events in any Category - Patient Level by Race (Safety Analysis Set)

		Number (%) of patients [a]				
		NIAGARA				
		Neoadjuvant period		Overall period		D Pan-tumor Pool
AE Category	Race group	D + G+C (N1 = 353) (N2 = 6) (N3 = 150) (N4 = 7) (N5 = 14)	G+C (N1 = 355) (N2 = 4) (N3 = 144) (N4 = 1) (N5 = 22)	D + G+C (N1 = 353) (N2 = 6) (N3 = 150) (N4 = 7) (N5 = 14)	G+C (N1 = 355) (N2 = 4) (N3 = 144) (N4 = 1) (N5 = 22)	(N1 = 2691) (N2 = 84) (N3 = 1121) (N4 = 72) (N5 = 77)
Any AE possibly related to any study treatment [b]	White	326 (92.4)	330 (93.0)	332 (94.1)	330 (93.0)	1574 (58.5)
	Black or African American	6 (100)	4 (100)	6 (100)	4 (100)	58 (69.0)
	Asian	141 (94.0)	130 (90.3)	144 (96.0)	130 (90.3)	613 (54.7)
	Other	6 (85.7)	1 (100)	6 (85.7)	1 (100)	47 (65.3)
	Missing	14 (100)	22 (100)	14 (100)	22 (100)	48 (62.3)
Any AE possibly related to Durvalumab [b]	White	174 (49.3)	NA	227 (64.3)	NA	1574 (58.5)
	Black or African American	5 (83.3)	NA	5 (83.3)	NA	58 (69.0)
	Asian	58 (38.7)	NA	82 (54.7)	NA	613 (54.7)
	Other	3 (42.9)	NA	4 (57.1)	NA	47 (65.3)
	Missing	8 (57.1)	NA	10 (71.4)	NA	48 (62.3)
Any AE of maximum CTCAE grade 3 or grade 4, possibly related to any study treatment [b,c]	White	130 (36.8)	150 (42.3)	142 (40.2)	151 (42.5)	311 (11.6)
	Black or African American	6 (100)	1 (25.0)	6 (100)	1 (25.0)	7 (8.3)
	Asian	57 (38.0)	51 (35.4)	59 (39.3)	51 (35.4)	133 (11.9)
	Other	1 (14.3)	0	1 (14.3)	0	10 (13.9)
	Missing	7 (50.0)	10 (45.5)	7 (50.0)	10 (45.5)	4 (5.2)
Any AE of maximum CTCAE grade 3 or grade 4, possibly related to Durvalumab [b,c]	White	30 (8.5)	NA	46 (13.0)	NA	311 (11.6)
	Black or African American	1 (16.7)	NA	1 (16.7)	NA	7 (8.3)
	Asian	8 (5.3)	NA	11 (7.3)	NA	133 (11.9)
	Other	1 (14.3)	NA	1 (14.3)	NA	10 (13.9)
	Missing	1 (7.1)	NA	2 (14.3)	NA	4 (5.2)
Any AE with outcome = death	White	5 (1.4)	9 (2.5)	22 (6.2)	24 (6.8)	162 (6.0)
	Black or African American	0	1 (25.0)	1 (16.7)	1 (25.0)	6 (7.1)
	Asian	1 (0.7)	0	4 (2.7)	3 (2.1)	39 (3.5)
	Other	0	0	0	0	4 (5.6)
	Missing	0	0	0	1 (4.5)	20 (26.0)
Any SAE (including events with outcome = death) [d]	White	79 (22.4)	83 (23.4)	224 (63.5)	201 (56.6)	993 (36.9)
	Black or African American	4 (66.7)	2 (50.0)	5 (83.3)	3 (75.0)	41 (48.8)
	Asian	37 (24.7)	27 (18.8)	83 (55.3)	72 (50.0)	334 (29.8)
	Other	1 (14.3)	1 (100)	5 (71.4)	1 (100)	35 (48.6)
	Missing	4 (28.6)	5 (22.7)	9 (64.3)	10 (45.5)	44 (57.1)

Table 85 Adverse Events in any Category - Patient Level by Race (Safety Analysis Set)

		Number (%) of patients [a]				
		NIAGARA				
		Neoadjuvant period		Overall period		D Pan-tumor Pool
AE Category	Race group	D + G+C (N1 = 353) (N2 = 6) (N3 = 150) (N4 = 7) (N5 = 14)	G+C (N1 = 355) (N2 = 4) (N3 = 144) (N4 = 1) (N5 = 22)	D + G+C (N1 = 353) (N2 = 6) (N3 = 150) (N4 = 7) (N5 = 14)	G+C (N1 = 355) (N2 = 4) (N3 = 144) (N4 = 1) (N5 = 22)	(N1 = 2691) (N2 = 84) (N3 = 1121) (N4 = 72) (N5 = 77)
Any AE leading to discontinuation of Durvalumab	White	33 (9.3)	NA	56 (15.9)	NA	282 (10.5)
	Black or African American	0	NA	1 (16.7)	NA	4 (4.8)
	Asian	16 (10.7)	NA	27 (18.0)	NA	91 (8.1)
	Other	0	NA	0	NA	5 (6.9)
	Missing	1 (7.1)	NA	2 (14.3)	NA	15 (19.5)
Any AE leading to discontinuation of any study treatment	White	56 (15.9)	58 (16.3)	76 (21.5)	58 (16.3)	282 (10.5)
	Black or African American	0	1 (25.0)	1 (16.7)	1 (25.0)	4 (4.8)
	Asian	21 (14.0)	13 (9.0)	32 (21.3)	13 (9.0)	91 (8.1)
	Other	0	0	0	0	5 (6.9)
	Missing	2 (14.3)	8 (36.4)	3 (21.4)	8 (36.4)	15 (19.5)

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 As assessed by the investigator. Missing responses are counted as related. Study treatment includes durvalumab, cisplatin, and gemcitabine, in this context surgery is not included as a study treatment.
c Maximum CTCAE grade per patient/treatment period/event is considered.
d Seriousness, as assessed by the investigator. An AE with missing seriousness is considered serious.
N1 = Total number of White patients, N2 = Total number of Black or African American patients, N3 = Total number of Asian patients, N4 = Total number of patients of "other" race, N5 = Total number of patients with missing race. Percentages are calculated from N1, N2, N3, N4, and N5 for patients of White, Black or African America, Asian, Other, and missing race, respectively.
Definitions of the NIAGARA Neoadjuvant and Overall periods are provided in Section 1.1.4.1.
Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.
Disease progression AEs reported in Study 1108 are not included in this summary.
All studies use CTCAE version 4.03, except for NIAGARA which uses version 5.0. MedDRA version 26.1.

ECOG PS

Table 86 Adverse Events in any Category - Patient Level by Baseline ECOG/WHO PS (Safety Analysis Set)

		Number (%) of patients [a]				
		NIAGARA				
		Neoadjuvant period		Overall period		D Pan-tumor Pool
AE Category	Baseline ECOG/WHO	D + G+C (N1 = 416) (N2 = 114) (N3 = 0)	G+C (N1 = 412) (N2 = 114) (N3 = 0)	D + G+C (N1 = 416) (N2 = 114) (N3 = 0)	G+C (N1 = 412) (N2 = 114) (N3 = 0)	(N1 = 1646) (N2 = 2394) (N3 = 5)
Any AE possibly related to durvalumab [b]	0	197 (47.4)	NA	259 (62.3)	NA	1022 (62.1)
	≥ 1	51 (44.7)	NA	69 (60.5)	NA	1314 (54.9)
	Missing	0	NA	0	NA	4 (80.0)
Any AE possibly related to any study treatment [b]	0	387 (93.0)	378 (91.7)	395 (95.0)	378 (91.7)	1022 (62.1)
	≥ 1	106 (93.0)	109 (95.6)	107 (93.9)	109 (95.6)	1314 (54.9)
	Missing	0	0	0	0	4 (80.0)

Table 86 Adverse Events in any Category - Patient Level by Baseline ECOG/WHO PS (Safety Analysis Set)

		Number (%) of patients [a]				
		NIAGARA				
		Neoadjuvant period		Overall period		D Pan-tumor Pool
AE Category	Baseline ECOG/WHO	D + G+C (N1 = 416) (N2 = 114) (N3 = 0)	G+C (N1 = 412) (N2 = 114) (N3 = 0)	D + G+C (N1 = 416) (N2 = 114) (N3 = 0)	G+C (N1 = 412) (N2 = 114) (N3 = 0)	(N1 = 1646) (N2 = 2394) (N3 = 5)
Any AE of maximum CTCAE grade 3 or grade 4, possibly related to durvalumab [b,c]	0	31 (7.5)	NA	48 (11.5)	NA	173 (10.5)
	≥ 1	10 (8.8)	NA	13 (11.4)	NA	291 (12.2)
	Missing	0	NA	0	NA	1 (20.0)
Any AE of maximum CTCAE grade 3 or grade 4, possibly related to any study treatment [b,c]	0	150 (36.1)	161 (39.1)	161 (38.7)	162 (39.3)	173 (10.5)
	≥ 1	51 (44.7)	51 (44.7)	54 (47.4)	51 (44.7)	291 (12.2)
	Missing	0	0	0	0	1 (20.0)
Any AE with outcome = death	0	3 (0.7)	6 (1.5)	16 (3.8)	18 (4.4)	70 (4.3)
	≥ 1	3 (2.6)	4 (3.5)	11 (9.6)	11 (9.6)	159 (6.6)
	Missing	0	0	0	0	2 (40.0)
Any SAE [d]	0	93 (22.4)	86 (20.9)	248 (59.6)	224 (54.4)	496 (30.1)
	≥ 1	32 (28.1)	32 (28.1)	78 (68.4)	63 (55.3)	949 (39.6)
	Missing	0	0	0	0	2 (40.0)
Any AE leading to discontinuation of durvalumab	0	43 (10.3)	NA	71 (17.1)	NA	129 (7.8)
	≥ 1	7 (6.1)	NA	15 (13.2)	NA	268 (11.2)
Any AE leading to discontinuation of any study treatment	0	64 (15.4)	59 (14.3)	90 (21.6)	59 (14.3)	129 (7.8)
	≥ 1	15 (13.2)	21 (18.4)	22 (19.3)	21 (18.4)	268 (11.2)

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 As assessed by the investigator. Missing responses are counted as related. Study treatment includes durvalumab, cisplatin, and gemcitabine, in this context surgery is not included as a study treatment.
c Maximum CTCAE grade per patient/treatment period/event is considered.
d Seriousness, as assessed by the investigator. An AE with missing seriousness is considered serious.
N1 = Total number of patients with baseline ECOG/WHO status of 0, N2 = Total number of patients with baseline ECOG/WHO status of ≥ 1, N3 = Total number of patients with missing baseline ECOG status. Percentages are calculated from N1, N2, and N3 for patients with Baseline ECOG/WHO status of 0, ≥ 1, and missing, respectively.
Definitions of the NIAGARA Neoadjuvant and Overall periods are provided in Section 1.1.4.1.
Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.
Disease progression AEs reported in Study 1108 are not included in this summary. All studies use CTCAE version 4.03, except for NIAGARA which uses version 5.0. MedDRA version 26.1.

Region

Table 87 Adverse Events in any Category - Patient Level by Baseline Geographic Region (Safety Analysis Set)

		Number (%) of patients [a]				
		NIAGARA				
		Neoadjuvant period		Overall period		D Pan-tumor Pool
AE Category	Geographic region group	D + G+C (N1 = 149) (N2 = 275) (N3 = 55) (N4 = 51) (N5 = 381)	G+C (N1 = 142) (N2 = 299) (N3 = 47) (N4 = 38) (N5 = 384)	D + G+C (N1 = 149) (N2 = 275) (N3 = 55) (N4 = 51) (N5 = 381)	G+C (N1 = 142) (N2 = 299) (N3 = 47) (N4 = 38) (N5 = 384)	(N1 = 1032) (N2 = 1756) (N3 = 1209) (N4 = 48) (N5 = 3013)
Any AE	Asia	146 (98.0)	139 (97.9)	147 (98.7)	142 (100)	949 (92.0)
	Europe	269 (97.8)	291 (97.3)	274 (99.6)	298 (99.7)	1645 (93.7)
	North America	55 (100)	47 (100)	55 (100)	47 (100)	1187 (98.2)
	South America	50 (98.0)	38 (100)	51 (100)	38 (100)	44 (91.7)
	Non-Asia Regions combined	374 (98.2)	376 (97.9)	380 (99.7)	383 (99.7)	2876 (95.5)
Any AE possibly related to any study treatment [b]	Asia	140 (94.0)	129 (90.8)	143 (96.0)	129 (90.8)	562 (54.5)
	Europe	252 (91.6)	273 (91.3)	257 (93.5)	273 (91.3)	991 (56.4)
	North America	52 (94.5)	47 (100)	53 (96.4)	47 (100)	754 (62.4)
	South America	49 (96.1)	38 (100)	49 (96.1)	38 (100)	33 (68.8)
	Non-Asia Regions combined	353 (92.7)	358 (93.2)	359 (94.2)	358 (93.2)	1778 (59.0)
Any AE of maximum CTCAE grade 3 or grade 4, possibly related to durvalumab [b,c]	Asia	8 (5.4)	NA	11 (7.4)	NA	129 (12.5)
	Europe	18 (6.5)	NA	31 (11.3)	NA	195 (11.1)
	North America	7 (12.7)	NA	7 (12.7)	NA	131 (10.8)
	South America	8 (15.7)	NA	12 (23.5)	NA	10 (20.8)
	Non-Asia Regions combined	33 (8.7)	NA	50 (13.1)	NA	336 (11.2)
Any AE of maximum CTCAE grade 3 or grade 4, possibly related to any study treatment [b,c]	Asia	56 (37.6)	50 (35.2)	58 (38.9)	50 (35.2)	129 (12.5)
	Europe	94 (34.2)	120 (40.1)	102 (37.1)	120 (40.1)	195 (11.1)
	North America	27 (49.1)	19 (40.4)	28 (50.9)	20 (42.6)	131 (10.8)
	South America	24 (47.1)	23 (60.5)	27 (52.9)	23 (60.5)	10 (20.8)
	Non-Asia Regions combined	145 (38.1)	162 (42.2)	157 (41.2)	163 (42.4)	336 (11.2)
Any AE with outcome = death	Asia	1 (0.7)	0	4 (2.7)	3 (2.1)	38 (3.7)
	Europe	4 (1.5)	8 (2.7)	16 (5.8)	18 (6.0)	110 (6.3)
	North America	0	0	2 (3.6)	0	76 (6.3)
	South America	1 (2.0)	2 (5.3)	5 (9.8)	8 (21.1)	7 (14.6)
	Non-Asia Regions combined	5 (1.3)	10 (2.6)	23 (6.0)	26 (6.8)	193 (6.4)
Any SAE [d]	Asia	37 (24.8)	26 (18.3)	82 (55.0)	71 (50.0)	308 (29.8)
	Europe	62 (22.5)	78 (26.1)	172 (62.5)	162 (54.2)	601 (34.2)
	North America	14 (25.5)	6 (12.8)	36 (65.5)	24 (51.1)	520 (43.0)
	South America	12 (23.5)	8 (21.1)	36 (70.6)	30 (78.9)	18 (37.5)
	Non-Asia Regions combined	88 (23.1)	92 (24.0)	244 (64.0)	216 (56.3)	1139 (37.8)
Any AE leading to discontinuation of durvalumab	Asia	16 (10.7)	NA	27 (18.1)	NA	89 (8.6)
	Europe	22 (8.0)	NA	39 (14.2)	NA	194 (11.0)
	North America	9 (16.4)	NA	11 (20.0)	NA	107 (8.9)
	South America	3 (5.9)	NA	9 (17.6)	NA	7 (14.6)
	Non-Asia Regions combined	34 (8.9)	NA	59 (15.5)	NA	308 (10.2)
Any AE leading to discontinuation of any study treatment	Asia	21 (14.1)	12 (8.5)	32 (21.5)	12 (8.5)	89 (8.6)
	Europe	41 (14.9)	55 (18.4)	56 (20.4)	55 (18.4)	194 (11.0)
	North America	11 (20.0)	7 (14.9)	13 (23.6)	7 (14.9)	107 (8.9)
	South America	6 (11.8)	6 (15.8)	11 (21.6)	6 (15.8)	7 (14.6)
	Non-Asia Regions combined	58 (15.2)	68 (17.7)	80 (21.0)	68 (17.7)	308 (10.2)

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 As assessed by the investigator. Missing responses are counted as related. Study treatment includes durvalumab, cisplatin, and gemcitabine, in this context surgery is not included as a study treatment.
c Maximum CTCAE grade per patient/treatment period/event is considered.
d Seriousness, as assessed by the investigator. An AE with missing seriousness is considered serious.
N1 = Total number of Asia patients, N2 = Total number of Europe patients, N3 = Total number of North America patients, N4 = Total number of South America patients, N5 = Total number of Non-Asia Region patients. Percentages are calculated from N1, N2, N3, N4, N5 for Asia, Europe, North America, South America and Non-Asia Regions, respectively.
Definitions of the NIAGARA Neoadjuvant and Overall periods are provided in Section 1.1.4.1.
Includes AEs with an onset date during this period and Aes with an onset date prior to dosing which worsen during this period.
Disease progression Aes reported in Study 1108 are not included in this summary. All studies use CTCAE version 4.03, except for NIAGARA which uses version 5.0. MedDRA version 26.1.

Safety in patients with impaired renal function:

Table 88 Adverse Events Based on Baseline Impaired Renal Function (Safety Analysis Set)

AE Category MedDRA Preferred Term	Number (%) of subjects [a,b]		
	NIAGARA		D Pan-tumor pool
	Overall period		
	D + G+C (N = 104)	G+C (N = 103)	(N = 314)
Any AE	103 (99.0)	103 (100)	300 (95.5)
Any AE with outcome = death	7 (6.7)	9 (8.7)	20 (6.4)
Any SAE (including events with outcome = death) [c]	69 (66.3)	66 (64.1)	126 (40.1)
Any SAE with in-patient hospitalization or prolongation of existing hospitalization	60 (57.7)	59 (57.3)	120 (38.2)
Any SAE life threatening	14 (13.5)	16 (15.5)	15 (4.8)
Any SAE with persistent or significant disability/incapacity	4 (3.8)	3 (2.9)	3 (1.0)
Any AE leading to discontinuation of any study treatment [d]	21 (20.2)	23 (22.3)	28 (8.9)
Anaemia	3 (2.9)	4 (3.9)	0
Asthenia	2 (1.9)	1 (1.0)	0
Chronic kidney disease	2 (1.9)	1 (1.0)	0
Acute kidney injury	1 (1.0)	1 (1.0)	1 (0.3)
Agranulocytosis	1 (1.0)	0	0
Cardiac failure	1 (1.0)	0	0
Cerebrovascular accident	1 (1.0)	0	1 (0.3)
Colitis ischaemic	1 (1.0)	0	0
Creatinine renal clearance decreased	1 (1.0)	2 (1.9)	0
Decreased appetite	1 (1.0)	0	0
Dermatitis	1 (1.0)	0	0
Eczema	1 (1.0)	0	0
Fatigue	1 (1.0)	0	1 (0.3)
Febrile neutropenia	1 (1.0)	0	0
Hypercreatininaemia	1 (1.0)	0	0
Leukopenia	1 (1.0)	0	0
Neuralgia	1 (1.0)	0	0
Neutropenia	1 (1.0)	2 (1.9)	0
Neutrophil count decreased	1 (1.0)	0	0
Oedema peripheral	1 (1.0)	0	0
Peripheral ischaemia	1 (1.0)	0	0
Platelet count decreased	1 (1.0)	0	0
Pulmonary embolism	1 (1.0)	0	0
Pyelonephritis	1 (1.0)	0	0

Table 88 Adverse Events Based on Baseline Impaired Renal Function (Safety Analysis Set)

AE Category MedDRA Preferred Term	Number (%) of subjects [a,b]		
	NIAGARA		D Pan-tumor pool
	Overall period		
	D + G+C (N = 104)	G+C (N = 103)	(N = 314)
Acute respiratory failure	0	0	1 (0.3)
Alanine aminotransferase increased	0	1 (1.0)	0
Amnesia	0	0	1 (0.3)
Ascites	0	0	1 (0.3)
Autoimmune hepatitis	0	0	1 (0.3)
Blood creatinine increased	0	4 (3.9)	0
Blood urea increased	0	1 (1.0)	0
Cerebral infarction	0	1 (1.0)	0
Colitis	0	0	1 (0.3)
Eastern Cooperative Oncology Group performance status worsened	0	1 (1.0)	0
Embolism	0	0	1 (0.3)
Gamma-glutamyltransferase increased	0	0	1 (0.3)
General physical health deterioration	0	1 (1.0)	0
Hepatitis	0	0	1 (0.3)
Immune thrombocytopenia	0	0	1 (0.3)
Ischaemic stroke	0	1 (1.0)	0
Lipase increased	0	0	1 (0.3)
Mental status changes	0	0	1 (0.3)
Oesophageal perforation	0	0	1 (0.3)
Osteomyelitis	0	0	1 (0.3)
Pneumocystis jirovecii pneumonia	0	0	1 (0.3)
Pneumonia aspiration	0	0	2 (0.6)
Pneumonia bacterial	0	0	1 (0.3)
Pneumonitis	0	0	3 (1.0)
Polymyalgia rheumatica	0	0	1 (0.3)
Pyrexia	0	2 (1.9)	0
Radiation pneumonitis	0	0	1 (0.3)
Renal tubular acidosis	0	0	1 (0.3)
Spinal cord compression	0	0	1 (0.3)
Thrombocytopenia	0	1 (1.0)	0
Thyroiditis	0	0	1 (0.3)
Tubulointerstitial nephritis	0	0	1 (0.3)
Vertebrobasilar stroke	0	1 (1.0)	0

Table 88 Adverse Events Based on Baseline Impaired Renal Function (Safety Analysis Set)

AE Category MedDRA Preferred Term	Number (%) of subjects [a,b] NIAGARA Overall period D + G+C (N = 104)	 G+C (N = 103)	 D Pan-tumor pool (N = 314)
White blood cell count decreased	0	1 (1.0)	0

a Baseline renal impaired subjects include those with CrCl < 60 mL/min.

b Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories.

c Seriousness, as assessed by the investigator. An AE with missing seriousness is considered serious.

Preferred terms are sorted by descending frequency in the NIAGARA overall D + G+C treatment group.

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

Note: Overall Period includes AEs between date of first dose of study treatment and the earliest of: 90 days after the last dose of treatment or surgery (Arm 1) or last adjuvant study visit (Arm 2) or date of first dose of subsequent anticancer therapy or date of DCO.

Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.

Disease progression AEs reported in Study 1108 are not included in this summary.
MedDRA version 26.1.

Safety in patients with impaired hepatic function:

Table 89 Adverse Events Based on Baseline Impaired Hepatic Function (Safety Analysis Set)

AE Category MedDRA Preferred Term	Number (%) of subjects [a,b] NIAGARA Overall period D + G+C (N = 42)	 G+C (N = 46)	 D Pan-tumor pool (N = 824)
Any AE	42 (100)	46 (100)	770 (93.4)
Any AE with outcome = death	2 (4.8)	1 (2.2)	67 (8.1)
Any SAE (including events with outcome = death) [c]	28 (66.7)	26 (56.5)	324 (39.3)
Any SAE with in-patient hospitalization or prolongation of existing hospitalization	26 (61.9)	26 (56.5)	298 (36.2)
Any SAE life threatening	5 (11.9)	4 (8.7)	53 (6.4)
Any SAE with persistent or significant disability/incapacity	1 (2.4)	0	11 (1.3)
Any AE leading to discontinuation of any study treatment [d]	3 (7.1)	8 (17.4)	93 (11.3)
Blood creatinine increased	1 (2.4)	0	0
Leukopenia	1 (2.4)	0	0
Neutrophil count decreased	1 (2.4)	0	0
Abdominal pain	0	0	1 (0.1)
Acute hepatic failure	0	0	1 (0.1)
Acute kidney injury	0	0	2 (0.2)
Alanine aminotransferase increased	0	0	4 (0.5)
Anaemia	0	0	1 (0.1)
Angioedema	0	0	1 (0.1)
Aortic stenosis	0	0	1 (0.1)
Ascites	0	0	2 (0.2)
Aspartate aminotransferase increased	0	0	3 (0.4)

Table 89 Adverse Events Based on Baseline Impaired Hepatic Function (Safety Analysis Set)

	Number (%) of subjects [a,b]		
	NIAGARA		
	Overall period		D Pan-tumor pool
AE Category MedDRA Preferred Term	D + G+C (N = 42)	G+C (N = 46)	(N = 824)
Asthenia	0	1 (2.2)	2 (0.2)
Autoimmune hepatitis	0	0	2 (0.2)
Autoimmune lung disease	0	0	1 (0.1)
Biliary obstruction	0	0	1 (0.1)
Blood alkaline phosphatase increased	0	0	1 (0.1)
Blood bilirubin increased	0	0	1 (0.1)
Blood urea increased	0	1 (2.2)	0
Cardiac arrest	0	0	1 (0.1)
Cardio-respiratory arrest	0	0	1 (0.1)
Cerebral ischaemia	0	0	1 (0.1)
Cerebrovascular accident	0	0	1 (0.1)
Colitis	0	0	1 (0.1)
Death	0	0	1 (0.1)
Dehydration	0	0	2 (0.2)
Diarrhoea	0	0	2 (0.2)
Drug hypersensitivity	0	0	1 (0.1)
Dysphagia	0	0	1 (0.1)
Embolism	0	0	1 (0.1)
Epstein-Barr virus infection	0	0	1 (0.1)
Erythema	0	0	1 (0.1)
Escherichia sepsis	0	1 (2.2)	0
Febrile neutropenia	0	1 (2.2)	0
Gastric ulcer perforation	0	0	1 (0.1)
Gastrointestinal haemorrhage	0	0	2 (0.2)
General physical health deterioration	0	0	5 (0.6)
Haemorrhage	0	0	1 (0.1)
Hepatic cirrhosis	0	0	1 (0.1)
Hepatic cytolysis	0	0	1 (0.1)
Hepatic failure	0	0	2 (0.2)
Hepatic function abnormal	0	0	5 (0.6)
Hepatitis	0	0	3 (0.4)
Hepatitis acute	0	0	1 (0.1)
Hyperbilirubinaemia	0	0	1 (0.1)
Hypopituitarism	0	0	1 (0.1)
Ileus	0	0	1 (0.1)
Immune thrombocytopenia	0	0	1 (0.1)
Interstitial lung disease	0	0	1 (0.1)
Ischaemic stroke	0	0	1 (0.1)
Myasthenia gravis	0	0	1 (0.1)
Myocarditis	0	0	2 (0.2)

Table 89 Adverse Events Based on Baseline Impaired Hepatic Function (Safety Analysis Set)

	Number (%) of subjects [a,b]		
	NIAGARA		
	Overall period		D Pan-tumor pool
AE Category MedDRA Preferred Term	D + G+C (N = 42)	G+C (N = 46)	(N = 824)
Myositis	0	0	1 (0.1)
Nephritis	0	0	1 (0.1)
Neuritis	0	0	1 (0.1)
Neuropathy peripheral	0	0	1 (0.1)
Neutropenia	0	1 (2.2)	0
Oesophageal adenocarcinoma stage 0	0	0	1 (0.1)
Oesophageal varices haemorrhage	0	0	2 (0.2)
Oral cavity fistula	0	0	1 (0.1)
Platelet count decreased	0	0	2 (0.2)
Pneumocystis jirovecii pneumonia	0	0	1 (0.1)
Pneumonia	0	0	1 (0.1)
Pneumonia adenoviral	0	0	1 (0.1)
Pulmonary embolism	0	0	2 (0.2)
Rash	0	0	2 (0.2)
Renal failure	0	0	1 (0.1)
Sacral pain	0	0	1 (0.1)
Sepsis	0	0	1 (0.1)
Septic shock	0	0	2 (0.2)
Spinal cord compression	0	0	1 (0.1)
Spontaneous bacterial peritonitis	0	0	1 (0.1)
Subdural haemorrhage	0	0	1 (0.1)
Sudden death	0	0	1 (0.1)
Thrombocytopenia	0	1 (2.2)	1 (0.1)
Thyroid disorder	0	0	1 (0.1)
Transaminases increased	0	0	2 (0.2)
Tubulointerstitial nephritis	0	0	1 (0.1)
White blood cell count decreased	0	2 (4.3)	0

a Baseline hepatically impaired subjects include those with bilirubin ≤ ULN and AST > ULN or bilirubin > 1 × ULN and any AST; ULN values for bilirubin and AST vary across studies.

For AST: Study 1108 has ULN values between 30 to 59 U/L; Japan Study 2 has ULN values between 30 to 40.2 U/L; Study 22 has ULN values between 30 to 50 U/L; all other D Pan-tumor pool studies and NIAGARA have a ULN of 33 U/L.

For bilirubin: Study 1108 has ULN values between 15.39 to 27.36 µmol/L; Japan Study 2 has ULN values between 15.4 to 25.7 µmol/L; Study 22 has ULN values between 15.39 to 32.0112 µmol/L; all other D Pan-tumor pool studies and NIAGARA have a ULN of 21 µmol/L.

Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories.

Seriousness, as assessed by the investigator. An AE with missing seriousness is considered serious.

Preferred terms are sorted by descending frequency in the NIAGARA overall D + G+C treatment group.

N = Total number of subjects with baseline impaired hepatic function.

Percentages are based on the total number of subjects in the treatment group with baseline impaired hepatic function (N).

Note: Overall Period includes AEs between date of first dose of study treatment and the earliest of: 90 days after the last dose of treatment or surgery (Arm 1) or last adjuvant study visit (Arm 2) or date of first dose of subsequent anticancer therapy or date of DCO.

Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.

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

MedDRA version 26.1.

Safety related to drug-drug interactions and other interactions

Durvalumab is an immunoglobulin; therefore, no formal PK drug-drug interaction studies have been conducted. Pharmacokinetic drug-drug interaction of durvalumab with other therapeutics is not anticipated given that durvalumab is not primarily cleared via hepatic or renal pathways.

Safety in ADA+ and ADA- patients

Table 90 Patients with at least one treatment-emergent AE in any Category by Durvalumab ADA Category (ADA-evaluable Analysis Set, IA-2, 29-Apr-2024)

AE category [a]	D + G+C (N = 453)			
	TE-ADA+ [b]	nAb+	ADA+ [c]	ADA- [d]
Number of ADA-evaluable patients in the category	8	6	37	416
Any AE	8 (100)	6 (100)	37 (100)	414 (99.5)
Any AE possibly related to treatment [e]	7 (87.5)	6 (100)	36 (97.3)	397 (95.4)
Any AE of CTCAE Grade 3 or 4	5 (62.5)	5 (83.3)	25 (67.6)	293 (70.4)
Any AE of CTCAE Grade 3 or 4, possibly related to treatment [e]	4 (50.0)	2 (33.3)	15 (40.5)	170 (40.9)
Any AE with outcome = death	0	0	0	21 (5.0)
Any AE with outcome = death, possibly related to treatment [e]	0	0	0	2 (0.5)
Any SAE (including events with outcome = death)	2 (25.0)	4 (66.7)	22 (59.5)	262 (63.0)
Any SAE (including events with outcome = death), possibly related to treatment [e]	1 (12.5)	1 (16.7)	5 (13.5)	71 (17.1)
Any AE leading to discontinuation of study treatment [f]	1 (12.5)	1 (16.7)	6 (16.2)	86 (20.7)
Any AE leading to discontinuation of study treatment, possibly related to treatment [e]	1 (12.5)	1 (16.7)	6 (16.2)	63 (15.1)
Any AESI/AEPI	8 (100)	6 (100)	37 (100)	414 (99.5)
Any AESI/AEPI, possibly related to treatment [e]	7 (87.5)	6 (100)	36 (97.3)	397 (95.4)
Any AE leading to drug interruption [f]	5 (62.5)	2 (33.3)	17 (45.9)	155 (37.3)
Any imAEs [g]	3 (37.5)	1 (16.7)	12 (32.4)	203 (48.8)
Any infusion reaction AEs [g]	0	0	3 (8.1)	36 (8.7)

[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] TE-ADA+ is defined as either treatment-induced (postbaseline ADA positive only) or treatment-boosted ADA (baseline positive ADA titer that was increased by ≥ 4 fold following drug administration).

[c] ADA+, ie, positive ADA result at any time, baseline or postbaseline.

[d] ADA-, ie, without any positive ADA results (at baseline or postbaseline).

[e] Possibly related to any of the study treatments, as assessed by the Investigator. Missing responses are counted as related.

Discontinuation due to adverse events

Table 91 Adverse events leading to discontinuation of any study treatment (Reported for > patients in either arm) by PT (Overall Period) (Full Analysis Set; IA-2, 29-Apr-2024)

MedDRA preferred term	Number (%) of patients [a]	
	Overall period	
	D + G+C (N = 530)	G+C (N = 526)
Patients with any AE leading to discontinuation of treatment [b]	112 (21.1)	80 (15.2)
Neutropenia	9 (1.7)	11 (2.1)
Anaemia	7 (1.3)	7 (1.3)
Blood creatinine increased	7 (1.3)	4 (0.8)
Chronic kidney disease	6 (1.1)	3 (0.6)
Acute kidney injury	5 (0.9)	2 (0.4)
Asthenia	4 (0.8)	4 (0.8)
Pyrexia	3 (0.6)	2 (0.4)
Nephritis	3 (0.6)	0
Pneumonitis	3 (0.6)	0
Platelet count decreased	3 (0.6)	0
Thrombocytopenia	2 (0.4)	4 (0.8)
Neutrophil count decreased	2 (0.4)	3 (0.6)
Alanine aminotransferase increased	2 (0.4)	3 (0.6)

[a] Number (%) of patients with an AE leading to discontinuation of study treatment, sorted by decreasing frequency of PT in the D + G+C arm. Patients with multiple AEs leading to discontinuation are counted once for each PT.

[b] Action taken; drug permanently discontinued.

Definition of the overall period is provided in Section 12.2.1.

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Table 92 Adverse events leading to discontinuation of any study treatment (Reported for >2 patients in either arm) by PT (neoadjuvant period) (Safety Analysis Set; IA-2, DCO 29-APR-2024)

MedDRA preferred term	Number (%) of patients [a]	
	Neoadjuvant period	
	D + G+C (N = 530)	G+C (N = 526)
Patients with any AE leading to discontinuation of treatment [b]	79 (14.9)	80 (15.2)
Neutropenia	9 (1.7)	11 (2.1)
Anaemia	6 (1.1)	7 (1.3)
Blood creatinine increased	6 (1.1)	4 (0.8)
Asthenia	4 (0.8)	4 (0.8)
Acute kidney injury	3 (0.6)	2 (0.4)
Platelet count decreased	3 (0.6)	0
Thrombocytopenia	2 (0.4)	4 (0.8)
Chronic kidney disease	2 (0.4)	3 (0.6)
Alanine aminotransferase increased	2 (0.4)	3 (0.6)
Neutrophil count decreased	2 (0.4)	3 (0.6)

[a] Number (%) of patients with an AE leading to discontinuation of study treatment, sorted by decreasing frequency of PT in the D + G+C arm. Patients with multiple AEs leading to discontinuation are counted once for each PT.

[b] Action taken; drug permanently discontinued.

Definition of the neoadjuvant period is provided in Section 12.2.1.

MedDRA version 26.1.

Table 93 Adverse events leading to discontinuation of any study treatment (reported for ≥2 patients in either arm) by PT (Adjuvant period) (Safety Analysis Set; IA-2, 29-Apr-2024)

MedDRA preferred term	Number (%) of patients [a]	
	Adjuvant period	
	D + G+C (N = 383)	G+C (N = 383)
Patients with any AE leading to discontinuation of treatment [b]	30 (7.8)	0
Pneumonitis	2 (0.5)	0
Acute kidney injury	2 (0.5)	0
Diarrhoea	2 (0.5)	0
Nephritis	2 (0.5)	0
Fatigue	2 (0.5)	0
Decreased appetite	2 (0.5)	0
Chronic kidney disease	2 (0.5)	0

[a] Number (%) of patients with an AE leading to discontinuation of study treatment, sorted by decreasing frequency of PT in the D + G+C arm. Patients with multiple AEs leading to discontinuation are counted once for each PT.

[b] Action taken; drug permanently discontinued.

Definition of the adjuvant period is provided in Section 12.2.1.

MedDRA version 26.1.

Table 94 Adverse Events Leading to Discontinuation of Durvalumab in the NIAGARA Study and D Pan-tumor Pool (Reported for ≥ 2 Patients in NIAGARA Overall Period) (Safety Analysis Set)

	NIAGARA neoadjuvant period D + G+C (N = 530, Dur = 131.1)		NIAGARA adjuvant period D + G+C (N = 383, Dur = 212.1)		NIAGARA overall period D + G+C (N = 530, Dur = 540.3)		D Pan-tumor pool (N = 4045, Dur = 2240.4)	
	n (%) [a]	Event rate (per 100 PY) [b]	n (%) [a]	Event rate (per 100 PY) [b]	n (%) [a]	Event rate (per 100 PY) [b]	n (% [a])	Event rate (per 100 PY) [b]
Patients with any AE leading to discontinuation of durvalumab	50 (9.4)	38.1	30 (7.8)	14.1	86 (16.2)	15.9	397 (9.8)	17.7
COVID-19	1 (0.2)	0.8	0	0	2 (0.4)	0.4	0	0
Sepsis	2 (0.4)	1.5	0	0	2 (0.4)	0.4	7 (0.2)	0.3
Anaemia	2 (0.4)	1.5	1 (0.3)	0.5	3 (0.6)	0.6	6 (0.1)	0.3
Neutropenia	3 (0.6)	2.3	0	0	3 (0.6)	0.6	1 (<0.1)	<0.1
Thyroiditis	2 (0.4)	1.5	0	0	2 (0.4)	0.4	1 (<0.1)	<0.1
Decreased appetite	0	0	2 (0.5)	0.9	2 (0.4)	0.4	1 (<0.1)	<0.1
Cardiac failure	1 (0.2)	0.8	1 (0.3)	0.5	2 (0.4)	0.4	2 (<0.1)	0.1
Pneumonitis	1 (0.2)	0.8	2 (0.5)	0.9	3 (0.6)	0.6	36 (0.9)	1.6
Diarrhoea	0	0	2 (0.5)	0.9	2 (0.4)	0.4	8 (0.2)	0.4
Acute kidney injury	3 (0.6)	2.3	2 (0.5)	0.9	5 (0.9)	0.9	5 (0.1)	0.2
Chronic kidney disease	1 (0.2)	0.8	2 (0.5)	0.9	5 (0.9)	0.9	1 (<0.1)	<0.1
Nephritis	1 (0.2)	0.8	2 (0.5)	0.9	3 (0.6)	0.6	4 (0.1)	0.2
Asthenia	3 (0.6)	2.3	0	0	3 (0.6)	0.6	4 (0.1)	0.2
Fatigue	0	0	2 (0.5)	0.9	2 (0.4)	0.4	6 (0.1)	0.3
Malaise	2 (0.4)	1.5	0	0	2 (0.4)	0.4	0	0
Pyrexia	1 (0.2)	0.8	0	0	2 (0.4)	0.4	0	0
Alanine aminotransferase increased	2 (0.4)	1.5	0	0	2 (0.4)	0.4	7 (0.2)	0.3
Blood creatinine increased	5 (0.9)	3.8	1 (0.3)	0.5	6 (1.1)	1.1	3 (0.1)	0.1

a Number (%) of patients with AEs, sorted by international order for system organ class and alphabetically for preferred term.
b Number of patients with AEs divided by the total number of years at risk for AEs across all patients within a group, multiplied by 100.
Study treatment includes durvalumab, cisplatin, and gemcitabine, in this context surgery is not included as a study treatment.
Patients with multiple AEs are counted once for each system organ class / preferred term.
Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.
Disease progression AEs reported in Study 1108 are not included in this summary.
Percentages are based on the total numbers of patients in the treatment group (N).
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Surgery

The proportion of patients who did not undergo cystectomy was 63 (11.8%) patients in the D + G+C arm vs 84 (15.8%) patients in the G+C arm. The most common reason for patients not undergoing on-study cystectomy was patient decision (6.0% vs 6.8%), disease progression (1.7% vs 1.7%), study discontinuation (0.6% vs 2.3%), **due to an AE (1.1% vs 1.3%),** and death (0.9% vs 1.5%) (see Table 14.2.8.1, CSR).

Surgical Delays:

For patients who underwent on-study cystectomy, the proportion of patients who had an AE in the neoadjuvant period that led to a delay in cystectomy was 1.7% in the D + G+C arm vs 1.1% in the G+C arm.

Adverse Events Possibly Related to Surgery: The proportion of patients with an AE possibly related to surgery, as assessed by the Investigator, was similar for both treatment arms (60.4% in the D + G+C arm vs 59.2% in the G+C arm). The proportion of patients with AEs of CTCAE Grade 3 or 4 considered possibly related to surgery by the Investigator were 29.8% in the D + G+C arm and 26.0% in the G+C arm. A total of 10 (2.1%) of patients in the D + G+C arm and 8 (1.8%) of patients in the G+C arm had AEs leading to death considered related to surgery by the Investigator (see Table 14.3.2.1.2, CSR 5.3.5.1). The most commonly reported AE with onset or worsening in the NIAGARA post-surgery period was urinary tract infection (17.4% in the D + G+C arm vs 15.9% in the G+C arm) (see Table 14.3.2.3.2, CSR).

Post-surgical complications:

The Clavien-Dindo assessment was used to grade surgical complications and was introduced during CSP Version 2.0 (23 April 2019), therefore it was not completed for all patients.

Table 95 Complications for patients undergoing cystectomy using Clavien-Dindo classification (Safety Analysis Set) DCO 29Apr2024

	Number (%) of patients	
Clavien Dindo Classification	D+G+C (N=530)	G+C (N=526)
Patients with radical cystectomy [a]	467	441
Grade 0	171 (36.6)	165 (37.4)
Grade I	81 (17.3)	82 (18.6)
Grade II	105 (22.5)	101 (22.9)
Grade III	53 (11.3)	48 (10.9)
Grade IIIa	29 (6.2)	28 (6.3)
Grade IIIb	24 (5.1)	19 (4.3)
Unspecified	0	1 (0.2)
Grade IV	19 (4.1)	11 (2.5)
Grade IVa	15 (3.2)	10 (2.3)
Grade IVb	3 (0.6)	1 (0.2)
Unspecified	1 (0.2)	0
Grade V	5 (1.1)	8 (1.8)
Missing	33 (7.1)	26 (5.9)

C = Cisplatin, D = Durvalumab, G = Gemcitabine
[a] Patients who had radical cystectomy before 1st protocol amendment (23APR2019) and don't have Clavien-Dindo grade are excluded.
Percentages are calculated from the number of patients who had radical cystectomy.

The proportion of patients who underwent surgery had a Clavien-Dindo assessment was similar in each treatment arm: 467 patients in the D + G+C arm vs 441 patients in the G+C arm. Overall, 296/467 (63.6%) vs 276/441 (62.6%) patients had any complications during surgery (Clavien-Dindo Grade >1). Most of the surgical complications were Grade I (81/467 [17.3%] in the D + G+C arm and 82/441 [18.6%] in the G+C arm) or Grade II (105/467 [22.5%] in the D + G+C arm and 101/441 [22.9%] in the G+C arm).

Table 96 Serious adverse events by system organ class and preferred term (Safety Analysis Set; post-surgery period)

System organ class / MedDRA Preferred term	Number (%) of patients [a] D+G+C (N=470)	G+C (N=446)
Patients with any SAE	213 (45.3)	178 (39.9)
INFECTIONS AND INFESTATIONS	107 (22.8)	92 (20.6)
Abdominal abscess	3 (0.6)	2 (0.4)
Abdominal infection	0	1 (0.2)
Abscess	1 (0.2)	0
Bacteraemia	2 (0.4)	2 (0.4)
Bacterial abdominal infection	0	1 (0.2)
Bacterial sepsis	1 (0.2)	0
Bacteroides bacteraemia	0	1 (0.2)
Bronchitis	0	1 (0.2)
COVID-19	4 (0.9)	1 (0.2)
COVID-19 pneumonia	0	1 (0.2)
Candida infection	1 (0.2)	0
Cellulitis	0	1 (0.2)
Clostridium difficile colitis	2 (0.4)	0
Clostridium difficile infection	1 (0.2)	1 (0.2)
Cystitis	0	1 (0.2)
Diarrhoea infectious	1 (0.2)	0
Escherichia infection	1 (0.2)	0
Fungaemia	1 (0.2)	1 (0.2)
Fungal endocarditis	0	1 (0.2)
Fungal peritonitis	0	1 (0.2)
Gastroenteritis	1 (0.2)	0
Infected lymphocele	1 (0.2)	0
Infection	2 (0.4)	0
Kidney infection	1 (0.2)	2 (0.4)
Osteomyelitis	1 (0.2)	0
Pelvic abscess	1 (0.2)	1 (0.2)
Pelvic infection	1 (0.2)	1 (0.2)
Perineal abscess	0	1 (0.2)
Perinephric abscess	0	1 (0.2)
Peritonitis	1 (0.2)	0
Pneumonia	5 (1.1)	1 (0.2)
Pneumonia aspiration	2 (0.4)	0
Pneumonia mycoplasmal	1 (0.2)	0
Post procedural infection	1 (0.2)	1 (0.2)
Postoperative abscess	0	2 (0.4)

Postoperative wound infection	2 (0.4)	0
Pseudomembranous colitis	0	1 (0.2)
Pyelonephritis	14 (3.0)	17 (3.8)
Pyelonephritis acute	2 (0.4)	3 (0.7)
Retroperitoneal abscess	1 (0.2)	0
Sepsis	13 (2.8)	10 (2.2)
Septic shock	7 (1.5)	4 (0.9)
Staphylococcal infection	0	1 (0.2)
Urethritis	1 (0.2)	0
Urinary tract infection	42 (8.9)	40 (9.0)
Urosepsis	12 (2.6)	8 (1.8)
Wound infection	1 (0.2)	1 (0.2)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	63 (13.4)	42 (9.4)
Chronic lymphocytic leukaemia	0	1 (0.2)
Lung neoplasm malignant	0	1 (0.2)
Neuroendocrine tumour	0	2 (0.4)
Prostate cancer	35 (7.4)	27 (6.1)
Prostate cancer stage I	4 (0.9)	0
Prostate cancer stage II	21 (4.5)	10 (2.2)
Prostate cancer stage III	2 (0.4)	0
Prostate cancer stage IV	1 (0.2)	1 (0.2)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	3 (0.6)	2 (0.4)
Anaemia	2 (0.4)	2 (0.4)
Leukocytosis	1 (0.2)	0
IMMUNE SYSTEM DISORDERS	0	1 (0.2)
Anaphylactic shock	0	1 (0.2)
ENDOCRINE DISORDERS	0	1 (0.2)
Inappropriate antidiuretic hormone secretion	0	1 (0.2)
METABOLISM AND NUTRITION DISORDERS	5 (1.1)	4 (0.9)
Dehydration	1 (0.2)	1 (0.2)
Hypercalcaemia	1 (0.2)	0
Hyperkalaemia	1 (0.2)	1 (0.2)
Hypochloraemia	0	1 (0.2)
Hypoglycaemia	1 (0.2)	0
Malnutrition	1 (0.2)	0
Metabolic acidosis	0	2 (0.4)
NERVOUS SYSTEM DISORDERS	6 (1.3)	4 (0.9)
Diabetic coma	1 (0.2)	0
IIIrd nerve paralysis	1 (0.2)	0
Ischaemic stroke	1 (0.2)	0
Seizure	1 (0.2)	2 (0.4)
Syncope	1 (0.2)	1 (0.2)
Transient ischaemic attack	1 (0.2)	0
Uraemic encephalopathy	0	1 (0.2)
CARDIAC DISORDERS	11 (2.3)	1 (0.2)
Acute myocardial infarction	1 (0.2)	1 (0.2)
Atrial fibrillation	1 (0.2)	0
Cardiac arrest	2 (0.4)	0
Cardiac failure	1 (0.2)	0
Cardio-respiratory arrest	2 (0.4)	0

Cardiogenic shock	1 (0.2)	0
Myocardial infarction	1 (0.2)	0
Myocardial ischaemia	1 (0.2)	0
Sinus node dysfunction	1 (0.2)	0
Ventricular fibrillation	1 (0.2)	0
VASCULAR DISORDERS	14 (3.0)	10 (2.2)
Arterioenteric fistula	0	1 (0.2)
Deep vein thrombosis	2 (0.4)	2 (0.4)
Distributive shock	0	1 (0.2)
Embolism	2 (0.4)	0
Femoral artery embolism	1 (0.2)	0
Hypotension	3 (0.6)	1 (0.2)
Lymphocele	6 (1.3)	5 (1.1)
Shock haemorrhagic	1 (0.2)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	11 (2.3)	6 (1.3)
Acute respiratory distress syndrome	2 (0.4)	0
Acute respiratory failure	0	2 (0.4)
Aspiration	1 (0.2)	1 (0.2)
Dyspnoea	1 (0.2)	1 (0.2)
Pulmonary embolism	6 (1.3)	2 (0.4)
Pulmonary oedema	1 (0.2)	0
GASTROINTESTINAL DISORDERS	30 (6.4)	23 (5.2)
Abdominal distension	1 (0.2)	0
Abdominal hernia	0	2 (0.4)
Abdominal hernia obstructive	1 (0.2)	0
Abdominal pain	0	1 (0.2)
Colitis	1 (0.2)	0
Constipation	1 (0.2)	1 (0.2)
Diarrhoea	3 (0.6)	1 (0.2)
Enterocutaneous fistula	1 (0.2)	0
Fistula of small intestine	0	2 (0.4)
Gastrointestinal haemorrhage	1 (0.2)	0
Gastrointestinal necrosis	0	1 (0.2)
Gastrointestinal obstruction	1 (0.2)	1 (0.2)
Gastrointestinal perforation	1 (0.2)	0
Hernial eventration	2 (0.4)	0
Ileal perforation	0	1 (0.2)
Ileus	4 (0.9)	4 (0.9)
Ileus paralytic	3 (0.6)	2 (0.4)
Intestinal fistula	1 (0.2)	0
Intestinal obstruction	0	4 (0.9)
Intestinal perforation	1 (0.2)	0
Intestinal strangulation	1 (0.2)	0
Mechanical ileus	0	1 (0.2)
Nausea	1 (0.2)	0
Small intestinal obstruction	5 (1.1)	1 (0.2)
Small intestinal perforation	1 (0.2)	1 (0.2)
Volvulus of small bowel	1 (0.2)	0
Vomiting	0	1 (0.2)
HEPATOBILIARY DISORDERS	1 (0.2)	0
Chronic hepatic failure	1 (0.2)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.2)	1 (0.2)

Pathological fracture	0	1 (0.2)
Polymyalgia rheumatica	1 (0.2)	0
RENAL AND URINARY DISORDERS	27 (5.7)	28 (6.3)
Acute kidney injury	9 (1.9)	11 (2.5)
Haematuria	0	1 (0.2)
Hydronephrosis	5 (1.1)	5 (1.1)
Nephritis	1 (0.2)	1 (0.2)
Nephrolithiasis	1 (0.2)	1 (0.2)
Perinephric collection	0	1 (0.2)
Renal failure	4 (0.9)	3 (0.7)
Renal impairment	1 (0.2)	0
Ureteric stenosis	0	1 (0.2)
Ureterolithiasis	0	2 (0.4)
Urethral stenosis	1 (0.2)	0
Urinary fistula	0	1 (0.2)
Urinary retention	1 (0.2)	1 (0.2)
Urinary tract inflammation	1 (0.2)	0
Urinary tract obstruction	3 (0.6)	1 (0.2)
Vesicourethral fistula	1 (0.2)	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	2 (0.4)	5 (1.1)
Benign prostatic hyperplasia	0	1 (0.2)
Pelvic fluid collection	1 (0.2)	2 (0.4)
Prostatic dysplasia	1 (0.2)	0
Vaginal fistula	0	1 (0.2)
Vaginal prolapse	0	1 (0.2)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	5 (1.1)	6 (1.3)
Asthenia	0	1 (0.2)
Death	0	2 (0.4)
Dehiscence	1 (0.2)	0
General physical health deterioration	1 (0.2)	0
Multiple organ dysfunction syndrome	0	2 (0.4)
Oedema peripheral	1 (0.2)	0
Pyrexia	1 (0.2)	1 (0.2)
Sudden cardiac death	1 (0.2)	0

INVESTIGATIONS	3 (0.6)	1 (0.2)
Blood creatinine increased	1 (0.2)	0
Candida test positive	1 (0.2)	0
Gastrointestinal stoma output increased	0	1 (0.2)
Platelet count decreased	1 (0.2)	0
SARS-CoV-2 test positive	1 (0.2)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	19 (4.0)	18 (4.0)
Abdominal injury	1 (0.2)	0
Abdominal wound dehiscence	1 (0.2)	0
Anastomotic fistula	0	1 (0.2)
Anastomotic leak	0	1 (0.2)
Femur fracture	0	1 (0.2)
Gastrointestinal anastomotic leak	1 (0.2)	1 (0.2)
Incisional hernia	0	1 (0.2)
Post procedural complication	2 (0.4)	0
Post procedural fever	1 (0.2)	0
Post procedural haematoma	0	1 (0.2)
Post procedural haemorrhage	0	1 (0.2)
Post procedural urine leak	0	2 (0.4)
Postoperative ileus	3 (0.6)	0
Postoperative wound complication	1 (0.2)	0
Procedural haemorrhage	0	2 (0.4)
Rectal injury	1 (0.2)	1 (0.2)
Stenosis of vesicourethral anastomosis	0	1 (0.2)
Suture related complication	0	1 (0.2)
Ureteric anastomosis complication	2 (0.4)	1 (0.2)
Urethral injury	1 (0.2)	0
Urostomy complication	0	1 (0.2)
Wound dehiscence	4 (0.9)	2 (0.4)
Wound evisceration	1 (0.2)	0
PRODUCT ISSUES	2 (0.4)	1 (0.2)
Device dislocation	2 (0.4)	0
Device occlusion	0	1 (0.2)

C = Cisplatin, D = Durvalumab, G = Gemcitabine, SAE = Serious Adverse Event
a Number (%) of patients with SAEs, sorted by international order for system organ class and alphabetical order for preferred term.
Patients with multiple SAEs are counted once for each system organ class / preferred term.
Includes AEs between date of surgery and the earliest of: 90 days after radical cystectomy; date of first dose of subsequent anti-cancer therapy; date of DCO.
Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.
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Post marketing experience

As of 30 April 2024, durvalumab is approved in 4 countries for the treatment of locally advanced or metastatic urothelial carcinoma. Additionally, durvalumab has been approved for the treatment of Stage III, locally advanced unresectable NSCLC in 94 countries, and in combination with chemotherapy as first-line treatment of ES-SCLC in 93 countries.
Durvalumab is also approved in combination with tremelimumab and platinum-based chemotherapy for first-line treatment of patients with metastatic NSCLC in 48 countries: in combination with tremelimumab for the treatment of unresectable hepatocellular carcinoma in 54 countries, and in combination with gemcitabine and cisplatin for the treatment of locally advanced or metastatic biliary tract cancer in 78 countries.

As of 30 April 2024, the cumulative world-wide post-approval patient exposure since launch is estimated to be 176966 patient-years. No new safety concerns have been identified based on post-marketing safety reports.

2.5.1. Discussion on clinical safety

The safety population in NIAGARA study consists of 1056 patients with bladder cancer randomised to receive either 4 cycles of platinum-based neoadjuvant chemotherapy and durvalumab followed by surgery

and adjuvant durvalumab monotherapy for 8 cycles OR platinum-based neoadjuvant chemotherapy and surgery without adjuvant treatment. The D+G+C arm contains 530 patients who received neoadjuvant treatment, while the G+C arm contains 526 patients. The numbers of patients who entered the adjuvant period are identical in both arms (383 patients received durvalumab in the D+G+C arm). Safety results are derived from the IA2 with DCO of 29 April 2024.

As supportive evidence, data from 13 clinical trials of durvalumab monotherapy in different solid tumors are presented. This is acceptable and provides context of additional risk of the combination of D with chemotherapy and surgery. Baseline demographic of NIAGARA study population were well-balanced between arms; however, the NIAGARA's study population constitutes slightly younger and more fit population compared to the expected characteristics of patients with muscle invasive bladder cancer eligible for the neoadjuvant chemotherapy.

The median duration of follow-up of 41 months is deemed sufficient for the assessment of toxicity of durvalumab in the perioperative setting. Patients in both study arms received the median of 4 cycles of treatment in the neoadjuvant period, slightly higher proportion of patients in D+G+C completed full course of the neoadjuvant treatment (78.7% vs. 74% in the D+G+C and G+C arms, respectively). The median number of D infusions was 8 (range 1-8) in the adjuvant phase of the pivotal study. Most patients who initiated the adjuvant treatment received all 8 pre-planned cycles of D. As of the IA-2 DCO (29 April 2024), 379 (71.1%) patients and 333 (62.8%) patients in the durvalumab + chemo and chemo arms, respectively, were ongoing in the study, in survival follow-up. The safety follow-up time was 90 days after the last dose of study treatment, or date of surgery (whichever occurred later), date of first dose of subsequent anticancer therapy, or date of DCO. The total number of years at risk for an AE (which includes the 90-day follow-up for patients) was 540.3 years in the D+G+C arm and 551.7 years in the G+C arm.

Nearly all patients, across both arms, in the pivotal study experienced adverse events in the overall study period. The addition of D to neoadjuvant G+C did not result in an increase of any AEs, grade 3-5 AEs, infusion reactions, surgery not done/delayed and discontinuation of the study treatment. However, slightly higher rates of SAEs, AESIs in the D+G+C in the neoadjuvant period are observed. As expected, D maintenance resulted in higher toxicity during the adjuvant period, as the patients included in the G+C arm did not receive any treatment. This is manifested by higher rates of any AEs, SAEs, grade 3-4 AEs, AESI and immune-mediated AEs. Comparing the overall period of NIAGARA study to D- Pan tumor pool, higher incidences of AEs grade 3-4, SAEs, AEs leading to dose modification and discontinuation were observed. Similar rates of any AEs and deaths due to AE were reported in the D+G+C arm and the D pan-tumor pool.

The most commonly reported **AEs** in the D+G+C arm (for the overall period) included: nausea (53.6%), anaemia (38.7%), constipation (38.7%), fatigue (36%), urinary tract infection (30%), decreased appetite (26.6%), neutropenia (25.8%), pyrexia (20.8%), diarrhoea (20.6%), vomiting (19.2%), blood creatinine increased (18.5%), asthenia (17.5%) and neutrophil count decreased (15.3%). The reported frequencies in the experimental arm are generally comparable to those in the G+C arm suggesting that the chemotherapy backbone from both arms contributes significantly to the most commonly reported AEs. However, urinary tract infection (UTI), was reported at higher rate in overall period (30.0% vs 29.1%), [(10.9% vs 10.6%) in the neoadjuvant period; (18.0% vs 17.0%) in the adjuvant period and also in comparison to the durvalumab monotherapy pool (6.7%). However, the slightly higher incidence of UTI in the durvalumab group was related to pre-existing comorbidities and to the surgical procedures, and thus not considered related to durvalumab treatment. The addition of D to chemotherapy resulted in increased (5% difference in the D+G+C vs. G+C arm) incidence of nausea, diarrhoea, pruritus, rash, abdominal pain, hypothyroidism, and dyspnoea. The toxicity profile of durvalumab in combination with chemotherapy differs significantly from durvalumab monotherapy (D Pan-tumor pool) in terms of most commonly reported AEs.

Adverse events of **grade 3+4 events** reported during the overall study period in patients treated with D+G+C included: neutropenia (14.3%), urinary tract infection (14.2%), anaemia (13.8%) and neutrophil count decreased (7.0%). The reported frequencies were of similar magnitude in the D+G+C arm compared to the G+C and occurred during the neoadjuvant part of the study suggesting, that chemotherapy plays a contributory role in the most commonly reported grade 3+4 AEs. During the adjuvant period similar rates of grade 3+4 AEs were observed with urinary tract infection being the most common occurring in 7.6% and 6.8% of patients in the D+G+C and G+C, respectively. Comparing overall period of NIAGARA study to the D Pan-tumor pool higher incidence of grade 3+4 AEs is observed. This is to be expected given the platinum-based backbone of the treatment, which contributes to the toxicity of this regimen.

The incidence of **adverse drug reactions** in the D+G+C arm (overall period) was higher in the NIAGARA study than in D Pan-tumor pool and nearly identical compared to the G+C arm and D+ CTx pool. The increased frequency of ADRs in the D+G+C arm compared to the G+C arm were observed for nausea (53.6% vs. 48.5%), abdominal pain (20.6% vs 13.5%), diarrhoea (20.6% vs. 14.1%), pyrexia (20.8% vs. 16.5%), rash (20.9% vs. 9.7%), increase in creatinine (18.5% vs. 14.6%), pruritis (15.1% vs. 7.2%), hypothyroidism (12.6% vs. 2.3%) and arthralgia (10.4% vs. 6.7%). The causality of some of ADRs cannot be fully determined, as these overlap with known chemotherapy and durvalumab toxicity and therefore it could be anticipated that the addition of D to the platinum regime would lead to increase in the GI/haematological AEs. The frequency of Grade 3+4 ADRs in the overall period was similar between treatment arms in the pivotal study and as expected higher compared to D pan-tumor pool.

The frequency of **SAEs** reported during the overall period in the D+G+C arm was higher than in the G+C arm, both for any SAEs (61.5% vs. 54.6%) and for SAEs assessed to be possibly related to any study treatment (16.2% vs. 12%). Compared to D pan-tumor pool, the combination of durvalumab and chemotherapy is more toxic with nearly twofold increase of SAEs. During the overall period of NIAGARA, the most frequent SAEs by SOC in D+G+C arm were infections and infestations (28.9%), neoplasms (12.6%), renal and urinary disorders (12.5%) and GI disorders (10%). The majority of events resolved, in total 21 out of 153 patients in D+G+C arm died due to SAE. During the neoadjuvant period SAEs that were more frequent in the experimental arm were infections and infestations (7.0% vs. 6.3%), respiratory disorders (2.8% vs. 1.1%), investigations (2.3% vs. 1.9%). Some difference in incidence between treatment arms in the neoadjuvant period are noticed with pneumonia, urosepsis, embolism/pulmonary embolism and blood creatine increased being more frequent present in the D+G+C arm, however small number of events in each category preclude any meaningful comparison. During the adjuvant period 26.4% compared to 22.2% of patients in the D+G+C and G+C arms experienced SAEs. The most frequent SAEs in both arms were infections and infestations (12.3% in both arms) and renal and urinary disorders (8.1% in D+G+C vs 6.5% in the G+C arms, respectively). Three AEs with an outcome of death were seen in the D+G arm, of which two occurred in the neoadjuvant phase and one occurred in the post-surgery period.

At IA2 DCO (29 April 2024) in the ITT population 136 **deaths** (25.5% of study population) in the D+G+C and 169 (31.9% of patients) occurred int the overall period of the NIAGARA study. The proportion of patients who died due to their baseline disease was lower in the D + C+G arm compared to the G + C arm (83 patients [15.6%] vs 112 patients [21.1%], respectively). This indicates that patients receiving D+G+C have higher risk of death from other causes than bladder cancer, which is concerning in the curative setting. Deaths on treatment or within 90 days of last dose were more frequent in the D+G+C arm compared to G+C arm (31 patients [5.8%] vs. 19 [3.6%]). The most common causes of death during that period in D+G+C and G+C arms were AEs (18 patients [3.4%] and 14 [2.7%]) and baseline disease (11 patients [2.1%] and 1 [0.2%]). During the overall period of study (Safety analysis dataset), numbers of deaths were comparable between the study arms: deaths after end of safety follow-up period and not due to disease under investigation [23 (4.3%) vs 22 (4.2%)], deaths due to AE with outcome of

death only [25 (4.7%) vs 25 (4.8%)], deaths due to the disease under investigation and AE with outcome of death [2 (0.4%) vs 3 (0.6%)], unknown reasons [2 (0.4%) vs 6 (1.1%)] and other deaths [1 (0.2%) vs 2 (0.4%)]. The majority of AEs with outcome of death occurred in the post-surgery period (15/27 events in the D+G+C arm and 13/29 events in the G+C arm), which is to be expected due to risk of surgical procedure, general anaesthesia and postoperative complications. During the neoadjuvant period 6 and 10 patients in the experimental and control arm died due to adverse event, however only 3 and 2 deaths respectively, were considered possibly related to treatment. Similar proportions of deaths are observed for the adjuvant period (7 vs. 6), regardless of its causality to treatment or not, it is reassuring that adjuvant durvalumab seemingly does not increase the AE related mortality of patients.

Overall, the addition of durvalumab to SoC followed by adjuvant D resulted in higher risk of **AESI/AEPI** in NIAGARA (71% vs. 54%), which is to be expected knowing the toxicity profiles of durvalumab and chemotherapy. Higher proportions of patients in the D+G+C arm (overall period) experienced dermatitis/rash (34.2% vs. 16.9%), diarrhoea/colitis (21.5% vs. 14.6%), renal events (20.6% vs. 16.3%), hypothyroid events (12.8% vs. 2.5%), other rare/miscellaneous (12.8% vs. 8.2%) and pancreatic events (10% vs. 6.7%). The incidence of pneumonitis was generally low in NIAGARA study (2.1% in the D+G+C arm vs. 0.8% in the G+C arm, respectively). The majority of AESI/AEPI events across arms occurred in the neoadjuvant period (262/377 and 222/284) and some of these worsen during the adjuvant period, which makes it challenging on assessing the "true" toxicity of each phase of NIAGARA study. In the adjuvant period of NIAGARA 208/383 patients in the D+G+C arm developed or had AESI/AEPI which worsened compared to 84/383 patients in the G+C arm, respectively. Higher rates of dermatitis or rash (34.2% vs. 24.4%), diarrhea or colitis (21.5% vs. 17%), renal events (20.6% vs. 4.1%) and pancreatic events (10% vs. 3.3%) were observed in D+G+C arm in NIAGARA compared to D-Pan Tumor. Increase in AESI/AEPI is anticipated in this clinical setting and therefore careful selection of patients who could possibly benefit from the perioperative treatment is of high importance. Overall, no new safety risk for durvalumab in combination with platinum-based chemotherapy in the neoadjuvant period followed by the maintenance of durvalumab were observed in NIAGARA, which is reassuring.

The risk of experiencing an **ImAE** during the overall period was 20.9% for patients receiving D+G+C compared to 3% for those receiving G+C. For comparison, the risk of ImAEs in the D Pan-tumor pool was 17.7%. The majority of events were of grade 1 or 2 and none of events lead to death. 10.8% of patients in the D+G+C arm received corticosteroid treatment compared to 1.3% in the G+C arm. The events resolved in 45(8.5%) patients and of not-resolved events (66 patients), only 4 patients had grade 3 events (pneumonitis, hepatic event, renal event and hypothyroid event). ImAEs lead to discontinuations of study treatment in 4.3% of patients in the D+G+C, which was higher compared to D Pan-tumor pool (2.8%). One of the reasons behind this could be a longer exposure to durvalumab in the NIAGARA study compared to other studies included in the D Pan-tumor pool and therefore is considered acceptable. The most frequent immunological events were hypothyroidism (10.4%), dermatitis or rash (2.3%), renal events (1.7%), diarrhoea or colitis (1.5%) and other rare miscellaneous (1.5%). Pneumonitis events were observed in 7 patients (1.3%) with 3 events leading to the discontinuation of durvalumab. The incidence of pneumonitis was lower in the NIAGARA compared to D pan-tumor pool, which is reassuring. Except of hypothyroidism, dermatitis or rash, renal events, other rare/miscellaneous events, the frequencies of ImAEs were similar or lower in the NIAGARA study. Overall, no new immune-mediated events were observed during the NIAGARA study. Infusion reactions were uncommon (in <10% of patients in both arms) in the NIAGARA study. No events lead to death and the majority resolved, which is reassuring.

Changes in **haematology** parameters are mostly consistent with what would be expected from the known and expected toxicity with chemotherapy. No significant differences between the D+G+C and G+C arms were noted. Shifts in nearly all clinical chemistry parameters to CTCAE Grade 3 or 4 were reported in similar proportions of patients in the D+G+C and G+C arms. Higher frequency of shifts to CTCAE

Grade 3 or 4 in the D+G+C arm compared to the G+C arm was observed for amylase (7.5% vs. 3.4%) and creatinine (9.5% vs. 6.7%). Both pancreatitis and nephritis are known risks of durvalumab. In addition, the risk of change in creatinine level is multifactorial due to known nephrotoxicity of cisplatin, baseline disease with the greater risk of urinary tract infections, surgery complications and addition of durvalumab. The frequency of shifts in clinical chemistry parameters to CTCAE Grade 3 and 4 was in general lower between the D+G+C arm in NIAGARA and the D Pan-tumor Pool. Higher rates of shifts to grade 3 or 4 in the D+G+C arm compared to D Pan-tumor were observed for amylase, creatinine, lipase, magnesium, sodium and potassium. These might be related to backbone chemotherapy, combination with Durvalumab and the clinical setting. Liver transaminase elevations were comparable between treatment arms in NIAGARA and the Pan-tumor pool. More patients in the D+G+C arm (44 [8.3%]) compared to the G+C arm (37 [7%]) and the Pan- tumor (242 [6%]) experienced increase of $\geq 3 \times$ to $\leq 5 \times$ ULN for ALT or AST. In total 13 cases were potential Hy's Law cases (8 in the experimental arm and 5 in the control arm). Three of the potential Hy's Law cases in the D+G+C arm were considered to be true ones by the MAH. In NIAGARA, elevated TSH values and low TSH values were observed in greater proportions of patients in the D+G+C arm compared to the G+C arm and was comparable to the D Pan-tumor Pool. Similar proportions of patients in both treatment arms in NIAGARA had shifts from normal kidney function at baseline to moderate (10.4% vs 9.8% in the D+G+C and G+C arms, respectively), severe (0.8% vs 1.2%), and kidney failure (0.4% vs 0.2%). The chance of this impairment of renal function being reversible was slightly higher in the D+G+C arm compared to the G+C arm (59.9% vs. 55%). Shifts in renal impairments were more frequent in the D+G+C arm in NIAGARA in comparison to D Pan-tumor. This is anticipated with known toxicity profile of backbone chemotherapy, disease under study and the perioperative setting. Overall it is reassuring that there is no obvious increase of the renal impairments and the risk of irreversible worsening of renal function is not increased with the addition of durvalumab to SoC in patients with MIBC.

A trend towards increasing toxicity with increasing **age** was noted in the D+G+C arm. This is evident with higher proportions of patients experiencing any AEs related to any study treatment years, higher frequencies of SAEs in the D + G+C arm, AEs leading to discontinuation of durvalumab and increased risk of death. Frequencies of nearly all AEs categories are higher compared to frequencies in the D Pan-tumor pool, which is anticipated knowing the toxicity of platinum-based chemotherapy, longer exposure to D and the clinical setting. However, the observed trend of increased toxicity with older age is of concern, especially in light of slightly younger study population of NIAGARA emphasizing the need of careful selection of patients who could potentially benefit from the addition of durvalumab to SoC. Section 4.8 of the SmPC includes a statement data on safety for patients 75 years and older are too limited to draw a conclusion on this population, and the NIAGARA study has been reflected in this statement. Nearly all patients with baseline impaired renal function experienced any AE, few fatal events were observed. No trend for increased toxicity with addition of D to SoC is observed, which is reassuring.

Higher rates of **discontinuations** of any treatment due to AE were observed in the D+G+C arm compared to G+C arm in the overall period of NIAGARA study (21.1% vs. 15.2%). The majority of events occurred during the neoadjuvant phase of treatment across both treatment arms and these were similar in frequencies (14.9% vs. 15%), which is reassuring. 30 (7.8%) patients discontinued adjuvant treatment in NIAGARA. The rate of discontinuation of durvalumab due to any AE was considerably higher in the D+G+C arm compared to D Pan-tumor pool (16.2% vs. 9.8%). Discontinuations of D were more frequent in the neoadjuvant than adjuvant period of NIAGARA (9.4% vs. 7.8%). The majority of AES were predominately related to kidney function or haematological events. Overall, the increase in these in NIAGARA in comparison to the D Pan-tumor pool would be expected given the baseline disease, perioperative setting, backbone chemotherapy and longer exposure to durvalumab. Dose interruptions occurred more frequently in D+G+C arm (57.5% vs. 47%). No new safety risks were observed in NIAGARA.

The planned **surgery** (radical cystectomy) was not performed for 63 (11.8%) and 84 (15.8%) patients in the D+G+C and G+C arms, respectively. This imbalance is mostly driven by patient's decision, discontinuation of study, and death, which occurred more frequently in the control arm of NIAGARA. In general, this reflects the caveats of neoadjuvant approach in oncology, which might lead to "loosing" patients, who were candidates for curative surgery upfront during the preoperative period. Similar proportions of patients (1.7% vs. 1.1%) in both arms in NIAGARA had their surgery delayed due to AE in the neoadjuvant period indicating that the addition of durvalumab to SoC does not significantly impact the timing of surgery. However, there is a trend toward increased toxicity possibly related to surgery in the D+G+C arm with increased frequencies of grade 3-4 AEs and deaths (10 vs. 8 patients in the D+G+C and G+C arms, respectively). The incidence of SAEs (45.3% vs. 39.9%) in the post-surgery period is also higher in the D+G+C arm compared the G+C arm, with increase in infections and infestations (22.8% vs. 20.6%), neoplasms (13.4% vs. 9.4%), GI disorders (6.4% vs. 5.2%). In conclusion, the addition of durvalumab to SoC in the perioperative treatment of resectable MIBC is associated with inscreased surgical and post-operative toxicity, however the limited magnitude of this toxicity precludes drawing meaningful conclusions regarding its impact on the benefit-risk and no further regulatory actions are warranted.

An uncertainty remains that AEs may have been counted both in the pre-surgery and adjuvant periods because there could be an overlap between both periods. Therefore, the number of patients with events in the neoadjuvant and adjuvant periods may not add up to the overall period. There is a risk of underestimation of toxicity from the neoadjuvant period and also overestimation and the same time, where some of events could have been doublecounted. Due to overlapping of the study phases it is impossible to assess toxcicty of each of the study phases separately. However, the impact of this uncertainty on the benefit-risk is limited and no further regulatory actions are warranted.

On 11 April 2024, the MAH accepted the EMA request based on PRAC recommendation (EPITT: 19955) to update section 4.8 of the SmPC with information regarding the class effect of pancreatic exocrine insufficiency (PEI) based on reports from other immune checkpoint inhibitors. Upon further review of the safety and clinical data to identify potential ADRs of pancreatic exocrine insufficiency with durvalumab, 2 cases of PEI were identified (1 in the montherapy pool and 1 in the Imfinzi+chemotherapy pool). As a consequence, the sentence on section 4.8 of the SmPC informing of cases reported during treatment with other immune checkpoint inhibitors which might also occure during treatment with durvalumab, has been deleted. Pancreatic exocrine insufficiency is considered an ADR for durvalumab and it has been added to the table of ADRs in section 4.8 of the SmPC with frequency rare.

The safety pool of IMFINZI in combination with chemotherapy was updated based on pooled data in 1769 patients from 5 studies (TOPAZ-1, CASPIAN, DUO-E, AEGEAN, and NIAGARA) and this was reflected in the section 4.8 of the SmPC.

2.5.2. Conclusions on clinical safety

The addition of neoadjuvant durvalumab to gemcitabine and cisplatin in adult patients with resectable MIBC followed by adjuvant durvalumab as monotherapy after radical cystectomy led to higher rates of Grade 3/4 AE, serious events, treatment discontinuations, immune-mediated AE and serious post-surgery complications. Of note, durvalumab did not impact the disposition of patients undergoing surgery. The trend of increased toxicity with higher age is noted emphasizing the need for careful selection of patients with resectable MIBC who could benefit from this perioperative regimen. Section 4.8 of the SmPC includes a statement that data on safety for patients 75 years and older are too limited to draw a conclusion on this population, and the NIAGARA study has been reflected in this statement. Overall, no new safety concerns were identified in the NIAGARA study.

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 MAH submitted an updated RMP version (version 13.2) with this application. The main proposed RMP changes were the following:

- Addition of the proposed new indication with corresponding dosage information:
    - IMFINZI in combination with gemcitabine and cisplatin as neoadjuvant treatment, followed by IMFINZI as monotherapy adjuvant treatment after radical cystectomy, for treatment of adults with resectable muscle invasive bladder cancer (MIBC).

    - For MICB: 1500 mg[j] in combination with chemotherapy Q3W for 4 cycles prior to surgery, followed by 1500 mg[j] Q4W as monotherapy for up to 8 cycles after surgery, until disease progression that precludes definitive surgery or unacceptable toxicity (in the neoadjuvant phase), or until recurrence, unacceptable toxicity, or a maximum of 8 cycles after surgery (in the adjuvant phase).
      (j) MIBC patients with a body weight of 30 kg or less must receive weight-based dosing of IMFINZI at 20mg/kg.

- Inclusion of a section on bladder cancer in Part II, Module SI: "Epidemiology of the indication and target population", to cover the proposed indication of MIBC.

- Addition of exposure data from the NIAGARA study in support of the new indication.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 13.2 is acceptable.

2.7. Changes to the Product Information

As a consequence of this variation, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet (PL) is updated accordingly. In addition, the applicant has implemented changes based on the recent updates to the excipient guideline. Please refer to Attachment 1 which includes all changes to the Product Information.

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 MAH and has been found acceptable for the following reasons:

The variation for durvalumab (IMFINZI) to be used in combination with gemcitabine and cisplatin as neoadjuvant treatment, followed by adjuvant durvalumab as monotherapy after radical cystectomy, for the treatment of adults with resectable muscle invasive bladder cancer (MIBC) affects the Package Leaflet (PL) for IMFINZI 50 mg/mL concentrate for solution for infusion in Section 1 (What IMFINZI is and what it is used for), Section 2 (What you need to know before you are given IMFINZI), and Section 4 (Possible side effects). Overall, the wording in the PL is similar to the text previously tested during the IMFINZI

MAA. IMFINZI is administered as an IV infusion by a medical professional and it is considered that the changes are not significant enough to warrant an additional user consultation for this new indication.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The approved indication is the following:

IMFINZI in combination with gemcitabine and cisplatin as neoadjuvant treatment, followed by IMFINZI as monotherapy adjuvant treatment after radical cystectomy, is indicated for the treatment of adults with resectable muscle invasive bladder cancer (MIBC).

3.1.1. Disease or condition

The disease investigated was resectable muscle-invasive bladder cancer (MIBC), stage T2N0-1M0 to T4aN0-1M0 (corresponding to AJCC Stage II or IIIa, 8th edition) and transitional cell and mixed transitional/non-transitional cell histologies (TCC) of the bladder.

MIBC accounts for approximately 25% to 30% of newly diagnosed bladder cancer (Babjuk et al. 2019, Boccardo and Palmeri 2006, Burger et al. 2013). Even with the use of neoadjuvant chemotherapy, disease recurrence rates after radical cystectomy are still very high and occur in approximately 40% to 45% of patients within 3 years (Pfister et al. 2022). The prognosis of urothelial bladder cancer depends on multiple factors, but the TNM stage at diagnosis is the single most important prognostic factor of urinary bladder carcinoma. The 5-year overall survival for pT2 is 50%, and pT3 is 20% (Leslie SW et al. 2025). The number of positive lymph nodes is associated with increased risk of cancer-specific death (HR 1.9 for N1 disease; HR 4.3 for ≥ 2 LNs) (Tarin et al. 2012 doi: 10.1016/j.eururo.2012.01.049).

3.1.2. Available therapies and unmet medical need

According to the 2021 ESMO Clinical Practice Guideline on bladder cancer, neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy (RC) with pelvic lymph node dissection is the standard of care for resectable MIBC staged cT2-T4a, N0-1, M0 (AJCC Stage II or IIIA).

The use of platinum-based neoadjuvant chemotherapy for bladder cancer is supported by a meta-analysis of 11 randomised trials, showing a 5% absolute increase in 5-year OS and a 9% absolute increase in 5-year DFS compared with radical cystectomy alone (Advanced Bladder cancer Meta-analysis collaboration 2005 DOI: 10.1016/j.eururo.2005.04.006). Cisplatin-gemcitabine or accelerated methotrexate, vinblastine, adriamycin and cisplatin (accelerated MVAC) are the most widely given neoadjuvant regimens and the optimal number of treatment cycles to be given has not been established (2021 ESMO Clinical Guideline on bladder cancer). While neoadjuvant chemotherapy (NAC) is recommended, the evidence for adjuvant chemotherapy is weak. Adjuvant chemotherapy for patients who have received neoadjuvant chemotherapy is currently not recommended.

Although immunotherapy has been investigated in the adjuvant setting of bladder cancer, OS data are awaited and this approach is currently not recommended in the ESMO guidelines.

3.1.3. Main clinical studies

The single pivotal study for this extension of indication for durvalumab is the NIAGARA Study, an ongoing Phase III, randomised, open-label, multi-center, global study to determine the efficacy and safety of neoadjuvant durvalumab in combination with gemcitabine and cisplatin prior to radical cystectomy for MIBC, followed by adjuvant durvalumab (D + G+C arm), compared with neoadjuvant gemcitabine and cisplatin prior to radical cystectomy and no adjuvant treatment (G+C arm) (see Figure 2 Flow Chart of Study Design.

The dual primary endpoints were pathological complete response (pCR) and event free survival (EFS) assessed by BICR. The main secondary endpoints were overall survival (OS), disease free survival (DFS) and metastasis free survival (MFS). OS and OS at 5 years (OS5) were the only alpha-controlled secondary endpoints.

The study included 1063 patients randomized 1:1 (ITT).

3.2. Favourable effects

- **EFS** by BICR (EFS maturity 40.7%, second interim analysis): The durvalumab arm showed superiority with 35.1% EFS events versus 46.4% in the comparator arm (HR 0.68, 95% CI 0.558-0.817). At 36 months there is an approximately 10% difference in EFS rate in favour of durvalumab (63.7% versus 53.6%).
- **OS** (OS maturity 28.7%, second interim analysis): the durvalumab arm showed superiority for OS (HR 0.75, 95% CI 0.594-0.934). Median OS is not reached in either arm. The Kaplan-Meier curves separate at 6 months and this separation is sustained. The median duration of follow-up for OS was 42.3 months and 39.6 months in the durvalumab and control arm respectively. While OS data might be considered immature at 28.7%, OS was statistically significant at the IA analysis submitted, therefore any later OS data would be descriptive in nature.
- pCR showed no statistically significant difference in pCR rate (per central pathology review) between the two treatment arms, where a numerical difference in favour of the durvalumab-arm was observed (37.3% versus 27.5%).
- The addition of neoadjuvant durvalumab did not prevent patients from undergoing surgery, which is considered critical in this curative setting. The proportion of patients who underwent radical cystectomy was similar in both arms (88.0% in the D +G+C arm vs 83.2% in the D+G arm), and median time to radical cystectomy was almost identical (16.3 weeks vs. 16.1 weeks).

3.3. Uncertainties and limitations about favourable effects

- The benefit of durvalumab on EFS appears to be primarily driven by the prognostically worse, higher-risk subgroup of patients with clinical stage >T2N0 (n=635 patients), with an EFS HR of 0.61 (95% CI 0.477-0.778, p-value = 0.0001) in favour of durvalumab. In contrast, EFS superiority of durvalumab was not formally demonstrated in the lower-risk subgroup T2NO (n=428 patients), with an EFS HR of 0.81, (95% CI 0.595 – 1.096, p-value = 0.1694). Similarly, the positive effect of durvalumab on OS appears to be primarily driven by the > T2N0 subgroup, with an HR of 0.67 (95% CI 0.501-0.894). OS superiority (OS maturity of 28.7%) was not formally demonstrated in the T2N0 subgroup (HR 0.89; 95% CI 0.612–1.275). The differential effect of EFS and OS seen in these two stage subgroups is supported by a scientific rationale, i.e. that in the lower-risk subgroup with fewer expected events (e.g., relapse or death), durvalumab has a lower absolute risk reduction. While the benefit-risk is considered positive in both

subgroups, the differential effects in EFS and OS between clinical stage T2N0 and >T2N0 are clinically relevant for prescribers. Therefore, EFS and OS efficacy data for these two subgroups are reflected in section 5.1 of the SmPC. The MAH will present OS results for the ITT population and for both stage subgroups separately at 5 years (**REC**).

- Due to the study design, it is impossible to disentagle the contribution of durvalumab to each treatment phase. Whether neoadjuvant and/or adjuvant durvalumab are both needed is unknown based on the study. Therefore, the study results can only be discussed in the context of an overall peri-operative setting, i.e., including neoadjuvant AND adjuvant treatment for resectable MIBC.
- The benefit of durvalumab appears to be independent of PD-L1 expression, however, patient classification according to the predefined categories of PD-L1 expression was hampered due to inconsistency in measuring outcomes of the immune cell (IC) component.

3.4. Unfavourable effects

- Well-known immune-related adverse events were seen. The risk of experiencing an imAE during the overall trial period was 20.9% for patients on the durva + chemo arm compared to 3.0% for those on the chemo arm, the majority were low Grade and Grade 3 or 4 only 16 (3.0%) and 1 (0.2%) in the durva + chemo and chemo arms, respectively in the overall period.
- Increase in frequencies of SAE in the D+G+C arm compared to G+C arm (61.5% vs. 54.6%)
- AEs leading to death were similar between arms (27 in D+G+C arm vs. 29 in the G+C arm). One death was related to durvalumab as assessed by investigator.
- Higher rates of discontinuations (21.1% vs. 15.2%). The risk of any AE leading to dose modification (delay or interruption) of any study treatment was also greater in the durva + chemo arm compared to the chemo arm (57.5% vs. 47.0%) in the overall period.
- Post-surgery SAEs were more frequent in D+G+C arm.
- Increased risk of toxicity with higher age.

3.5. Uncertainties and limitations about unfavourable effects

- The reasons for not receiving adjuvant treatment were not collected prospectively in the NIAGARA trial, and were only available for 38 patients (out of 86) in which the reasons identified were not mutually exclusive. A reliable interpretation of these results was thus not possible. This could have potentially underestimated the safety and tolerability in a real-world setting, which could translate into an even lower completion rate of the perioperative regimen, particularly in older patients.

3.6. Effects Table

Table 97 Effects Table for perioperative Imfinzi in combination with gemcitabine and cisplatin for the treatment of adults with resectable MIBC (data cut-off: 29 April 2024)

Effect	Short description	Unit	Treatment D+ G + C N=533	Control G+C N=530	Uncertainties / Strength of evidence	References
Favourable Effects						

Effect	Short description	Unit	Treatment D+ G + C N=533	Control G+C N=530	Uncertainties / Strength of evidence	References
EFS (per BICR or central pathology review)	Event free survival	Median. % of patients with events having occurred	35.1% Median follow-up 34.7	46.6% Median follow-up 27.7	HR 0.68, 95% CI 0.558-0.817 (maturity 40.7%)	Section 2.4.
OS	Overall survival	Median (Months)	Not reached Median follow-up 42.3	Not reached Median follow-up 39.6	HR 0,75, 95% CI 0.594-0.934 (maturity 28.7%)	
pCR	Pathological complete response	% of patients with pCR	37.3%	27.5%	HR 1.49, 95% CI: 1.138 – 1.958	
Unfavourable Effects						
Grade 3-4	High grade AE	%	69.4	67.5	Sufficient median follow-up (~ 4years)	Section 2.5.
SAE	Serious AEs	%	61.5	54.6		
Death due to AE	AEs leading to death	%	5.1	5.5		
AEs leading to disc.	AEs leading to discontinuation	%	21.1	15.2		
ImAEs	Any immune-related AEs	%	20.9	3		
SAE post-surgery period	Serious AEs from surgery date up to 90 days	%	45.3	39.9	Overlap with adjuvant period	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The current standard of care for resectable MIBC is neoadjuvant chemotherapy followed by radical cystectomy. Stage at diagnosis is the single most important prognostic factor and the reported 5-year overall survival for stage T2 and T3 is 50% and 20% respectively. There is thus a high unmet medical need in this patient population.

The addition of neoadjuvant durvalumab to gemcitabine and cisplatin in adults with resectable MIBC, followed by adjuvant durvalumab monotherapy after radical cystectomy led to a statistically significant improvement in EFS of 11.3% at DCO (EFS maturity of 40.7%). The second interim analysis of OS is supportive hereof, with an HR of 0.75 in favour of durvalumab (OS maturity of 28.7%). While OS data might be considered immature at 28.7%, OS was statistically significant at the IA analysis submitted, therefore any later OS data would be descriptive in nature. The difference in EFS is greatest in the

prognostically worse, higher-risk subgroup with clinical stage >T2N0 subgroup (n=635) with an HR of 0.60, 95% CI: 0.472 – 0.770, and is present, but less pronounced, in the prognostically better, lower-risk T2N0 subgroup (n=428) with an HR of 0.81, 95% CI: 0.594 – 1.096. EFS and OS efficacy data for these subgroups are included in Section 5.1 of the SmPC. The MAH will present OS results for the ITT population and for both stage subgroups separately at 5 years (**REC**).

Results were also favourable for the pre-planned subgroup with borderline renal function (18% of ITT), although more uncertain due to a broad confidence interval.

The study was not able to identify PD-L1 expression as a predictive biomarker of treatment effect of durvalumab.

Other secondary objectives also favoured the experimental arm, and subgroup and sensitivity analyses were in general consistent with the main study results.

Several protocol amendments were implemented once the study was ongoing, and these modified (among others) the study population, the number of events needed for final analysis and censoring rules. However, the MAH has adequately explained how bias from these amendments was prevented, and these justifications are considered acceptable. Sensitivity analyses support the robustness of the efficacy results.

The toxicity profile of durvalumab has been extensively investigated in several trials. In the NIAGARA study, the addition of durvalumab to gemcitabine and cisplatin as neoadjuvant treartment, led to higher rates of grade 3/4 AE, serious events, discontinuations, immune-mediated AE and serious post-surgery complications. The trend of increased toxicity with higher age is noted, emphasizing the need for careful selection of patients with MIBC who could benefit from this preoperative regimen. Section 4.8 of the SmPC includes a statement that data on safety for patients 75 years and older are too limited to draw a conclusion on this population, and the NIAGARA study has been reflected in this statement. No new safety concerns were identified in the NIAGARA study.

3.7.2. Balance of benefits and risks

Overall, the NIAGARA study relevantly addresses the unmet medical need in the population investigated, showing a benefit in EFS, which is considered clinically meaningful and which is supported by positive OS results. The study design does not allow for a distinction between the contribution of the neoadjuvant versus adjuvant durvalumab to the treatment effect and therefore the study results can only be discussed in the context of an overall peri-operative setting, i.e., including neoadjuvant AND adjuvant treatment for resectable MIBC. No new safety concerns were identified, and the toxicity of durvalumab in combination with chemotherapy reported in the NIAGARA trial is overall consistent with the already known safety profile of durvalumab.

3.8. Conclusions

The overall B/R of durvalumab in combination with gemcitabine and cisplatin as neoadjuvant treatment, followed by durvalumab as monotherapy adjuvant treatment after radical cystectomy for the treatment of adults with resectable MIBC is considered positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus, 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 and IIIB

Extension of indication to include IMFINZI in combination with gemcitabine and cisplatin as neoadjuvant treatment, followed by IMFINZI as monotherapy adjuvant treatment after radical cystectomy, for the treatment of adults with resectable muscle invasive bladder cancer (MIBC), based on an ongoing pivotal study D933RC00001 (NIAGARA); this is a phase 3, randomized, open-label, multi-center, global study to determine the efficacy and safety of durvalumab in combination with gemcitabine + cisplatin for neoadjuvant treatment followed by durvalumab alone for adjuvant treatment in patients with muscle-invasive bladder cancer. As a consequence, sections 4.1, 4.2, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly. The RMP version 13.2 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes and update the PI according to the Excipients Guideline.

Amendments to the marketing authorisation

5. In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Imfinzi-H-C-004771-II-0073'

Attachments

1. SmPC, Package Leaflet (changes highlighted) of IMFINZI, with changes highlighted as adopted by the CHMP on 22 May 2025.

Appendix