14 October 2021
EMA/CHMP/618201/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lenvima

International non-proprietary name: lenvatinib

Procedure No. EMEA/H/C/003727/II/0042

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

ADA	Antidrug antibody
AE	Adverse event(s)
AEOSI	Adverse events of special interest
BICR	Blinded Independent Central Review
CHMP	Committee for Medical Products for Human Use
CI	Confidence interval
CR	Complete response
CSAE	Clinically Significant Adverse Event(s)
DDI	Drug-drug interaction
dMMR	Defective mismatch repair
DOR	Duration of response
DTC	Differentiated thyroid cancer
EC	Endometrial carcinoma
EMA CHMP	European Medicines Agency: Committee for Medicinal Products for Human Use
ESGO	European Society of Gynaecological Oncology
ESP	European Society of Pathology
ESTRO	European Society for Radiotherapy and Oncology
EU	European Union
FDA	US Food and Drug Administration
FGFRs	Fibroblast growth factor receptors
HCC	Hepatocellular carcinoma
HNSCC	Head and neck squamous cell carcinoma
IA1	First interim analysis
IFN	Interferon
IL-2	Interleukin-2
IND	Investigational New Drug
ITT	Intent-to-treat population
IV	Intravenously
KIT	Receptor tyrosine kinase type III
LC-MS/MS	Liquid chromatography-tandem mass spectrometry/mass spectrometry

mAb	Monoclonal antibody
MMR	Mismatch repair status
MSI-H	Microsatellite instability - high
NMSP	No specific molecular profile
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PDGFRα	Platelet derived growth factor receptor alpha
PD-1	Programmed death 1 receptor
PD-L1	Programmed death, ligand 1
PD-L2	Programmed death, ligand 2
PFS	Progression-free survival
PK	Pharmacokinetic(s)
pMMR	Mismatch repair proficient
POLE	DNA polymerase epsilon
PR	Partial response
qd	Once daily
RCC	Renal cell carcinoma
RSD	Reference safety data
RTK	Receptor tyrosine kinase
sBLA	Supplemental biologic license application
sNDA	Supplemental new drug application
Study 111/KEYNOTE-146	Eisai study number E7080-A001-111/Merck Study number KEYNOTE-146
Study 309/KEYNOTE-775	Eisai study number E7080-G000-309/Merck Study number KEYNOTE-775
TAM	Tumor-associated macrophage
TNFα	Tumor necrosis factor-α
TKI	Tyrosine kinase inhibitor
TPC	Treatment of physician’s choice
US	United States
VEGFR	Vascular endothelial growth factor receptor

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eisai GmbH submitted to the European Medicines Agency on 10 March 2021 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 lenvatinib in combination with pembrolizumab for the treatment of adult patients with advanced endometrial carcinoma (EC) who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation; as a consequence, sections 4.1, 4.2, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 14.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to make minor editorial changes to the SmPC and update the list of local representatives in the Package Leaflet in line with the latest QRD template version 10.2.

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 EMA Decisions P/0210/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0210/2020 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the 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.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 9 November 2017 (EMEA/H/SA/1375/6/2017/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: Karin Janssen van Doorn Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	10 March 2021
Start of procedure:	27 March 2021
CHMP Rapporteur Assessment Report	26 May 2021
PRAC Rapporteur Assessment Report	27 May 2021
PRAC Outcome	10 June 2021
CHMP members comments	14 June 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 June 2021
Request for supplementary information (RSI)	24 June 2021
CHMP Rapporteur Assessment Report	24 August 2021
CHMP members comments	6 September 2021
Updated CHMP Rapporteur Assessment Report	10 September 2021
2nd Request for supplementary information (RSI)	16 September 2021
CHMP Rapporteur Assessment Report	29 September 2021
CHMP members comments	4 October 2021
Updated CHMP Rapporteur Assessment Report	8 October 2021
Opinion	14 October 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Carcinoma of the uterine corpus, often called endometrial cancer is the sixth most common cancer among women worldwide. In 2021, an estimated 66,570 new cases are expected to be diagnosed and

approximately 12,940 women are expected to die of uterine cancer in the US, including EC and uterine sarcoma. In Europe, the estimated number of new cases and deaths from EC in 2018 were 121,600 and 26,000, respectively.

The MAH applied for an extension of indication for lenvatinib in combination with pembrolizumab in second line endometrial carcinoma patients:

"LENVIMA in combination with pembrolizumab is indicated for the treatment of adult patients with advanced endometrial carcinoma (EC) who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation (see section 5.1)."

Finally approved indication:

"LENVIMA in combination with pembrolizumab is indicated for the treatment of adult patients with advanced or recurrent endometrial carcinoma (EC) who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and are not candidates for curative surgery or radiation.'

Epidemiology and risk factors, screening tools/prevention

Adenocarcinoma of the endometrium (lining of the uterus) is the most common histologic type of uterine cancer. Endometrial adenocarcinomas are often classified into 2 histologic categories — Type 1 or Type 2. Type 1 tumors are more common and less aggressive, accounting for 70% to 80% of new cases, with endometrioid histology being the most common. In contrast, Type 2 tumors typically have a poorer prognosis and are not clearly associated with estrogen stimulation. These tumors consist of higher-grade adenocarcinomas and often have nonendometrioid histologies (eg, clear cell and serous cell types). In the recurrent setting, high-grade, aggressive tumors like serous and clear cell become more prevalent.

Biologic features

A recent finding has been the identification of tumors with shortening or lengthening of small repetitive elements in DNA, a condition called microsatellite instability. Microsatellite instability is a result of the inability of DNA mismatch repair enzymes to repair random mutations leading to tumorigenesis. The majority of patients (approximately 85%) with previously treated EC will have tumors that are not MSI-H or dMMR.

Clinical presentation, diagnosis and stage/prognosis

The prognosis for EC is significantly influenced by disease stage. At diagnosis, 67% have localized disease, while 21% have regional disease, and approximately 9% have distant metastases Patients with localized disease have a 5-year survival rate of 95%, whereas those with regional and distant metastatic disease have 5-year survival rates of 69% and 16.8%, respectively. Despite the favorable outcomes associated with early detection, approximately 20% of EC cases recur with poor prognosis. The population of patients with recurrent EC represents a heterogeneous mix of different histological subtypes and grades, stages at initial diagnosis, prior therapy, duration of recurrence-free intervals, and site(s) of recurrence (distant or local). In general, the prognosis is dismal for women diagnosed with advanced or recurrent disease, with a median survival of only 12 months.

Management

Treatment of EC may vary depending on the grade, histology, stage of the disease, and MSI/MMR status. Currently, the mainstay of first-line treatment of EC is surgery with hysterectomy and bilateral salpingo-oophorectomy, with or without radiotherapy and/or chemotherapy. Per NCCN guidelines, platinum-based chemotherapy is the standard first-line systemic therapy for patients with metastatic, recurrent, or high-risk disease. Some subgroups of patients based on molecular profiling may benefit less from chemotherapy, as suggested by a retrospective analysis on the PORTEC-3 study including dMMR tumors that demonstrated worse outcomes compared with pMMR tumors (POLE-mutated and NSMP).

The ESGO/ESTRO/ESP guidelines for the management of patients with advanced EC includes the following guidance for the systemic treatment of EC:

- The standard first-line chemotherapy is carboplatin with paclitaxel.
- There is no standard of care for second-line chemotherapy. Doxorubicin and paclitaxel are considered the most active therapies. In patients with a long platinum-free interval, reintroduction of platinum can be considered.
- Anti-PD-1-based immune therapy with pembrolizumab could be considered for second line therapy of MSI-high/dMMR carcinomas.
- The combination of pembrolizumab and the multi-tyrosine-kinase inhibitor lenvatinib could be considered for second-line treatment of microsatellite-stable carcinomas. However, its use may be limited due to regulatory approvals or reimbursement in different countries. Clinical study participation should be offered to all patients with disease relapse.

Before the combination of lenvatinib plus pembrolizumab received accelerated or equivalent approval in 2019 in the US, Australia, and Canada for treatment of advanced EC that is not MSI-H or dMMR, there was no approved therapy or generally accepted standard treatment approach for second-line EC. Pembrolizumab as monotherapy is approved in several countries since 2017 for a select subset of patients with MSI-H or dMMR solid tumors including those with EC. Dostarlimab as monotherapy received a positive CHMP opinion on 25 February 2021 for the treatment of adult patients with recurrent or advanced mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) endometrial cancer (EC) that has progressed on or following prior treatment with a platinum containing regimen.

Cytotoxic chemotherapy is the de facto second-line treatment for advanced EC despite being associated with low response rates (≤15%), short PFS (4 months), and substantial toxicity resulting in poor overall survival and quality of life. While pembrolizumab monotherapy received accelerated approval or equivalent in some countries for MSI H/dMMR solid tumors including EC, this was based on the results of KEYNOTE 158, a Phase 2, single-arm study; therefore, improvement in OS compared with other therapies used in these patients, including chemotherapy has not been evaluated.

Updated results of KEYNOTE-158 (data cut-off date 05 October 2020) in participants with advanced EC with dMMR tumors demonstrated that the ORR was 48.1%, the CR rate was 13.9%, and the median PFS seen with pembrolizumab monotherapy was 13.1 months, however, approximately 30% of participants experienced a PFS event at 3 months, illustrating the aggressive nature of previously treated EC.

2.1.2. About the product

Lenvatinib is a TKI active against both VEGFR, VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4) and FGFR, FGFR1, 2, 3, and 4. Lenvatinib also inhibits other RTKs that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including the PDGFRα, KIT, and RET.

Lenvatinib has been approved in the EU for the treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer (RR-DTC) and hepatocellular carcinoma (HCC) under the tradename Lenvima and under the tradename Kisplyx for advanced and/or metastatic renal cell carcinoma (RCC; 2nd line).

Pembrolizumab has been approved in the EU as monotherapy for the treatment of patients with melanoma (stage III, advanced or metastatic), non-small cell lung carcinoma, relapsed or refractory classical Hodgkin lymphoma, locally advanced or metastatic urothelial carcinoma, recurrent or metastatic head and neck squamous cell carcinoma and metastatic microsatellite-instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (see EPAR Keytruda).

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

The MAH received Scientific advice from the CHMP on 9 November 2017 (EMEA/H/SA/1375/6/2017/II). This Scientific advice pertained to clinical development aspects of the dossier.

- The CHMP suggested to include ECOG PS2 patients, as inclusion of only patients with ECOG PS 0 or 1 would preclude a significant number of real-world endometrial cancer patients being treated in second-line setting. This was however not followed. As discussed below, the inclusion/exclusion criteria of KEYNOTE-775 study reflect only the fitter subpopulation with diagnosis of advanced endometrial carcinoma.

- PFS did not seem acceptable as a primary endpoint. Given the dismal prognosis of this condition and considering that no further efficient options would confound OS, there are no reasons to justify using PFS for a decision if an effect on OS is not established. In this study, PFS and OS are dual primary. Within this submission, both PFS and OS reached statistical significance at IA1.

- With regard to contribution of each component, the provided information at that time seem to support the hypothesis of synergism; the proposed study and with an outcome of positive risk-benefit would in principle support a MAA, provided the guidance for one pivotal trial applications is respected.

2.1.4. General comments on compliance with GLP

The additional pharmacodynamics studies were not performed in compliance with GLP, which is considered acceptable in line with the ICH guidelines.

2.2. Non-clinical aspects

2.2.1. Introduction

To support this submission for lenvatinib in combination with pembrolizumab, four *in vivo* primary pharmacodynamics studies conducted with lenvatinib, rat anti-murine programmed cell death 1 (PD-1) monoclonal antibody (mAb), clone RMP1-14, as a surrogate antibody for pembrolizumab, and the combination of lenvatinib with anti-PD-1 mAb were submitted. The following *in vivo* primary pharmacodynamic studies were submitted:

• Antitumor activity in combination with anti-PD-1 mAb in the RAG murine RCC, LL/2 murine Lewis lung carcinoma, Hepa1-6 murine HCC, and CT26 murine colon carcinoma isograft models

• Effects of lenvatinib in combination with anti-murine PD-1 mAb on the populations of tumour-associated macrophages and cytotoxic T cells in the tumour microenvironment in a murine tumour isograft model

• Effects of CD8+ T-cell depleting anti-murine CD8α mAb on the antitumor activity of lenvatinib in murine tumour isograft models

• Effects of interferon-γ (IFN- γ) neutralizing anti-murine IFN-γ mAb on the antitumor activity of lenvatinib and lenvatinib in combination with anti-murine PD-1 mAb in a murine tumour isograft model.

2.2.2. Pharmacology

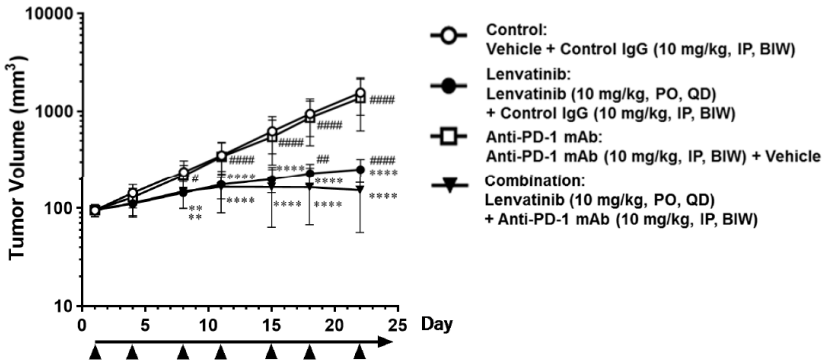
Primary pharmacodynamic studies

1) Antitumor Activity of Lenvatinib in Combination with Anti-Murine PD-1 mAb in the RAG Murine Renal Cell Carcinoma Isograft Model

Table 1: Antitumor Activity of Lenvatinib in Combination with Anti-Murine PD-1 mAb in the RAG Murine Renal Cell Carcinoma Isograft Model

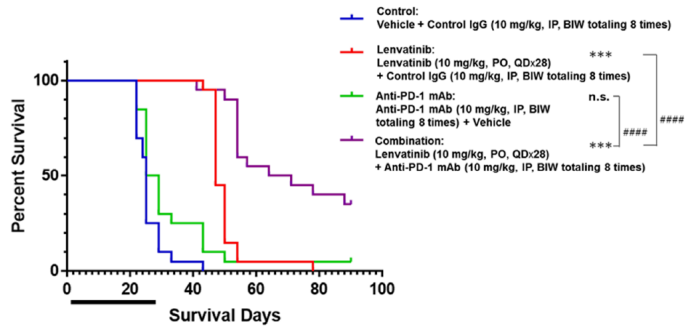
Type of Study	Methods	Species/ Strain	Number/ Gender	Route	Dose or Concentration	Observations	Study/ Report No.
Antitumor activity in murine cancer isograft model	Isografts were generated by SC inoculation of the murine cancer cells into immunocompetent mice. Dosing was initiated after 7 days. The TV and the body weight of mice were measured once or twice per week until Day 90.	Mouse/ BALB/c AnNCrlCrlj Mouse/ RAG (RCC)	20 female / group	lenvatinib: PO, QD×28 anti-PD-1 mAb: IP, twice per week totaling 8 times	lenvatinib: 10 mg/kg anti-PD-1 mAb: 10 mg/kg	Lenvatinib and lenvatinib in combination with anti-PD-1 mAb showed significant TGI and prolonged survival compared to control group, and the TGI and prolonged survival of the combination was significantly greater than that of each monotherapy. Severe BWL was not noted in any treated groups on Days 1 – 28. Median survival times of control, lenvatinib, anti-PD-1 mAb, and the combination groups were 25, 47, 27, and 67.5 days, respectively.	M18018

Figure 1. Antitumor Activity of lenvatinib in combination with Anti-PD-1 mAb Against the RAG Murine RCC Isografts



Each point represents the mean ±SD of 20 animals. Horizontal arrow signifies the dosing period for lenvatinib. The ▲ signifies the dosing day of anti-PD-1 mAb or control IgG. BIW = twice per week, IgG = immunoglobulin G, mAb = monoclonal antibody, QD = once daily, RCC = renal cell carcinoma. ***P*<0.01, *****P*<0.0001 versus control group (repeated measures ANOVA followed by Dunnett type multiple comparison test after logarithmic transformation). #*P*<0.05, ##*P*<0.01, ####*P*<0.0001 versus combination group (repeated measures ANOVA followed by Dunnett type multiple comparison test after logarithmic transformation). Source: Study No. M18018.

Figure 2. Survival of Mice Following Treatment with lenvatinib in Combination with Anti-PD-1 mAb in the RAG Murine RCC Isograft Model



Each line represents the percent survival of 20 animals per group through Day 90. The horizontal bar signifies the dosing period of lenvatinib and anti-PD-1 mAb. A total of 66 mice were euthanized on Days 22 – 90 because their TV was >2000 mm^3. In the control group, 3/20 mice were found dead on Days 24 – 25. In the combination group, 2/20 mice were found dead on Days 41 and 54, and 1/20 mice was euthanized on Day 78 due to hemorrhage-related tumor rupture. BIW = twice per week, IgG = immunoglobulin G, mAb = monoclonal antibody, n.s. = not significant, QD×28 = once daily for 28 days, RCC = renal cell carcinoma, TV = tumor volume. ****P*<0.001 versus control (log-rank test with Bonferroni's correction), n.s. versus control (log-rank test with Bonferroni's correction). ####*P*<0.0001 versus combination (log-rank test). Source: Study No. M18018.

Comparable results were obtained when evaluating the antitumour activity of lenvatinib in combination with anti-Murine PD-1 mAb in the **LL/2 (LLC1) Murine Lewis Lung Carcinoma Isograft Model and in an the Hepa1-6 Murine HCC Isograft Model (data not shown).**

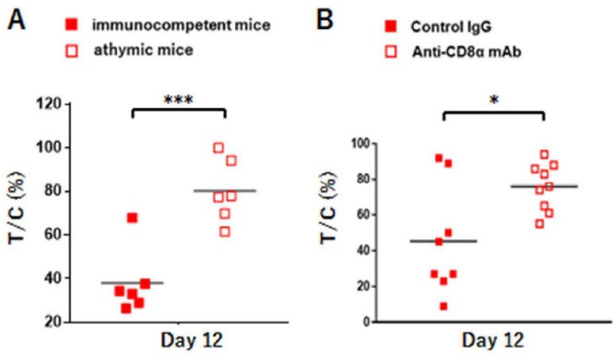
2) Antitumor and Immunomodulatory Activity of Lenvatinib in the CT26 Murine Colon Carcinoma Isograft Model

Table 2: Antitumor and Immunomodulatory Activity of Lenvatinib in the CT26 Murine Colon Carcinoma Isograft Model

Antitumor and immuno-modulatory activity in murine cancer isograft model	(Exp. 1-1) Isografts were generated by SC inoculation of the murine cancer cells into immunocompetent or athymic mice. Dosing was initiated when the respective mean TV was 80 or 77 mm^3 (Day 1). The TV was measured on Day 12. (Exp. 1-2). Isografts were generated by SC inoculation of the murine cancer cells into immunocompetent mice. Six days after the cancer cell inoculation, control IgG or anti-CD8α mAb was injected twice per week. After a further 2 days, dosing with lenvatinib was initiated (Day 1). The TV was measured on Day 12.	Mouse/ BALB/c AnNCrlCrlj, CAnN.Cg-*Foxn1*^{nu}/ CrlCrlj Mouse/ CT26 (colon carcinoma)	6 female / group (Exp.1-1) 8 or 9 female / group (Exp.1-2)	lenvatinib PO, QD×11 control IgG (rat IgG2b) or anti-murine CD8α mAb: twice per week totaling 4 times (Exp.1-2)	lenvatinib: 10 mg/kg control IgG (rat IgG2b) or anti-murine CD8α mAb: 200 μg/animal (Exp.1-2)	(Exp. 1-1) Lenvatinib showed TGI against the isografts in immunocompetent mice with mean T/C of 38% on Day 12. The TGI in athymic mice (mean T/C = 80% on Day 12) was significantly lower than that in the immunocompetent mice. (Exp. 1-2) Lenvatinib showed TGI against the isografts in immunocompetent mice injected with control IgG with mean T/C of 45% on Day 12. The TGI was significantly reduced in the mice injected with anti-CD8α mAb with mean T/C = 76% on Day 12.	Kato, et al., 2019 W-20190067
	(Exp. 2-1) Isografts were generated by SC inoculation of the murine cancer cells into immunocompetent mice. Dosing was initiated when mean TV was 33 mm^3 (Day 1). The TV and the body weight of mice were measured twice per week. (Body weight data are reported in Study No. W-20190067) (Exp. 2-2) Isografts were generated by SC inoculation of the murine cancer cells into immunocompetent mice. Dosing was initiated on Day 1, and tumors were resected on Day 8. Immune cell populations were analyzed by flow cytometer. TAM, IFN-γ$^+$CD8$^+$ T cells, and GzmB$^+$CD8$^+$ T cells were identified as CD45$^+$CD11b$^+$Ly6G$^-$Ly6C$^-$ F4/80$^+$, CD45$^+$CD3$^+$CD8$^+$ IFN-γ$^+$, and CD45$^+$CD3$^+$CD8$^+$GzmB$^+$, respectively.	Mouse/ BALB/c AnNCrlCrlj, Mouse/ CT26 (colon carcinoma)	8 female / group (Exp.2-1) 6 female / group (Exp.2-2)	lenvatinib: PO, QD×25 for monotherapy, QD×28 for combination therapy (Exp. 2-1) PO, QD×7 (Exp. 2-2) anti-PD-1 mAb: IP, Q3D×7 for monotherapy, Q3D×10 for combination-therapy (Exp.2-1) IP, Q3D×2 (Exp.2-2)	lenvatinib: 10 mg/kg anti-PD-1 mAb: 200 μg/animal	(Exp. 2-1) Lenvatinib and anti-PD-1 mAb monotherapies showed significant TGI compared with the vehicle control. The TGI of the combination of lenvatinib and anti-PD-1 mAb was greater than that of each monotherapy on Day 19. Severe BWL was not noted in any treated group. (Exp. 2-2) The population of TAM was significantly decreased, and the populations of IFN-γ$^+$CD8$^+$ T cell and GzmB$^+$CD8$^+$ T cell were significantly increased in the tumors of both lenvatinib monotherapy and the combination therapy compared with those of vehicle-control. The GzmB$^+$CD8$^+$ T cell population expressing a cytotoxic enzyme, GzmB, was significantly increased following treatment with the combination compared with that of lenvatinib monotherapy.	
	(Exp. 3) Isografts were generated by SC inoculation of the murine cancer cells to immunocompetent mice. After 8 days (Day 1), control IgG or anti-IFN-γ mAb was injected on Days 1, 5, 8, 12, and 15. Dosing was initiated on Day 2. The TV was measured 2 or 3 times per week.	Mouse/ BALB/c AnNCrlCrlj, Mouse/ CT26 (colon carcinoma)	7 female / group	lenvatinib: PO, QD×14 anti-PD-1 mAb: IP, twice per week totaling 4 times control IgG (rat IgG1) or anti-IFN-γ mAb: IP, Days 1, 5, 8, 12, and 15	lenvatinib: 10 mg/kg anti-PD-1 mAb: 200 μg/animal control IgG (rat IgG1) or anti-IFN-γ mAb: 300 μg/animal	(Exp. 3) Lenvatinib, anti-PD-1 mAb, and their combination showed TGI in the isograft models injected with control IgG. The TGI of lenvatinib monotherapy and the combination was significantly decreased in mice injected with anti-IFN-γ mAb. The TGI of anti-PD-1 mAb monotherapy was not affected. These results suggested that the IFN-γ signaling contributed to the antitumor activity of lenvatinib and the combination of lenvatinib and anti-PD-1 mAb.	

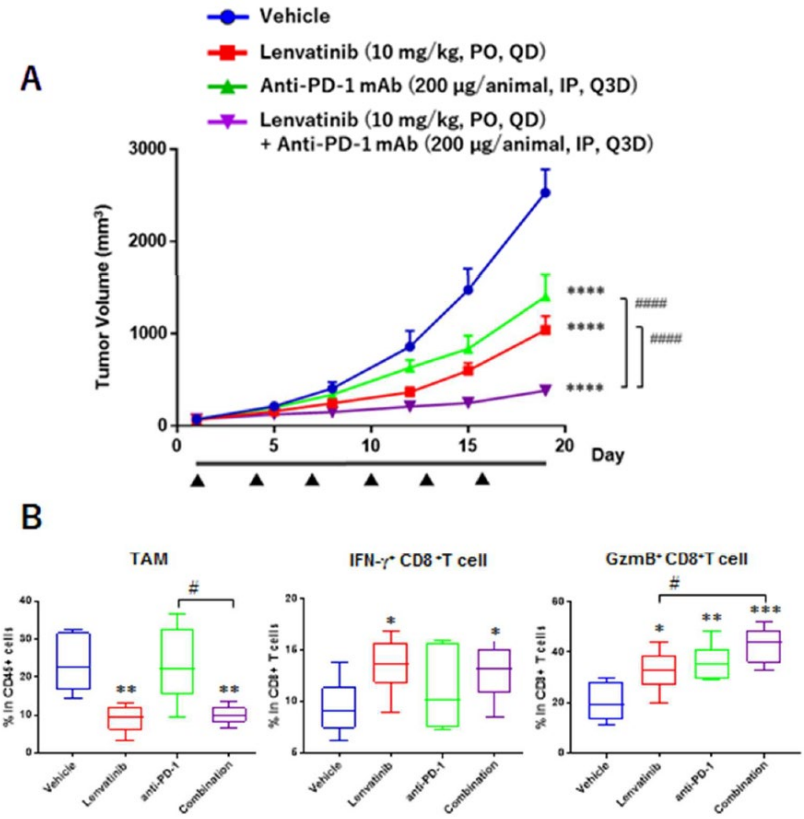
Doses described for lenvatinib are expressed as those of the salt form.
anti-CD8α mAb = rat anti-murine CD8α mAb, anti-IFN-γ mAb = rat anti-murine IFN-γ mAb, anti-PD-1 mAb = rat anti-murine PD-1 mAb, BWL = body weight loss, Exp. = experiment, HCC = hepatocellular carcinoma, IFN-γ = interferon-γ, IgG = immunoglobulin G, IP = intraperitoneal, mAb = monoclonal antibody, PD-1 = programmed cell death 1, QD×X = once daily for X days, QnD×m = once every n days totaling m times, RCC = renal cell carcinoma, TAM = tumor associated macrophage, T/C = treatment/control, TGI = tumor growth inhibition, TV = tumor volume.

Figure 3. Antitumor and Immunomodulatory Activity of Lenvatinib Against the CT26 Murine Colon Carcinoma Isografts in Immunocompetent Mice



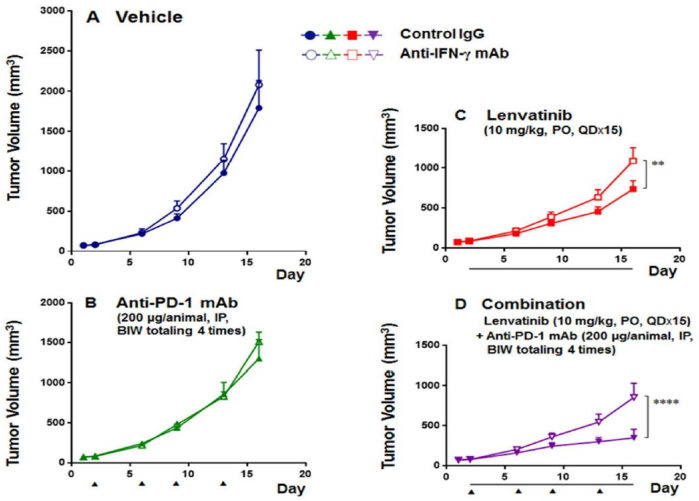
A: Antitumor activity of lenvatinib (10 mg/kg PO, QD×11) against the isografts in immunocompetent and athymic mice.
B: Effect of prior and concomitant injection with $CD8^+$ T cell-depleting antibody on antitumor activity of lenvatinib (10 mg/kg PO, QD×11) against isografts in immunocompetent mice.
Each symbol shows individual T/C (%), and each line shows the mean of 6 animals (A), or 8 animals (control IgG) or 9 animals (anti-CD8α mAb) (B). IgG = immunoglobulin G, mAb = monoclonal antibody, QD×11 = once daily for 11 days, T/C = treatment/control.
*P<0.05, ***P<0.001 (unpaired t test). Source: Kato, et al., 2019.

Figure 4. Antitumor and Immunomodulatory Activity of Lenvatinib in Combination With Anti-PD-1 mAb Against the CT26 Murine Colon Carcinoma Isografts



A: Tumor growth curves. Each point represents the mean +SEM of 8 animals. The horizontal bar signifies the dosing period for lenvatinib. The ▲ signifies the day of dosing of the anti-PD-1 mAb. mAb = monoclonal antibody, QD = once daily, Q3D = once every 3 days. ****P<0.0001versus vehicle control on Day 19 (repeated measures ANOVA followed by Dunnett type multiple comparison test), ####P<0.0001 versus the combination on Day 19 (repeated measures ANOVA followed by Dunnett type multiple comparison test). B: Box-and-whisker plot of changes in the populations for TAM, IFN-γ$^+$CD8$^+$ T cells, and GzmB$^+$CD8$^+$ T cells in tumor on Day 8. Lenvatinib (10 mg/kg) was administered orally once daily for 7 days, and anti-PD-1 mAb was administered intraperitoneally once every 3 days totaling 2 times. The center-line is the median value of 6 animals, the edges of the boxes are the 25th and 75th percentiles, and the extremes are the range of the data. GzmB = granzyme B, IFN-γ = interferon-γ, mAb = monoclonal antibody, TAM = tumor-associated macrophage. *P<0.05, **P<0.01, ***P<0.001 versus vehicle control (unpaired t test), #P<0.05 versus the combination (unpaired t test). Source: Kato, et al., 2019.

Figure 5. Effects of Prior and Concomitant Injection of IFN-γ Neutralizing Antibody on the Antitumor Activity of Lenvatinib in Combination with Anti-PD-1 mAb Against the CT26 Murine Colon Carcinoma Isografts



Each point represents the mean +SEM of 7 animals. The horizontal bar signifies the dosing period for lenvatinib. The ▲ signifies the day of dosing of anti-PD-1 mAb. BIW = twice per week, IFN-γ = interferon-γ, IgG = immunoglobulin G, mAb = monoclonal antibody, QD×14 = once daily for 14 days. $^{**}P<0.01$, $^{****}P<0.0001$ versus control IgG (repeated measures ANOVA followed by Dunnett type multiple comparison test). Source: Kato, et al., 2019.

2.2.3. Ecotoxicity/environmental risk assessment

Based on previous environmental risk assessments (ERA), lenvatinib has not been identified as a PBT (persistent, bioaccumulative and toxic) or a vPvB substance (very persistent and bioaccumulative) and there are no environmental concerns expected for lenvatinib.

An additional ERA was performed to evaluate the potential environmental risk ($PEC_{SURFACEWATER}$) from the use of lenvatinib for the additional indication of second line EC, as well as for different combinations of indications. The individual $PEC_{SURFACEWATER}$ value of lenvatinib for second line EC is below the action limit of 0.01 µg/L. Based on worst-case assumptions for patient populations eligible for treatment, the total of the lenvatinib $PEC_{SURFACEWATER}$ values for all the indications (RR-DTC, HCC, 1L or 2L RCC & 2L EC) just exceeds the action limit of 0.01 µg/L. However, refining the calculation for the patient population eligible for 2nd line treatment for EC resulted in $PEC_{SURFACEWATER}$ values below the action limit for all combinations. In conclusion, lenvatinib is unlikely to represent a risk for the environment when used in accordance with the Summary of Product Characteristics.

2.2.4. Discussion on non-clinical aspects

Lenvatinib is an oral multiple RTK inhibitor that selectively inhibits the kinase activities of VEGF receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other proangiogenic and oncogenic pathway-related RTKs including FGF receptors FGFR1, 2, 3, and 4; the PDGF receptor PDGFRα; KIT; and RET. *In vivo* human tumour xenograft studies in athymic mice have shown that lenvatinib exerts antitumor activity against various tumour types including RCC, thyroid cancer, HCC, non-small cell lung cancer, melanoma, colorectal cancer, gastric cancer, and ovarian cancer, mainly through its potent inhibition of tumour angiogenesis driven by VEGFR and FGFR signalling.

The new non-clinical studies conducted with lenvatinib investigated the antitumor activity of lenvatinib and the combination of lenvatinib with an anti-PD-1 mAb (used as a surrogate antibody for pembrolizumab), in murine tumour isograft models of RCC, HCC, colon carcinoma and lung carcinoma. No non-clinical studies were performed in murine model of endometrial cancer, but this is considered acceptable in line with ICH S9. In addition, the immunomodulatory activity of lenvatinib in murine tumour isograft models using immunocompetent mice and athymic mice was investigated to determine the effects of lenvatinib on the host immune systems in the tumour microenvironment.

Lenvatinib (10 mg/kg) in combination with anti-PD-1 mAb (10 mg/kg, 200 µg/animal, or 500 µg/animal) showed significant tumour growth inhibition compared to the control group against the isografts of RAG murine RCC, LL/2 murine Lewis lung carcinoma, Hepa1-6 murine HCC, and CT26 murine colon carcinoma in immunocompetent mice. Lenvatinib monotherapy and lenvatinib in combination with anti-PD-1 mAb showed inhibition of tumour growth, however, the antitumor activity of the combination of lenvatinib and anti-PD-1 mAb was only slightly greater than that of lenvatinib monotherapy in every model investigated. Severe body weight loss (i.e., >20% compared to the initial day of dosing) was not noted for any treatment groups in these models.

Lenvatinib showed greater antitumor activity in immunocompetent mice than in athymic mice in the Hepa1-6 and CT26 isograft models, and antitumor activity in immunocompetent mice was significantly decreased by $CD8^+$ T-cell depletion with the prior and concomitant injection of an anti-CD8α mAb in both models. Flow cytometric analysis revealed that the population of tumour-associated macrophages in the tumour microenvironment was significantly decreased and populations of IFN-γ^+CD8^+ T cells and granzyme B^+CD8^+ T cells (both considered activated cytotoxic T cells) were significantly increased in the groups treated with lenvatinib and lenvatinib plus anti- PD-1 mAb. However, these experiments could not convincingly demonstrate an additive effect of anti-PD-1 treatment to the lenvatinib monotherapy.

In addition, the antitumor activity of lenvatinib as well as lenvatinib plus anti-PD-1 mAb was significantly reduced by the prior and concomitant injection of an IFN-γ neutralizing anti-murine IFN-γ mAb, but the antitumor activity of anti-PD-1 mAb monotherapy was not changed by anti-IFN-γ mAb in this model.

These results suggested that in addition to its anti-angiogenesis activity, the immunomodulatory activity of lenvatinib involving the decrease of immunosuppressive tumour-associated macrophages, increase of activated cytotoxic T cells, and an activation of IFN-γ signalling contributes to its antitumor activity in immunocompetent mice.

No new PK or toxicology studies were conducted with lenvatinib or pembrolizumab to support this application, which is considered acceptable based on the available clinical data on lenvatinib and pembrolizumab.

No formal drug-drug interaction studies have been conducted with lenvatinib and pembrolizumab. However, since pembrolizumab is enzymatically catabolized to individual amino acids while lenvatinib is cleared via aldehyde oxidase and cytochrome P450 mediated metabolism, as well as spontaneous hydrolysis, no metabolic drug interactions are expected.

Because pembrolizumab was well tolerated in chronic toxicity studies, the potential of a toxicologic interaction with lenvatinib is considered low.

The toxicities observed with the two agents were consistent with their respective mechanisms of action, and the combination of lenvatinib plus an anti-PD-1 mAb (surrogate for pembrolizumab) was well tolerated when studied in mouse isograft models. No significant mortality or body weight loss was observed in these studies.

In the chronic toxicity studies in rats and cynomolgus monkeys with lenvatinib, target organ toxicity was primarily observed in the kidneys, gastro-intestinal tract, artery/arteriole in various organs, bone, and

male and female reproductive organs (testis and ovary) in both species, and in the incisor and adrenals in rats. All these findings were expected, as similar findings have already been reported in animals treated with receptor tyrosine kinase inhibitors and are considered related to the pharmacologic (antiangiogenic) effects of lenvatinib. These findings were reversible and most were not evident at the end of a recovery period of 4 weeks. The no observed adverse effect levels (NOAELs) for the 26- and 39-week toxicity studies in rats and cynomolgus monkeys, respectively, were the lowest doses tested in those studies (0.4 and 0.1 mg/kg, respectively). The exposure margins at the NOAELs based on systemic exposure (area under the concentration-time curve from time zero to 24 hours; $AUC_{(0-24)}$) compared to exposures at the maximum recommended human dose (24 mg) were 0.7- to 0.8-fold in rats and 0.1-fold in monkeys.

Overall, the clinical adverse effect profiles of both agents have been well characterized in the various clinical trials conducted with each agent. In addition, the efficacy, safety and tolerability of lenvatinib in combination with pembrolizumab is being evaluated in completed/ongoing clinical studies (KEYNOTE-146 and KEYNOTE-523 Phase 1b studies in subjects with solid tumours including EC, KEYNOTE-581 Phase 3 in advanced RCC, KEYNOTE-775 Phase 3 study in subjects with EC). Additional data for the ERA regarding the prevalence of the disease population targeted by the second line EC, as well as for different combinations of indications were provided. Based on the updated data submitted in this application, the new indication does not lead to a significant increase in environmental exposure further to the use of lenvatinib. Considering the above data, lenvatinib is not expected to pose a risk to the environment.

2.2.5. Conclusion on the non-clinical aspects

The available pharmacodynamic studies in mice tumour isograft models (RCC, HCC, colon carcinoma and lung carcinoma) showed that the antitumor activity of the combination therapy of lenvatinib and the anti-PD-1 mAb (pembrolizumab) was greater than either monotherapy, however the difference to lenvatinib monotherapy was not striking.

Nevertheless, the previously established antiangiogenic activity of lenvatinib resulting from the inhibition of VEGFR and FGFR signalling and its immunomodulatory activity with a different mode of action from a PD-1 immune checkpoint inhibitor (decrease of TAMs, increase of activated cytotoxic T cells and activation of IFN-γ signalling) could lead to an additive effect of both components. No non-clinical studies were performed in murine model of endometrial cancer, but this is considered acceptable in line with ICH S9 and taking into account the ongoing/completed clinical trials of lenvatinib in combination with pembrolizumab in subjects with EC.

The updated data submitted with this application does not lead to a significant increase in environmental exposure further to the use of lenvatinib. Considering the above data from the environmental risk assessment, lenvatinib is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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 was provided.

- **Tabular overview of clinical studies**

Study	Design	Participant Population	Primary Endpoint(s)	Status
Study E7080-A001-111/KEYNOTE-146	A Multicenter, Open-Label Phase 1b/2 Trial of Lenvatinib (E7080) Plus Pembrolizumab in Subjects with Selected Solid Tumors	124 participants with endometrial carcinoma were enrolled. The endometrial carcinoma cohort has completed enrollment. Participants must have had histologically and/or cytologically confirmed metastatic selected solid tumors that had progressed after treatment (if previously treated). **Phase 1b**: no limit to number of prior treatments; **Phase 2 expansion:** 0 to 2 prior treatments.	**Phase 1b**: Determination of the MTD for lenvatinib plus pembrolizumab 200 mg IV Q3W pembrolizumab. **Phase 2-Expansion:** ORR($Week_{24}$)	Ongoing
Study E7080-G000-309/KEYNOTE-775	A Multicenter, Open-label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination with Pembrolizumab Versus Treatment of Physician's Choice in Participants With Advanced Endometrial Cancer	827 participants were randomized (697 pMMR and 130 dMMR participants). Participants must have had radiographic evidence of disease progression after 1 prior systemic, platinum-based chemotherapy regimen for endometrial carcinoma. Participants may have received up to 1 additional line of platinum-based chemotherapy if given in the neoadjuvant or adjuvant treatment setting.	PFS OS	Fully Enrolled Ongoing
Study E7080-G000-313/MK-7902-001	A Phase 3 Randomized, Open-Label, Study of Pembrolizumab (MK-3475) Plus Lenvatinib Versus Chemotherapy for First-line Treatment of Advanced or Recurrent Endometrial Carcinoma	Approximately 720 total participants will be enrolled (approximately 612 pMMR and 108 dMMR participants).	PFS OS	Enrolling Ongoing
dMMR = defective mismatch repair; IV Q3W = intravenously every 3 weeks; MTD = Maximum Tolerated Dose; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; pMMR = mismatch repair proficient.				

2.3.2. Pharmacokinetics

Data from additional studies in support of the new indication were included. No new results were presented related to the effect of intrinsic factors or related to drug-drug interactions, except an updated population PK analysis (CPMS-E7080-015P-v1) based on pooled PK data from 22 studies, including Study 309/KEYNOTE-775. Additional clinical pharmacology information is available from previous submissions made in support of the following indications:

- Differentiated thyroid cancer (DTC).
- Second line (2L) renal cell carcinoma (RCC) (following one prior anti-angiogenic therapy), in combination with everolimus.
- First line (1L) RCC, in combination with pembrolizumab.
- First line hepatocellular carcinoma (monotherapy).

- First line HCC, in combination with pembrolizumab.

Bioanalytical methods

Bioanalytical methods used for the determination of lenvatinib concentration in human plasma

The main biopharmaceutics information has been previously presented in the submissions for DTC, second line RCC in combination with everolimus and HCC.

A sensitive, specific, and reproducible method was developed and validated for the determination of lenvatinib (free base concentration) in human plasma (sodium heparinized) and was previously reported in DTC, 2L RCC, HCC and 1L RCC indications. This method was transferred from one laboratory to another where it was fully validated (18718AUWZ) with successful cross-validation (study RPT05042).

ADME

An updated lenvatinib population PK analysis including data from updated lenvatinib population PK information from participants treated with lenvatinib plus pembrolizumab in Study 309/KEYNOTE-775 was provided.

Pembrolizumab PK and ADA were not collected in Study 309/KEYNOTE-775.

Study KEYNOTE-775/E7080-G000-309 (hereafter Study 309/KEYNOTE-775)

The study is a multicenter, Open-label, Randomized, Phase 3 Trial to compare the Efficacy and Safety of lenvatinib in Combination with Pembrolizumab Versus Treatment of Physician's Choice in Participants with Advanced Endometrial Cancer.

One of the secondary objectives is to characterize the population pharmacokinetics (PK) of lenvatinib when co-administered with pembrolizumab in pMMR participants and in all-comer participants, especially to compare the PK of lenvatinib in subjects with advanced EC (Study KEYNOTE-775/309) to that in subjects with other types of cancer across available studies of the lenvatinib clinical program and assess the effect of concomitant pembrolizumab on the PK of lenvatinib.

Table 3: Study 309/KEYNOTE-775

Study No. (Status)	Study Design and Objective	Treatments Dose of Lenvatinib, Dosage Form, Route, Product ID	Subjects No. of Subjects (M/F)	Results/ Conclusions
Clinical Pharmacology Studies: Clinical Safety and Efficacy Studies				
KN775/ E7080-G000-309	A Multicenter, Open label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination with Pembrolizumab Versus Treatment of Physician's Choice	Doses: Lenvatinib: 20 mg QD, PO 4-mg and 10-mg oral capsules Pembrolizumab: 200 mg, Q4W Days, IV	Number of Subjects Treated:794 Ongoing (No. on Treatment at Data Cutoff): 134 Final PFS analysis: this is IA1 not final analysis	Population PK and PK/safety analyses for lenvatinib are reported in CPMS-E7080-015R-v1.

IA1=Interim Analysis 1, IV = intravenous, M/F = male/female, no. = number, PFS = progression-free survival, PK = pharmacokinetic, PO = per oral, Q4W = every 4 weeks, QD = once a day (drug dosing), y = year.
Source: CSR for Study KN-775/E7080-G000-309.

CPMS-E7080-015P-v1

Population PK analysis of lenvatinib was based on pooled PK data from the 22 studies, including Study Study 309/KEYNOTE-775 in EC subjects. In the previous PK analysis (CPMS-E7080- 013R), lenvatinib

PK was best described by a 3-compartment model with simultaneous first and zero order absorption and linear elimination from the central compartment parameterized for CL/F, apparent volume of the central compartment (V1/F), apparent volume of peripheral compartments (V2/F and V3/F), inter-compartmental clearance between V1/F and V2/F and V1/F and V3/F (Q2/F and Q3/F), absorption rate constant (Ka), and duration of zero-order absorption (D1) and relative bioavailability (F1rel).

The PK model included the following covariates: body weight on clearances and volume parameters, healthy subjects on CL/F, RCC and HCC subjects on CL/F, albumin <30 g/L and alkaline phosphatase (ALP) > upper limit of normal (ULN) on CL/F, cytochrome P450 (CYP)3A4 inhibitors on CL/F, and capsule formulation on relative bioavailability (F1rel).

In the current analysis, due to the large dataset, which resulted in a very long run time, Ka, D1, F1rel, V3/F and effect of healthy subjects and CYP3A inhibitors on CL/F were similar to those from many previous PK analyses.

As such, these parameters were fixed to those from the recent PK analysis (CPMS-E7080-013R) and only effects of albumin, ALP and tumour type were re-evaluated in the PK model in addition to the effect of sex and co-medication of pembrolizumab (categorical) on CL/F. Estimation of model parameters was performed using first order conditional estimation method with interaction (FOCEI).

The final PK model was a 3-compartment model with simultaneous zero and first order absorption and first order elimination from the central compartment parameterized for CL/F, V1/F, V2/F, V3/F, Q1, Q2, Ka, D1, and F1rel for capsule formulation compared to tablet.

The full covariate model included body weight as an allometric constant on clearances and volume parameters, albumin < 30 g/L and ALP > ULN on CL/F, and concomitant CYP3A4 inhibitors on CL/F. Lenvatinib CL/F differences for EC, DTC, RCC, HCC and healthy subjects, as well as sex and concomitant pembrolizumab were also included in the full covariate model. Population PK parameter estimates from the final model are presented in the table below.

Table 4: Population Pharmacokinetic Parameter Estimates of Lenvatinib

Parameter	NONMEM Estimates		
	Point Estimate	%RSE	95% Confidence Interval
$CL/F\ [L/h] = \Theta_{CL} * (WGT/74)^{0.75} * \Theta_{IINHIB}^{INHIB} * \Theta_{ALP}^{ALP} * \Theta_{ALB}^{ALB} * \Theta_{HV}^{HV} * \Theta_{DTC}^{DTC} * \Theta_{HCC}^{HCC} * \Theta_{RCC}^{RCC} * \Theta_{EC}^{EC} * \Theta_{Pembro}^{Pembro} * \Theta_{SEX}^{SEX}$			
Basal CL/F for subjects with other type of solid tumor in L/h [Θ_{CL}]	6.65	2.06	6.38 – 6.92
Effect of CYP3A4 inhibitors on CL/F [Θ_{INHIB}]	0.896 Fixed	–	–
Effect of ALP (>ULN) on CL/F [Θ_{ALP}]	0.939	0.724	0.926 – 0.952
Effect of ALB (<30 g/L) on CL/F [Θ_{ALB}]	0.856	1.92	0.824 – 0.888
Effect of healthy subjects on CL/F [Θ_{HV}]	1.19 Fixed	–	–
Effect of DTC population on CL/F [Θ_{DTC}]	0.970	2.74	0.918 – 1.02
Effect of HCC population on CL/F [Θ_{HCC}]	0.824	2.71	0.780 – 0.868
Effect of RCC population on CL/F [Θ_{RCC}]	0.802	2.31	0.766 – 0.838
Effect of EC population on CL/F [Θ_{EC}]	0.751	3.64	0.697 – 0.805
Effect on concomitant pembrolizumab on CL/F [Θ_{Pembro}]	1.07	2.20	1.02 – 1.12
Effect on females on CL/F [Θ_{SEX}]	0.886	1.64	0.858 – 0.914
$V1/F\ [L] = \Theta_{V1} * WGT/74$			
Basal V1/F in L [Θ_{V1}]	45.1	1.49	43.8 – 46.4
$V2/F\ [L] = \Theta_{V2} * WGT/74$			
Basal V2/F in L [Θ_{V2}]	21.7	3.76	20.1 – 23.3
$V3/F\ [L] = \Theta_{V3} * WGT/74$			
Basal V3/F in L [Θ_{V3}]	30.9 Fixed	–	–
$Q1/F\ [L/h] = \Theta_{Q1} * (WGT/74)^{0.75}$			
Basal Q1/F in L/h [Θ_{Q1}]	3.61	2.55	3.43 – 3.79
$Q2/F\ [L/h] = \Theta_{Q2} * (WGT/74)^{0.75}$			
Basal Q2/F in L/h [Θ_{Q2}]	0.847	2.73	0.802 – 0.892

Parameter	NONMEM Estimates		
	Point Estimate	%RSE	95% Confidence Interval
Ka [1/h] = Θ_{Ka}			
Basal Ka in 1/h [Θ_{Ka}]	0.803 Fixed	–	–
D1 [h] = Θ_{D1}			
Basal D1 in h [Θ_{D1}]	1.27 Fixed	–	–
F1 = Θ_{F1}			
Relative bioavailability of capsule vs tablet formulation [Θ_{F1}]	0.882 Fixed	–	–
Inter-individual variability (%CV)			
CL/F	33.5	3.00	–
V1/F	43.6	4.64	–
V2/F	65.0	9.81	–
V3/F	33.9	8.14	–
Ka	52.0	12.5	–
D1	104	4.56	–
Residual variability			
Proportional (%CV) (Clin pharm studies)	16.6	0.960	–
Proportional (%CV) (Patients studies)	40.2	1.07	–
Proportional (%CV) (TAD ≤ 2 h)	48.5	2.95	–
Additional (ng/mL) (TAD ≤ 2 h)	17.5	0.915	–

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100;

The %CV for both inter-subject and proportional residual variability is an approximation taken as the square root of the variance * 100; CL/F = apparent clearance, V1/F = apparent volume of central compartment; V2/F and V3/F = apparent volume of peripheral compartment; Q1 = inter-compartment clearance between V1 and V2; Q2 = inter-compartment clearance between V1 and V3; Ka = absorption rate constant; D1 = duration of zero order absorption; F1 = relative bioavailability of capsule to tablet formulation; TAD = Time after dose; CI = confidence interval; WGT = weight (kg); INHIB = CYP3A4 inhibitors; ALB =albumin, 0 (≥ ALB 30 g/L) or 1 (< ALB 30 g/L); ALP = Alkaline phosphatase measurement (IU/L) 0 (ALP ≤ upper limit of normal) or 1 (ALP > upper limit of normal value); HV = 0 (cancer patients) or 1 (healthy subjects); DTC = 0 (non-DTC patients) or 1 (DTC patients); RCC = 0 (non-RCC patients) or 1 (RCC patients); HCC = 0 (non-HCC patients) or 1 (HCC patients); EC = 0 (non-EC patients) or 1 (EC patients); Pembro = pembrolizumab, ULN = upper limit of normal

Source: Table 9 of CPMS-E7080-015R-v1

Individual lenvatinib CL/F and AUC for EC subjects receiving lenvatinib 20 mg in combination with pembrolizumab in Study 309/KEYNOTE-775are summarized in **Table** 5. The median values and range of parameter values were comparable with CL/F and AUC dose normalized to 20 mg in subjects with RCC and other tumour types received lenvatinib monotherapy or concomitantly with everolimus or pembrolizumab in the pooled PK dataset (**Table** 6).

Table 5: Summary of Individual Model-Predicted Lenvatinib Pharmacokinetic Parameters in EC Subjects from Lenvatinib + Pembrolizumab Arm (Arm A) in Study 309/KEYNOTE-775

Starting Dose	Parameter (unit)	N	Mean	SD	Median	Min	Max
20 mg	CL/F (L/h)	403	4.69	1.39	4.60	1.78	10.15
20 mg	AUC (ng•h/mL)	403	4134	1350	3835	1738	9932

AUC = area under the concentration × time curve, CL/F = apparent clearance, EC = endometrial carcinoma, N = number, SD = standard deviation
Source: Table 10 of CPMS-E7080-015R-v1

Table 6: Summary of Individual Model-Predicted Lenvatinib CL/F and AUC Dose-Normalized to 20 mg by Tumour Type in Subjects Receiving Lenvatinib Monotherapy or Concomitantly with Pembrolizumab or Everolimus in Pooled PK Dataset

Tumor type	Parameter (unit)	N	Mean	SD	Median	Min	Max
RCC	CL/F (L/h)	1188	5.73	2.02	5.49	1.36	14.38
	AUC (ng•h/mL)	1188	3520	1438	3215	1227	13017
DTC	CL/F (L/h)	542	6.42	2.00	6.22	1.66	15.18
	AUC (ng•h/mL)	542	3115	1099	2907	1162	10656
HCC	CL/F (L/h)	534	4.94	1.50	4.78	1.54	10.22
	AUC (ng•h/mL)	534	4007	1381	3747	1726	11474
Other solid tumors	CL/F (L/h)	161	6.45	2.87	5.89	1.47	19.3
	AUC (ng•h/mL)	161	3633	1619	3372	1036	13588

AUC = area under the concentration × time curve, CL/F = apparent total clearance following oral administration, DTC = differentiated thyroid cancer, HCC = hepatic cell carcinoma, N = number, SD = standard deviation, PK = pharamcokinetic, RCC = renal cell carcinoma
Source: Table 11 of CPMS-E7080-015R-v1

Goodness-of-fit-plots for the final PK model for lenvatinib based on the pooled dataset were presented (data not shown). The scatter plots of CWRES vs. population predicted concentrations and vs. time showed the CWRES to be distributed around zero. Plots of ETA (CL/F) vs covariates (tumour type and concomitant pembrolizumab) appeared to be normally distributed with a mean of 0. The Final PK model was also evaluated using pcVPC.

Special populations

No additional information was provided (see discussion on clinical pharmacology).

Pharmacokinetic interaction studies

No additional information was provided (see discussion on clinical pharmacology).

PK data of pembrolizumab have been collected in a number of other studies investigating the same combination therapy (pembrolizumab and lenvatinib) including KEYNOTE-581 / E7080-G000-307 in 1L RCC where PK results confirmed no impact to the exposures of pembrolizumab and lenvatinib in presence of each other in the combination setting.

2.3.3. Discussion on clinical pharmacology

Clinical pharmacokinetics

Bioanalytical methods

Lenvatinib method validation (Project n. 187184AUWZ) as well as the bioanalytical report (MK-3475-775) were submitted. The method for the determination of MK-7902 was proven to be precise, accurate, sensitive and selective over the validated range from 0.25 to 250 ng/mL. Dilution integrity was shown using QC samples at 2500 ng/mL, diluted 20 folds and showed that it does not affect precision and accuracy. The method is considered reliable and reproducible, and the analyte and the internal standard were stable under all conditions tested. Long-Term stability of lenvatinib in matrix (human sodium heparinized plasma) has been evaluated and demonstrated for a period of 6, 153, 343 and 675 days at -20ºC and -80°C, whereas the maximum sample storage duration from collection to analysis of study samples was 927 days at -20ºC.

Long-term stability data available so far (i.e. up to 675 days) were provided. Since only 6 samples are not covered by long-term stability data, which accounts for 0.2% of the total samples analysed, no impact on the outcome of BA study is expected. Long term stability data up to 927 days will be available early 2022.

Only 2452 samples out of 4423 were analysed which corresponds to more than half samples. It is adequately clarified that the Aliquot 2 samples were back-up samples that were only used if the Aliquot 1 sample was not available or not viable. An adequate justification was also provided by the applicant to explain why 6 samples were not analyzed.

Three different instruments for LC-MS/MS analysis, coded LC MS MS 4000 01, LC MS MS 4000 13 and LC MS MS 4000 17 were used; Multiple LC MS/MS systems were used and found to be equivalent during assay development and the performances (calibration curves, Y intercept, slope) were comparable across systems. It was also clarified that no changes were made to the validated instrument platform and therefore partial validations were not warranted.

Lenvatinib POP PK analysis

An updated lenvatinib population PK analysis (CPMS-E7080-015R-v1) including data from updated lenvatinib population PK information from participants treated with lenvatinib plus pembrolizumab in Study 309/KEYNOTE-775 was provided. The PK of lenvatinib was described by a 3-compartment model with elimination from the central compartment and simultaneous first and zero order absorption. The model was parameterized for CL/F, V1/F, Q2/F, V2/F, Q3/F, V3/F, Ka, D1 and F1. The final pooled lenvatinib PK dataset included 25738 observations from a total of 3025 subjects. For EC subjects, there were 2178 lenvatinib concentrations available from 403 subjects from Study 309/KEYNOTE-775. The updated lenvatinib PK profile containing data from Study 309/KEYNOTE-775 is consistent with the current population PK profile of lenvatinib.

Of note, a lot of Lenvatinib observations were excluded from PK Dataset as "outlier, inconsistent with the PK profile. It was clarified that only 1.4% of total observations were excluded due to BLQ TAD< 200h. It is agreed that exclusion of these BLQ samples does not bias the parameter estimates.

According to the provided model, EC subjects had 24.9% lower apparent total clearance following extravascular (e.g. oral) administration (CL/F) than that in subjects with other types of solid tumour excluding DTC, RCC and HCC. The lower CL of lenvatinib observed in EC patients would appear not to be due to the effect of the combination with pembrolizumab, as lenvatinib CL is equal in both the presence (yes) and absence (no) of pembrolizumab, indicating that there is no effect of pembrolizumab co-administration on lenvatinib. The reason why the CL of lenvatinib is lower in EC patients compared with RCC and HCC patients is currently unknown. However, as the magnitude of this effect in EC patients (24.9%) is within the inter-subject variability for CL (33.5%), this is of no apparent clinical relevance.

Concomitant pembrolizumab dosing had no clinically relevant effect on lenvatinib pharmacokinetic (PK). There was a statistically significant small effect of gender on lenvatinib PK, which is not considered clinically relevant.

Goodness-of-fit-plots for the final PK model for lenvatinib based on the pooled dataset were presented, the scatter plots of CWRES vs. population predicted concentrations and vs. time showed the CWRES to be distributed around zero.

Plots of ETA (CL/F) vs covariates (tumour type and concomitant pembrolizumab) appeared to be normally distributed with a mean of 0.

During the first round, the Final PK model was also evaluated using pcVPC. Prediction-Corrected Visual Predictive Check of Observed and Predicted Lenvatinib concentrations in overall population considered in the final model (popPK analysis of lenvatinib from all studies) both including and excluding Study 309/KEYNOTE-775 (pcVPC including the 21 studies considered other than Study 309/KEYNOTE-775 and also pcVPC for all subjects considered from the 22 studies included in the updated final popPK model) were provided.

In summary, the final model fitting performance on EC data is overall acceptable.

The information on special populations is unchanged from the original DTC (Lenvima) and RCC (Kisplyx) indications. It has been reflected in section 4.2 of the SmPC that no adjustment of starting dose was required on the basis of hepatic function or renal function in Study 309/KEYNOTE775. Dose adjustments in this population may be necessary on the basis of individual tolerability.

No pharmacokinetic interaction studies were provided. In general, the potential of DDI between biologics and small molecules is negligible. Given the divergent metabolic pathways for both compounds, no DDI liability is expected on pembrolizumab and lenvatinib when administered in combination with each other. Based on the review of the submitted data, no change in the SmPC is needed from a PK perspective, except in section 5.2., the subsection on age, sex, weight and race which has been revised to reflect that based on a population pharmacokinetic analysis of patients receiving up to 24 mg lenvatinib once daily, age, sex, weight, and race (Japanese vs. other, Caucasian vs. other) had no clinically relevant effects on clearance (see section 4.2).

Finally, as the pembrolizumab dosage of 400 mg Q6W has been approved for all adult indications for monotherapy and combination indications in the US and the EU, the 400 mg Q6W dosing regimen is expected to have a similar benefit-risk profile as the 200 mg Q3W (or 2 mg/kg Q3W) dosing regimen in the clinical use of pembrolizumab in combination with lenvatinib in adults with advanced EC. Therefore, the alternate 400 mg Q6W dosing has been included in the Lenvima SmPC section 4.2.

2.3.4. Conclusions on clinical pharmacology

The updated lenvatinib PK model containing data from Study 309/KEYNOTE-775 was consistent with the current population PK profile of lenvatinib.

2.4. Clinical efficacy

2.4.1. Dose response study

Study E7080-A001-111/KEYNOTE-146

The proposed clinical dose is lenvatinib 20 mg QD combined with pembrolizumab 200 mg IV Q3W for the patients with confirmed advanced EC. This dose was defined based on the efficacy and safety results from the phase 1b/2 E7080-A001-111/KEYNOTE-146 study.

Study E7080-A001-111/KEYNOTE-146 is a multicenter, open-label, Phase 1b/2 study of the combination of lenvatinib plus pembrolizumab in subjects with metastatic solid tumour including EC.

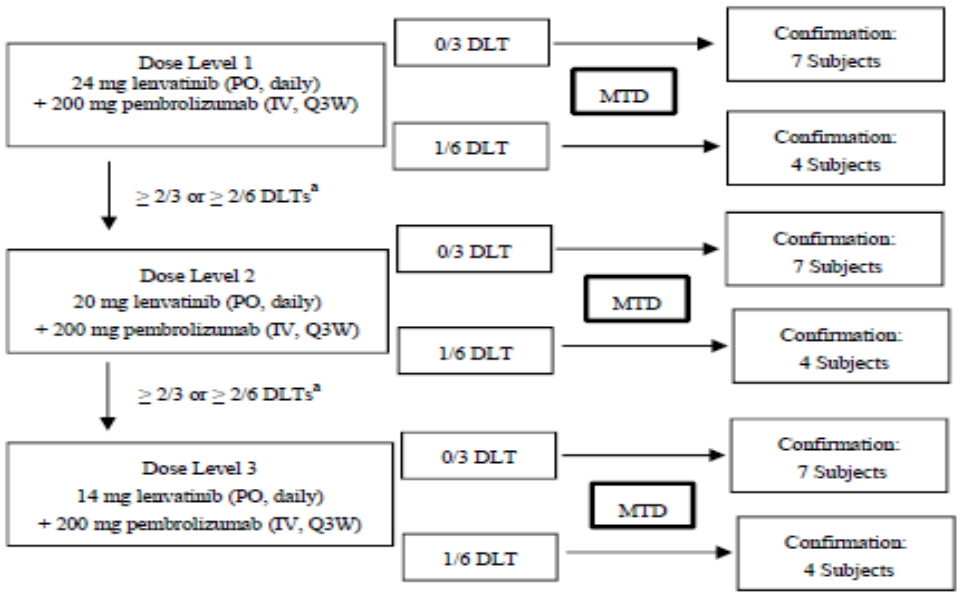


Figure *6*: Study E7080-A001-111 Phase 1b design schematic - Determination and Confirmation of the MTD

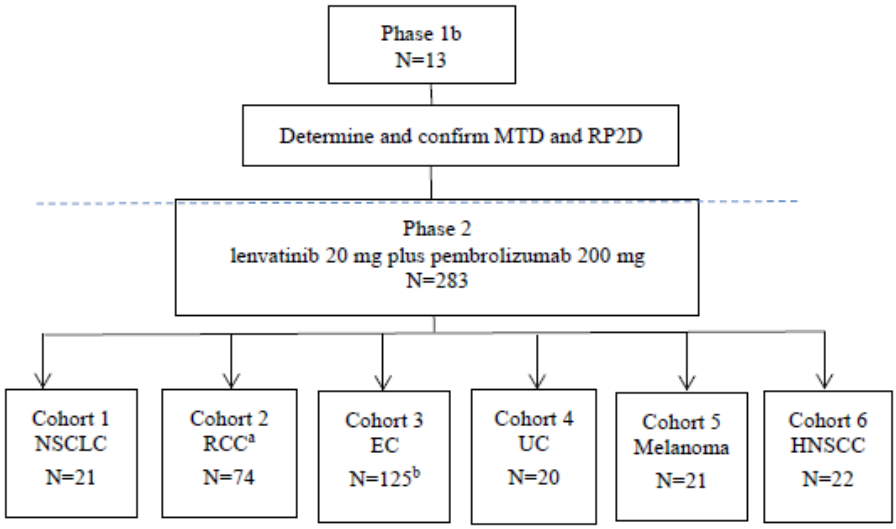


Figure *7:* Study E7080-A001-111 Phase 2 design schematic – cohort expansion in selected tumours

In the phase 2 stage, a total of 108 patients received lenvatinib 20 mg QD plus pembrolizumab 200 mg Q3W as the second-Line or later line treatment (EC 2L+).

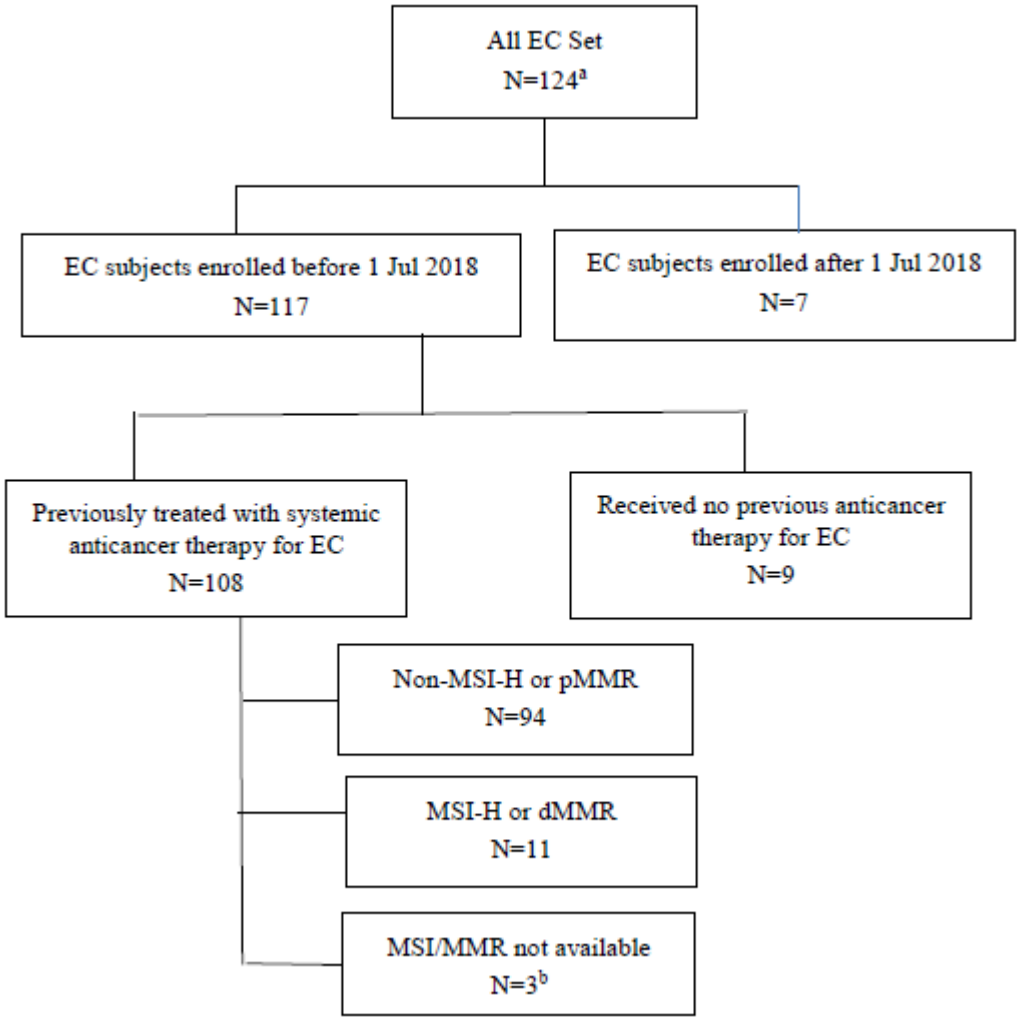


Figure *8*: Enrollment in the Endometrial Carcinoma Cohort in Study E7080-A001-111, Including the EC 2L+ Set

Table 7: Data Analysis Sets in the Endometrial Carcinoma Cohort in Study E7080-A001-111

	Lenvatinib 20 mg QD +Pembrolizumab 200 mg Q3W n (%)					
	EC 2L+					
	Total (N=108)	Non-MSI-H/ pMMR (N=94)	MSI-H/ dMMR (N=11)	All EC (N=124)	Non-EC (N=159)	All EC + Non-EC (N=283)
Full Analysis Set	108 (100.0)	94 (100.0)	11 (100.0)	124 (100.0)	159 (100.0)	283 (100.0)
Safety Analysis Set	108 (100.0)	94 (100.0)	11 (100.0)	124 (100.0)	159 (100.0)	283 (100.0)
Endometrial Carcinoma (EC) Analysis Set	108 (100.0)	94 (100.0)	11 (100.0)	124 (100.0)	NA	NA

Data cutoff date: 10 Jan 2019.

Table 8: Summary of Tumour Response per RECIST 1.1 by Independent Imaging Review – Endometrial Carcinoma Set

Parameter	Lenvatinib 20 mg QD + Pembrolizumab 200 mg Q3W			
	EC 2L+			
	Total (N=108)	Non-MSI-H/ pMMR (N=94)	MSI-H/ dMMR (N=11)	All EC (N=124)
Best Overall Response (BOR), n (%)[a,b]				
Complete Response (CR)	11 (10.2)	10 (10.6)	1 (9.1)	12 (9.7)
Partial Response (PR)	33 (30.6)	26 (27.7)	6 (54.5)	40 (32.3)
Stable Disease (SD)	42 (38.9)	38 (40.4)	3 (27.3)	48 (38.7)
Progressive Disease (PD)	14 (13.0)	12 (12.8)	1 (9.1)	15 (12.1)
Not Evaluable (NE)[c]	8 (7.4)	8 (8.5)	0 (0.0)	9 (7.3)
Unknown (UNK)[d]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Objective Response Rate (CR + PR), n (%)[a]	44 (40.7)	36 (38.3)	7 (63.6)	52 (41.9)
95% CI of Objective Response Rate[d]	(31.4, 50.6)	(28.5, 48.9)	(30.8, 89.1)	(33.1, 51.1)
Disease Control Rate (CR + PR + SD), n (%)[a]	86 (79.6)	74 (78.7)	10 (90.9)	100 (80.6)
95% CI of Disease Control Rate[e]	(70.8, 86.8)	(69.1, 86.5)	(58.7, 99.8)	(72.6, 87.2)
Clinical Benefit Rate (CR + PR + Durable SD), n (%)[a]	61 (56.5)	52 (55.3)	8 (72.7)	70 (56.5)
95% CI of Clinical Benefit Rate[e]	(46.6, 66.0)	(44.7, 65.6)	(39.0, 94.0)	(47.3, 65.3)
Maximum Tumor Shrinkage in Sum of Diameters of Target Lesions, n/m[f] (%)				
>0%	84/98 (85.7)	72/84 (85.7)	10/11 (90.9)	97/112 (86.6)
≥50%	33/98 (33.7)	26/84 (31.0)	6/11 (54.5)	39/112 (34.8)
≥75%	15/98 (15.3)	13/84 (15.5)	1/11 (9.1)	16/112 (14.3)

Data cutoff date: 10 Jan 2019.

No new safety signal or risk was identified for either lenvatinib or pembrolizumab or the combination from this trial. Observed toxicities were generally similar to those previously reported with either study drug when used as monotherapy, except for an overall higher incidence of AEOSIs observed for the combination of lenvatinib plus pembrolizumab versus pembrolizumab monotherapy, primarily driven by a higher frequency of hypothyroidism.

2.4.2. Main study

Study E7080-G000-309 (Study 309)/KEYNOTE-775

A Multicenter, Open-label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination with Pembrolizumab Versus Treatment of Physician's Choice in Participants with Advanced Endometrial Cancer

Methods

This is an ongoing multicenter, open-label, randomized, Phase 3 trial to compare the efficacy and safety of pembrolizumab plus lenvatinib versus treatment of physician's choice (TPC) in the patients with advanced endometrial carcinoma.

Participants were 1:1 ratio randomly assigned to receive either pembrolizumab plus lenvatinib or TPC with either doxorubicin or paclitaxel.

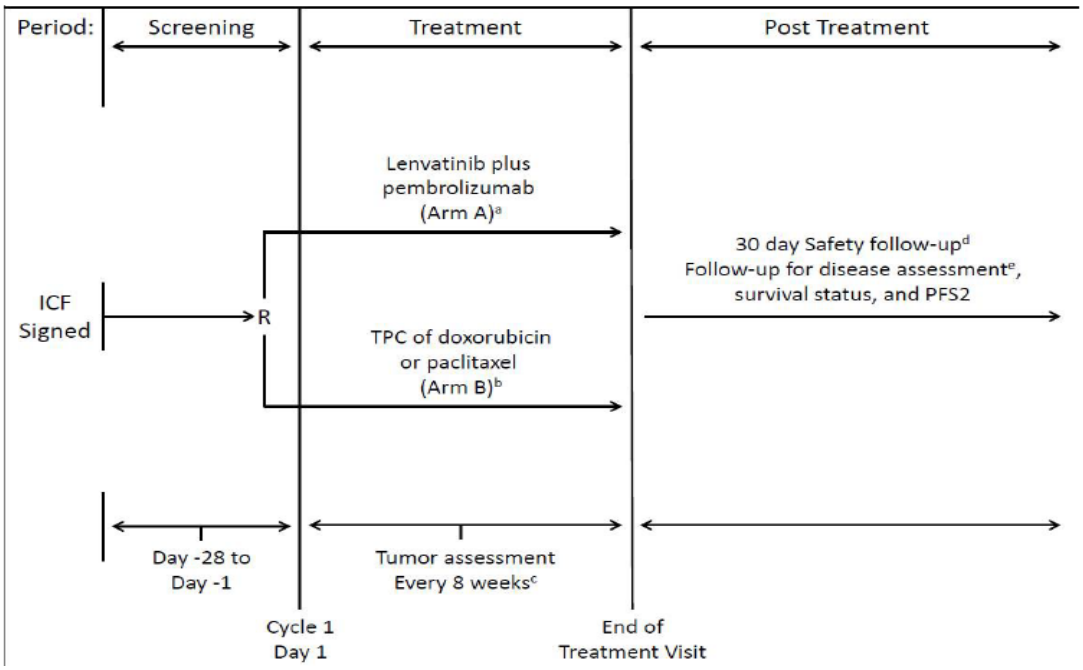


Figure 9: Study 309/KEYNOTE-775 design schematic

Study participants

Key Inclusion Criteria

- Histologically confirmed diagnosis of endometrial carcinoma; documented evidence of advanced, recurrent or metastatic EC.

- Radiographic evidence of disease progression after 1 prior systemic, platinum-based chemotherapy regimen for EC. Participants may have received up to 1 additional line of platinum-based chemotherapy if given in the neoadjuvant or adjuvant treatment setting. Note: There is no restriction regarding prior hormonal therapy.

- Available historical or fresh tumor biopsy specimen for determination of MMR status.

- At least 1 measurable target lesion according to RECIST 1.1 and confirmed by BICR, including the following criteria: Non-nodal lesion that measures ≥1.0 cm in the longest diameter; Lymph node (LN) lesion that measures as ≥1.5 cm in the short axis; The lesion is suitable for repeat measurement using computed tomography/magnetic resonance imaging (CT/MRI). Lesions that have had external beam radiotherapy (EBRT) or locoregional therapy must show radiographic evidence of subsequent growth.

- ECOG performance status of 0 or 1 within 7 days of starting study treatment.

- Female participant age ≥18 years is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:

a.) Not a WOCBP as defined in Appendix 2 of the protocol, OR

b.) A WOCBP who agrees to follow the contraceptive guidance in Appendix 2 during the treatment period and for at least 120 days (for participants treated with lenvatinib plus pembrolizumab) or at least 180 days (for participants treated with TPC) after the last dose of study treatment.

- Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as BP ≤150/90 mm Hg at Screening and no change in antihypertensive medications within 1 week before C1D1.

- Have adequate organ function. Specimens must be collected within 7 days prior to the start of study treatment.

Key Exclusion Criteria

- Carcinosarcoma (malignant mixed Műllerian tumor), endometrial leiomyosarcoma and endometrial stromal sarcomas.

- Participants with CNS metastases are not eligible, unless they have completed local therapy (eg, whole brain radiation therapy [WBRT], surgery or radiosurgery) and have discontinued the use of corticosteroids for this indication for at least 4 weeks before starting treatment in this study. Any signs (eg, radiologic) or symptoms of CNS metastases must be stable for at least 4 weeks before starting study treatment.

- Active malignancy (except for endometrial cancer, definitively treated in-situ carcinomas [e.g. breast, cervix, bladder], or basal or squamous cell carcinoma of the skin) within the past 24 months.

- Gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of lenvatinib; has a pre-existing Grade ≥3 gastrointestinal or non-gastrointestinal fistula.

- Radiographic evidence of major blood vessel invasion/infiltration. The degree of tumor invasion/infiltration of major blood vessels should be considered because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis following lenvatinib therapy.

- Clinically significant hemoptysis or tumor bleeding within 2 weeks prior to the first dose of study drug.

- Significant cardiovascular impairment within 12 months of the first dose of study drug: such as history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction or cerebrovascular accident (CVA) stroke, or cardiac arrhythmia associated with hemodynamic instability.

- Active infection (any infection requiring systemic treatment).

- Participants who have not recovered adequately from any toxicity and/or complications from major surgery prior to starting therapy.

- Participants known to be positive for Human Immunodeficiency Virus (HIV). No HIV testing is required unless mandated by local heath authority

- Known active Hepatitis B (eg, HBsAg reactive) or Hepatitis C (eg, HCV RNA [qualitative] is detected). No testing for hepatitis B or C is required unless mandated by local health authority. Refer to Appendix 9 for country-specific requirements.

- Has a history of (non-infectious) pneumonitis that required treatment with steroids, or has current pneumonitis.

- Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.

- Active autoimmune disease (with the exception of psoriasis) that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment; has had an allogenic tissue/solid organ transplant.

- Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [β-hCG] (or hCG) test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG [or hCG]). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.

- Participants with proteinuria >1+ on urine dipstick testing will undergo 24-h urine collection for quantitative assessment of proteinuria. Participants with urine protein ≥1 g/24 h will be ineligible.

- Prolongation of QTc interval to >480 ms; left ventricular ejection fraction (LVEF) below the institutional (or local laboratory) normal range as determined by multigated acquisition scan (MUGA) or echocardiogram (ECHO)

Prior/Concomitant Therapy

- Greater than 1 prior systemic chemotherapy regimen (other than adjuvant or neoadjuvant) for EC. Participants may receive up to 2 regimens of platinum-based chemotherapy in total, as long as one is given in the neoadjuvant or adjuvant treatment setting.

- Prior anticancer treatment within 28 days (or 5 times the half-life time, whichever is shorter). All acute toxicities related to prior treatments must be resolved to Grade ≤1, except for alopecia and Grade ≤2 peripheral neuropathy.

- Prior treatment with any treatment targeting VEGF-directed angiogenesis, any anti-PD-1, anti-PD-L1, or anti-PD-L2 agent; participants who received prior treatment with an agent directed to a stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX 40, CD137) other than an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent, and who discontinued from that treatment due to a Grade 3 or higher immune-related adverse event (irAE).

- Prior radiation therapy within 21 days prior to start of study treatment with the exception of palliative radiotherapy to bone lesions, which is allowed if completed 2 weeks prior to study treatment start. Participants must have recovered from all radiation-related toxicities and/or complications prior to randomization.

- Received a live vaccine within 30 days of planned start of study treatment (C1D1). Intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

- Prior enrollment on a clinical study evaluating pembrolizumab and lenvatinib for endometrial carcinoma, regardless of treatment received.

Treatments

The eligible patients were randomised to one of the following two treatment arms in a 1:1 ratio:

• Arm A: lenvatinib 20 mg QD plus pembrolizumab 200 mg Q3W

• Arm B: Treatment of Physician's Choice (TPC)

Table 9: Study 309/KEYNOTE-775 treatments

Study Treatment Name	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Use
Lenvatinib	Capsule	10 mg, 4 mg[a]	20 mg	Orally QD	Experimental
Pembrolizumab	Solution for infusion	25 mg/mL	200 mg Q3W	IV	Experimental
Doxorubicin	Solution for infusion	Variable	60 mg/m^2 Q3W	IV	Comparator
Paclitaxel	Solution for infusion	Variable	80 mg/m^2 QW[c]	IV	Comparator

Abbreviations: IV = intravenous; Q3W = every 3 weeks; QD = once daily; QW = every week.

a. 4 mg capsules provided for successive dose reduction of lenvatinib, if needed, as described in Section 6.6.1.

b. Provided centrally by the Sponsor except in specific countries where commercial product may be sourced locally.

c. 28-day cycle with weekly administration; 3 weeks on and 1 week off.

Objectives/outcomes/endpoints

Objective/Hypothesis	Endpoint
Primary	
Objective: To demonstrate that lenvatinib in combination with pembrolizumab is superior to Treatment of Physician's Choice (TPC) in improving progression-free survival (PFS). *Hypothesis (H1):* The combination of lenvatinib and pembrolizumab is superior to TPC as assessed by PFS in pMMR participants. *Hypothesis (H4):* The combination of lenvatinib and pembrolizumab is superior to TPC as assessed by PFS in all-comer participants.	**PFS**, defined as the time from date of randomization to the date of the first documentation of disease progression, as determined by blinded independent central review (BICR) per RECIST 1.1, or death from any cause (whichever occurs first).
Objective: To demonstrate that lenvatinib in combination with pembrolizumab is superior to TPC in improving overall survival (OS).	**OS**, defined as the time from date of randomization to date of death from any cause.

Hypothesis (H2): The combination of lenvatinib and pembrolizumab is superior to TPC as assessed by OS in pMMR participants. *Hypothesis (H5):* The combination of lenvatinib and pembrolizumab is superior to TPC as assessed by OS in all-comer participants.	
Secondary	
Objective: To compare the objective response rate (ORR) of participants treated with lenvatinib in combination with pembrolizumab versus TPC by BICR. *Hypothesis (H3):* The combination of lenvatinib and pembrolizumab is superior to TPC as assessed by ORR in pMMR participants. *Hypothesis (H6):* The combination of lenvatinib and pembrolizumab is superior to TPC as assessed by ORR in all-comer participants.	**ORR**, defined as the proportion of participants who have best overall response of either complete response (CR) or partial response (PR), as determined by BICR per RECIST 1.1.
Objective: To evaluate the impact of treatment on Health-Related Quality of Life (HRQoL) as assessed by using the global score of the European Organization for the Research and Treatment of Cancer (EORTC) QLQ- C30 for participants treated with lenvatinib in combination with pembrolizumab versus TPC in pMMR and in all-comer participants.	**HRQoL** will be assessed using the global score of the EORTC QLQ-C30.
Objective: To assess safety and tolerability of treatment with lenvatinib in combination with pembrolizumab versus TPC in pMMR participants and in all-comer participants.	Incidence of treatment-emergent adverse events (TEAEs), serious AEs (SAEs), and immune-related AEs. Proportion of participants discontinuing study treatment due to TEAEs. Time to treatment failure due to toxicity, defined as the time from the date of randomization to the date that a participant discontinues study treatment due to TEAEs.
Objective: To characterize the population pharmacokinetics (PK) of lenvatinib when co-administered with pembrolizumab in pMMR participants and in all-comer participants.	Plasma concentration of lenvatinib versus time.
Objective: To assess the relationship between exposure to lenvatinib and safety events related to lenvatinib in pMMR participants and in all-comer participants.	Clearance and area under the concentration-time curve (AUC) for lenvatinib.

Objective/Hypothesis	Endpoint
Exploratory	
Objective: To compare the ORR of participants treated with lenvatinib in combination with pembrolizumab versus TPC.	ORR, defined as the proportion of participants who have best overall response of either CR or PR, as determined by investigator per RECIST 1.1.
Objective: To compare the PFS of participants treated with lenvatinib in combination with pembrolizumab versus TPC.	PFS, defined as the time from date of randomization to the date of the first documentation of disease progression, as determined by investigator per RECIST 1.1, or death from any cause, whichever occurs first.
Objective: To assess duration of response (DOR) in both treatment arms in pMMR participants and in all-comer participants.	DOR, defined as the time from the date a response was first documented until the date of the first documentation of disease progression, by BICR and investigator assessment of objective radiographic disease assessment per RECIST 1.1, or date of death, whichever occurs first.
Objective: To assess disease control rate (DCR) and clinical benefit rate (CBR) of participants treated with lenvatinib in combination with pembrolizumab versus TPC in pMMR participants and in all-comer participants.	DCR, defined as the proportion of participants who have best overall response of CR, PR, or stable disease (SD) by BICR and investigator assessment per RECIST 1.1. SD must be achieved at ≥7 weeks after randomization to be considered best overall response. CBR, defined as the proportion of participants who have best overall response of CR, PR, or SD by BICR and investigator assessment per RECIST 1.1 (duration of SD ≥23 weeks after randomization).
Objective: To assess efficacy outcomes using modified RECIST 1.1 for immune-based therapeutics (iRECIST) in participants treated with lenvatinib in combination with pembrolizumab versus TPC by investigator assessment in pMMR participants and in all-comer participants.	PFS, ORR, DOR, DCR, and CBR as determined by investigator assessment using iRECIST. PFS using iRECIST will be defined as the time from the date of randomization to the date of the first documentation of confirmed immune-related progressive disease (iPD) or death (whichever occurs first).
Objective: To assess PFS on next line therapy (PFS2) by investigator assessment in pMMR participants and in all-comer participants.	PFS2, defined as the time from randomization to disease progression, as determined by investigator assessment, on next-line of treatment or death (whichever occurs first).
Objective: To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of lenvatinib and	Molecular (genomic, metabolic, and/or proteomic) determinants of response or resistance to treatments, using blood and/or tumor tissue.

pembrolizumab in pMMR participants and in all-comer participants.	

Sample size

The sample size is estimated based on the primary endpoints PFS and OS.

A total of approximately 780 participants (including 660 participants from pMMR and 120 participants from dMMR participants) were planned to be randomized in a 1:1 ratio (approximately 330 participants from pMMR and 60 participants from dMMR participants in each treatment arm).

The study was considered to have completed enrollment when 660 pMMR participants have enrolled. Enrollment of dMMR participants was planned to be capped at 120.

Sample size and power calculations are based on pMMR participants:

The study is designed to have 90% power to detect a statistically significant difference in OS at one-sided α=0.0245 and as a result, the study will also have at least 99% power to detect a statistical significant difference in PFS at one-sided α=0.0005.

Assuming an accrual period of 19 months and a follow-up period of 24 months, a total of 660 participants are required to observe 526 death events by the time of 43 months after the first participant is randomized (19 months enrollment plus 24 months follow-up period).

For OS, a total of 526 OS events are required to detect a statistically significant difference at 0.0245 level with 90% power, under the following assumptions that: 1) the hazard ratio is 0.75 (median OS is 16.4 months in Arm A and 12.3 months in Arm B), 2) the first interim analysis is performed when approximately 368 OS events are observed (i.e. 70% of the total target death events), 3) the second interim analysis is performed when approximately 463 OS events are observed (i.e. 88% of the total target death events), and 4) Lan-DeMets spending function with O'Brien-Fleming boundary is used.

The final PFS analysis is planned to be performed at the time of the first OS interim analysis (IA1) at 27 months after the first participant is randomized. A total of 564 PFS events are estimated to be observed to detect a statistically significant difference at 0.0005 level with >99% power under the assumption that the hazard ratio is 0.55 (median PFS is 7.3 months in Arm A and 4 months in Arm B).

Power calculations are based on pMMR and dMMR participants combined (all comer):

Assuming an accrual period of 19 months and a follow-up period of 24 months, a total of 780 participants are required in the all comer population to observe 618 death events by the time of 43 months after the first participant is randomized (19 months enrollment plus 24 months follow-up period). For OS, a total of 618 OS events are required to detect a statistically significant difference at 0.02205 level with 93.5% power, under the following assumptions that: 1) the hazard ratio is 0.75 (median OS is 16.4 months in Arm A and 12.3 months in Arm B), 2) the first interim analysis is performed when approximately 433 OS events are observed (i.e. 70% of the total target death events), 3) the second interim analysis is performed when approximately 544 OS events are observed (i.e. 88% of the total target death events), and 4) Lan-DeMets spending function with O'Brien-Fleming boundary is used.

Randomisation

Treatment allocation/randomization occurred centrally using an interactive response technology (IRT) system. Participants will be assigned randomly in a 1:1 ratio to either Arm A or Arm B. Treatment allocation/randomization was stratified according to the following factors:

1. MMR status (pMMR or dMMR)

2. ECOG performance status (0 or 1)

3. Geographic region (Region 1 [Europe, USA, Canada, Australia, New Zealand, and Israel] or Region 2 [rest of the world])

4. Prior history of pelvic radiation (yes or no)

First, participants will be stratified according to MMR status. Then, only within the pMMR stratum, participants will be further stratified according to ECOG performance status, geographic region, and prior history of pelvic radiation. A total of 9 strata will be utilized for the study.

Blinding (masking)

This study 309/KEYNOTE-775 is an open-label study.

Statistical methods

The Intention-to-Treat (ITT) population served as the population for the primary efficacy analyses. Efficacy analyses were planned to be performed in two subsets of subjects: All-comer participants and pMMR participants. In addition, select analyses may be performed for dMMR participants. All analyses performed in dMMR participants will be based on unstratified models for each endpoint. Although MMR status is a stratification factor in the trial, summary of pMMR and dMMR participants will be based on actual MMR status defined by immunohistochemistry (IHC) performed by a central vendor on tumor tissue provided by sites. If a participant is stratified as dMMR, but is determined to be pMMR by IHC, then stratification factors for the participant will be imputed based on clinical data.

Efficacy results for pMMR participants and all-comer participants that will be deemed to be statistically significant after consideration of the Type I error control strategy described below. Nominal p-values will be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity.

The stratification factors used for randomization (see below) will be applied to all stratified analyses, in particular, the stratified log-rank test, stratified Cox model, and stratified Miettinen and Nurminen method. In the event that there are small strata, for the purpose of analysis, strata will be combined to ensure sufficient number of participants, responses and events in each stratum.

Since, stratification is layered in this study, first according to the MMR status for all subjects and then by ECOG, region and pelvic radiation history only within the pMMR stratum, the stratification will be different for the pMMR and all-comer analyses. All stratified analyses based on the all-comer population will include all 4 stratification variables in the model (9 strata), while the model for the pMMR population will include stratification variables for ECOG, region and pelvic radiation history (8 strata).

Analysis sets

The All-comer Full Analysis Set (FAS) consists of all randomized participants who have received at least one dose of study medication, and have completed at least one PRO assessment beyond baseline.

Participants in the All-comer Full Analysis Set who have pMMR status are included in the pMMR Full Analysis Set.

Unless otherwise specified, all the analyses were performed for the pMMR Full Analysis Set as well as the All-comer Full Analysis Set.

Multiplicity testing strategy

The study initially allocated α = 0.0005, one-sided, to test PFS for pMMR participants and initially allocated α =0.0245, one-sided, to test OS for pMMR participants between the 2 treatment arms. If the null hypothesis for PFS for pMMR was rejected, α = 0.0005 was then passed to the test for PFS for all-comer participants. And if the null hypothesis for PFS for all-comer participants was rejected, α = 0.0005 was then passed to the test for OS for pMMR; therefore, OS for pMMR was tested at α =0.025. The study was considered positive if either testing of PFS or testing of OS was significant in pMMR participants.

The total family-wise error rate (Type-I error) among the dual-primary PFS and OS and the secondary ORR endpoints is strongly controlled at one-sided 0.025 level. The multiplicity strategy will follow the graphical approach of Maurer and Bretz (Figure below) shows the initial one-sided α-allocation for each hypothesis in the ellipse representing the hypothesis. The initial weights for reallocation from each hypothesis to the others are represented in the boxes on the lines connecting hypotheses.

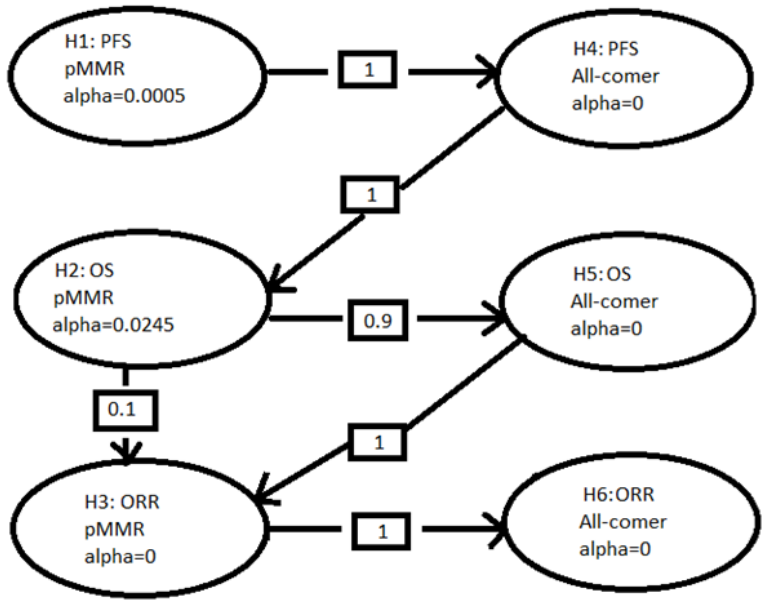


Figure *10*: Multiplicity Graph for Type I Error Control of Study Hypotheses

Abbreviations: ORR = objective response rate; OS = overall survival; PFS = progression-free survival; pMMR = mismatch repair proficient.

The non-parametric Kaplan-Meier method was used to estimate the PFS curve and survival curves respectively and the treatment differences in PFS and OS were assessed by the stratified log-rank test. Stratified Miettinen and Nurminen's method was used for comparison of the ORR between two treatment groups.

For PFS, OS, and ORR, the following subgroups will be summarized: Age (<65,≥65); Age (<65, ≥65 to <75, ≥75 to <85, ≥85); Race (White, Asian, Other): ECOG Status (0, 1): Region (Region 1, Region2); Prior History of Pelvic Radiation (Yes, No); Histology (Endometrioid, Non-endometrioid); Prior Lines of Therapy (1, 2, ≥3); MMR Status (pMMR, dMMR).

The safety monitoring and efficacy interim analyses were conducted by the external DMC.

Censoring rules for PFS are presented below.

Table 10: Censoring Rules for Primary Analysis of Progression-Free Survival Based on RECIST 1.1

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
PD or death documented after ≤ 1 missed disease assessment, and before new anti-cancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
Death or progression immediately after ≥ 2 consecutive missed disease assessments, or after new anti-cancer therapy	Censored at last disease assessment prior to the earlier date of ≥ 2 consecutive missed disease assessment and new anti-cancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death
No PD and no death; and new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than complete response; otherwise censored at last disease assessment if still on study treatment or completed study treatment.
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment	Progressed at date of new anticancer treatment if new anti-cancer treatment is initiated; otherwise progressed at treatment discontinuation if treatment is discontinued due to reasons other than complete response; otherwise censored at last disease assessment if still on study therapy or completed the study therapy
Abbreviations: PD = progressive disease; RECIST = Response Evaluation Criteria in Solid Tumors.			

The safety analyses were conducted using all subjects as treated (APaT) population, which included all randomized subjects who received at least 1 dose of study treatment. The analysis of safety results will follow a tiered approach. The tiers differed with respect to the analyses that was being performed including methods of statistical inferential test and descriptive statistics.

Two interim analyses are planned in this study:

- Interim Analysis 1 (IA1)
  - ✓ Primary purpose: final efficacy analysis for PFS and interim efficacy analysis for OS
- Interim Analysis 2 (IA2)
  - ✓ Primary purpose: interim efficacy analysis for OS
- Final Analysis (FA)

Primary purpose: final efficacy analysis for OS

Table 11: Summary of Interim and Final Analysis Strategy for the pMMR Participants

Analyses	Key Endpoints	Timing	Estimated Time after First Participant Randomized	Primary Purpose of Analysis
IA1	PFS OS	Both ~368 OS events and at least 6 months after last participant randomized	~27 months	Final PFS analysis Interim OS analysis
IA2	OS	Both ~463 OS events and at least 12 months after last participant randomized	~35 months	Interim OS analysis
FA	OS	Both ~526 OS events and at least 18 months after last participant randomized †	~43 months †	Final OS analysis

Abbreviations: FA = final analysis; IA1 = interim analysis 1; IA2 = interim analysis 2;

† Note that if events accrue slower than expected for the FA, the Sponsor may conduct the analysis up to 3 months after the estimated timing of the FA (ie., ~46 months after first participant randomized).

Table 12: Boundary Properties for Planned Analyses of OS Based on Potential Alpha-Levels to be Used for Testing in the pMMR Participants

Analysis	Value	α =0.0245	α =0.025
IA1 N: 660 OS events: 368 (70%*) Month: 27	Z	2.448	2.440
	p (1-sided) †	0.0072	0.0073
	HR at bound ‡	0.7747	0.7753
	P(Cross) if HR=1 §	0.0072	0.0073
	P(Cross) if HR=0.75 ‖	0.6234	0.6259
IA2 N: 660 OS Events: 463 (88%*) Month: 35	Z	2.187	2.178
	p (1-sided) †	0.0144	0.0147
	HR at bound ‡	0.8160	0.8167
	P(Cross) if HR=1 §	0.0165	0.0169
	P(Cross) if HR=0.75 ‖	0.8260	0.8285
FA N: 660 OS Events: 526 Month: 43	Z	2.069	2.061
	p (1-sided) †	0.0193	0.0196
	HR at bound ‡	0.8348	0.8355
	P(Cross) if HR=1 §	0.0245	0.0250
	P(Cross) if HR=0.75 ‖	0.9009	0.9025

Abbreviation: HR = hazard ratio; IA= interim analysis; FA= final analysis. The number of events and timings are estimated. * Percentage of total planned events at the interim analysis.

† p (1-sided) is the nominal α for group sequential testing.

‡ HR at bound is the approximate observed HR required to reach an efficacy bound.

§ P(Cross) if HR=1 is the probability of crossing a bound under the null hypothesis.

‖ P(Cross) if HR=0.75 is the probability of crossing a bound under the alternative hypothesis

Results

Participant flow

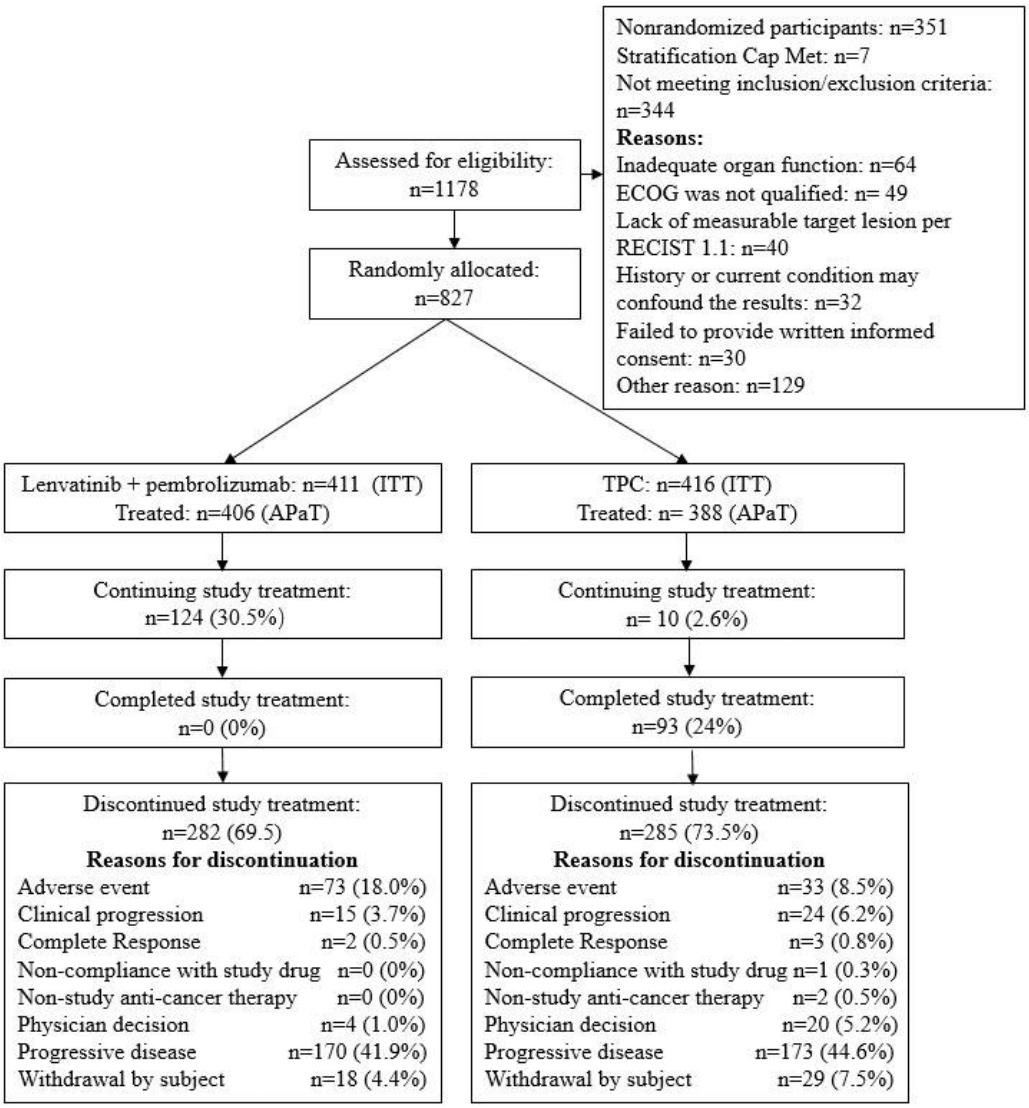


Figure *11*: Participant Flow Diagram (KEYNOTE-775) in All-comer Participants

Abbreviations: APaT=all participants as treated; ITT=intent to treat; ECOG= Eastern Cooperative Oncology Group; RECIST=Response Evaluation Criteria in Solid Tumor.

Recruitment

Participants with advanced endometrial carcinoma were randomly assigned from 11-JUN-2018 to 03-FEB-2020 across 167 global sites in 21 countries. At the data cutoff date of 26-OCT-2020 for the first interim analysis, 827 participants were randomized (411 in lenvatinib plus pembrolizumab group, 416 in TPC group).

Conduct of the study

All changes in the conduct of the study were implemented by protocol amendment(s), generally listed as follows (see the details in protocol amendments). There were no changes in the planned conduct of the study due to the COVID-19 pandemic before data cutoff (26-OCT-2020).

Protocol amendments

Table 13: Protocol amendments Study 309/KEYNOTE-775

Document	Date of Issue	Key changes
Original protocol	13-Feb-2018	Not applicable.
Amendment 01	21-Mar-2018	Germany-specific amendment to address country-specific request for HIV/HBV/HCV testing and pregnancy testing at screening.
Amendment 02	06-Jun-2018	United Kingdom-specific amendment to address country-specific requests for HIV/HBV/HCV testing at screening and contraception use.
Amendment 03	31-Aug-2018	Global protocol amendment to provide clarity with respect to the number of prior lines of treatment in order to be eligible for the study.
Amendment 04	01-Oct-2018	Germany-specific amendment to address country-specific requests for HIV/HBV/HCV testing and pregnancy testing and to incorporate changes implemented in Amendment 03 to provide clarity with respect to the number of prior lines of treatment in order to be eligible for the study.
Amendment 05	02-Oct-2018	United Kingdom-specific amendment to address country-specific requests for HIV/HBV/HCV testing and to incorporate changes implemented in Amendment 03 to provide clarity with respect to the number of prior lines of treatment in order to be eligible for the study.
Amendment 06	18-Feb-2020	Revision to the statistical analysis plan to add an interim efficacy analysis to evaluate the superiority of PFS and OS.
Amendment 07	12-Jun-2020	Revision to the statistical analysis plan to revise the timing of interim efficacy analysis following communications with health authorities.

Protocol deviations

Protocol deviations were classified as per the ICH E3 classification of protocol deviations as important (those that may significantly impact the quality or integrity of key study data or that may significantly affect a participant's rights, safety, or well-being) or not important. Important protocol deviations were further classified as either clinically important (deviations that may compromise critical data analyses pertaining to primary efficacy and/or safety endpoints or the participant's safety) or not clinically important.

Important protocol deviations were reported for 51 participants in this study. The number of participants with important deviations was 27 (6.6%) in the lenvatinib plus pembrolizumab and 24 (5.8%) in the TPC groups respectively.

Of the important protocol deviations, 20 participants had deviations that were considered to be clinically important and are categorized as follows:

• Study intervention (n=7 for lenvatinib plus pembrolizumab; n=5 for TPC)

• Received improperly stored study intervention (n=6 for lenvatinib plus pembrolizumab; n=3 for TPC)

• Study intervention was dispensed that was not assigned in the allocation schedule (n=1 for lenvatinib plus pembrolizumab; n=2 for TPC). For the 3 participants with important protocol deviations under this category, they received the wrong dosage of medications.

• Discontinuation criteria were met, but participants were not discontinued from the study medication (n=5 for lenvatinib plus pembrolizumab; n=3 for TPC)

• Prohibited medication (n=1 for TPC)

No participant's data were excluded from analyses due to an important protocol deviation.

Table 14: Summary of Important Protocol Deviations Considered to be Clinically Important (ITT Population)

	Lenvatinib + Pembrolizumab		TPC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	411		416		827	
with one or more important protocol deviations	27	(6.6)	24	(5.8)	51	(6.2)
with no important protocol deviations	384	(93.4)	392	(94.2)	776	(93.8)
Discontinuation Criteria	**5**	**(1.2)**	**3**	**(0.7)**	**8**	**(1.0)**
Participant developed study intervention discontinuation criteria, but was not discontinued from study intervention.	4	(1.0)	3	(0.7)	7	(0.8)
Participant developed trial specific discontinuation criteria but was not discontinued from the trial.	1	(0.2)	0	(0.0)	1	(0.1)
Inclusion/ Exclusion Criteria	**1**	**(0.2)**	**0**	**(0.0)**	**1**	**(0.1)**
Participants prior therapy for endometrial cancer must include at least 1 prior platinum based systemic therapy.	1	(0.2)	0	(0.0)	1	(0.1)
Prohibited Medications	**0**	**(0.0)**	**1**	**(0.2)**	**1**	**(0.1)**
Concurrent anticancer therapies such as chemotherapy, targeted therapies (e.g.tyrosine kinase inhibitors), hormonal therapy directed at EC, radiotherapy (with the exception of palliative radiotherapy as specified in Section 6.5.1), antitumor interventions (surgical resection, surgical debulking of tumor, etc.), live vaccines (within 30 days) or concurrent investigational therapies, while on treatment or before study entry during screening unless allowed per protocol.	0	(0.0)	1	(0.2)	1	(0.1)
Safety Reporting	**15**	**(3.6)**	**17**	**(4.1)**	**32**	**(3.9)**
Participant had a reportable Safety Event and/or follow up Safety Event information that was not reported per the timelines outlined in the protocol.	15	(3.6)	17	(4.1)	32	(3.9)
Study Intervention	**7**	**(1.7)**	**5**	**(1.2)**	**12**	**(1.5)**
Participant was administered improperly stored study intervention that was deemed unacceptable for use.	6	(1.5)	3	(0.7)	9	(1.1)
Study Intervention	**7**	**(1.7)**	**5**	**(1.2)**	**12**	**(1.5)**
Participant was dispensed study intervention other than what was assigned in the allocation schedule, i.e. incorrect medication or potential cross-treatment.	1	(0.2)	2	(0.5)	3	(0.4)

Every participant is counted a single time for each applicable row and column.
TPC = Treatment Physician's Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

Source: [P775V01MK3475: adam-adsl] [P775V01MK3475: sdtm-dv; suppdv]

Baseline data

All randomized participants were female with a diagnosis of advanced EC who had been treated with at least 1 prior platinum-based chemotherapy regimen (except for 1 participant).

The baseline demographic characteristics of participants with pMMR EC, all-comer, and dMMR participants were generally balanced between the 2 treatment groups, had a median age 65 years (65.0 years in Lenvatinib plus pembrolizumab arm and 66.0 years in TPC arm respectively; 64 in the dMMR subgroup).

Most patients (61.3%) are white, 21.4% are Asian, and had an ECOG performance status of 0 (58.9%). 84.3% patients (346 in Lenvatinib plus pembrolizumab and 351 in TPC arm) had a pMMR tumour.

The baseline disease characteristics of participants with pMMR EC and all-comer participants were generally balanced between the 2 treatment groups and were reflective of the patient population with advanced EC. Of 827 all-comer participants, 497 participants had endometroid carcinoma, and 330 participants had non-endometroid carcinoma. Of 697 pMMR participants, 386 had endometroid carcinoma, and 311 had non-endometroid carcinoma. Of 130 dMMR participants, 111 had endometroid carcinoma, and 19 had non-endometroid carcinoma.

Table 15: Participant Characteristics in All-comer Participants (ITT Population)

	Lenvatinib + Pembrolizumab		TPC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	411		416		827	
Sex						
Female	411	(100.0)	416	(100.0)	827	(100.0)
Age (Years)						
< 65	206	(50.1)	204	(49.0)	410	(49.6)
>= 65	205	(49.9)	212	(51.0)	417	(50.4)
Mean	63.2		63.8		63.5	
SD	9.1		9.2		9.1	
Median	64.0		65.0		65.0	
Range	30 to 82		35 to 86		30 to 86	
Race						
American Indian Or Alaska	4	(1.0)	7	(1.7)	11	(1.3)
Native Asian	85	(20.7)	92	(22.1)	177	(21.4)
Black Or African	17	(4.1)	14	(3.4)	31	(3.7)
American Multiple	7	(1.7)	13	(3.1)	20	(2.4)
American Indian Or Alaska Native Black Or African American	1	(0.2)	2	(0.5)	3	(0.4)
American Indian Or Alaska Native	5	(1.2)	8	(1.9)	13	(1.6)
White Black Or African American	1	(0.2)	3	(0.7)	4	(0.5)
White	1	(0.2)	0	(0.0)	1	(0.1)
Native Hawaiian Or Other Pacific	261	(63.5)	246	(59.1)	507	(61.3)
Islander White	36	(8.8)	44	(10.6)	80	(9.7)
Missing						
Ethnicity						
Hispanic Or Latino	60	(14.6)	73	(17.5)	133	(16.1)
Not Hispanic Or Latino	308	(74.9)	287	(69.0)	595	(71.9)
Not Reported	34	(8.3)	46	(11.1)	80	(9.7)
Unknown	9	(2.2)	10	(2.4)	19	(2.3)
Age (Years) Group						
< 75	376	(91.5)	373	(89.7)	749	(90.6)
>= 75	35	(8.5)	43	(10.3)	78	(9.4)
Age (Years) at Initial Diagnosis						
< 65	253	(61.6)	255	(61.3)	508	(61.4)
>= 65	158	(38.4)	161	(38.7)	319	(38.6)

Age (Years) at Initial Diagnosis						
Participants with data	411		416		827	
Mean	61.3		61.5		61.4	
SD	9.1		9.3		9.2	
Median	62.4		62.1		62.3	
Range	30 to 81		27 to 84		27 to 84	
Region [a]						
Region 1	234	(56.9)	240	(57.7)	474	(57.3)
Region 2	177	(43.1)	176	(42.3)	353	(42.7)
MMR Status						
pMMR	346	(84.2)	351	(84.4)	697	(84.3)
dMMR	65	(15.8)	65	(15.6)	130	(15.7)
ECOG						
0	246	(59.9)	241	(57.9)	487	(58.9)
1	164	(39.9)	175	(42.1)	339	(41.0)
3	1	(0.2)	0	(0.0)	1	(0.1)
Prior History of Pelvic Radiation						
Yes	168	(40.9)	173	(41.6)	341	(41.2)
No	243	(59.1)	243	(58.4)	486	(58.8)
Elapsed Time (Years) from Initial Diagnosis						
Participants with data	411		416		827	
Mean	2.4		2.9		2.7	
SD	2.4		2.8		2.6	
Median	1.7		2.1		1.9	
Range	0 to 21		0 to 26		0 to 26	
Histology of Initial Diagnosis						
Clear Cell Carcinoma	30	(7.3)	17	(4.1)	47	(5.7)
Endometrioid Carcinoma	83	(20.2)	103	(24.8)	186	(22.5)
Endometrioid Carcinoma With Differentiation	7	(1.7)	7	(1.7)	14	(1.7)
High Grade Endometrioid Carcinoma	94	(22.9)	90	(21.6)	184	(22.2)
High Grade Mucinous Carcinoma	0	(0.0)	1	(0.2)	1	(0.1)
High Grade Serous	65	(15.8)	65	(15.6)	130	(15.7)
Low Grade Endometrioid Carcinoma	59	(14.4)	54	(13.0)	113	(13.7)
Low Grade Mucinous Carcinoma	1	(0.2)	0	(0.0)	1	(0.1)
Mixed	22	(5.4)	16	(3.8)	38	(4.6)
Neuroendocrine	2	(0.5)	0	(0.0)	2	(0.2)
Serous Carcinoma	38	(9.2)	50	(12.0)	88	(10.6)
Unclassified	0	(0.0)	3	(0.7)	3	(0.4)
Undifferentiated Histology	4	(1.0)	3	(0.7)	7	(0.8)
Other	6	(1.5)	7	(1.7)	13	(1.6)
FIGO Stage at Initial Diagnosis						
I	10	(2.4)	11	(2.6)	21	(2.5)
IA	54	(13.1)	64	(15.4)	118	(14.3)
IB	47	(11.4)	64	(15.4)	111	(13.4)
II	32	(7.8)	26	(6.3)	58	(7.0)
III	5	(1.2)	8	(1.9)	13	(1.6)
IIIA	28	(6.8)	33	(7.9)	61	(7.4)
IIIB	11	(2.7)	11	(2.6)	22	(2.7)
IIIC	30	(7.3)	24	(5.8)	54	(6.5)
IIIC1	17	(4.1)	25	(6.0)	42	(5.1)
IIIC2	27	(6.6)	27	(6.5)	54	(6.5)
IV	27	(6.6)	26	(6.3)	53	(6.4)

IVA	7	(1.7)	8	(1.9)	15	(1.8)
IVB	116	(28.2)	89	(21.4)	205	(24.8)
Brain Metastasis [c]						
Yes	2	(0.5)	2	(0.5)	4	(0.5)
No	409	(99.5)	414	(99.5)	823	(99.5)
Bone Metastasis [c]						
Yes	39	(9.5)	33	(7.9)	72	(8.7)
No	372	(90.5)	383	(92.1)	755	(91.3)
Liver Metastasis [c]						
Yes	101	(24.6)	98	(23.6)	199	(24.1)
No	310	(75.4)	318	(76.4)	628	(75.9)
Lung Metastasis [c]						
Yes	164	(39.9)	152	(36.5)	316	(38.2)
No	247	(60.1)	264	(63.5)	511	(61.8)
Intra-abdominal Metastasis [b] [c]						
Yes	164	(39.9)	166	(39.9)	330	(39.9)
No	247	(60.1)	250	(60.1)	497	(60.1)
Lymph node Metastasis [c]						
Yes	224	(54.5)	225	(54.1)	449	(54.3)
No	187	(45.5)	191	(45.9)	378	(45.7)

[a] Region 1: Europe, USA, Canada, Australia, New Zealand, Israel; Region 2: Rest of World.

[b] Includes reported locations of colon, abdominal cavity, omentum, small intestine, peritoneal cavity, and peritoneum. Does not include lymph nodes or other organs.

[c] Lesion location as determined by investigator review.

TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel. Database Cutoff Date: 26OCT2020

Table 16: Participant Characteristics in pMMR Participants (ITT Population)

	Lenvatinib + Pembrolizumab		TPC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	346		351		697	
Sex						
Female	346	(100.0)	351	(100.0)	697	(100.0)
Age (Years)						
< 65	171	(49.4)	165	(47.0)	336	(48.2)
>= 65	175	(50.6)	186	(53.0)	361	(51.8)
Mean	63.3		64.0		63.7	
SD	8.9		9.2		9.0	
Median	65.0		66.0		65.0	
Range	30 to 82		35 to 86		30 to 86	
Race						

American Indian Or Alaska	4	(1.2)	6	(1.7)	10	(1.4)
Native Asian	74	(21.4)	80	(22.8)	154	(22.1)
Black Or African	15	(4.3)	9	(2.6)	24	(3.4)
American Multiple	3	(0.9)	9	(2.6)	12	(1.7)
American Indian Or Alaska Native Black Or African American	0	(0.0)	1	(0.3)	1	(0.1)
American Indian Or Alaska Native	3	(0.9)	5	(1.4)	8	(1.1)
White Black Or African American	0	(0.0)	3	(0.9)	3	(0.4)
White	1	(0.3)	0	(0.0)	1	(0.1)
Native Hawaiian Or Other Pacific	220	(63.6)	211	(60.1)	431	(61.8)
Islander White	29	(8.4)	36	(10.3)	65	(9.3)
Ethnicity						
Hispanic Or Latino	48	(13.9)	58	(16.5)	106	(15.2)
Not Hispanic Or Latino	261	(75.4)	247	(70.4)	508	(72.9)
Not Reported	28	(8.1)	37	(10.5)	65	(9.3)
Unknown	9	(2.6)	9	(2.6)	18	(2.6)
Age (Years) Group						
< 75	318	(91.9)	312	(88.9)	630	(90.4)
>= 75	28	(8.1)	39	(11.1)	67	(9.6)
Age (Years) at Initial Diagnosis						
< 65	212	(61.3)	211	(60.1)	423	(60.7)
>= 65	134	(38.7)	140	(39.9)	274	(39.3)
Age (Years) at Initial Diagnosis						
Participants with data	346		351		697	
Mean	61.3		61.7		61.5	
SD	9.0		9.4		9.2	
Median	62.5		62.9		62.6	
Range	30 to 81		27 to 84		27 to 84	
Region [a]						
Region 1	202	(58.4)	204	(58.1)	406	(58.2)
Region 2	144	(41.6)	147	(41.9)	291	(41.8)
MMR Status						
pMMR	346	(100.0)	351	(100.0)	697	(100.0)
ECOG						
0	212	(61.3)	207	(59.0)	419	(60.1)
1	133	(38.4)	144	(41.0)	277	(39.7)
3	1	(0.3)	0	(0.0)	1	(0.1)
Prior History of Pelvic Radiation						
Yes	136	(39.3)	139	(39.6)	275	(39.5)
No	210	(60.7)	212	(60.4)	422	(60.5)
Elapsed Time (Years) from Initial Diagnosis						
Participants with data	346		351		697	
Mean	2.5		2.9		2.7	
SD	2.4		2.8		2.6	
Median	1.7		2.1		1.9	
Range	0 to 21		0 to 26		0 to 26	
Histology of Initial Diagnosis						
Clear Cell Carcinoma	29	(8.4)	17	(4.8)	46	(6.6)
Endometrioid Carcinoma	60	(17.3)	74	(21.1)	134	(19.2)
Endometrioid Carcinoma With Differentiation	5	(1.4)	6	(1.7)	11	(1.6)
High Grade Endometrioid Carcinoma	73	(21.1)	77	(21.9)	150	(21.5)

High Grade Mucinous Carcinoma	0	(0.0)	1	(0.3)	1	(0.1)
High Grade Serous	62	(17.9)	64	(18.2)	126	(18.1)
Low Grade Endometrioid Carcinoma	50	(14.5)	41	(11.7)	91	(13.1)
Low Grade Mucinous Carcinoma	1	(0.3)	0	(0.0)	1	(0.1)
Mixed	18	(5.2)	13	(3.7)	31	(4.4)
Neuroendocrine	2	(0.6)	0	(0.0)	2	(0.3)
Serous Carcinoma	37	(10.7)	48	(13.7)	85	(12.2)
Unclassified	0	(0.0)	2	(0.6)	2	(0.3)
Undifferentiated Histology	4	(1.2)	2	(0.6)	6	(0.9)
Other	5	(1.4)	6	(1.7)	11	(1.6)
FIGO Stage at Initial Diagnosis						
I	9	(2.6)	10	(2.8)	19	(2.7)
IA	41	(11.8)	53	(15.1)	94	(13.5)
IB	40	(11.6)	51	(14.5)	91	(13.1)
II	30	(8.7)	22	(6.3)	52	(7.5)
III	5	(1.4)	6	(1.7)	11	(1.6)
IIIA	23	(6.6)	29	(8.3)	52	(7.5)
IIIB	11	(3.2)	8	(2.3)	19	(2.7)
IIIC	22	(6.4)	20	(5.7)	42	(6.0)
IIIC1	14	(4.0)	20	(5.7)	34	(4.9)
IIIC2	22	(6.4)	20	(5.7)	42	(6.0)
IV	25	(7.2)	23	(6.6)	48	(6.9)
IVA	4	(1.2)	7	(2.0)	11	(1.6)
IVB	100	(28.9)	82	(23.4)	182	(26.1)
Brain Metastasis [c]						
Yes	1	(0.3)	2	(0.6)	3	(0.4)
No	345	(99.7)	349	(99.4)	694	(99.6)
Bone Metastasis [c]						
Yes	33	(9.5)	28	(8.0)	61	(8.8)
No	313	(90.5)	323	(92.0)	636	(91.2)
Liver Metastasis [c]						
Yes	90	(26.0)	90	(25.6)	180	(25.8)
No	256	(74.0)	261	(74.4)	517	(74.2)
Lung Metastasis [c]						
Yes	140	(40.5)	130	(37.0)	270	(38.7)
No	206	(59.5)	221	(63.0)	427	(61.3)
Intra-abdominal Metastasis [b] [c]						
Yes	143	(41.3)	141	(40.2)	284	(40.7)
No	203	(58.7)	210	(59.8)	413	(59.3)
Lymph node Metastasis [c]						
Yes	183	(52.9)	191	(54.4)	374	(53.7)
No	163	(47.1)	160	(45.6)	323	(46.3)

[a] Region 1: Europe, USA, Canada, Australia, New Zealand, Israel; Region 2: Rest of World.

[b] Includes reported locations of colon, abdominal cavity, omentum, small intestine, peritoneal cavity, and peritoneum. Does not include lymph nodes or other organs.

[c] Lesion location as determined by investigator review.

DCO: 26OCT2020 Source: [P775V01MK3475: adam-adsl]

Table 17: Prior Therapies for Endometrial Cancer (ITT Population)

	Lenvatinib + Pembrolizumab		TPC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	411		416		827	
Prior Lines of Systemic Therapy						
1	297	(72.3)	27	(66.6)	574	(69.4)
2	103	(25.1)	12	(30.3)	229	(27.7)
>=3	11	(2.7)	13	(3.1)	24	(2.9)
Prior Lines of Platinum Based Therapy						
0	1	(0.2)	0	(0.0)	1	(0.1)
1	326	(79.3)	31	(75.7)	641	(77.5)
2	83	(20.2)	10	(24.3)	184	(22.2)
>=3	1	(0.2)	0	(0.0)	1	(0.1)
Neo-adjuvant/Adjuvant						
Yes	224	(54.5)	25	(60.3)	475	(57.4)
No	187	(45.5)	16	(39.7)	352	(42.6)
Primary Therapy						
Yes	74	(18.0)	48	(11.5)	122	(14.8)
No	337	(82.0)	36	(88.5)	705	(85.2)
Progressive Disease/Relapse						
Yes	197	(47.9)	21	(51.4)	411	(49.7)
No	214	(52.1)	20	(48.6)	416	(50.3)
Palliative Hormonal Therapy						
Yes	36	(8.8)	44	(10.6)	80	(9.7)
No	375	(91.2)	37	(89.4)	747	(90.3)
Prior Systemic Therapies Received by Setting [a]						
Neo-adjuvant/adjuvant only	144	(35.0)	15	(38.2)	303	(36.6)
Primary therapy	69	(16.8)	43	(10.3)	112	(13.5)
Progressive disease/relapse only	114	(27.7)	11	(28.1)	231	(27.9)
Treatment in both neo-adjuvant/adjuvant and PD/relapse setting	79	(19.2)	92	(22.1)	171	(20.7)
Not Applicable	5	(1.2)	5	(1.2)	10	(1.2)
Interval from End of Most Recent Therapy to First Dose (mos)						
Participants with data	406		388		794	
Mean	7.6		8.5		8.0	
SD	8.9		11.4		10.2	
Median	4.8		5.4		5.0	
Range	0 to 74		0 to 100		0 to 100	
History of Prior Hysterectomy						
Yes	296	(72.0)	32	(79.1)	625	(75.6)
No	115	(28.0)	87	(20.9)	202	(24.4)
History of Prior External Beam Radiotherapy						
Yes	189	(46.0)	19	(47.8)	388	(46.9)
No	222	(54.0)	21	(52.2)	439	(53.1)
History of Prior Brachytherapy						
Yes	103	(25.1)	12	(29.3)	225	(27.2)
No	308	(74.9)	29	(70.7)	602	(72.8)

a Does not include the therapeutic setting of palliative hormonal therapy.TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel. Database Cutoff Date: 26OCT2020 Source: [P775V01MK3475: adam-adsl]

In general, the lenvatinib plus pembrolizumab and TPC groups were balanced for baseline clinical characteristics, prior systemic therapies for EC and concomitant medications, in all randomized patient population as well as in pMMR patient subgroup. Patients recruited globally. White and Asian population account for the majority of patients enrolled Median Age (range) is 65.0 years (65.0 years in Lenvatinib plus pembrolizumab arm and 66.0 years in TPC arm respectively). Most patients (about 60%) are white, one fifth are Asian, and more than half patients had an ECOG performance status of 0 in both treatment groups. No differences on the distribution of metastatic lesions were observed.

Numbers analysed

Efficacy Analysis Population

Efficacy analyses were based on the ITT population, which included participants in the treatment arm to which they were randomly assigned, regardless of whether they received treatment. The following ITT populations were included: all-comer participants and pMMR participants. No participants were excluded from the analyses. The analyses included 1 participant who was stratified with a dMMR status, but actually had a pMMR status; stratification factors for this participant are derived from actual ECOG performance status, geographic region, and prior history of pelvic radiation.

PRO Analysis Population

The HRQoL analyses are based on the HRQoL Full Analysis Set (PRO FAS) population, defined as all randomized participants who had at least one HRQoL assessment available for the specific endpoint and had received at least 1 dose of study intervention. Participants were analyzed in the treatment group to which they were randomized. HRQoL analysis populations included an all-comer FAS and a pMMR FAS.

Safety Analysis Population

Safety analyses were based on the APaT population, which included all randomly assigned participants who received at least 1 dose of study treatment. APaT populations: all-comer and pMMR participants.

Table 18: Study Population in All-comer Participants

	Lenvatinib + Pembrolizumab	TPC	Total
Number of Participants Screened			1178
Number of Participants Randomized (ITT)	411	416	827
Number of Participants Received Treatment (Actual Treatment) (APaT)	406	388	794
Number of Participants Randomized and Did not Receive Treatment	5	28	33
TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel. Database Cutoff Date: 26OCT2020			

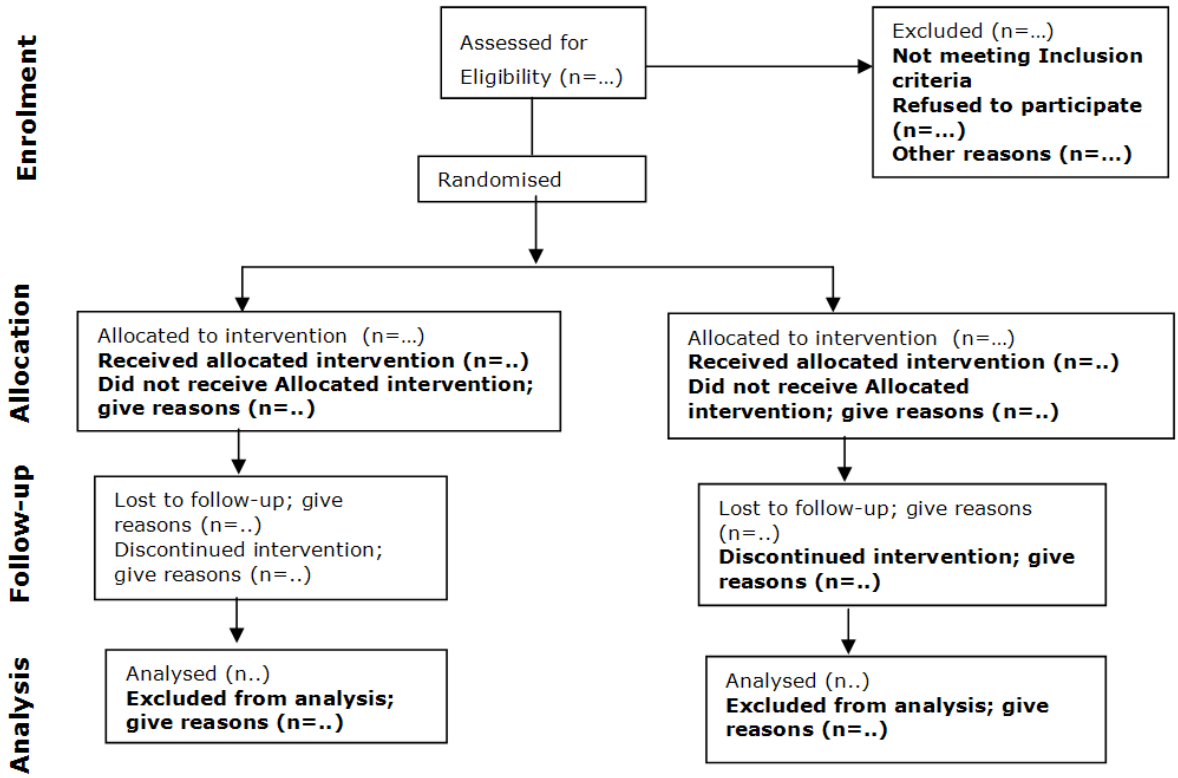
Source: [P775V01MK3475: adam-adsl]

Table 19: Study Population in pMMR Participants

	Lenvatinib + Pembrolizumab	TPC	Total
Number of Participants Randomized (ITT)	346	351	697
Number of Participants Received Treatment (Actual Treatment) (APaT)	342	325	667
Number of Participants Randomized and Did not Receive Treatment	4	26	30
TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel. Database Cutoff Date: 26OCT2020			

Source: [P775V01MK3475: adam-adsl]

Participant flow



Outcomes and estimation

The MAH provided the results of IA1- final efficacy analysis for PFS and interim efficacy analysis for OS in both pMMR and all-comer participants. As of the data cutoff date (26-OCT-2020), the median duration of follow-up was 12 months in the lenvatinib plus pembrolizumab group and 10.8 months in the TPC group.

Table 20: Summary of Follow-up Duration in pMMR Participants (ITT Population)

Follow-up duration (months)[a]	Lenvatinib + Pembrolizumab (N=346)	TPC (N=351)	Total (N=697)
Median (Range)	12.0 (0.3, 26.9)	10.8 (0.3, 26.3)	11.4 (0.3, 26.9)
Mean (SD)	12.5 (6.3)	11.2 (5.7)	11.8 (6.0)

[a] Follow-up duration is defined as the time from randomization to the date of death or the database cutoff date if the participant is still alive.
TPC = Treatment Physician's Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

Source: [P775V01MK3475: adam-adsl]

Table 21: Summary of Follow-up Duration in All-comer Participants (ITT Population)

Follow-up duration (months)[a]	Lenvatinib + Pembrolizumab (N=411)	TPC (N=416)	Total (N=827)
Median (Range)	12.2 (0.3, 26.9)	10.7 (0.3, 26.3)	11.4 (0.3, 26.9)
Mean (SD)	12.7 (6.3)	11.0 (5.9)	11.8 (6.1)

[a] Follow-up duration is defined as the time from randomization to the date of death or the database cutoff date if the participant is still alive.
TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

Source: [P775V01MK3475: adam-adsl]

PFS primary endpoint

pMMR

Table 22: PFS by BICR Assessment per RECIST 1.1 in pMMR Participants (ITT)

Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median PFS [a] (months) (95% CI)	PFS Rate at 6 months in % [a] (95% CI)
Lenvatinib + Pembrolizumab	346	247 (71.4)	2538.0	9.7	6.6 (5.6, 7.4)	52.1 (46.5, 57.3)
TPC	351	238 (67.8)	1458.8	16.3	3.8 (3.6, 5.0)	36.2 (30.5, 41.9)
Pairwise Comparisons					Hazard Ratio[b] (95% CI)[b]	p-Value
Lenvatinib + Pembrolizumab vs. TPC					0.60 (0.50, 0.72)	<0.0001[c]

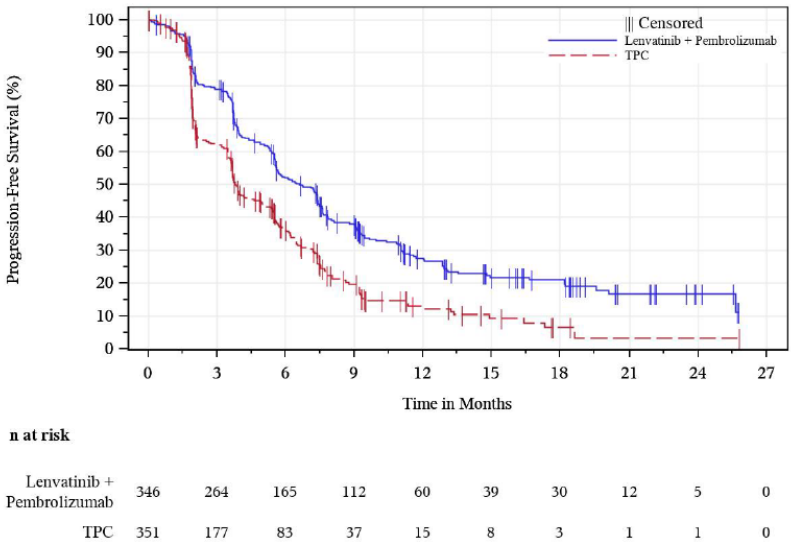
a From product-limit (Kaplan-Meier) method for censored data. b Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by ECOG performance status, geographic region, and prior history of pelvic radiation. c One-sided p-value based on log-rank test stratified by ECOG performance status, geographic region, and prior history of pelvic radiation. Analysis includes one participant who was stratified with a dMMR status, but actually had a pMMR status; stratification factors for this participant are derived from actual ECOG performance status, geographic region, and prior history of pelvic radiation. BICR= Blinded Independent Central Review. TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel. Database Cutoff Date: 26OCT2020

Table 23: Summary Of PFS Rate Over Time Based on BICR Assessment per RECIST 1.1 (Primary Censoring Rule) in pMMR Participants

	Lenvatinib + Pembrolizumab (N=346) % (95% CI)[a]	TPC (N=351) % (95% CI)[a]
Summary of Progression-Free Survival rate at time point		
6 months	52.1 (46.5, 57.3)	36.2 (30.5, 41.9)
12 months	27.6 (22.5, 32.8)	13.1 (8.9, 18.3)
18 months	21.1 (16.3, 26.3)	6.6 (3.0, 12.1)
24 months	16.8 (11.8, 22.4)	3.3 (0.5, 11.4)

[a] From product-limit (Kaplan-Meier) method for censored data.
BICR = Blinded Independent Central Review.
TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

Source: [P775V01MK3475: adam-adsl; adtte]



n at risk

Lenvatinib + Pembrolizumab	346	264	165	112	60	39	30	12	5	0
TPC	351	177	83	37	15	8	3	1	1	0

Figure *12*: Kaplan-Meier Estimates of Progression-Free Survival Based on BICR Assessment per RECIST 1.1 (Primary Censoring Rule) in pMMR Participants (ITT Population)

All-comers

Table 24: PFS by BICR Assessment per RECIST 1.1 in All-comer Participants (ITT)

Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median PFS [a] (months) (95% CI)	PFS Rate at 6 months in % [a] (95% CI)
Lenvatinib + Pembrolizumab	411	281 (68.4)	3178.9	8.8	7.2 (5.7, 7.6)	53.5 (48.4, 58.3)
TPC	416	286 (68.8)	1726.5	16.6	3.8 (3.6, 4.2)	34.3 (29.2, 39.4)
Pairwise Comparisons					Hazard Ratio[b] (95% CI)[b]	p-Value
Lenvatinib + Pembrolizumab vs. TPC					0.56 (0.47, 0.66)	<0.0001[c]

a From product-limit (Kaplan-Meier) method for censored data. b Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation. c One-sided p-value based on log-rank test stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation. Database Cutoff Date: 26OCT2020

Table 25: Summary Of PFS Rate Over Time Based on BICR Assessment per RECIST 1.1 (Primary Censoring Rule) in All-comer Participants

	Lenvatinib + Pembrolizumab (N=411) % (95% CI)[a]	TPC (N=416) % (95% CI)[a]
Summary of Progression-Free Survival rate at time point		
6 months	53.5 (48.4, 58.3)	34.3 (29.2, 39.4)
12 months	31.2 (26.4, 36.0)	13.2 (9.3, 17.8)
18 months	25.0 (20.4, 29.9)	7.6 (4.1, 12.6)
24 months	20.9 (16.0, 26.2)	3.8 (0.6, 12.7)

[a] From product-limit (Kaplan-Meier) method for censored data.
BICR = Blinded Independent Central Review.
TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

Source: [P775V01MK3475: adam-adsl; adtte]

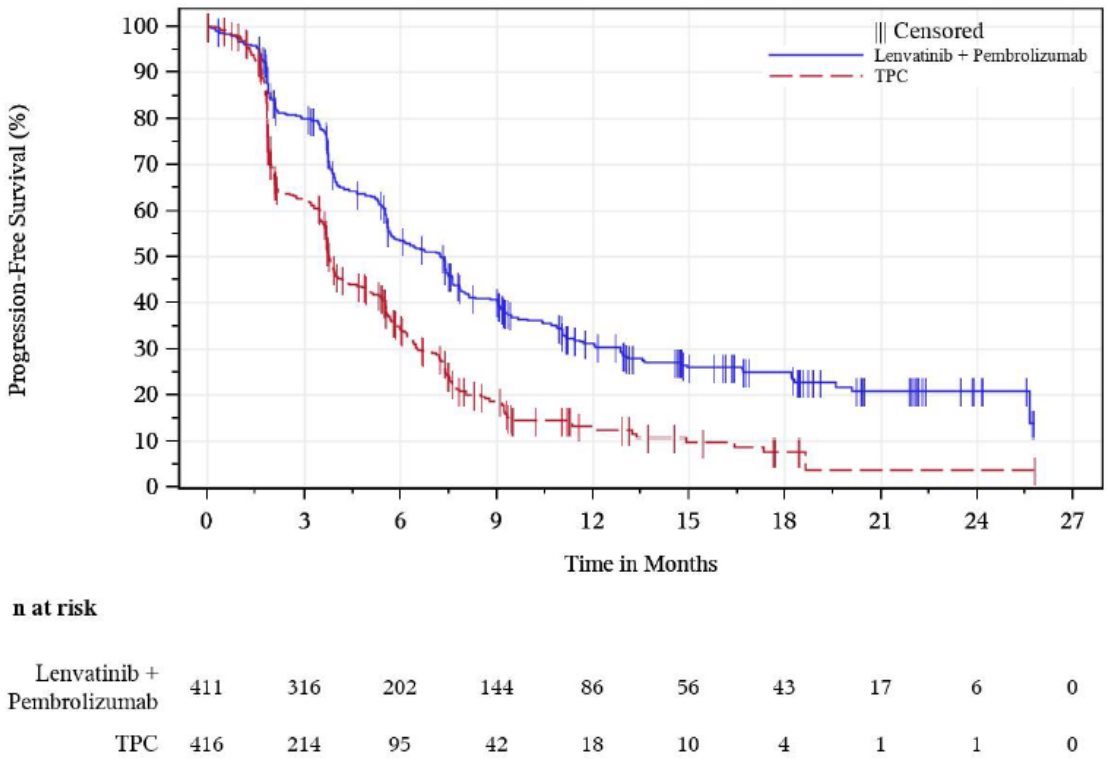


Figure *13*: Kaplan-Meier Estimates of Progression-Free Survival Based on BICR Assessment per RECIST 1.1 (Primary Censoring Rule) in All-comer Participants (ITT Population)

OS primary endpoint

At IA1, the median OS in the lenvatinib plus pembrolizumab group was 18.3 months, showing a statistically significant improvement compared with that in the TPC group 11.4 months, HR of 0.62 (95% CI: 0.51, 0.75; p<0.0001) crossed the pre-specified boundary for statistical significance at IA1 of ≤0.0064.

pMMR

Table 26: OS in pMMR Participants (ITT)

Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median OS [a] (months) (95% CI)	OS Rate at 12 months in % [a] (95% CI)
Lenvatinib + Pembrolizumab	346	165 (47.7)	4128.6	4.0	17.4 (14.2, 19.9)	61.6 (56.1, 66.6)
TPC	351	203 (57.8)	3564.8	5.7	12.0 (10.8, 13.3)	49.5 (43.8, 55.0)
Pairwise Comparisons					Hazard Ratio[b] (95% CI)[b]	p-Value
Lenvatinib + Pembrolizumab vs. TPC					0.68 (0.56, 0.84)	0.0001[c]

a From product-limit (Kaplan-Meier) method for censored data. b Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by ECOG performance status, geographic region, and prior history of pelvic radiation. c One-sided p-value based on log-rank test stratified by ECOG performance status, geographic region, and prior history of pelvic radiation. Analysis includes one participant who was stratified with a dMMR status, but actually had a pMMR status; stratification factors for this participant are derived from actual ECOG performance status, geographic region, and prior history of pelvic radiation. Database Cutoff Date: 26OCT2020

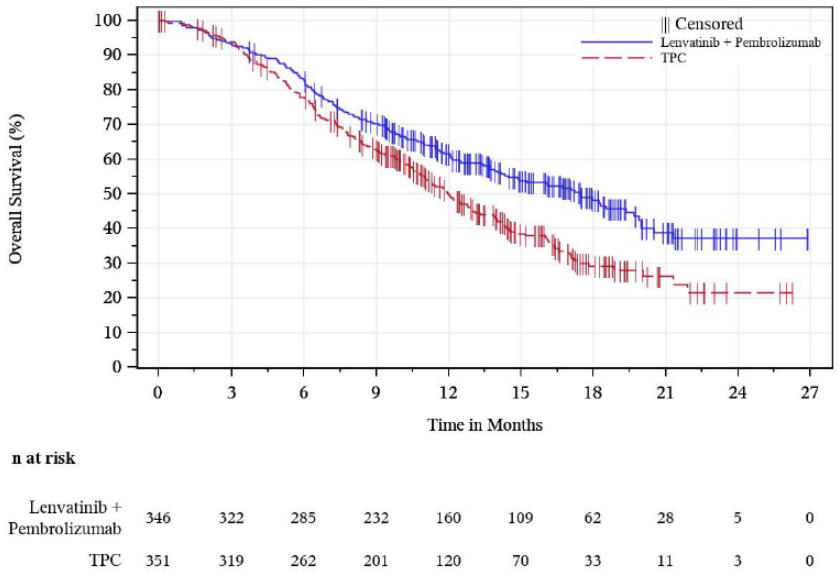


Figure 14: Kaplan-Meier Estimates of Overall Survival in pMMR Participants (ITT Population)

All-comer

Table 27: OS in All-comer Participants (ITT)

Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median OS [a] (months) (95% CI)	OS Rate at 12 months in % [a] (95% CI)
Lenvatinib + Pembrolizumab	411	188 (45.7)	5009.2	3.8	18.3 (15.2, 20.5)	62.5 (57.5, 67.1)
TPC	416	245 (58.9)	4122.6	5.9	11.4 (10.5, 12.9)	47.9 (42.7, 53.0)
Pairwise Comparisons					Hazard Ratio[b] (95% CI)[b]	p-Value
Lenvatinib + Pembrolizumab vs. TPC					0.62 (0.51, 0.75)	<0.0001[c]

a From product-limit (Kaplan-Meier) method for censored data. b Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation. c One-sided p-value based on log-rank test stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation. Database Cutoff Date: 26OCT2020

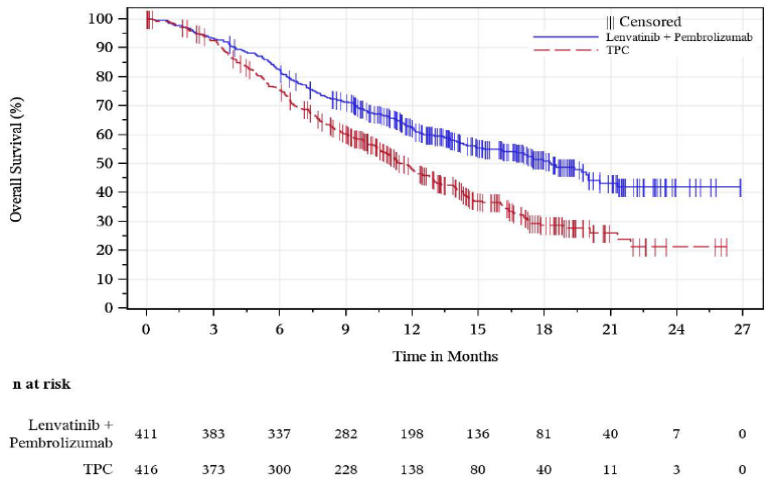


Figure *15*: Kaplan-Meier Estimates of Overall Survival in All-comer Participants (ITT)

Secondary Efficacy Endpoints

Objective response rate (ORR)

In all randomised patients, ORR was 31.9% in the lenvatinib plus pembrolizumab group and 14.7% in the TPC group respectively, with an estimated difference of 17.2% (95% CI: 11.5, 22.9; p<0.0001)

For pMMR patients, ORR was 30.3% in the lenvatinib plus pembrolizumab group and 15.1% in the TPC group respectively, with an estimated difference of 15.2% (95% CI: 9.1, 21.4.7; p<0.0001)

Quality of Life (EORTC QLQ-30)

The global health status/quality of life (GHS/QoL) score of EORTC QLQ-30 was a secondary endpoint. The schedule for PRO data collection is described in supplemental SAP-01 (17 NOV 2020) and was planned to occur at least until week 24. At each scheduled visit, three instruments, EORTC QLQ-C30, EORTC QLQ-EN24 and EQ-5D, were collected.

In pMMR participants, completion rate of the EORTC QLQ-C30 was above 95% in both the lenvatinib plus pembrolizumab and TPC groups at baseline. The completion rate for pMMR participants remained above 60% through Week 12 (77.8% vs 61.7% for the lenvatinib plus pembrolizumab and TPC groups, respectively). Compliance rates at baseline were also above 96% in both arms. Compliance remained high through Week 12 (91.8% for lenvatinib plus pembrolizumab group and 86.9% for TPC group).

In All-comer Participants, completion rate of the EORTC QLQ-C30 was above 95% in both the lenvatinib plus pembrolizumab and TPC groups at baseline. The completion rate for all-comer participants remained above 60% through Week 12 (79.9% vs 62.4% for the lenvatinib plus pembrolizumab and TPC groups, respectively). Completion rates dropped gradually for both arms as the trial progressed likely because of the reduction in the number of patients scheduled to finish the questionnaires at each time point as a result of disease progression, adverse event, or death. Compliance rates at baseline were also above 96% in both arms. Compliance remained high through Week 12 (91.8% for Lenvatinib plus pembrolizumab and 86.9% for TPC).

The completion rates and compliance rates in both pMMR and all-comer participants for EORTC QLQ-EN24 and EQ-5D were consistent with those for EORTC QLQ-C30.

In both Al-comer patients and pMMR population, the differences in score change from baseline to week 12 for EORTC-QLQ-C30 GHS/QoL scale between lenvatinib plus pembrolizumab and TPC groups were not significantly different.

Table 28: Analysis of Change from Baseline in EORTC QLQ-C30 Global Health Status to Week 12 (All-comer Full Analysis Set)

	Baseline		Week 12		Change from Baseline to Week 12	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[a]
Lenvatinib + Pembrolizumab	370	65.74 (21.87)	310	60.56 (21.35)	386	-5.97 (-8.36, -3.58)
TPC	351	65.69 (22.71)	227	62.70 (21.08)	363	-6.98 (-9.63, -4.33)

Pairwise Comparison	Difference in LS Means[a] (95% CI)	p-Value[a]
Lenvatinib + Pembrolizumab vs. TPC	1.01 (-2.28, 4.31)	0.5460

[a] Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction, stratification factors MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation.
For baseline and Week 12, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.
TPC = Treatment Physician's Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

Source: [P775V01MK3475: adam-adsl; adpro]

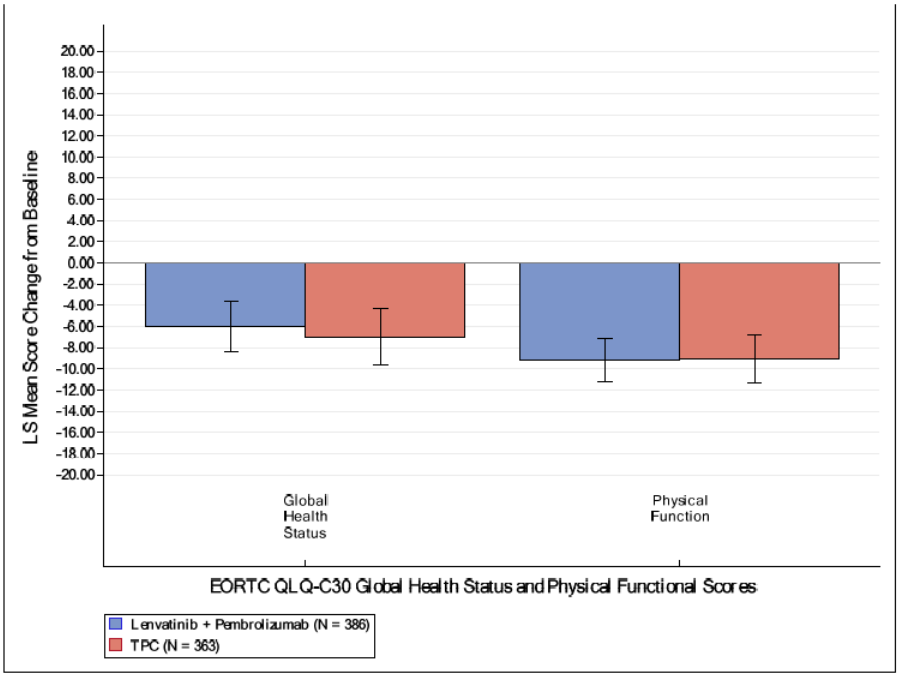


Figure *16*: Change from Baseline to Week 12 and 95% CI in EORTC QLC-C30 Global Health Status and Physical Functional Scores (All-comer Full Analysis Set)

Exploratory endpoints

Duration of Response (DOR) and Time to Response (TTR)

Table 29: Summary of Time to Response and DOR Based on BICR Assessment per RECIST 1.1 in Participants with Confirmed Response in pMMR Participants (ITT Population)

	Lenvatinib + Pembrolizumab (N=346)	TPC (N=351)
Number of participants with response[a]	105	53
Time to Response (months)		
Mean (SD)	3.2 (1.8)	3.0 (1.3)
Median (Range)	2.1 (1.5-9.4)	3.5 (1.0-7.4)
Response Duration[b] (months)		
Median (Range)	9.2 (1.6+ - 23.7+)	5.7 (0.0+ - 24.2+)

a Includes participants with complete response or partial response b From product-limit (Kaplan-Meier) method for censored data. "+" indicates there is no progressive disease by the time of last disease assessment.

Database Cutoff Date: 26OCT2020 Source: [P775V01MK3475: adam-adsl; adtte; adrs]

Table 30: Summary of Time to Response and DOR Based on BICR Assessment per RECIST 1.1 in Participants with Confirmed Response in All-comer Participants (ITT Population)

	Lenvatinib + Pembrolizumab (N=411)	TPC (N=416)
Number of participants with response[a]	131	61
Time to Response (months)		
Mean (SD)	3.3 (2.1)	2.9 (1.2)
Median (Range)	2.1 (1.5-16.3)	2.1 (1.0-7.4)
Response Duration[b] (months)		
Median (Range)	14.4 (1.6+ - 23.7+)	5.7 (0.0+ - 24.2+)

a Includes participants with complete response or partial response b From product-limit (Kaplan-Meier) method for censored data. "+" indicates there is no progressive disease by the time of last disease assessment.

Database Cutoff Date: 26OCT2020 Source: [P775V01MK3475: adam-adsl; adtte; adrs]

Ancillary analyses

PFS sensitivity analyses

Table 31: Analysis of Progression-Free Survival Based on BICR Assessment per RECIST 1.1 (Sensitivity Censoring Rule 1) in All-comer Participants (ITT Population)

Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median PFS [a] (months) (95% CI)	PFS Rate at 6 months in % [a] (95% CI)
Lenvatinib + Pembrolizumab	411	301 (73.2)	3308.0	9.1	7.2 (5.7, 7.6)	53.6 (48.6, 58.3)
TPC	416	337 (81.0)	2110.0	16.0	3.9 (3.7, 5.4)	38.2 (33.3, 43.1)
Pairwise Comparisons					Hazard Ratiob (95% CI)[b]	p-Value
Lenvatinib + Pembrolizumab vs. TPC					0.58 (0.49, 0.68)	<0.0001c

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation.
[c] One-sided p-value based on log-rank test stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation.
BICR= Blinded Independent Central Review.
TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

Source: [P775V01MK3475: adam-adsl; adtte]

Table 32: Analysis of Progression-Free Survival Based on BICR Assessment per RECIST 1.1 (Sensitivity Censoring Rule 2) in All-comer Participants (ITT Population)

Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median PFS [a] (months) (95% CI)	PFS Rate at 6 months in % [a] (95% CI)
Lenvatinib + Pembrolizumab	411	328 (79.8)	3285.4	10.0	6.4 (5.6, 7.4)	51.6 (46.6, 56.3)
TPC	416	391 (94.0)	2080.0	18.8	3.8 (3.6, 4.2)	34.4 (29.8, 39.0)
Pairwise Comparisons					Hazard Ratiob (95% CI)[b]	p-Value
Lenvatinib + Pembrolizumab vs. TPC					0.53 (0.45, 0.61)	<0.0001c

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation.
[c] One-sided p-value based on log-rank test stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation.
BICR= Blinded Independent Central Review.
TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

Source: [P775V01MK3475: adam-adsl; adtte]

Table 33: Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Primary Censoring Rule) in All-comer Participants (ITT Population)

Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median PFS [a] (months) (95% CI)	PFS Rate at 6 months in % [a] (95% CI)
Lenvatinib + Pembrolizumab	411	293 (71.3)	3273.9	8.9	7.3 (5.7, 7.6)	54.0 (49.0, 58.8)
TPC	416	302 (72.6)	1849.2	16.3	4.2 (3.7, 5.4)	33.6 (28.6, 38.6)
Pairwise Comparisons					Hazard Ratiob (95% CI)[b]	p-Value
Lenvatinib + Pembrolizumab vs. TPC					0.56 (0.47, 0.66)	<0.0001c

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation.
[c] One-sided p-value based on log-rank test stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation.
TPC = Treatment Physician's Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

Source: [P775V01MK3475: adam-adsl; adtte]

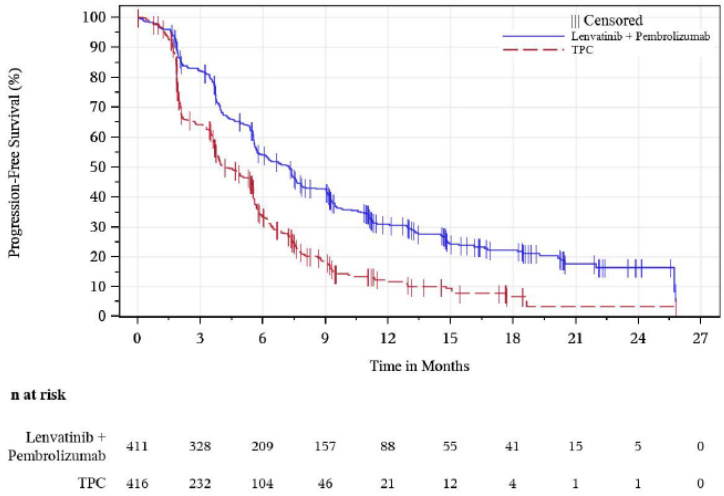


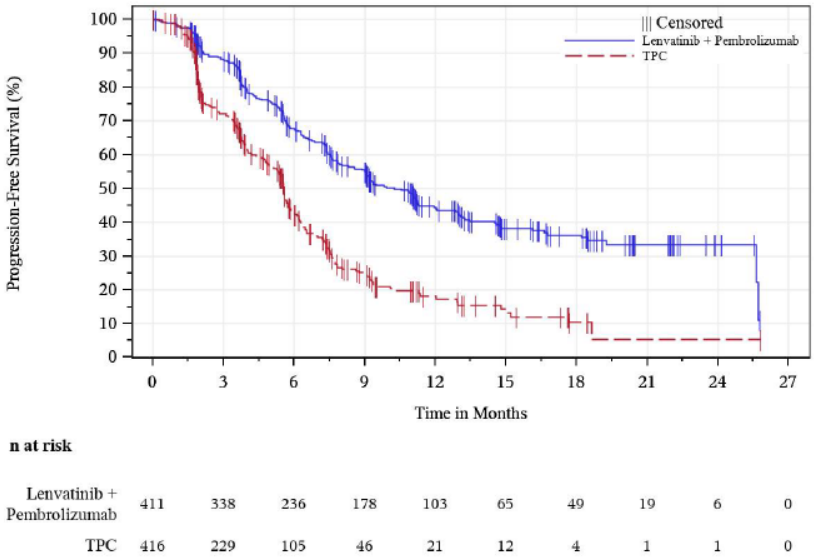
Figure *17*: Kaplan-Meier Estimates of PFS Based on Investigator Assessment per RECIST 1.1 (Primary Censoring Rule) in All-comer Participants (ITT Population)

Table 34: Analysis of Progression-Free Survival Based on Investigator Assessment per iRECIST (Primary Censoring Rule) in All-comer Participants (ITT Population)

Treatment	N	Number of Events (%)	Person-month	Event Rate/ 100 Person-months	Median PFS [a] (months) (95% CI)	PFS Rate at 6 months in % [a] (95% CI)
Lenvatinib + Pembrolizumab	411	214 (52.1)	3560.6	6.0	10.3 (9.0, 12.0)	67.7 (62.7, 72.2)
TPC	416	239 (57.5)	1854.6	12.9	5.6 (5.3, 5.7)	42.8 (37.1, 48.4)
Pairwise Comparisons					Hazard Ratiob (95% CI)[b]	p-Value
Lenvatinib + Pembrolizumab vs. TPC					0.47 (0.39, 0.57)	<0.0001c

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation.
[c] One-sided p-value based on log-rank test stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation.
TPC = Treatment Physician's Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

Source: [P775V01MK3475: adam-adsl; adtte]



n at risk

Lenvatinib + Pembrolizumab	411	338	236	178	103	65	49	19	6	0
TPC	416	229	105	46	21	12	4	1	1	0

Figure *18*: Kaplan-Meier Estimates of PFS Based on Investigator Assessment per iRECIST (Primary Censoring Rule) in All-comer Participants (ITT Population)

Subgroup analyses

Table 35: PFS by Subgroup Factors Based on BICR Assessment per RECIST 1.1 (Primary Censoring Rule) in All-comer Participants (ITT Population)

	Lenvatinib + Pembrolizumab (N=411)			TPC (N=416)			Lenvatinib + Pembrolizumab vs. TPC
	N	Number of Events	(%)	N	Number of Events	(%)	Hazard Ratio (95% CI)[a]
Overall	411	281	(68.4)	416	286	(68.8)	0.56 (0.47, 0.66)
Age Group 1							
< 65	206	138	(67.0)	204	146	(71.6)	0.49 (0.38, 0.62)
>= 65	205	143	(69.8)	212	140	(66.0)	0.61 (0.48, 0.78)
Age Group 2							
< 65	206	138	(67.0)	204	146	(71.6)	0.49 (0.38, 0.62)
65-74	170	118	(69.4)	169	112	(66.3)	0.62 (0.47, 0.80)
>= 75	35	25	(71.4)	43	28	(65.1)	0.58 (0.33, 1.02)
Race							
White	261	177	(67.8)	246	163	(66.3)	0.56 (0.45, 0.70)
Asian	85	59	(69.4)	92	62	(67.4)	0.63 (0.44, 0.91)
Other	29	20	(69.0)	34	28	(82.4)	0.42 (0.23, 0.78)
Region							
Region 1	234	160	(68.4)	240	169	(70.4)	0.50 (0.40, 0.63)
Region 2	177	121	(68.4)	176	117	(66.5)	0.61 (0.47, 0.79)
pMMR Status							
pMMR	346	247	(71.4)	351	238	(67.8)	0.60 (0.50, 0.72)
dMMR Status							
dMMR	65	34	(52.3)	65	48	(73.8)	0.36 (0.23, 0.57)
ECOG Status							
0	246	166	(67.5)	241	162	(67.2)	0.53 (0.42, 0.66)
1	164	115	(70.1)	175	124	(70.9)	0.58 (0.45, 0.75)
Prior History of Pelvic Radiation							
Yes	168	111	(66.1)	173	114	(65.9)	0.52 (0.40, 0.69)
No	243	170	(70.0)	243	172	(70.8)	0.56 (0.45, 0.69)
Histology							
Endometrioid	243	150	(61.7)	254	173	(68.1)	0.52 (0.41, 0.65)
Non-endometrioid	168	131	(78.0)	162	113	(69.8)	0.56 (0.43, 0.73)
Prior Lines of Therapy							
1	297	207	(69.7)	277	203	(73.3)	0.49 (0.40, 0.60)
2	103	71	(68.9)	126	79	(62.7)	0.66 (0.48, 0.92)
>=3	11	3	(27.3)	13	4	(30.8)	0.51 (0.11, 2.30)

[a] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
Subgroup analyses were conducted using an unstratified Cox model, with the exception of the 'Overall' and 'pMMR' rows, which utilized the same stratified Cox models as conducted for the primary analysis of All-comer and pMMR participants, respectively.
Database Cutoff Date: 26OCT2020

[P775V01MK3475: adam-adsl; adtte]

PFS

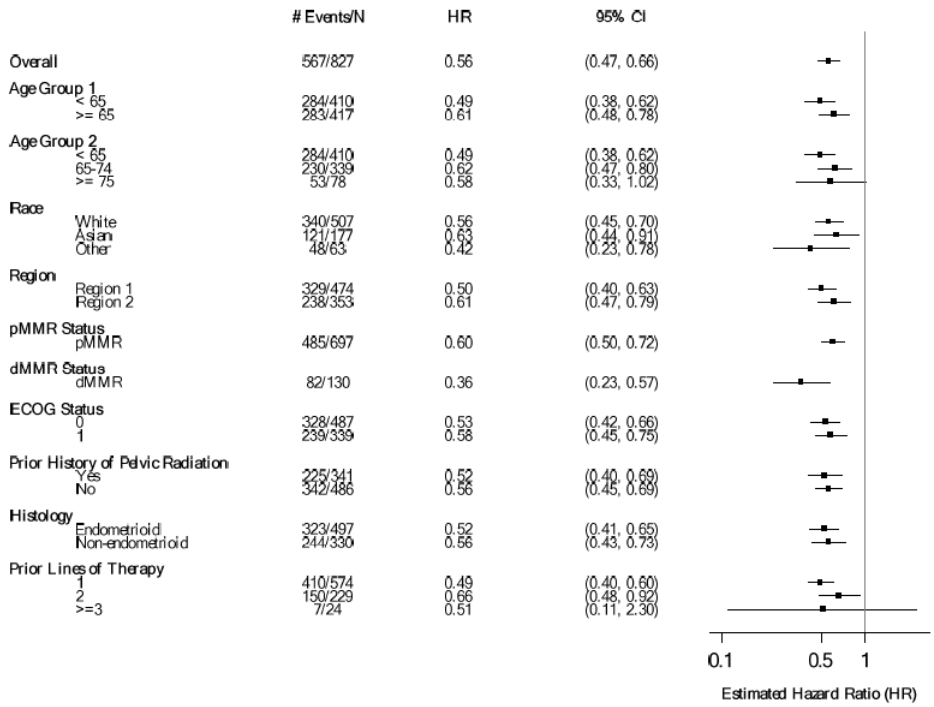


Figure *19*: PFS by Subgroup Factors Based on BICR Assessment per RECIST 1.1 (Primary Censoring Rule) in All-comer Participants (ITT Population)

Note: Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel or Region 2: rest of the world

Database Cutoff Date: 26OCT2020 Source: [P775V01MK3475: adam-adsl; adtte]

OS

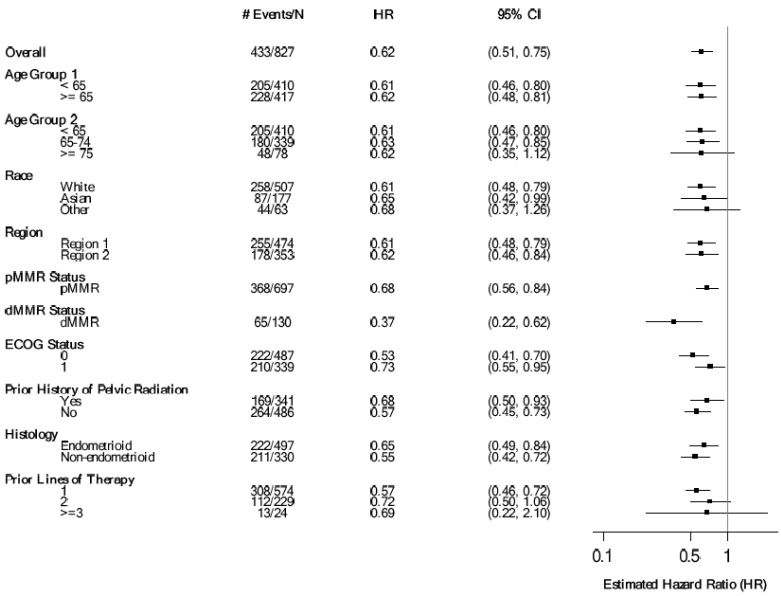


Figure *20*: OS by Subgroup Factors in All-comer Participants (ITT Population)

MMR status (pMMR or dMMR)

In the study 309, 130 enrolled patients had dMMR EC (65 in each group) and the analyses of primary and secondary efficacy endpoints were based on the ITT population (n=130). The dMMR subgroup was

not prespecified in the multiplicity strategy for Type I error control, so only nominal p-values are provided for the efficacy endpoints.

The clinical characteristics in dMMR participants were comparable between the two treatment groups, with a median age of 65 years, nearly 60% white race as well as almost 20% Asian, and had half patients with ECOG performance status of 0.

Table 36: Study 309: Disease characteristics in dMMR participants (ITT population)

	Lenvatinib + Pembrolizuma		TPC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	65		65		130	
Prior History of Pelvic Radiation						
Yes	32	(49.2)	34	(52.3)	66	(50.8)
No	33	(50.8)	31	(47.7)	64	(49.2)
Elapsed Time (Years) from Initial Diagnosis						
Participants with data	65		65		130	
Mean	2.2		2.9		2.5	
SD	2.0		2.6		2.3	
Median	1.7		2.4		1.9	
Range	0 to 13		0 to 17		0 to 17	
Histology of Initial Diagnosis						
Clear Cell Carcinoma	1	(1.5)	0	(0.0)	1	(0.8)
Endometrioid Carcinoma	23	(35.4)	29	(44.6)	52	(40.0)
Endometrioid Carcinoma With	2	(3.1)	1	(1.5)	3	(2.3)
Differentiation						
High Grade Endometrioid Carcinoma	21	(32.3)	13	(20.0)	34	(26.2)
High Grade Serous	3	(4.6)	1	(1.5)	4	(3.1)
Low Grade Endometrioid Carcinoma	9	(13.8)	13	(20.0)	22	(16.9)
Mixed	4	(6.2)	3	(4.6)	7	(5.4)
Serous Carcinoma	1	(1.5)	2	(3.1)	3	(2.3)
Unclassified	0	(0.0)	1	(1.5)	1	(0.8)
Undifferentiated Histology	0	(0.0)	1	(1.5)	1	(0.8)
Other	1	(1.5)	1	(1.5)	2	(1.5)
FIGO Stage at Initial Diagnosis						
I	1	(1.5)	1	(1.5)	2	(1.5)
IA	13	(20.0)	11	(16.9)	24	(18.5)
IB	7	(10.8)	13	(20.0)	20	(15.4)
II	2	(3.1)	4	(6.2)	6	(4.6)
III	0	(0.0)	2	(3.1)	2	(1.5)
IIIA	5	(7.7)	4	(6.2)	9	(6.9)
IIIB	0	(0.0)	3	(4.6)	3	(2.3)
IIIC	8	(12.3)	4	(6.2)	12	(9.2)
IIIC1	3	(4.6)	5	(7.7)	8	(6.2)
IIIC2	5	(7.7)	7	(10.8)	12	(9.2)
IV	2	(3.1)	3	(4.6)	5	(3.8)
IVA	3	(4.6)	1	(1.5)	4	(3.1)
IVB	16	(24.6)	7	(10.8)	23	(17.7)
Brain Metastasis [C]						
Yes	1	(1.5)	0	(0.0)	1	(0.8)
No	64	(98.5)	65	(100.0)	129	(99.2)
Bone Metastasis [C]						
Yes	6	(9.2)	5	(7.7)	11	(8.5)

No	59	(90.8)	60	(92.3)	119	(91.5)
Liver Metastasis [c]						
Yes	11	(16.9)	8	(12.3)	19	(14.6)
No	54	(83.1)	57	(87.7)	111	(85.4)
Lung Metastasis [c]						
Yes	24	(36.9)	22	(33.8)	46	(35.4)
No	41	(63.1)	43	(66.2)	84	(64.6)
Intra-abdominal Metastasis [b] [c]						
Yes	21	(32.3)	25	(38.5)	46	(35.4)
No	44	(67.7)	40	(61.5)	84	(64.6)
Lymph node Metastasis [c]						
Yes	41	(63.1)	34	(52.3)	75	(57.7)
No	24	(36.9)	31	(47.7)	55	(42.3)

[a] Region 1: Europe, USA, Canada, Australia, New Zealand, Israel; Region 2: Rest of World.

[b] Includes reported locations of colon, abdominal cavity, omentum, small intestine, peritoneal cavity, and peritoneum. Does not include lymph nodes or other organs.

[c] Lesion location as determined by investigator review.

Database Cutoff Date: 26OCT2020

Source: [P775V01MK3475: adam-adsl]

Table 37: Study 309: Summary of Efficacy Results Based on BICR Assessment per RECIST 1.1 in dMMR Participants

Endpoint	Lenvatinib + Pembrolizumab (N=65)	TPC (Chemotherapy) (N=65)
PFS[a]		
Median PFS, months (95% CI)	10.7 (5.6, NR)	3.7 (3.1, 4.4)
HR (95% CI)[b], p-value [c]	0.36 (0.23, 0.57), <0.0001	
OS[a]		
Median OS, months (95% CI)	NR (NR, NR)	8.6 (5.5, 12.9)
HR (95% CI)[b], p-value [c]	0.37 (0.22, 0.62), <0.0001	
ORR		
Response Rate (%) (95% CI)	40.0 (28.0, 52.9)	12.3 (5.5, 22.8)
Difference in % vs. TPC (95% CI)[d], p-value[e]	27.7 (12.9, 41.7), 0.0002	

Abbreviations: BICR = blinded independent central review; CI = confidence interval; dMMR = mismatch repair deficient; HR = hazard ratio; NR = not reached; OS = overall survival; PFS = progression-free survival; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; TPC = treatment physician´s choice of doxorubicin or paclitaxel.

[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.

[c] One-sided p-value based on log-rank test.

[d] Based on Miettinen & Nurminen method.

[e] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.

Source: [Ref. 5.3.5.1: P775V01MK3475: Table 11-24, 11-25, 11-26].

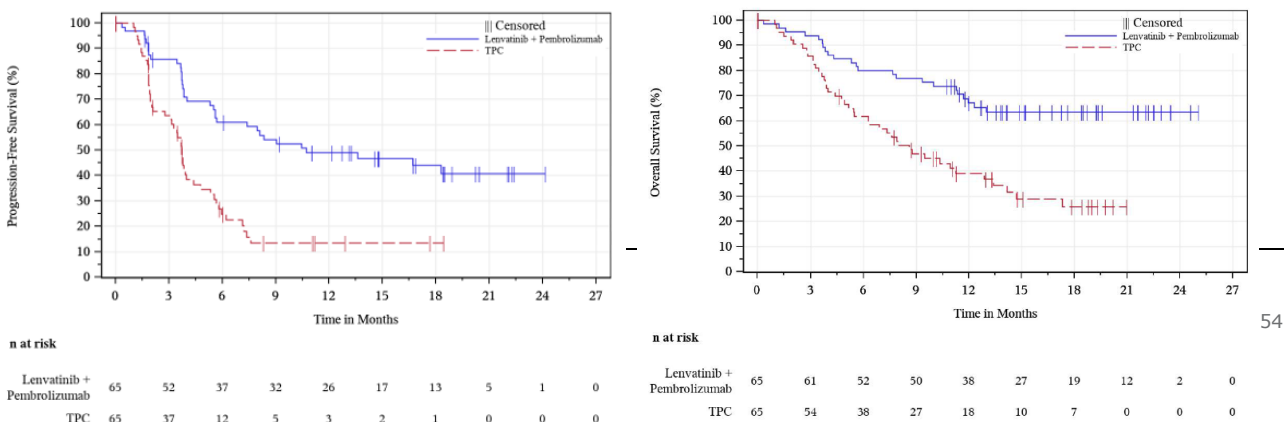


Figure *21*: Kaplan-Meier Estimates of PFS Based on BICR Assessment per RECIST 1.1 (Primary Censoring Rule) and OS in dMMR Participants (ITT Population)

Table 38: Study 309: Summary of Efficacy Results for the Lenvatinib + Pembrolizumab Group: Endometrial Carcinoma All-Comer Population, pMMR Population and dMMR Population

	Lenvatinib + Pembrolizumab		
Endpoint	**All-Comer Population (N=411)**	**pMMR Population (N=346)**	**dMMR Population (N=65)**
Overall Survival			
Median OS[a], months (95% CI)	18.3 (15.2, 20.5)	17.4 (14.2, 19.9)	NR (NR, NR)
Progression Free Survival (BICR Assessment per RECIST 1.1)			
Median PFS[a], months (95% CI)	7.2 (5.7, 7.6)	6.6 (5.6, 7.4)	10.7 (5.6, NR)
Objective Response Rate (BICR Assessment per RECIST 1.1)			
% (95% CI)	31.9 (27.4, 36.6)	30.3 (25.5, 35.5)	40.0 (28.0, 52.9)
CR, n (%) (95% CI)	27 (6.6) (4.4, 9.4)	18 (5.2) (3.1, 8.1)	9 (13.8) (6.5, 24.7)
Median Duration of Response months (range)	N=131 14.4 (1.6+ - 23.7+)	N=105 9.2 (1.6+ - 23.7+)	N=26 NR (2.1+ – 20.4+)

BICR = blinded independent central review; CI = confidence interval; CR = complete response; dMMR = mismatch repair deficient; ECOG = Eastern Cooperative Oncology Group; NR = not reached; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; pMMR = mismatch repair proficient; RECIST = Response Evaluation Criteria in Solid Tumors version; TPC = treatment of physician's choice.
a: From product-limit (Kaplan-Meier) method for censored data.
Data cutoff: 26-OCT-2020. Source: [P775V01MK3475: adam-adsl; adtte; adrs].

Subsequent Systemic Anti-Cancer Treatment

For all randomised patients, 28% patients in the lenvatinib plus pembrolizumab group and 48% patients in the TPC group received at least 1 subsequent systemic anticancer therapy. 7.7% patients (n=32) in the TPC group switched to lenvatinib and pembrolizumab afterwards. Compared with the lenvatinib and pembrolizumab group, more patients in TPC group switched to the subsequent PD 1/PD L1 checkpoint and VEGF/ VEGFR inhibition treatment (PD 1/PD L1 checkpoint: 12.7% patients (n=53) vs 1.0% patients (n=4), VEGF/VEGFR inhibitor: 11.1% patients (n=46) VS 2.4% patient (n=10)). Of note, 2 patients in the lenvatinib plus pembrolizumab group received subsequent oncologic surgeries compared with 13 cases in TPC group. A total of 82 patients (9.9%) received subsequent radiation, including 27 case in combination treatment group (6.6%) and 55 cases in TPC (13.2%). In pMMR patients, the similar differences on the subsequent systemic treatment were observed.

Ancillary analyses

Summary of main study(ies)

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

Table 39: Summary of Efficacy for trial 309/KEYNOTE-775

Title: A Multicenter, Open-label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination with Pembrolizumab Versus Treatment of Physician's Choice in Participants with Advanced Endometrial Cancer			
Study identifier	P775V01MK3475 (IND: 118808 EudraCT number: 2017- 004387-35; NCT number: 03517449)		
Design	Phase 3, two-arm, multicenter, open-label, randomized, controlled study		
	Duration of main phase: Duration of run-in phase: Duration of extension phase:		Enrollment started on 11-JUN-2018; Data cut off: 26-OCT-2020. Study ongoing. not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Lenvatinib + Pembrolizumab N=411		Lenvatinib 20 mg orally (PO) once daily (QD) plus pembrolizumab 200 mg intravenously (IV) every 3 weeks (Q3W)
	TPC N=416		Doxorubicin 60 mg/m^2 IV Q3W or Paclitaxel 80 mg/m^2 IV every week, 3 weeks on/1 week off
Endpoints and definitions	Dual Primary endpoint	PFS	PFS, defined as the time from date of randomization to the date of the first documentation of disease progression, as determined by BICR per RECIST 1.1, or death from any cause (whichever occurred first).
	Dual Primary Endpoint	OS	OS, defined as the time from date of randomization to date of death from any cause.
	Secondary	ORR	ORR, defined as the proportion of participants who have best overall response of either CR or PR, as determined by BICR per RECIST 1.1.
Database lock	20-NOV-2020		
Results and Analysis			
Analysis description	**Primary Analysis** (Interim Analysis 1)		
Analysis population and time point description	Intent-to-treat (ITT) population		
Descriptive statistics and estimate variability	**ITT Population – All Randomised**		
	Treatment group	Lenvatinib + Pembrolizumab	TPC
	Number of subjects	411	416
	PFS median (months)	7.2	3.8

	95% CI	5.7, 7.6	3.6, 4.2
	OS median (months)	18.3	11.4
	95% CI	15.2, 20.5	10.5, 12.9
	ORR (%)	31.9	14.7
	95% CI	27.4, 36.6	11.4, 18.4
Effect estimate per comparison	PFS (primary endpoint)	Comparison groups	Lenvatinib + Pembrolizumab TPC
		HR	0.56
		95% CI	0.47, 0.66
		P-value*	<0.0001
	OS (primary endpoint)	Comparison groups	Lenvatinib + Pembrolizumab TPC
		HR	0.62
		95% CI	0.51, 0.75
		P-value*	<0.0001
	ORR (secondary endpoint)	Comparison groups	Lenvatinib + Pembrolizumab TPC
		ORR (%)	17.2
		95% CI	11.5, 22.9
		P-value*	<0.0001
Descriptive statistics and estimate variability	**ITT Population – pMMR**		
	Treatment group	Lenvatinib + Pembrolizumab	TPC
	Number of subjects	346	351
	PFS median (months)	6.6	3.8
	95% CI	5.6, 7.4	3.6, 5.0
	OS median (months)	17.4	12.0
	95% CI	14.2, 19.9	10.8, 13.3
	ORR (%)	30.3	15.1
	95% CI	25.5, 35.5	11.5, 19.3
Effect estimate per comparison	PFS (primary endpoint)	Comparison groups	Lenvatinib + Pembrolizumab TPC
		HR	0.60
		95% CI	0.50, 0.72
		P-value*	<0.0001
	OS (primary endpoint)	Comparison groups	Lenvatinib + Pembrolizumab TPC
		HR	0.68

		95% CI	0.56, 0.84
		P-value	<0.0001
	ORR (secondary endpoint)	Comparison groups	Lenvatinib + Pembrolizumab TPC
		ORR (%)	15.2
		95% CI	9.1, 21.4
		P-value*	<0.0001
Analysis description	**Subgroup Analysis -dMMR Participants (ITT Population)**		
Descriptive statistics and estimate variability	Treatment group	Lenvatinib + Pembrolizumab	TPC
	Number of subjects	65	65
	PFS median (months)	10.7	3.7
	95% CI	5.6, Not reached (NR)	3,1 4.4
	OS median (months)	NR	8.6
	95% CI	NR, NR	5.5, 12.9
	ORR (%)	40.0	12.3
	95% CI	28.0, 52.9	5.5, 22.8
Effect estimate per comparison	PFS	Comparison groups	Lenvatinib + Pembrolizumab TPC
		HR	0.36
		95% CI	0.23, 0.57
		P-value*	<0.0001
	OS	Comparison groups	Lenvatinib + Pembrolizumab TPC
		HR	0.37
		95% CI	0.22, 0.62
		P-value*	<0.0001
	ORR	Comparison groups	Lenvatinib + Pembrolizumab TPC
		ORR (%)	27.7
		95% CI	12.9, 41.7
		P-value*	0.0002

* All p-values are one-sided

Supportive study(ies)

Data from Study 204, KEYNOTE-028, and KEYNOTE-158 are provided to demonstrate the individual contributions of lenvatinib and pembrolizumab to that of the combination.

Table 40: Summary of Study Designs of Clinical Studies

Study	Design	Number of Participants	Data Cutoff Date
Study E7080-G000-204 CSR	Phase 2, global, open-label, single-arm study of lenvatinib monotherapy in participants with advanced endometrial carcinoma and PD after first-line platinum-based chemotherapy.	N=133 MMR status not determined	21-MAY-2012
KEYNOTE-158 CSR	Phase 2 multicohort, multicenter, open-label, study of pembrolizumab monotherapy in participants with multiple types of advanced solid tumors, including endometrial carcinoma regardless of PD-L1 expression, which had progressed after standard of care therapy.	**Cohort D**: N=107 pMMR: n=90 dMMR: n=11 Unknown: n=6 **Cohort K:** N=79 dMMR	06-DEC-2018
KEYNOTE-028 CSR	Phase 1b multicohort, multicenter, open-label study of pembrolizumab monotherapy in participants with PD-L1 positive advanced solid tumors, including endometrial carcinoma.	N=24 pMMR: n=18 dMMR: n=1 Unknown: n=5	23-JAN-2019
KEYNOTE-158 Statistical Report	Phase 2 multicohort, multicenter, open-label, study of pembrolizumab monotherapy in participants with multiple types of advanced solid tumors, including endometrial carcinoma regardless of PD-L1 expression, which had progressed after standard of care therapy.	N=79 dMMR with ≥6 months of follow up. Cohort D dMMR: n=11 Cohort K dMMR: n=68	**Updated dMMR statistical analysis**: 05-OCT-2020
Abbreviations: dMMR = mismatch repair deficient; MMR = mismatch repair; MSI-H = microsatellite instability-high; PD = progressive disease; PD-L1= programmed cell death ligand 1; pMMR = mismatch repair proficient; TPC = treatment physician´s choice of doxorubicin or paclitaxel. Source: [Ref. 5.3.5.2: PE204V01: Table 8]) [Ref. 5.3.5.2: P158V05MK3475: Table 14.1-13] [Ref. 5.3.5.2: P028V06MK3475: Table 10-3] [Ref. 5.3.5.2: P158MK3475ENDO: Table 4-5].			

Table 41: Key Baseline Characteristics Across Study 309/KEYNOTE-775 and Monotherapy Studies

	309/KEYNOTE-775 pMMR (N=346)	309/KEYNOTE-775 dMMR (N=65)	204[a] (N=133)	KEYNOTE-158 pMMR/MSS[b] (N=90)	KEYNOTE-158 dMMR/ MSI-H[c] (N=79)	KEYNOTE-028 (N=24)
Age (year)						
Median	65.0	64.0	• 62.0	• 63.0	• 64.0	67.0
Min, Max	30 to 82	38 to 81	• 38, 80	• 41, 80	• 42 to 86	34, 87
Sex, n (%)						
Female	346 (100.0)	65 (100.0)	• 133 (100.0)	• 90 (100.0)	• 79 (100)	24 (100.0)
Race, n (%)						
• White	• 220 (63.6)	• 41 (63.1)	• 112 (84.2)	• 67 (74.4)	• 68 (86.1)	17 (70.8)
• Black or African American	• 15 (4.3)	• 2 (3.1)	• 10 (7.5)	• 9 (10.0)	• 3 (3.8)	1 (4.2)
• Asian	• 74 (21.4)	• 11 (16.9)	• 6 (4.5)	• 14 (15.6)	• 4 (5.1)	3 (12.5)
• American Indian or Alaska Native	• 4 (1.2)	• 0	• 1 (0.8)	• 0	• 1 (1.3)	0
• Native Hawaiian or Other Pacific Islander	• 1 (0.3)	• 0	• 2 (1.5)	• 0	• 0	0
Other	3 (0.9)	4 (6.2)	• 2 (1.5)	• 0	• 2 (2.5)	0
Missing	29 (8.4)	7 (10.8)	• NA	• 0	• 1 (1.3)	3 (12.5)
ECOG PS at Baseline						
0	212 (61.3)	34 (52.3)	• 50 (37.6)	• 43 (47.8)	• 31 (39.2)	7 (29.2)
1	133 (38.4)	31 (47.7)	• 71 (53.4)	• 47 (52.2)	• 48 (60.8)	17 (70.8)
2	NA	0	• 12 (9.0)	• NA	• 0	NA
3	1 (0.3)[d]	0	• NA	• NA	• 0	NA
MMR/MSI-H Status, n (%)						
pMMR	346 (100)	0	• NC	• 90 (100)	• NA	18 (75.0)
dMMR	NA	65 (100)	• NC	• NA	• 79 (100)	1 (4.2)
Missing	0	NA	• NC	• 0 (0)	• NA	5 (20.8)
Number of prior anticancer medication regimens, n (%)						
1	244 (70.5)	NA	• 132 (99.2)	• 26 (28.9)	• 38 (48.1)	7 (29.2)
2	92 (26.6)	NA	• 1 (0.8)	• 21 (23.3)	• 19 (24.1)	6 (25.0)
≥3	10 (2.9)	NA	• 0	• 43 (47.8)	• 22 (27.8)	11 (45.8)
PD-L1 status, n (%)						
Positive	NC	NC	• NC	• 56 (62.2)	• 17 (21.5)	24 (100.0)
Negative	NC	NC	• NC	• 32 (35.6)	• 6 (7.6)	NA
NA/NE	NC	NC	• NC	• 2 (2.2)	• 56 (70.9)	NA

Abbreviations: dMMR = mismatch repair deficient; ECOG PS = Eastern Cooperative Oncology Group performance status; MMR = mismatch repair; MSI-H = microsatellite instability-high; MSS = microsatellite stable; NA = not applicable/available; NC = not collected; NE = not evaluable; PD-L1 = programmed death ligand 1; pMMR = mismatch repair proficient.

f In Study 204, MMR status in participants was not assessed.

g Data cutoff date: 06-OCT-2018.

h Data cutoff date: 05-OCT-2020.

i This participant was enrolled in error.

Source: Study 309/KEYNOTE-775: [Ref. 5.3.5.1: P775V01MK3475: Table 10-6, 11-23, 14.2-19]; Study 204: [Ref. 5.3.5.2: PE204V01: Table 10, 12] ; KEYNOTE-158 (data cutoff date: 06-OCT-2018): [Ref. 5.3.5.2: P158V05MK3475: Table 14.1-13]; KEYNOTE-158 (data cutoff date: 05-OCT-2020): [Ref. 5.3.5.2: P158MK3475ENDO: Table 4-5]; KEYNOTE-028: [Ref. 5.3.5.2: P028V06MK3475: Table 10-3].

Table 42: Summary of Efficacy Results in Subjects with pMMR Endometrial Carcinoma in Study 309/KEYNOTE-775 and KEYNOTE-158, and in All Subjects in Study 204 and KEYNOTE-028

Parameters	Study 309/KEYNOTE-775 Combination Therapy[a]	Lenvatinib Monotherapy Study-204[b]	Pembrolizumab Monotherapy	
			KEYNOTE-028[c]	KEYNOTE158
Therapy	Lenvatinib +Pembrolizumab	Lenvatinib (24 mg)	Pembrolizumab	Pembrolizumab
Population	≥1 previous systemic therapy	PD after 1 prior systemic platinum-based chemotherapy	PD-L1+ Advanced EC with ≥1 previous systemic therapy	Advanced EC ≥1 previous systemic therapy
No. of subjects	pMMR (N=346)	(N=133)	(N=24)	pMMR[d] (N=90)
Median OS (months) (95% CI)	17.4 (14.2, 19.9)	10.6 (8.9, 14.9)	13.6 (2.2, 25.2)	10.1 (7.7, 14.9)
Median PFS (months), (95% CI)	6.6 (5.6, 7.4)	5.6 (3.7, 6.3)	1.8 (1.6, 2.7)	2.1 (2.1, 2.2)
ORR (%) (95% CI)	30.3 (25.5, 35.5)	14.3 (8.8, 21.4)	9.5 (1.2, 30.4)	7.8 (3.2, 15.4)
CR n (%)	18 (5.2)	1 (0.8)	1 (4.8)	0 (0.0)
Median DOR (months), (range)	9.2 (1.6+ - 23.7+)	7.2 (4.5 to NE)	NR	NR

DOR = duration of response; NE = not estimable; NR = not reached; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; pMMR = mismatch repair proficient; TPC = treatment of physician's choice.
a: Data cutoff date: 26-OCT-2020.
b: Data cutoff date: 21-MAY-2012 (for primary analysis); 6 Nov 2012 for OS in Study 204 (based on the updated analysis of OS, 6 months after the cutoff for the primary analysis). In Study 204, subjects were not assessed for MMR status.
c: Data cutoff date: 23-JAN-2019. For KEYNOTE-028, all subjects are included (pMMR n+18; dMMR n=1; unknown n=5)
d: Data cutoff date: 06-DEC-2018.
Source: Module 2.5.

Table 43: Summary of Efficacy Results in Subjects with dMMR Endometrial Carcinoma in Study 309 and KEYNOTE-158, and in All Subjects in Study 204 and KEYNOTE-028

Parameters	Study 309/KEYNOTE-775[a] Combination Therapy	Study 309/KEYNOTE-775[a] TPC (Chemotherapy)	KEYNOTE158 Pembrolizumab Monotherapy (data cutoff date: 06-DEC-2018)	KEYNOTE158 Pembrolizumab Monotherapy (data cutoff date: 05-OCT-2020)
No. of participants	MSI-H/dMMR (N = 65)	MSI-H/dMMR (N = 65)	MSI-H/dMMR (N = 49)	MSI-H/dMMR (N = 79)
ORR, (%) (95% CI)	40.0 (28.0, 52.9)	12.3 (5.5, 22.8)	57.1 (42.2, 71.2)	48.1 (36.7, 59.6)
CR, n (%)	9 (13.8)	2 (3.1)	8 (16.3)	11 (13.9)
PR, n (%)	17 (26.2)	6 (9.2)	20 (40.8)	27 (34.2)
DOR (months) Median (Range: min, max)	n=26[b] NR (2.1+ - 20.4+)	n=8[b] 4.1 (1.9+ - 15.6+)	n=28[b] NR (2.9, 27.0+)	n=38[b] NR (2.9 - 49.7+)[c]
Median PFS (months) (95% CI)	10.7 (5.6, NR)	3.7 (3.1, 4.4)	25.7 (4.9, NE)	13.1 (4.3, 34.4)
Median OS (months) (95% CI)	NR (NR, NR)	8.6 (5.5, 12.9)	NR (27.2, NE)	NR (27.2, NR)
Follow-up duration (months) median (range)	13.5 (0.4, 25.1)	8.8 (1.0, 23.8)	24.4 (0.5, 34.2)	16.5 (0.5, 56.1)

Abbreviations: CI = confidence interval; CR = complete response; dMMR = mismatch repair deficient; DOR = duration of response; max = maximum; min = minimum; MSI-H = microsatellite instability-high; NE = not evaluable; NR = not reached; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; TPC = treatment of physician's choice.

j Data cutoff date: 26-OCT-2020.

k Number of participants with responses.

l "+" indicates there is no progressive disease by the time of last disease assessment.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Dose response study

The lenvatinib dose of 20 mg QD used in combination with pembrolizumab 200 mg Q3W in treating advanced EC was established in a Phase 1b/2 Study E7080-A001-111/KEYNOTE-146. In the dose-finding phase, 3 subjects received 24 mg QD of lenvatinib (i.e. the recommended monotherapy dose in DTC) however due to DLT (G3 arthralgia and G3 fatigue) the dose was de-escalated to 20 mg QD, no further DLT were observed and this was considered the RP2D. Pembrolizumab was used only at its recommended dose of 200 mg /Q3W. In the KEYNOTE-775, approximately 66% of subjects had to reduce the dose of lenvatinib due to side effect.

Pivotal study

This application is based on the results of a single pivotal phase 3 trial Study 309/KEYNOTE-775.

The open-label design is not optimal, though understood in the context of the differences of treatment in the two arms and different toxicities. The blinded review of images to determine ORR and PFS is endorsed. In the control arm more patients did not receive the treatment they were randomized to and more patients discontinued therapy due to subject or physician's decision.

780 participants were planned to be randomized, and a total of 827 participants were actually enrolled in this study (697 pMMR and 130 dMMR).

The number of OS and PFS events at each respective final analyses has increased (in particular PFS) with the last protocol amendment 7 compared to the original protocol and prior amendments, which were mainly related to the additional follow-up.

The total family-wise error rate (Type-I error) among the 2 primary PFS and OS analyses, ORR analysis, and for pMMR and all-comer participants was controlled at one-sided 0.025 level. Doxorubicin and paclitaxel were still regarded as valid second-line treatment options after platinum-based first-line treatment of endometrial cancer during the scientific advice.

In this study, all patients were first stratified by MMR status, then only within the pMMR stratum, participants were further stratified with 3 stratification factors, according to ECOG performance status (0 or 1), geographic region (Region 1 [Europe, US, Canada, Australia, New Zealand, and Israel] or Region 2 [rest of the world]), and prior history of pelvic radiation (yes or no), which were considered important prognostic factors for this study population.

Either lenvatinib in combination with pembrolizumab or TPC chemotherapy were used in patients who have disease progression after prior systemic therapy, and are not eligible for curative surgery or radiation. More precisely, per the inclusion criterion 3, the eligible patients should have previously been treated with a total of 1 or 2 prior systemic, platinum-based chemotherapy regimens for EC (including up to one prior line of chemotherapy in adjuvant and/or neoadjuvant setting), which is currently considered the standard first-line treatment in EC and received nearly by all patients. Therefore, the indication was modified in order to specify the use of prior platinum-based therapy and add "recurrent" to the wording in the Lenvima SmPC section 4.1.

Approximately 35% of subjects in both arms received study treatment as first line for advanced/metastatic setting, after relapse to platinum-based chemotherapy received as (neo)adjuvant therapy. This population appear balanced between the two arms regarding platinum-free interval (PFI), with overall few patients with PFI≥12 months, as expected. Benefit of lenvatinib + pembrolizumab as compared to standard chemotherapy is retained also in patients treated in first line.

Only patients with ECOG performance status 0 or 1 were enrolled in this trial. The exclusion of patients with ECOG ≥2 from clinical studies (except for thyroid carcinoma) is mentioned in section 4.4 of the SmPC. In the description of Study 309- KEYNOTE-775 study in section 5.1 of the SmPC the baseline ECOG is reported as "ECOG PS of 0 (59%) or 1 (41%)". The combination may be used also in less fit patients based on physician's judgment thanks to the manageable safety profile of the treatment.

In terms of the prior treatments, the lenvatinib plus pembrolizumab and TPC groups were comparable for all reported prior therapies used for EC including the pMMR population. Per inclusion criteria, there was no restriction regarding prior hormonal therapy. The use of prior hormonal therapy was low in both all-comer participants (9.7%) and pMMR participants (9.3%) and generally comparable between the 2 treatment groups.

Despite both doxorubicin and paclitaxel were deemed as prevailing treatment options after platinum-based first-line treatment of endometrial cancer, heterogeneity within this control group due to different objective response to advanced EC in the second line is of concern. Less than 30% of subjects in the control arm received paclitaxel (both in the ITT as well as in the pMMR population). For patients in the control arm receiving paclitaxel outcome is similar regardless whether they have received paclitaxel previously.

When analyzed by chemotherapy chosen prior to randomization for all randomized participant, an advantage of the lenvatinib + pembrolizumab combination is maintained vs each control chemotherapy paclitaxel and doxorubicin, with the exception of a modestly shorter OS for patients treated with lenvatinib and pembrolizumab compared with participants treated with paclitaxel. However, the

performance of patients treated with doxorubicin in the control arm appear unexpectedly inferior to patients who received paclitaxel. Considering the number of patients who received paclitaxel is limited, no definitive conclusion could be drawn on it.

Efficacy data and additional analyses

At the data cut-off date of 26 October 2020, within all 827 randomised patients, 411 patients received lenvatinib plus pembrolizumab and 416 received TPC. The results of the Interim Analysis 1 (i.e. final for PFS, interim for OS) were provided. The median duration of follow up in the overall population of 11.4 months (range 0.3, 26.9).

Baseline characteristics

The baseline characteristics was generally well balanced between the 2 arms in unselected patients. Median age (range) is 65.0 years (65.0 years in lenvatinib plus pembrolizumab arm and 66.0 years in TPC arm, respectively). Most patients (about 60%) are white, one fifth are Asian, and more than half patients had an ECOG performance status of 0 in both treatment groups. No differences on the distribution of metastatic lesions were found. Similar prior anti-cancer therapies were given between groups.

A biomarker-defined patient population (negative selection) represents 84.3% of the all-comers population. 697 patients (346 in Lenvatinib plus pembrolizumab and 351 in TPC arm) had a pMMR tumour, while the remaining patients had dMMR tumours defined by a biomarker assay. Similarly, there were no notable differences in the baseline characteristics between two arms in pMMR and dMMR patients.

In total, all randomised 827 patients were included as ITT population for primary analysis (411 in Lenvatinib plus pembrolizumab group and 416 in TPC group), 697 patients were analysed as pMMR ITT population.

As histology is a prognostic factor, the available data on histology (endometrioid/non endometrioid) were provided in all the populations in Study 309/KEYNOTE-775 and supportive studies. Most participants were enrolled with an endometrioid histology. No relevant differences are seen in histology (endometrioid vs non endometrioid). In the dMMR population of KEYNOTE-775 study, most of the subjects have also endometrioid histology, which is in line with the characteristics of dMMR EC.

Primary endpoint

At the time of data cut-off date (26 October 2020), the median follow-up duration was about 11 months in each treatment group. In lenvatinib plus pembrolizumab group, 184 (44.8%) deaths were observed among 406 treated patients. In TPC group, 236 deaths (56.7%) were observed in 388 treated patients. Overall, 124 patients (30.5%) in the combination treatment group and 10 (2.6%) in TPC group continued the study treatment.

For all randomised patients, a gain of 3.4 months (7.2 months vs 3.8 months) in median PFS by BICR was shown in patients treated with lenvatinib plus pembrolizumab compared with TPC, with HR of 0.56 (95% CI: 0.47, 0.66; p<0.0001, one-sided).

An alike proportion of patients in both arms had PD due to progression of a target or non-target lesion, or developing new lesions. Overall, 101 (24.6%) patients in the combination therapy group vs 35 (8.4%) patients in the TPC group were progression-free at the time of analysis.

Both PFS rates over time and the shape of KM curves for PFS indicated the superiority in PFS outcome in lenvatinib plus pembrolizumab over TPC. The effect was maintained throughout the duration of the evaluation period in all randomised patients.

The efficacy results for the TPC arm (doxorubicin and paclitaxel) in the all-comers population are consistent with those from other randomized Phase 3 studies in a similar treatment setting.

The results for the PFS by investigator assessment (HR 0.56; 95% CI 0.47 to 0.66; p<0.0001, one sided; median PFS 7.3 months vs 4.2 months for Lenvatinib plus pembrolizumab vs TPC, respectively) were consistent with the PFS analysis by BICR. The median PFS based on investigator assessment per iRECIST in the lenvatinib plus pembrolizumab group was substantially longer than that of TPC group (10.3 months vs 5.6 months, HR 0.56, 95% CI 0.39 to 0.57 p<0.0001, one-sided). Both sensitivity analyses support primary analysis. The rate of agreement between INV and BICR was approximately 80-85%.

The median OS in the lenvatinib plus pembrolizumab group was 18.3 months, indicating an improvement compared the median OS in TPC group of 11.4 months, HR of 0.62 (95% CI: 0.51, 0.75; p<0.0001, one-sided). However, OS analysis is not mature yet as in lenvatinib plus pembrolizumab and TPC groups, 44.8% and 56.7% maturity was reported, respectively.

In the pMMR population, a statistically significant improvement in median PFS by BICR was shown for the lenvatinib plus pembrolizumab treatment compared with TPC (median PFS of 6.6 months vs 3.8 months, HR of 0.60 (95% CI: 0.50, 0.72; p<0.0001, one-sided). The favouring trend of the PFS rates over time and KM curves supported better efficacy of lenvatinib plus pembrolizumab over TPC consistently throughout the duration of the evaluation period. The results from both sensitivity analyses with a different set of censoring rules supported the robustness of PFS results in pMMR population.

Even though the median OS improvement was found in the lenvatinib plus pembrolizumab group over TPC in all comers and in the pMMR population, OS data is not fully mature yet and this limits the efficacy estimation at this moment. The MAH is recommended to submit the results from the final OS analysis in the overall population and by MMR biomarker by Q4 2022.

The significant superiority in terms of PFS and OS is maintained after multiplicity correction in all randomised patients and pMMR subgroup.

The subsequent treatment after progression, especially PD-1/PD-L1 checkpoint inhibitors and/ or VEGF/ VEGFR inhibitors use, has to be considered as a confounding factor for the long-term survival data analysis. Despite more patients in TPC group received the subsequent systemic treatment (including PD-1/PD-L1 checkpoint and VEGF/ VEGFR inhibition) compared with the combination treatment group, the improved outcomes for OS in the lenvatinib plus pembrolizumab group compared with the TPC group were still observed.

Approximately 30% of subjects in the pembrolizumab + lenvatinib arm received treatment beyond RECIST 1.1-defined and investigator assessed disease progression for a median of 2.8 months, compared to <5% in the control arm who continued chemotherapy for a median of 1.7 months. This difference is not unexpected, as indicated in the Keytruda SmPC "It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed."

Efficacy data in patients who continued treatment with lenvatinib and/or pembrolizumab beyond RECIST 1.1 disease progression were consistent with the primary analysis, raising no concern. However, the number of participants in the TPC arm who continued treatment with chemotherapy beyond disease progression by Investigator Assessment (n=16) is small and thus a meaningful analysis cannot be performed.

Among patients discontinuing due to AE, subsequent therapies were administered less frequently after lenvatinib + pembrolizumab compared to patients in the control arm (23.3% vs 39.4%). There is insufficient data to determine why participants did not start subsequent systemic anticancer therapy

following discontinuation of study treatment due to AE, as well as limited information on subsequent anticancer therapies may have been available for participants who discontinued study treatment due to an AE and then withdrew consent from further participation in the study.

Time from discontinuation due to AE to disease progression was shorter in the lenvatinib + pembrolizumab arm than in the control arm, however the outcome in terms of OS and PFS of patients who discontinued treatment due to AE in the two arms appear similar.

Secondary endpoints

The results of secondary endpoints generally support the PFS and OS results.

In all randomised patients, ORR was 31.9% in the lenvatinib plus pembrolizumab group and 14.7% in the TPC group respectively, with an estimated difference of 17.2% (95% CI: 11.5, 22.9; p<0.0001). For pMMR patients, ORR was 30.3% in the lenvatinib plus pembrolizumab group and 15.1% in the TPC group respectively, with an estimated difference of 15.2% (95% CI: 9.1, 21.4.7; p<0.0001). ORR results supported the relevant results on PFS and OS favouring lenvatinib plus pembrolizumab treatment.

Exploratory Endpoints

For all randomised patients, the median TTR in both treatment groups are the same: 2.1 months; however in pMMR population, the median TTR for doxorubicin-treated patients is longer at 3.6 vs 2.1 months in the all comers. These data should be interpreted with caution due to the limited number of responding patients for whom TTR is calculated.

For other endpoints, lenvatinib plus pembrolizumab treatment prolonged median DOR, DCR, CBR and PFS2 relative to TPC.

Patient reported outcomes (PRO)

The main PRO variable for HRQoL analysis was Global HRQoL score (global health status/QoL) of the EORTC QLQ-C30 reviewed as a secondary endpoint. EORTC QLQ-C30 physical functioning score, EORTC QLQ EN24 urological symptoms score, and EuroQoL EQ-5D-5L VAS score were exploratory endpoints.

In both all randomised patients and pMMR population, comparable score change from baseline to week 12 for EORTC-QLQ-C30 GHS/QoL scale was informative to ensure a similar impact on quality of life for both lenvatinib plus pembrolizumab and TPC groups.

The overall compliance rates for the QLQ-C30 were high in both treatment arms up to 12 weeks. The treatment arms were balanced in terms of baseline scores. Within the all-comers population, the adjusted mean change from baseline in EORTC QLQ-C30 global HRQoL score at week 12 was -5.97 in the combination treatment group (386 evaluable patients) and -6.98 in TPC group (363 evaluable patients), with a corresponding estimated difference of LS mean score change from baseline between two treatment groups at Week 12 was (1.01 points; 95% CI: -2.28, 4.31, p=0.5460).

In pMMR population, there was also no significant difference observed in LS mean score change from baseline between two treatment groups at Week 12 was (1.16 points; 95% CI: -2.49, 4.81, p=0.5316).

EORTC QLQ-30 physical functioning scores and EQ-5D-5L VAS scores decreased slightly in both the lenvatinib plus pembrolizumab group and TPC group and were generally similar between the 2 groups during the evaluation period EORTC QLQ-EN24 urological symptoms scores were maintained over time and were also generally similar between two treatment groups.

In conclusion, no major differences are seen between arms in the PRO. However, PRO data in the context of an open-label study should be interpreted with caution.

Subgroup analyses

In the subgroup analyses for all randomised patients and pMMR population, the treatment benefit for PFS and OS for lenvatinib plus pembrolizumab compared with TPC is generally consistent across the major subgroups. There is a sign that non-white patients and the patients who have received more than one line previous systemic therapies are less likely to benefit from lenvatinib plus pembrolizumab treatment over TPC, but the number of patients is limited to draw any firm conclusion.

dMMR

In Study 309/KEYNOTE-775, dMMR participants represent a relatively small subset of the all-comers population, reflecting its low prevalence in clinical practice. Despite the upper 95% CI for the PFS and OS are still not reached at time of data cutoff date, the currently available data indicated PFS and OS benefit, similarly to both ITT populations.

The median follow-up duration was 13.5 months in the lenvatinib plus pembrolizumab group and 8.8 months in the TPC group. In dMMR patients, the median PFS in the lenvatinib plus pembrolizumab group was 10.7 months compared with 3.7 months in the TPC group, HR 0.36 (0.23, 0.57), p<0.0001. The median OS in the lenvatinib plus pembrolizumab group was not reached compared to 8.6 months in the TPC group, HR 0.37 (0.22, 0.62) p<0.0001.

The improved ORR (per RECIST 1.1 by BICR) was observed in the lenvatinib plus pembrolizumab group (40.0%) compared with 12.3% for the TPC group, with an estimated difference of 27.7% (95% CI: 12.9, 41.7; nominal p=0.0002).

The median DOR assessed by BICR was not reached as of the IA1 data cutoff date in the lenvatinib plus pembrolizumab group and was 4.1 months in the TPC group. The median TTR (per RECIST 1.1 by BICR) was 2.9 months in the lenvatinib plus pembrolizumab group and 1.9 months in the TPC group.

Determination of MSI/MMR status

Available tumour samples were tested centrally to determine tumour MSI status. Tumour MSI status was determined by IHC. Tumour MMR status was determined using the Ventana MMR IHC assay.

All patients were assessed centrally for MMR status with IHC, using a clinical trial assay (CTA) of Roche Tissue Diagnostics. All four MMR proteins (MLH1, MSH2, MSH6 and PMS2) were tested, as usually recommended. Compared to MSI PCR results, its precision (repeatability and reproducibility) met the acceptance criteria.

Additionally, if available, local testing results for both MSI and MMR status were also collected. Overall, MSI/MMR status was derived based on central assessment if both central and local assessments results were available, and then based on central MMR IHC testing if both MMR and MSI status were available. If central testing results were not available, then local testing results were used to derive MSI and MMR status. Similar to central testing, if both local MSI and MMR results were available, MMR results were used to derive MSI/MMR status.

In the EC 2L+ Set, 104 of the 108 subjects submitted tumour samples (no tumour samples were obtained from 4 subjects). Central testing results for MMR/MSI status were available for 97 subjects (7 samples did not meet testing criteria). There were 86 Non-MSI-H/pMMR (45 Non-MSI-H and 41 pMMR) and 11 MSI-H/dMMR (6 MSI-H and 5 dMMR) tumours. Among the 86 Non-MSI-H/pMMR centrally tested samples, 12 samples were tested by both assay platforms, and the results were 100% concordant. Among the 11 subjects whose tumor MSI/MMR status was not available by central testing, 8 subjects (7 Non-MSI-H

and 1 pMMR) had local testing results available, for a total of 94 Non-MSI-H/pMMR subjects defining the EC 2L+ Set. For 3 subjects, there was no central or local MMR/MSI status available.

Among the 108 subjects in the EC 2L+ Set, 62 subjects (58 Non-MSI-H/pMMR and 4 MSI-H/dMMR) had MMR/MSI local testing results available with a high concordance to central testing results (95% concordance, n=59; 5% discordance, n=3). Among the 94 Non-MSI-H/pMMR subjects, 58 had local testing results available with a high concordance to central testing results (96.6% concordance, n=56; 3.4% discordance n=2).

PD-L1 status was not assessed in Study 309/KEYNOTE-775.

Supportive study

The results from an ongoing phase 1b/2 E7080-A001-111/KEYNOTE-146 trial in which a total of 108 patients received lenvatinib 20 mg QD plus pembrolizumab 200 mg Q3W as the second-Line or later line treatment at stage II, whose results support the demonstration of the efficacy of combination treatment activity in advanced EC.

Contribution of components within lenvatinib-pembrolizumab combination

The pivotal trial did not include the monotherapy arms and no direct comparative data are available.

Results from Study 204, KEYNOTE-158, and KEYNOTE-028 were provided in order to provide evidence of the contribution of lenvatinib and pembrolizumab monotherapies to the efficacy of the combination. KEYNOTE-158 is a phase 2 study of pembrolizumab monotherapy in participants with multiple types of advanced solid tumors progressing after standard of care therapy. Efficacy results for a total of 79 dMMR and 90 dMMR endometrial cancer patients have been provided, together with 24 subjects who received pembrolizumab in the phase 1 study KEYNOTE-028. The evidence for lenvatinib monotherapy comes from 133 patients treated within the phase II single arm Study-204, for whom however the MMR status was not determined. The dose of lenvatinib used in Study-204 (24 mg OD) was higher than what was used in the combination with pembrolizumab in KEYNOTE-775 (20 mg OD). On the contrary, the same dose of pembrolizumab (200 mg Q3W) was used in KEYNOTE-775 and -158. When comparing the baseline characteristics of the four studies, some differences are noted, most relevant being that patients in KEYNOTE-775 have better performance status compared to patients enrolled in the supportive studies, and that patients in the pembrolizumab monotherapy studies KEYNOTE-158 and -028 were more pretreated. It cannot be excluded that this could have possibly improved the outcome of KEYNOTE-775 population with respect to subjects receiving monotherapy in the supportive studies. The lack of data on PD-L1 expression in KEYNOTE-775 at this stage is a limit for data interpretation. The key efficacy results of the combination and monotherapy studies are summarized below:

- The ORR for lenvatinib plus pembrolizumab in pMMR participants with advanced EC was higher relative to what was observed for either lenvatinib monotherapy in Study 204 or pembrolizumab monotherapy in KEYNOTE-028 and KEYNOTE-158. The lower bound of the 95% CI of the ORR for lenvatinib plus pembrolizumab was greater than that of the observed point estimate for either lenvatinib or pembrolizumab administered as monotherapy.

- The observed CR rate was higher in participants who received lenvatinib plus pembrolizumab compared with those who received lenvatinib monotherapy in Study 204 or pembrolizumab monotherapy in KEYNOTE-158 and KEYNOTE-028.

- Among responders, the median DOR for lenvatinib plus pembrolizumab in pMMR participants with advanced EC was longer compared with lenvatinib monotherapy in Study 204. The median DOR was not reached for participants with advanced EC who received pembrolizumab monotherapy in KEYNOTE-158 and in KEYNOTE-028.

- The median PFS for lenvatinib plus pembrolizumab in pMMR participants with advanced EC was longer relative to what was observed for either lenvatinib monotherapy in Study 204 or pembrolizumab monotherapy in KEYNOTE-028 and KEYNOTE-158.

- As of the cut-off date, the median OS for lenvatinib and pembrolizumab in pMMR participants with advanced EC was longer relative to what was observed for either lenvatinib monotherapy in Study 204 or pembrolizumab monotherapy in KEYNOTE-028 and KEYNOTE-158.

In the pMMR subgroup, considering the ORR and PFS data reported in the supportive studies, and the apparent limited activity of both pembrolizumab and lenvatinib as single agents in previously treated advanced/metastatic endometrial cancer with pMMR based on single-arm data, the overall results seem to support the hypothesis that each component is contributing to the treatment effect in the combination regimen. The limit of cross-study comparison should be however noted. However, the limits of cross-study comparison hamper the possibility to draw definitive conclusions. No meaningful conclusion can be made with regards to OS, especially in view of some differences in baseline characteristics among studies, as well as the difficulties in evaluating time-related endpoints in single-arm studies.

In conclusion, it is acknowledged that the combination of lenvatinib plus pembrolizumab showed superiority to TPC with respect to PFS, OS and ORR for the treatment of dMMR participants in KEYNOTE-775, although the dMMR subgroup was not formally tested. The cross-study comparison, acknowledging its limitations, suggests that the activity of the pembrolizumab + lenvatinib combination is not significantly different as compared to pembrolizumab alone in dMMR EC population. While the lack of direct comparison of pembrolizumab monotherapy versus pembrolizumab and lenvatinib in 2L dMMR endometrial cancer is a limitation in the dossier, this study has shown a substantial improvement in all efficacy endpoints for pembrolizumab and lenvatinib against chemotherapy in dMMR endometrial cancer, which is fully acknowledged.

2.4.4. Conclusions on the clinical efficacy

Study 309/KEYNOTE-775 study showed a statistically significant and clinically meaningful advantage in OS and PFS of the combination pembrolizumab + lenvatinib as compared to standard chemotherapy (doxorubicin or paclitaxel, TPC) in advanced endometrial cancer patients progressed to at least one prior platinum-based therapy. Even though the median OS improvement was found in the lenvatinib plus pembrolizumab group over TPC, OS data is not fully mature yet and this limits the efficacy estimation at this moment. Therefore, the MAH is recommended to submit the results from the final OS analysis in the overall population and by MMR biomarker (expected in Q4 2022).

ORR for the combination was not outstanding but was doubled compared to the standard treatment. DOR, PFS2 and PFS sensitivity analyses further support the benefit of the combination.

2.5. Clinical safety

Introduction

Lenvima (Lenvatinib, Eisai) is already commercialized in monotherapy to treat differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC) and hepatocellular carcinoma (HCC).

The safety profile of lenvatinib is based on data from 452 DTC patients and 496 HCC patients; allowing characterisation only of common adverse drug reactions in DTC and HCC patients.

Keytruda (pembrolizumab, MSD) is already commercialized in monotherapy or in combination to treat melanoma, Non-small cell lung carcinoma (NSCLC), Classical Hodgkin lymphoma (cHL), Urothelial carcinoma, Head and neck squamous cell carcinoma (HNSCC), Renal cell carcinoma (RCC), and Colorectal cancer (CRC).

Pembrolizumab is most commonly associated with immune-related adverse reactions. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of pembrolizumab.

The safety of pembrolizumab as monotherapy has been evaluated in 6,185 patients with advanced melanoma, resected Stage III melanoma (adjuvant therapy), NSCLC, cHL, urothelial carcinoma, HNSCC, or CRC across four doses (2 mg/kg every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg every 2 or 3 weeks) in clinical studies.

In this patient population, the median observation time was 7.6 months (range: 1 day to 47 months) and the most frequent adverse reactions with pembrolizumab were fatigue (32%), nausea (21%), and diarrhoea (21%). The majority of adverse reactions reported for monotherapy were of Grades 1 or 2 severity. The most serious adverse reactions were immune-related adverse reactions and severe infusion-related reactions.

The safety profile of oral lenvatinib (E7080) 20 mg QD in combination with IV pembrolizumab (MK-3475) 200 mg Q3W has been studied for the treatment of patients with advanced EC who have disease progression following prior platinum-based systemic therapy.

The main safety results were provided from the pivotal, open-label, randomized Phase 3 study, Study 309/KEYNOTE-775 (KEYNOTE775). The safety profile of the combination of lenvatinib + pembrolizumab is compared to Physician´s Choice (doxorubicin or paclitaxel – TPC group).

Supportive data have been provided for comparison:

- Data from the non-Endometrial Carcinoma (EC) participants in Study 111/KEYNOTE-146 were selected for the Lenvatinib in combination with Pembrolizumab Non-EC Safety Dataset.

- Data from the Lenvatinib Monotherapy Safety Dataset: includes all subjects who received at least one dose of lenvatinib in E7080-G000-398, E7080-G000-303, E7080-G000-201, E7080-G000-204, E7080-G000-703, E7080-G000-203, E7080-G000-205, E7080-G000-206, E7080-J081-208, E7080-G000-209 and E7080-J081-105 (i.e. data from participants with various cancer including EC, with different data cut-off).

- Data from the Pembrolizumab Monotherapy Reference Safety Dataset (RSD): includes all subjects who received at least one dose of pembrolizumab in KEYNOTE001 Part B1, B2, B3, D, C, F1, F2, F3, KEYNOTE002 (original phase), KEYNOTE006, KEYNOTE010, KEYNOTE012 cohort B and B2, KEYNOTE013 cohort 3, KEYNOTE024, KEYNOTE040, KEYNOTE042, KEYNOTE045, KEYNOTE048, KEYNOTE052, KEYNOTE054, KEYNOTE055 and KEYNOTE087 (i.e. data from participants with various cancer including EC, with different data cut-off).

Analyses were conducted using the APaT population (all participants as treated) as of each study data cut-off (Study 309/KEYNOTE-775: 26-OCT-2020; Study 111/KEYNOTE-146: 10-JAN-2019).

Table 44: Summary of Clinical Safety Data Sets

Dataset	Population	Treatment	Nomenclature in Tables	Nomenclature in Text
Study 309/KEYNOTE-775 combination lenvatinib + pembrolizumab	N=406: Safety data from participants with advanced endometrial carcinoma who had disease progression following prior platinum-based systemic therapy, who received combination treatment with lenvatinib + pembrolizumab in Study 309/KEYNOTE-775.	Lenvatinib (20 mg QD) + pembrolizumab (200 mg Q3W)	KN775 Lenvatinib + Pembrolizumab[a]	Lenvatinib plus pembrolizumab group
Study 309/KEYNOTE-775 chemotherapy doxorubicin or paclitaxel	N=388: Safety data from participants with advanced endometrial carcinoma who had disease progression following prior platinum-based systemic therapy, who received combination chemotherapy treatment with doxorubicin and paclitaxel in Study 309/KEYNOTE-775.	Doxorubicin or paclitaxel	KN775 Treatment Physician's Choice[b]	TPC group
Combination lenvatinib + pembrolizumab - Nonendometrial	N=230: Pooled safety data from participants with confirmed metastatic selected solid tumor types (excluding endometrial carcinoma) treated with the lenvatinib + pembrolizumab combination in Study 111/KEYNOTE-146 (NSCLC, predominantly clear cell RCC, urothelial carcinoma, squamous cell carcinoma of the head and neck, or melanoma [excluding uveal melanoma]). NOTE: endometrial cohort is excluded from this dataset	Lenvatinib (20 mg QD) + pembrolizumab (200 mg Q3W)	KN146 Lenvatinib + Pembrolizumab (Non-Endometrial Cancer)	Lenvatinib and pembrolizumab non-EC group
Lenvatinib monotherapy	N=1119: Pooled safety data from participants treated with lenvatinib monotherapy in 11 studies including E7080-G000-201 (advanced thyroid cancers), E7080-G000-203 (malignant glioma), E7080-G000-204 (advanced endometrial carcinoma), E7080-G000-205 (RCC), E7080-G000-206 (advanced melanoma), E7080-G000-209 (K1F5B-RET-translocations in NSCLC and other cancers), E7080-G000-303 (DTC), E7080-G000-398 (advanced DTC), E7080-G000-703 (advanced NSCLC), E7080-J081-105 (advanced solid tumors), and E7080-J081-208 (thyroid cancer).	Lenvatinib monotherapy (24 mg QD)	Lenvatinib Monotherapy Safety Dataset	Lenvatinib monotherapy group
Pembrolizumab monotherapy reference safety	N=5884: Pooled safety data from participants treated with pembrolizumab monotherapy, including all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.	Pembrolizumab monotherapy (2 mg/kg Q3W; 10 mg/kg Q2W; 10 mg/kg Q3W; 200 mg Q3W)	Pembrolizumab Monotherapy Reference Safety Dataset[c]	Pembrolizumab monotherapy RSD

Abbreviations: DTC=differentiated thyroid cancer; EC=endometrial carcinoma; ISS=Integrated Summary of Safety; N=number; NSCLC=non-small cell lung cancer; Q2W=every 2 weeks; Q3W=every 3 weeks; QD=once daily; RCC=renal cell cancer; RSD=reference safety dataset; TPC=treatment of physician's choice.

a. Includes all participants who received at least 1 dose of lenvatinib + pembrolizumab in Study 309/KEYNOTE-775.
b. Includes all participants who received at least 1 dose of chemotherapy in Study 309/KEYNOTE-775.
c. The studies that comprise the pembrolizumab monotherapy RSD are listed in the footnotes of the data tables in this document and in the ISS.

Patient exposure

- ***Overall exposure***

As of the 26-OCT-2020 data cut-off, 406 participants received at least 1 dose of the lenvatinib plus pembrolizumab combination, compared to 388 participants who received at least 1 dose of the doxorubicin or paclitaxel chemotherapy in Study 309/KEYNOTE-775 (EC). There were 230 participants in the Lenvatinib plus Pembrolizumab Non-EC Safety Dataset (KEYNOTE-146), 1,119 participants in the lenvatinib monotherapy safety dataset, and 5,884 participants in the pembrolizumab monotherapy RSD.

The median duration of treatment was longer in the lenvatinib plus pembrolizumab EC group (7.59 months) compared to the TPC EC group (3.43 months), the lenvatinib monotherapy safety dataset (5.55 months) and the pembrolizumab monotherapy RSD (4.86 months) (table below)

The proportion of participants with duration of treatment was higher at each time point analyzed in the lenvatinib plus pembrolizumab EC group compared to the TPC EC group, and higher through the ≥6 month time point compared with the lenvatinib monotherapy group and the pembrolizumab monotherapy RSD (table below).

The median duration of treatment in the lenvatinib plus pembrolizumab EC group (7.59 months) was shorter compared with the lenvatinib plus pembrolizumab non-EC group (9.79 months) (table below). The length of follow-up was longer for Study 111/KEYNOTE-146 than for Study 309/KEYNOTE-775.

The median duration of lenvatinib exposure was longer in the lenvatinib plus pembrolizumab EC group (6.95 months) compared to the lenvatinib monotherapy safety dataset (5.55 months) and shorter than in the lenvatinib plus pembrolizumab non-EC group (9.59 months). The median duration of treatment with the combination (7.59 months) is comparable to that observed for lenvatinib in the combination group (6.95 months) in Study 309/KEYNOTE-775.

Table 45: Summary of Drug Exposure (APaT Population)

	KN775 Lenvatinib + Pembrolizumab (N=406)	KN775 Treatment Physician´s Choice (N=388)	KN146 Lenvatinib + Pembrolizumab (Non-Endometrial Cancer) (N=230)	Lenvatinib Monotherapy Safety Dataset[i] (N=1119)	Pembrolizumab Monotherapy Reference Safety Dataset[j] (N=5884)
Duration of Exposure (month)					
Mean	8.93	3.58	11.77	11.61	7.25
Median	7.59	3.43	9.79	5.55	4.86
SD	6.393	2.969	10.579	14.066	6.783
Range	0.03 to 26.84	0.03 to 25.79	0.10 to 50.40	0.03 to 78.66	0.03 to 30.39

Duration of exposure (month) is calculated as (last dose date - first dose date + 1) / 30.4367.

[i] Includes all subjects who received at least one dose of lenvatinib in E7080-G000-398, E7080-G000-303, E7080-G000-201, E7080-G000-204, E7080-G000-703, E7080-G000-203, E7080-G000-205, E7080-G000-206, E7080-J081-208, E7080-G000-209 and E7080-J081-105.

[j] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054:02OCT2017, E7080-G000-206: 01SEP2016)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, E7080-G000-703: 01SEP2016)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Thyroid (E7080-G000-398: 01SEP2016, E7080-G000-303: 01SEP2016, E7080-G000-201: 01SEP2016, E7080-J081-208: 01SEP2016)

Database cutoff date for Endometrial Cancer (KN775: 26OCT2020, E7080-G000-204: 01SEP2016)

Database cutoff date for Malignant Glioma (E7080-G000-203: 01SEP2016)

Database cutoff date for Renal Cell Carcinoma (E7080-G000-205: 15MAR2018)

Database cutoff date for Adenocarcinoma (E7080-G000-209: 01SEP2016)

Database cutoff date for Solid Tumor (KN146: 18AUG2020, E7080-J081-105: 01SEP2016)

Table 46: Drug Exposure by Duration (APaT Population)

	KN775 Lenvatinib + Pembrolizumab (N=406)			KN775 Treatment Physician´s Choice (N=388)			KN146 Lenvatinib + Pembrolizumab (Non-Endometrial Cancer) (N=230)			Lenvatinib Monotherapy Safety Dataset[1] (N=1119)			Pembrolizumab Monotherapy Reference Safety Dataset[1] (N=5884)		
	n	(%)	Person-time	n	(%)	Person-time	n	(%)	Person-time	n	(%)	Person-time	n	(%)	Person-time
Duration of Exposure (month)															
> 0	406	(100.0)	3,627.1	388	(100.0)	1,388.6	230	(100.0)	2,706.1	1,119	(100.0)	12,994.4	5,884	(100.0)	42,653.7
≥ 1	376	(92.6)	3,611.2	323	(83.2)	1,358.3	215	(93.5)	2,699.2	985	(88.0)	12,910.7	5,033	(85.5)	42,315.3
≥ 3	325	(80.0)	3,505.7	213	(54.9)	1,163.3	182	(79.1)	2,632.3	738	(66.0)	12,436.7	3,620	(61.5)	39,491.8
≥ 6	243	(59.9)	3,143.4	42	(10.8)	403.5	144	(62.6)	2,465.0	518	(46.3)	11,449.9	2,613	(44.4)	35,106.4
≥ 12	110	(27.1)	1,939.7	10	(2.6)	151.7	88	(38.3)	1,941.1	331	(29.6)	9,827.9	1,281	(21.8)	22,970.6
≥ 18	48	(11.8)	1,017.5	1	(0.3)	25.8	47	(20.4)	1,331.1	248	(22.2)	8,607.8	549	(9.3)	12,395.2

- ***Demographics and other characteristics***

Demographic and other baseline characteristics in Study 309/KEYNOTE-775 were generally well balanced between the lenvatinib plus pembrolizumab EC group and the TPC EC group (Table below). In the lenvatinib plus pembrolizumab EC group, all participants were female, and most were white (63.1%) or Asian (20.9%), with an ECOG performance status of 0 (60.1%), and a minority were based in the EU (28.1%). Half of them were under 65 year-of-age (yoa), and half of them over 65 yoa.

When the lenvatinib plus pembrolizumab EC group was compared with the lenvatinib plus pembrolizumab non-EC group, lenvatinib monotherapy group, and pembrolizumab monotherapy RSD, the following main differences were noted:

- Male participants were included in the other groups (overall over 50%).

- More participants in the lenvatinib plus pembrolizumab EC group were ≥65 years of age (49.5%) compared with the other groups (minimum of 37.4% in lenvatinib monotherapy group).

- Less participants in the lenvatinib plus pembrolizumab EC group were white (63.1%) compared with the other groups (maximum of 87.4% in the lenvatinib plus pembrolizumab non-EC group).

- More participants in the lenvatinib plus pembrolizumab EC group were Asian (20.9%) compared with the other groups (minimum of 1.3% in the lenvatinib plus pembrolizumab non-EC group).

- More participants in the lenvatinib plus pembrolizumab EC group were Hispanic or Latino (14.8%) compared with the other groups (minimum of 3.8% in the lenvatinib monotherapy group).

- More participants in the lenvatinib plus pembrolizumab EC group had an ECOG performance status of 0 (60.1%) compared with the other groups (minimum of 44% in lenvatinib monotherapy group).

- More participants in the lenvatinib plus pembrolizumab EC group were based in the EU (28.1%) compared with the lenvatinib plus pembrolizumab non-EC group (6.1%).

Table 47: Participant Characteristics (APaT Population)

	KN775 Lenvatinib + Pembrolizumab		KN775 Treatment Physician´s Choice		KN146 Lenvatinib + Pembrolizumab (Non-Endometrial Cancer)		Lenvatinib Monotherapy Safety Dataset[i]		Pembrolizumab Monotherapy Reference Safety Dataset[j]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	406		388		230		1,119		5,884	
Sex										
Male	0	(0.0)	0	(0.0)	173	(75.2)	554	(49.5)	3,887	(66.1)
Female	406	(100.0)	388	(100.0)	57	(24.8)	565	(50.5)	1,997	(33.9)
Age (Years)										
<65	205	(50.5)	192	(49.5)	127	(55.2)	700	(62.6)	3,385	(57.5)
>=65	201	(49.5)	196	(50.5)	103	(44.8)	419	(37.4)	2,499	(42.5)
Mean	63.2		63.8		61.7		59.8		60.6	
SD	9.1		9.3		11.1		11.6		13.2	
Median	64.0		65.0		63.0		61.0		62.0	
Range	30 to 82		35 to 86		31 to 87		21 to 89		15 to 94	
Race										
American Indian Or Alaska Native	4	(1.0)	7	(1.8)	0	(0.0)	2	(0.2)	29	(0.5)
Asian	85	(20.9)	86	(22.2)	3	(1.3)	178	(15.9)	658	(11.2)
Black Or African American	17	(4.2)	14	(3.6)	12	(5.2)	23	(2.1)	108	(1.8)
Multiracial	7	(1.7)	13	(3.4)	0	(0.0)	0	(0.0)	66	(1.1)
Native Hawaiian Or Other Pacific Islander	1	(0.2)	0	(0.0)	0	(0.0)	4	(0.4)	4	(0.1)
Other	0	(0.0)	0	(0.0)	10	(4.3)	12	(1.1)	0	(0.0)
White	256	(63.1)	225	(58.0)	201	(87.4)	900	(80.4)	4,444	(75.5)
Missing	36	(8.9)	43	(11.1)	4	(1.7)	0	(0.0)	575	(9.8)
Ethnicity										
Hispanic Or Latino	60	(14.8)	68	(17.5)	22	(9.6)	43	(3.8)	389	(6.6)
Not Hispanic Or Latino	304	(74.9)	266	(68.6)	208	(90.4)	1,069	(95.5)	4,690	(79.7)
Not Reported	33	(8.1)	45	(11.6)	0	(0.0)	1	(0.1)	181	(3.1)
Unknown	9	(2.2)	9	(2.3)	0	(0.0)	0	(0.0)	110	(1.9)
Missing	0	(0.0)	0	(0.0)	0	(0.0)	6	(0.5)	514	(8.7)
Age Category (year)										
<65	205	(50.5)	192	(49.5)	127	(55.2)	700	(62.6)	3,385	(57.5)
65-74	166	(40.9)	157	(40.5)	78	(33.9)	321	(28.7)	1,737	(29.5)
75-84	35	(8.6)	37	(9.5)	23	(10.0)	96	(8.6)	663	(11.3)
>=85	0	(0.0)	2	(0.5)	2	(0.9)	2	(0.2)	99	(1.7)
ECOG Performance Status										

[0] Normal Activity	244	(60.1)	224	(57.7)	105	(45.7)	492	(44.0)	2,761	(46.9)
[1] Symptoms, but ambulatory	162	(39.9)	164	(42.3)	125	(54.3)	452	(40.4)	2,931	(49.8)
Other/Missing	0	(0.0)	0	(0.0)	0	(0.0)	175	(15.6)	192	(3.3)
Geographic Region										
EU	114	(28.1)	128	(33.0)	14	(6.1)	385	(34.4)	2,092	(35.6)
Ex-EU	292	(71.9)	260	(67.0)	216	(93.9)	734	(65.6)	3,792	(64.4)

[i] Includes all subjects who received at least one dose of lenvatinib in E7080-G000-398, E7080-G000-303, E7080-G000-201, E7080-G000-204, E7080-G000-703, E7080-G000-203, E7080-G000-205, E7080-G000-206, E7080-J081-208, E7080-G000-209 and E7080-J081-105.

[j] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054:02OCT2017, E7080-G000-206: 01SEP2016)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, E7080-G000-703: 01SEP2016)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Thyroid (E7080-G000-398: 01SEP2016, E7080-G000-303: 01SEP2016, E7080-G000-201: 01SEP2016, E7080-J081-208: 01SEP2016)

Database cutoff date for Endometrial Cancer (KN775: 26OCT2020, E7080-G000-204: 01SEP2016)

Database cutoff date for Malignant Glioma (E7080-G000-203: 01SEP2016)

Database cutoff date for Renal Cell Carcinoma (E7080-G000-205: 15MAR2018)

Database cutoff date for Adenocarcinoma (E7080-G000-209: 01SEP2016)

Database cutoff date for Solid Tumor (KN146: 18AUG2020, E7080-J081-105: 01SEP2016)

Source: [ISS: adam-adsl]

- **Adverse events**

  - ***Overall safety***

In the lenvatinib plus pembrolizumab EC group and the TPC EC group, there were generally similar incidences of all AEs (99.8% vs. 99.5%, respectively), drug-related AEs (97.3% vs. 93.8%), and fatal AEs (5.7% vs. 4.9%), and drug related fatal AEs (1.5% vs. 2.1%); and higher incidences of all SAEs (52.7% vs. 30.4%), drug-related SAEs (33.3% vs. 14.2%), Grade 3 to 5 AEs (88.9% vs. 72.7%), drug-related Grade 3 to 5 AEs (77.8% vs. 59%), dose modification due to an AE (93.6% vs. 41.5%), dose interruption due to an AE (69.2% vs. 27.1%), dose reduction due to an AE (66.5% vs. 12.9%), and discontinuation due to an AEs (33% vs. 8%) (Table below).

In the lenvatinib plus pembrolizumab EC group and the lenvatinib monotherapy group, there were generally similar incidences of all AEs (99.8% vs. 99%, respectively), drug-related AEs (97.3% vs. 94.7%), all SAEs (52.7% vs. 54.8%), drug-related SAEs (33.3% vs. 29.5%), drug-related fatal AEs (1.5% vs. 2.4%), and discontinuation of lenvatinib due to AEs (30.8% vs. 26.7%); and higher incidences of Grade 3 to 5 AEs (88.9% vs. 80.3%), drug-related Grade 3 to 5 AEs (77.8% vs. 64.7%), and lenvatinib dose reduction due to an AE (66.5% vs. 47.5%).

In the lenvatinib plus pembrolizumab EC group and the pembrolizumab monotherapy RSD, there were generally similar incidences of all AEs (99.8% vs. 96.7%), drug-related fatal AEs (1.5% vs. 0.7%), and discontinuation of pembrolizumab due to AEs (18.7% vs. 13.4%); and higher incidences of drug-related AEs (97.3% vs. 70.2%), Grade 3 to 5 AEs (88.9% vs. 48.1%), drug-related Grade 3 to 5 AEs (77.8% vs 15.5%), SAEs (52.7% vs. 38.5%), drug-related SAEs (33.3% vs. 11.1%), and pembrolizumab dose interruption due to AEs (50% vs. 25.4%).

The overall AE summary profile of the lenvatinib plus pembrolizumab EC group was generally consistent with the lenvatinib plus pembrolizumab non-EC group, except for drug-related Grade 3 to 5 AEs, which was higher in the lenvatinib plus pembrolizumab EC group compared with the lenvatinib plus

pembrolizumab non-EC group (77.8% vs. 65.7%); and lower incidences of dose interruption of lenvatinib due to AEs (81.3% vs. 58.6%) and discontinuation of either drug due to a drug-related AE (26.6% vs. 17.4%).

Table 48: Adverse Event Summary (APaT Population)

	KN775 Lenvatinib + Pembrolizumab		KN775 Treatment Physician´s Choice		KN146 Lenvatinib + Pembrolizumab (Non-Endometrial Cancer)		Lenvatinib Monotherapy Safety Dataset[f]		Pembrolizumab Monotherapy Reference Safety Dataset[g]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	406		388		230		1,119		5,884	
with one or more adverse events	405	(99.8)	386	(99.5)	230	(100.0)	1,108	(99.0)	5,690	(96.7)
with no adverse event	1	(0.2)	2	(0.5)	0	(0.0)	11	(1.0)	194	(3.3)
with drug-related[e] adverse events	395	(97.3)	364	(93.8)	225	(97.8)	1,060	(94.7)	4,132	(70.2)
with toxicity grade 3-5 adverse events	361	(88.9)	282	(72.7)	203	(88.3)	899	(80.3)	2,829	(48.1)
with toxicity grade 3-5 drug-related adverse events	316	(77.8)	229	(59.0)	151	(65.7)	724	(64.7)	913	(15.5)
with serious adverse events	214	(52.7)	118	(30.4)	129	(56.1)	613	(54.8)	2,266	(38.5)
with serious drug-related adverse events	135	(33.3)	55	(14.2)	59	(25.7)	330	(29.5)	656	(11.1)
with dose interruption of any drug due to an adverse event	281	(69.2)	105	(27.1)	195	(84.8)	757	(67.6)	1,492	(25.4)
interruption of Pembrolizumab	203	(50.0)	--		122	(53.0)	--		1,492	(25.4)
interruption of Lenvatinib	238	(58.6)	--		187	(81.3)	757	(67.6)	--	
interruption of both Pembrolizumab and Lenvatinib	125	(30.8)	--		89	(38.7)	--		--	
with dose reduction of Lenvatinib due to an adverse event	270	(66.5)	--		152	(66.1)	531	(47.5)	--	
who died	23	(5.7)	19	(4.9)	24	(10.4)	97	(8.7)	312	(5.3)
who died due to a drug-related adverse event	6	(1.5)	8	(2.1)	5	(2.2)	27	(2.4)	39	(0.7)
discontinued any drug due to an adverse event	134	(33.0)	31	(8.0)	65	(28.3)	299	(26.7)	790	(13.4)
discontinued Pembrolizumab	76	(18.7)	--		55	(23.9)	--		790	(13.4)
discontinued Lenvatinib	125	(30.8)	--		57	(24.8)	299	(26.7)	--	
discontinued both Pembrolizumab and Lenvatinib	57	(14.0)	--		42	(18.3)	--		--	
discontinued any drug due to a drug-related adverse event	108	(26.6)	22	(5.7)	40	(17.4)	208	(18.6)	410	(7.0)
discontinued Pembrolizumab	40	(9.9)	--		--		--		410	(7.0)
discontinued Lenvatinib	92	(22.7)	--		--		208	(18.6)	--	
discontinued both Pembrolizumab and Lenvatinib	20	(4.9)	--		--		--		--	
discontinued any drug due to a serious adverse event	88	(21.7)	14	(3.6)	41	(17.8)	179	(16.0)	572	(9.7)
discontinued Pembrolizumab	60	(14.8)	--		35	(15.2)	--		572	(9.7)
discontinued Lenvatinib	81	(20.0)	--		36	(15.7)	179	(16.0)	--	
discontinued both Pembrolizumab and Lenvatinib	50	(12.3)	--		30	(13.0)	--		--	
discontinued any drug due to a serious drug-related adverse event	61	(15.0)	8	(2.1)	21	(9.1)	105	(9.4)	245	(4.2)
discontinued Pembrolizumab	28	(6.9)	--		--		--		245	(4.2)
discontinued Lenvatinib	50	(12.3)	--		--		105	(9.4)	--	
discontinued both Pembrolizumab and Lenvatinib	17	(4.2)	--		--		--		--	

[e] Determined by the investigator to be related to the drug.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
For KN775 dataset, non-serious adverse events up to 30 days of last dose and serious adverse events up to 120 days of last dose are included.
For KN146 dataset, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
For lenvatinib monotherapy safety dataset, both non-serious adverse events and serious adverse events up to 30 days of last dose are included.
For pembrolizumab monotherapy reference safety dataset, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
[f] Includes all subjects who received at least one dose of lenvatinib in E7080-G000-398, E7080-G000-303, E7080-G000-201, E7080-G000-204, E7080-G000-703, E7080-G000-203, E7080-G000-205, E7080-G000-206, E7080-J081-208, E7080-G000-209 and E7080-J081-105.
[g] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054:02OCT2017, E7080-G000-206: 01SEP2016)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, E7080-G000-703: 01SEP2016)
Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019)
Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)
Database cutoff date for Thyroid (E7080-G000-398: 01SEP2016, E7080-G000-303: 01SEP2016, E7080-G000-201: 01SEP2016, E7080-J081-208: 01SEP2016)
Database cutoff date for Endometrial Cancer (KN775: 26OCT2020, E7080-G000-204: 01SEP2016)
Database cutoff date for Malignant Glioma (E7080-G000-203: 01SEP2016)
Database cutoff date for Renal Cell Carcinoma (E7080-G000-205: 15MAR2018)
Database cutoff date for Adenocarcinoma (E7080-G000-209: 01SEP2016)
Database cutoff date for Solid Tumor (KN146: 18AUG2020, E7080-J081-105: 01SEP2016)

Source: [ISS: adam-adsl; adae]

Overall, the safety profile adjusted for exposure of lenvatinib plus pembrolizumab in Study 309/KEYNOTE-775 is generally similar to the comparative safety sets of TPC EC in Study 309/KEYNOTE-775, lenvatinib plus pembrolizumab in non-EC and lenvatinib monotherapy, but exposure adjusted differences were generally much higher compared with pembrolizumab monotherapy (table below).

When comparing the exposure-adjusted AE (rate: number of events / 100 person-months), in the lenvatinib plus pembrolizumab EC group and the TPC EC group (table below), there were generally similar rate of all SAEs (10.15 vs. 10.08), drug-related SAEs (5.15 vs. 4.08), and drug-related fatal AEs (0.15 vs. 0.45); lower rate of drug-related AEs (133.21 vs. 153.13), Grade 3 to 5 AEs (31.02 vs. 48.78), drug-related Grade 3 to 5 AEs (18.52 vs. 34.5) and fatal AEs (0.59 vs. 1.08); and higher rate of dose interruption due to an AE (21.18 vs. 11.5), discontinuation due to an AEs (5 vs. 2.32), to a drug-related AEs (3.98 vs. 1.76), to a SAEs (2.42 vs. 0.85), or to a drug-related SAEs (1.63 vs. 0.45), dose modification due to an AE (37.91 vs. 18.58), and dose reduction due to an AE (15.16 vs. 4.76).

In the lenvatinib plus pembrolizumab EC group and the lenvatinib monotherapy group, there were generally similar rate of all AEs (231.94 vs. 226.7), all SAEs (10.15 vs. 9.66), dose interruption due to AE (21.18 vs. 22.71), drug-related fatal AEs (0.15 vs. 0.21); lower rate of drug-related AEs (133.21 vs. 150.70), fatal AEs (0.59 vs. 0.72), and lenvatinib interruption due to AEs (15.72 vs. 22.71); and higher rate of drug-related SAEs (5.15 vs. 3.79), Grade 3 to 5 AEs (31.02 vs. 22.7), drug-related Grade 3 to 5 AEs (18.52 vs. 14.12), discontinuation due to AEs (5 vs. 3.07), to a drug-related AEs (3.98 vs. 2.08), to a SAEs (2.42 vs. 1.51), or to a drug-related SAEs (1.63 vs. 0.84), and lenvatinib dose reduction due to an AE (15.16 vs. 9.3).

In the lenvatinib plus pembrolizumab EC group and the pembrolizumab monotherapy RSD, there were generally similar rate of all SAEs (10.15 vs. 8.55), fatal AEs (0.59 vs. 0.67), and drug-related fatal AEs (0.15 vs. 0.08); and much higher rate of all AEs (231.94 vs. 128.64), drug-related AEs (133.21 vs. 40.27), Grade 3 to 5 AEs (31.02 vs. 12.87), drug-related Grade 3 to 5 AEs (18.52 vs 2.87), drug-related SAEs (5.15 vs. 1.91), dose interruption due to AE (21.18 vs. 5.59), pembrolizumab interruption due to AEs (11.28 vs. 5.59), and discontinuation due to AEs (5 vs. 1.8), to a drug-related AEs (3.98 vs. 0.94), to a SAEs (2.42 vs. 1.27), or to a drug-related SAEs (1.63 vs. 0.54).

The overall AE summary profile of the lenvatinib plus pembrolizumab EC group was generally consistent with the lenvatinib plus pembrolizumab non-EC group, except for lower rate of dose interruption of any drugs due to AEs (21.18 vs. 26.74), and lenvatinib interruption due to AEs (15.72 vs. 23.33); and higher rate in the lenvatinib plus pembrolizumab EC group compared with the lenvatinib plus pembrolizumab non-EC group observed for Grade 3 to 5 AEs (31.02 vs. 25.73), drug-related Grade 3 to 5 AEs (18.52 vs. 12.24), drug-related SAEs (5.15 vs. 2.85); discontinuation of due to AEs (5 vs. 3.1), to drug-related AEs (3.98 vs. 1.91), to a SAEs (2.42 vs. 1.74), or to a drug-related SAEs (1.63 vs. 0.87).

So, overall, Grade 3 to 5 AEs (including drug-related Grade 3 to 5 AEs) exposure-adjusted rate was higher in the lenvatinib plus pembrolizumab EC group compared with lenvatinib plus pembrolizumab non-EC, and both lenvatinib and pembrolizumab monotherapy datasets, but lower than in the TPC EC group. SAEs rates were similar between all datasets. Fatal AEs rates were similar between the lenvatinib plus pembrolizumab EC group, lenvatinib plus pembrolizumab non-EC, and both lenvatinib and pembrolizumab monotherapy datasets, but lower than in the TPC EC group. However, rate of discontinuation of any drugs due to AEs (including due to drug-related AEs) and to SAEs (including due to drug-related SAEs) was slightly higher in the lenvatinib plus pembrolizumab EC group compared to all other datasets.

Table 49: Exposure-Adjusted Adverse Event Summary (Including Multiple Occurrences of Events) (APaT Population)

	Event Count and Rate (Events/100 person-months)[a]									
	KN775 Lenvatinib + Pembrolizumab		KN775 Treatment Physician's Choice		KN146 Lenvatinib + Pembrolizumab (Non-Endometrial Cancer)		Lenvatinib Monotherapy Safety Dataset[f]		Pembrolizumab Monotherapy Reference Safety Dataset[g]	
Number of Subjects exposed	406		388		230		1119		5884	
Total exposure[b] in person-months	3919.48		1765.17		2875.54		14052.8		47883.8	
Total events (rate)										
with one or more adverse events	9091	(231.94)	4526	(256.41)	6680	(232.30)	31858	(226.70)	61600	(128.64)
with no adverse event	1	(0.03)	2	(0.11)	0	(0.00)	11	(0.08)	194	(0.41)
with drug-related[c] adverse events	5221	(133.21)	2703	(153.13)	3773	(131.21)	21177	(150.70)	19283	(40.27)
with toxicity grade 3-5 adverse events	1216	(31.02)	861	(48.78)	740	(25.73)	3190	(22.70)	6162	(12.87)
with toxicity grade 3-5 drug-related adverse events	726	(18.52)	609	(34.50)	352	(12.24)	1984	(14.12)	1374	(2.87)
with serious adverse events	398	(10.15)	178	(10.08)	284	(9.88)	1358	(9.66)	4094	(8.55)
with serious drug-related adverse events	202	(5.15)	72	(4.08)	82	(2.85)	533	(3.79)	916	(1.91)
with dose interruption of any drug due to an adverse event	830	(21.18)	203	(11.50)	769	(26.74)	3191	(22.71)	2677	(5.59)
interruption of Pembrolizumab	442	(11.28)	--		283	(9.84)	--		2677	(5.59)
interruption of Lenvatinib	616	(15.72)	--		671	(23.33)	3191	(22.71)	--	
interruption of both Pembrolizumab and Lenvatinib	228	(5.82)	--		185	(6.43)	--		--	
with dose reduction of Lenvatinib due to an adverse event	594	(15.16)	--		327	(11.37)	1307	(9.30)	--	
who died	23	(0.59)	19	(1.08)	28	(0.97)	101	(0.72)	319	(0.67)
who died due to a drug-related adverse event	6	(0.15)	8	(0.45)	5	(0.17)	29	(0.21)	39	(0.08)
discontinued any drug due to an adverse event	196	(5.00)	41	(2.32)	89	(3.10)	432	(3.07)	863	(1.80)
discontinued Pembrolizumab	101	(2.58)	--		71	(2.47)	--		863	(1.80)
discontinued Lenvatinib	164	(4.18)	--		73	(2.54)	432	(3.07)	--	
discontinued both Pembrolizumab and Lenvatinib	69	(1.76)	--		55	(1.91)	--		--	
discontinued any drug due to a drug-related adverse event	156	(3.98)	31	(1.76)	55	(1.91)	292	(2.08)	448	(0.94)
discontinued Pembrolizumab	56	(1.43)	--		--		--		448	(0.94)
discontinued Lenvatinib	124	(3.16)	--		--		292	(2.08)	--	
discontinued both Pembrolizumab and Lenvatinib	24	(0.61)	--		--		--		--	
discontinued any drug due to a serious adverse event	95	(2.42)	15	(0.85)	50	(1.74)	212	(1.51)	609	(1.27)
discontinued Pembrolizumab	61	(1.56)	--		42	(1.46)	--		609	(1.27)
discontinued Lenvatinib	85	(2.17)	--		45	(1.56)	212	(1.51)	--	
discontinued both Pembrolizumab and Lenvatinib	51	(1.30)	--		37	(1.29)	--		--	
discontinued any drug due to a serious drug-related adverse event	64	(1.63)	8	(0.45)	25	(0.87)	118	(0.84)	259	(0.54)
discontinued Pembrolizumab	29	(0.74)	--		--		--		259	(0.54)
discontinued Lenvatinib	53	(1.35)	--		--		118	(0.84)	--	
discontinued both Pembrolizumab and Lenvatinib	18	(0.46)	--		--		--		--	

[a] Event rate per 100 person-months of exposure = event count *100/person-months of exposure.
[b] Drug exposure is defined as the interval between the first dose date and the earlier of the last dose date + 30 or the database cutoff date.
[c] Determined by the investigator to be related to the drug.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
For KN775 dataset, non-serious adverse events up to 30 days of last dose and serious adverse events up to 120 days of last dose are included.
For KN146 dataset, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
For lenvatinib monotherapy safety dataset, both non-serious adverse events and serious adverse events up to 30 days of last dose are included.
For pembrolizumab monotherapy reference safety dataset, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
[f] Includes all subjects who received at least one dose of lenvatinib in E7080-G000-398, E7080-G000-303, E7080-G000-201, E7080-G000-204, E7080-G000-703, E7080-G000-203, E7080-G000-205, E7080-G000-206, E7080-J081-208, E7080-G000-209 and E7080-J081-105.
[g] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054:02OCT2017, E7080-G000-206: 01SEP2016)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, E7080-G000-703: 01SEP2016)
Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019)
Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)
Database cutoff date for Thyroid (E7080-G000-398: 01SEP2016, E7080-G000-303: 01SEP2016, E7080-G000-201: 01SEP2016, E7080-J081-208: 01SEP2016)
Database cutoff date for Endometrial Cancer (KN775: 26OCT2020, E7080-G000-204: 01SEP2016)
Database cutoff date for Malignant Glioma (E7080-G000-203: 01SEP2016)
Database cutoff date for Renal Cell Carcinoma (E7080-G000-205: 15MAR2018)
Database cutoff date for Adenocarcinoma (E7080-G000-209: 01SEP2016)
Database cutoff date for Solid Tumor (KN146: 18AUG2020, E7080-J081-105: 01SEP2016)
Source: [ISS: adam-adsl; adae]

- ***Most frequently reported AEs***

The overall incidence of AEs was similar between the lenvatinib plus pembrolizumab EC group (99.8%), TPC EC group (99.5%), the lenvatinib plus pembrolizumab non-EC group (100%), the lenvatinib monotherapy group (99%) and pembrolizumab monotherapy RSD (96.7%) (Table below). The most frequently reported AEs (incidence ≥30%) were:

- Lenvatinib plus pembrolizumab EC group: hypertension, hypothyroidism, diarrhoea, nausea, decreased appetite, vomiting, weight decreased, fatigue, and arthralgia

- TPC EC group: anaemia, nausea, neutropenia, and alopecia

The most frequent exposure-adjusted AEs in the lenvatinib plus pembrolizumab EC group (> 4 events / 100 person-months) were diarrhoea, hypertension, nausea, vomiting, hypothyroidism, decreased appetite, proteinuria, arthralgia, fatigue, and weight decreased. All these AEs are identified very common ADRs in section 4.8 of the SmPC.

When comparing the exposure-adjusted AEs, the overall rate was slightly lower in the lenvatinib plus pembrolizumab EC group (231.94) compared to the TPC EC group (256.41) (Table below). The following AEs were reported with an increased rate of at least 2 events / 100 person-months in the lenvatinib plus pembrolizumab EC group compared to the TPC EC group : Hypertension, Hypothyroidism, Diarrhoea, Weight decreased, Arthralgia, Proteinuria, AST increased, Dysphonia, and PPES. All these AEs are identified very common ADRs in the SmPC section 4.8.

The most frequently reported AEs in the lenvatinib plus pembrolizumab EC group were generally consistent with those observed in the lenvatinib plus pembrolizumab non-EC group, although the incidences varied for some of these AEs between the 2 groups.

In the lenvatinib plus pembrolizumab EC group compared with the lenvatinib monotherapy group and pembrolizumab monotherapy RSD, there was a marked higher incidence of the following AEs: hypothyroidism, anaemia, UTI, ALT increased, AST increased, hypomagnesemia, hypertriglyceridemia, lipase increased, mucosal inflammation, hyperthyroidism, Hypokalaemia, Blood thyroid stimulating hormone increased, blood alkaline phosphatase increased, platelet count decreased, blood creatinine increased, hyponatremia, neutropenia, leukopenia, and neutrophil count decreased.

Of these AEs, the following had a marked higher incidence in the lenvatinib plus pembrolizumab EC group compared with the lenvatinib plus pembrolizumab non-EC group: hypothyroidism, anaemia, UTI, ALT increased, AST increased, hypomagnesemia, mucosal inflammation, hyperthyroidism, Blood thyroid stimulating hormone increased, platelet count decreased, neutropenia, leukopenia, and neutrophil count decreased.

Table 50: Participants With Adverse Events by Decreasing Incidence (Incidence ⩾ 10% in One or More Treatment Groups) (APaT Population)

	KN775 Lenvatinib + Pembrolizumab		KN775 Treatment Physician's Choice		KN146 Lenvatinib + Pembrolizumab (Non-Endometrial Cancer)		Lenvatinib Monotherapy Safety Dataset[i]		Pembrolizumab Monotherapy Reference Safety Dataset[j]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	406		388		230		1,119		5,884	
with one or more adverse events	405	(99.8)	386	(99.5)	230	(100.0)	1,108	(99.0)	5,690	(96.7)
with no adverse events	1	(0.2)	2	(0.5)	0	(0.0)	11	(1.0)	194	(3.3)
Hypertension	260	(64.0)	20	(5.2)	97	(42.2)	672	(60.1)	295	(5.0)
Hypothyroidism	233	(57.4)	3	(0.8)	87	(37.8)	146	(13.0)	651	(11.1)
Diarrhoea	220	(54.2)	78	(20.1)	135	(58.7)	580	(51.8)	1,200	(20.4)
Nausea	201	(49.5)	179	(46.1)	116	(50.4)	475	(42.4)	1,213	(20.6)
Decreased appetite	182	(44.8)	82	(21.1)	113	(49.1)	509	(45.5)	1,136	(19.3)
Vomiting	149	(36.7)	81	(20.9)	77	(33.5)	373	(33.3)	732	(12.4)
Weight decreased	138	(34.0)	22	(5.7)	65	(28.3)	390	(34.9)	561	(9.5)
Fatigue	134	(33.0)	107	(27.6)	147	(63.9)	537	(48.0)	1,884	(32.0)
Arthralgia	124	(30.5)	31	(8.0)	93	(40.4)	343	(30.7)	1,104	(18.8)
Proteinuria	117	(28.8)	11	(2.8)	93	(40.4)	389	(34.8)	54	(0.9)
Anaemia	106	(26.1)	189	(48.7)	32	(13.9)	92	(8.2)	836	(14.2)
Constipation	105	(25.9)	96	(24.7)	70	(30.4)	300	(26.8)	995	(16.9)
Urinary tract infection	104	(25.6)	39	(10.1)	29	(12.6)	119	(10.6)	384	(6.5)
Headache	101	(24.9)	34	(8.8)	59	(25.7)	357	(31.9)	711	(12.1)
Asthenia	96	(23.6)	95	(24.5)	16	(7.0)	193	(17.2)	666	(11.3)
Dysphonia	93	(22.9)	2	(0.5)	82	(35.7)	351	(31.4)	127	(2.2)
Alanine aminotransferase increased	86	(21.2)	20	(5.2)	24	(10.4)	90	(8.0)	393	(6.7)
Palmar-plantar erythrodysaesthesia syndrome	86	(21.2)	3	(0.8)	53	(23.0)	233	(20.8)	19	(0.3)
Abdominal pain	83	(20.4)	53	(13.7)	46	(20.0)	229	(20.5)	480	(8.2)
Aspartate aminotransferase increased	80	(19.7)	17	(4.4)	24	(10.4)	82	(7.3)	384	(6.5)
Stomatitis	78	(19.2)	47	(12.1)	76	(33.0)	310	(27.7)	144	(2.4)
Hypomagnesaemia	72	(17.7)	26	(6.7)	28	(12.2)	51	(4.6)	160	(2.7)
Myalgia	72	(17.7)	19	(4.9)	27	(11.7)	168	(15.0)	430	(7.3)
Rash	61	(15.0)	13	(3.4)	35	(15.2)	162	(14.5)	904	(15.4)
Pyrexia	58	(14.3)	29	(7.5)	27	(11.7)	134	(12.0)	746	(12.7)
Abdominal pain upper	53	(13.1)	27	(7.0)	15	(6.5)	167	(14.9)	213	(3.6)
Cough	53	(13.1)	51	(13.1)	88	(38.3)	245	(21.9)	1,148	(19.5)
Hypokalaemia	53	(13.1)	26	(6.7)	22	(9.6)	96	(8.6)	270	(4.6)
Blood thyroid stimulating hormone increased	52	(12.8)	1	(0.3)	16	(7.0)	80	(7.1)	97	(1.6)
Hypertriglyceridaemia	51	(12.6)	11	(2.8)	31	(13.5)	35	(3.1)	88	(1.5)
Blood alkaline phosphatase increased	50	(12.3)	15	(3.9)	22	(9.6)	56	(5.0)	240	(4.1)

Platelet count decreased	50	(12.3)	22	(5.7)	12	(5.2)	55	(4.9)	73	(1.2)
Back pain	49	(12.1)	29	(7.5)	44	(19.1)	200	(17.9)	662	(11.3)
Mucosal inflammation	49	(12.1)	38	(9.8)	0	(0.0)	25	(2.2)	92	(1.6)
Oedema peripheral	49	(12.1)	36	(9.3)	44	(19.1)	193	(17.2)	512	(8.7)
Hyperthyroidism	47	(11.6)	4	(1.0)	11	(4.8)	29	(2.6)	247	(4.2)
Dyspnoea	46	(11.3)	42	(10.8)	63	(27.4)	202	(18.1)	989	(16.8)
Lipase increased	45	(11.1)	8	(2.1)	32	(13.9)	41	(3.7)	27	(0.5)
Pain in extremity	45	(11.1)	21	(5.4)	40	(17.4)	153	(13.7)	391	(6.6)
Blood creatinine increased	44	(10.8)	10	(2.6)	28	(12.2)	54	(4.8)	256	(4.4)
Thrombocytopenia	44	(10.8)	26	(6.7)	8	(3.5)	103	(9.2)	89	(1.5)
Dizziness	42	(10.3)	22	(5.7)	41	(17.8)	153	(13.7)	430	(7.3)
Pruritus	42	(10.3)	12	(3.1)	31	(13.5)	69	(6.2)	1,060	(18.0)
Dry mouth	40	(9.9)	11	(2.8)	29	(12.6)	147	(13.1)	284	(4.8)
Dysgeusia	40	(9.9)	27	(7.0)	24	(10.4)	79	(7.1)	110	(1.9)
Hyponatraemia	36	(8.9)	18	(4.6)	36	(15.7)	66	(5.9)	345	(5.9)
Insomnia	33	(8.1)	20	(5.2)	32	(13.9)	133	(11.9)	429	(7.3)
Epistaxis	32	(7.9)	10	(2.6)	27	(11.7)	140	(12.5)	83	(1.4)
Neutropenia	30	(7.4)	131	(33.8)	2	(0.9)	34	(3.0)	49	(0.8)
Dry skin	28	(6.9)	11	(2.8)	27	(11.7)	117	(10.5)	304	(5.2)
Leukopenia	28	(6.9)	51	(13.1)	2	(0.9)	32	(2.9)	46	(0.8)
Dyspepsia	27	(6.7)	19	(4.9)	25	(10.9)	113	(10.1)	149	(2.5)
Dehydration	26	(6.4)	8	(2.1)	34	(14.8)	105	(9.4)	208	(3.5)
Alopecia	22	(5.4)	120	(30.9)	6	(2.6)	90	(8.0)	87	(1.5)
Neutrophil count decreased	22	(5.4)	94	(24.2)	4	(1.7)	18	(1.6)	37	(0.6)
Oropharyngeal pain	22	(5.4)	9	(2.3)	43	(18.7)	119	(10.6)	196	(3.3)
Oral pain	20	(4.9)	3	(0.8)	23	(10.0)	79	(7.1)	45	(0.8)
White blood cell count decreased	20	(4.9)	60	(15.5)	3	(1.3)	26	(2.3)	57	(1.0)
Rash maculo-papular	15	(3.7)	2	(0.5)	32	(13.9)	15	(1.3)	202	(3.4)
Muscular weakness	13	(3.2)	5	(1.3)	27	(11.7)	79	(7.1)	157	(2.7)
Nasal congestion	7	(1.7)	5	(1.3)	27	(11.7)	23	(2.1)	150	(2.5)
Rhinorrhoea	3	(0.7)	4	(1.0)	26	(11.3)	36	(3.2)	114	(1.9)

Every participant is counted a single time for each applicable row and column.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

For KN775 dataset, non-serious adverse events up to 30 days of last dose and serious adverse events up to 120 days of last dose are included.

For KN146 dataset, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

For lenvatinib monotherapy safety dataset, both non-serious adverse events and serious adverse events up to 30 days of last dose are included.

For pembrolizumab monotherapy reference safety dataset, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

[i] Includes all subjects who received at least one dose of lenvatinib in E7080-G000-398, E7080-G000-303, E7080-G000-201, E7080-G000-204, E7080-G000-703, E7080-G000-203, E7080-G000-205, E7080-G000-206, E7080-J081-208, E7080-G000-209 and E7080-J081-105.

[j] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054:02OCT2017, E7080-G000-206: 01SEP2016)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, E7080-G000-703: 01SEP2016)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Thyroid (E7080-G000-398: 01SEP2016, E7080-G000-303: 01SEP2016, E7080-G000-201: 01SEP2016, E7080-J081-208: 01SEP2016)

Database cutoff date for Endometrial Cancer (KN775: 26OCT2020, E7080-G000-204: 01SEP2016)

Database cutoff date for Malignant Glioma (E7080-G000-203: 01SEP2016)

Database cutoff date for Renal Cell Carcinoma (E7080-G000-205: 15MAR2018)

Database cutoff date for Adenocarcinoma (E7080-G000-209: 01SEP2016)

Database cutoff date for Solid Tumor (KN146: 18AUG2020, E7080-J081-105: 01SEP2016)

Source: ISS: adam-adsl: adae1

Table 51: Exposure-Adjusted Adverse Events (Including Multiple Occurrences of Events) (Incidence ⩾ 10% in One or More Treatment Groups) in All-comer Participants (APaT Population)

	Event Count and Rate (Events/100 person-months)[a]	
	Lenvatinib + Pembrolizumab	TPC
Number of participants exposed	406	388
Total exposure[b] in person-months	3919.5	1765.2
Blood and lymphatic system disorders	**368 (9.4)**	**658 (37.3)**
Anaemia	147 (3.8)	239 (13.5)
Leukopenia	54 (1.4)	89 (5.0)
Neutropenia	60 (1.5)	216 (12.2)
Thrombocytopenia	52 (1.3)	31 (1.8)
Cardiac disorders	**79 (2.0)**	**53 (3.0)**
Endocrine disorders	**342 (8.7)**	**9 (0.5)**
Hyperthyroidism	47 (1.2)	4 (0.2)
Hypothyroidism	275 (7.0)	3 (0.2)
Eye disorders	**61 (1.6)**	**25 (1.4)**
Gastrointestinal disorders	**1,995 (50.9)**	**956 (54.2)**
Abdominal pain	107 (2.7)	61 (3.5)
Abdominal pain upper	68 (1.7)	33 (1.9)
Constipation	129 (3.3)	119 (6.7)
Diarrhoea	518 (13.2)	107 (6.1)
Nausea	306 (7.8)	299 (16.9)
Stomatitis	95 (2.4)	58 (3.3)
Vomiting	297 (7.6)	125 (7.1)
General disorders and administration site conditions	**667 (17.0)**	**513 (29.1)**
Asthenia	121 (3.1)	128 (7.3)
Fatigue	166 (4.2)	146 (8.3)
Mucosal inflammation	60 (1.5)	47 (2.7)
Oedema peripheral	60 (1.5)	39 (2.2)
Pyrexia	88 (2.2)	31 (1.8)
Hepatobiliary disorders	**66 (1.7)**	**3 (0.2)**
Infections and infestations	**478 (12.2)**	**247 (14.0)**
Urinary tract infection	153 (3.9)	50 (2.8)
Injury, poisoning and procedural complications	**63 (1.6)**	**28 (1.6)**
Investigations	**1,226 (31.3)**	**674 (38.2)**
Alanine aminotransferase increased	128 (3.3)	26 (1.5)
Aspartate aminotransferase increased	129 (3.3)	18 (1.0)
Blood alkaline phosphatase increased	71 (1.8)	19 (1.1)
Blood creatinine increased	58 (1.5)	10 (0.6)
Blood thyroid stimulating hormone increased	58 (1.5)	2 (0.1)
Lipase increased	60 (1.5)	9 (0.5)
Neutrophil count decreased	38 (1.0)	204 (11.6)
Platelet count decreased	79 (2.0)	27 (1.5)
Weight decreased	159 (4.1)	23 (1.3)
White blood cell count decreased	28 (0.7)	132 (7.5)
Metabolism and nutrition disorders	**885 (22.6)**	**317 (18.0)**
Decreased appetite	237 (6.0)	97 (5.5)
Hypertriglyceridaemia	77 (2.0)	11 (0.6)
Hypokalaemia	63 (1.6)	37 (2.1)
Hypomagnesaemia	116 (3.0)	27 (1.5)
Musculoskeletal and connective tissue disorders	**548 (14.0)**	**168 (9.5)**
Arthralgia	179 (4.6)	32 (1.8)
Back pain	59 (1.5)	36 (2.0)
Myalgia	92 (2.3)	24 (1.4)
Pain in extremity	61 (1.6)	25 (1.4)
Nervous system disorders	**373 (9.5)**	**194 (11.0)**
Dizziness	47 (1.2)	30 (1.7)
Headache	137 (3.5)	35 (2.0)
Psychiatric disorders	**89 (2.3)**	**47 (2.7)**
Renal and urinary disorders	**342 (8.7)**	**68 (3.9)**
Proteinuria	198 (5.1)	13 (0.7)
Reproductive system and breast disorders	**87 (2.2)**	**30 (1.7)**
Respiratory, thoracic and mediastinal disorders	**404 (10.3)**	**194 (11.0)**
Cough	64 (1.6)	55 (3.1)
Dysphonia	112 (2.9)	2 (0.1)

Respiratory, thoracic and mediastinal disorders	**404 (10.3)**	**194 (11.0)**
Dyspnoea	51 (1.3)	44 (2.5)
Skin and subcutaneous tissue disorders	**450 (11.5)**	**233 (13.2)**
Alopecia	22 (0.6)	120 (6.8)
Palmar-plantar erythrodysaesthesia syndrome	98 (2.5)	3 (0.2)
Pruritus	49 (1.3)	12 (0.7)
Rash	77 (2.0)	13 (0.7)
Vascular disorders	**502 (12.8)**	**89 (5.0)**
Hypertension	435 (11.1)	28 (1.6)

[a] Event rate per 100 person-months of exposure = event count *100/person-months of exposure.
[b] Drug exposure is defined as the interval between the first dose date + 1 day and the earlier of the last dose date + 30 or the database cutoff date.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 120 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

Source: [P775V01MK3475: adam-adsl; adae]

Section 4.8 of the SmPC was updated to include the population of Endometrial Carcinoma patients receiving lenvatinib plus pembrolizumab from the pooled dataset (N=530) in single arm study KEYNOTE-146 (cut-off date: 18AUG2020) and in phase III study KEYNOTE-775 (cut-off date: 26OCT2020) into a new column representing Lenvatinib plus Pembrolizumab combination Safety Dataset.

- ***All grade 3 to 5 AEs***

Table 52: Participants With Grade 3-5 Adverse Events by Decreasing Incidence (Incidence ⩾ 1% in One or More Treatment Groups) (APaT Population)

	KN775 Lenvatinib + Pembrolizumab		KN775 Treatment Physician´s Choice		KN146 Lenvatinib + Pembrolizumab (Non-Endometrial Cancer)		Lenvatinib Monotherapy Safety Dataset[a]		Pembrolizumab Monotherapy Reference Safety Dataset[b]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	406		388		230		1,119		5,884	
with one or more adverse events	361	(88.9)	282	(72.7)	203	(88.3)	899	(80.3)	2,829	(48.1)
with no adverse events	45	(11.1)	106	(27.3)	27	(11.7)	220	(19.7)	3,055	(51.9)
Hypertension	154	(37.9)	9	(2.3)	53	(23.0)	342	(30.6)	102	(1.7)
Weight decreased	42	(10.3)	1	(0.3)	11	(4.8)	80	(7.1)	30	(0.5)
Decreased appetite	32	(7.9)	2	(0.5)	9	(3.9)	41	(3.7)	74	(1.3)
Diarrhoea	31	(7.6)	8	(2.1)	22	(9.6)	82	(7.3)	79	(1.3)
Lipase increased	26	(6.4)	5	(1.3)	21	(9.1)	22	(2.0)	16	(0.3)
Anaemia	25	(6.2)	57	(14.7)	7	(3.0)	25	(2.2)	233	(4.0)
Asthenia	24	(5.9)	15	(3.9)	4	(1.7)	59	(5.3)	58	(1.0)
Proteinuria	22	(5.4)	1	(0.3)	21	(9.1)	99	(8.8)	1	(0.0)
Fatigue	21	(5.2)	12	(3.1)	24	(10.4)	102	(9.1)	144	(2.4)
Hypokalaemia	21	(5.2)	6	(1.5)	3	(1.3)	26	(2.3)	58	(1.0)
Alanine aminotransferase increased	19	(4.7)	3	(0.8)	3	(1.3)	15	(1.3)	61	(1.0)
Aspartate aminotransferase increased	18	(4.4)	3	(0.8)	5	(2.2)	9	(0.8)	65	(1.1)
Hyponatraemia	18	(4.4)	4	(1.0)	16	(7.0)	34	(3.0)	153	(2.6)
Urinary tract infection	16	(3.9)	4	(1.0)	5	(2.2)	10	(0.9)	73	(1.2)
Nausea	14	(3.4)	5	(1.3)	5	(2.2)	31	(2.8)	50	(0.8)
Acute kidney injury	12	(3.0)	4	(1.0)	5	(2.2)	17	(1.5)	51	(0.9)
Amylase increased	11	(2.7)	2	(0.5)	6	(2.6)	13	(1.2)	9	(0.2)
Palmar-plantar erythrodysaesthesia syndrome	11	(2.7)	0	(0.0)	1	(0.4)	22	(2.0)	1	(0.0)
Platelet count decreased	11	(2.7)	3	(0.8)	2	(0.9)	5	(0.4)	8	(0.1)
Pulmonary embolism	11	(2.7)	13	(3.4)	4	(1.7)	34	(3.0)	91	(1.5)
Vomiting	11	(2.7)	9	(2.3)	6	(2.6)	29	(2.6)	42	(0.7)
Abdominal pain	10	(2.5)	5	(1.3)	6	(2.6)	32	(2.9)	42	(0.7)
Neutrophil count decreased	10	(2.5)	83	(21.4)	3	(1.3)	2	(0.2)	8	(0.1)
Dehydration	9	(2.2)	1	(0.3)	12	(5.2)	39	(3.5)	62	(1.1)
Gamma-glutamyltransferase increased	9	(2.2)	2	(0.5)	0	(0.0)	8	(0.7)	35	(0.6)
Hyperglycaemia	9	(2.2)	2	(0.5)	4	(1.7)	10	(0.9)	64	(1.1)
Hypophosphataemia	9	(2.2)	3	(0.8)	9	(3.9)	3	(0.3)	41	(0.7)
Blood alkaline phosphatase increased	8	(2.0)	4	(1.0)	2	(0.9)	6	(0.5)	48	(0.8)
Hypertriglyceridaemia	8	(2.0)	1	(0.3)	11	(4.8)	7	(0.6)	16	(0.3)

Pain in extremity	8	(2.0)	1	(0.3)	1	(0.4)	9	(0.8)	18	(0.3)
Pneumonia	8	(2.0)	5	(1.3)	7	(3.0)	43	(3.8)	242	(4.1)
Stomatitis	8	(2.0)	2	(0.5)	1	(0.4)	24	(2.1)	9	(0.2)
Arthralgia	7	(1.7)	0	(0.0)	5	(2.2)	15	(1.3)	58	(1.0)
Cholecystitis	7	(1.7)	0	(0.0)	3	(1.3)	9	(0.8)	6	(0.1)
Colitis	7	(1.7)	1	(0.3)	4	(1.7)	6	(0.5)	60	(1.0)
Lymphocyte count decreased	7	(1.7)	14	(3.6)	1	(0.4)	7	(0.6)	30	(0.5)
Lymphopenia	7	(1.7)	13	(3.4)	0	(0.0)	8	(0.7)	16	(0.3)
Neutropenia	7	(1.7)	100	(25.8)	1	(0.4)	10	(0.9)	15	(0.3)
Blood bilirubin increased	6	(1.5)	4	(1.0)	2	(0.9)	4	(0.4)	23	(0.4)
Mucosal inflammation	6	(1.5)	3	(0.8)	0	(0.0)	0	(0.0)	9	(0.2)
Thrombocytopenia	6	(1.5)	5	(1.3)	1	(0.4)	18	(1.6)	16	(0.3)
White blood cell count decreased	6	(1.5)	41	(10.6)	1	(0.4)	3	(0.3)	4	(0.1)
Death	5	(1.2)	3	(0.8)	0	(0.0)	5	(0.4)	42	(0.7)
Female genital tract fistula	5	(1.2)	1	(0.3)	0	(0.0)	2	(0.2)	1	(0.0)
Hypoalbuminaemia	5	(1.2)	0	(0.0)	3	(1.3)	8	(0.7)	28	(0.5)
Hypothyroidism	5	(1.2)	0	(0.0)	0	(0.0)	8	(0.7)	7	(0.1)
Immune-mediated hepatitis	5	(1.2)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.0)
Intestinal obstruction	5	(1.2)	5	(1.3)	0	(0.0)	2	(0.2)	12	(0.2)
Sepsis	5	(1.2)	6	(1.5)	5	(2.2)	17	(1.5)	45	(0.8)
Blood creatine phosphokinase increased	4	(1.0)	0	(0.0)	0	(0.0)	1	(0.1)	14	(0.2)
Haematuria	4	(1.0)	2	(0.5)	2	(0.9)	1	(0.1)	19	(0.3)
Hepatotoxicity	4	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hyperkalaemia	4	(1.0)	1	(0.3)	6	(2.6)	9	(0.8)	25	(0.4)
Hypocalcaemia	4	(1.0)	1	(0.3)	3	(1.3)	26	(2.3)	9	(0.2)
Hypomagnesaemia	4	(1.0)	2	(0.5)	1	(0.4)	4	(0.4)	1	(0.0)
Pyrexia	4	(1.0)	0	(0.0)	1	(0.4)	2	(0.2)	27	(0.5)
Rash maculo-papular	4	(1.0)	0	(0.0)	3	(1.3)	0	(0.0)	16	(0.3)
Adrenal insufficiency	3	(0.7)	0	(0.0)	3	(1.3)	0	(0.0)	18	(0.3)
Constipation	3	(0.7)	2	(0.5)	7	(3.0)	8	(0.7)	24	(0.4)
Dyspnoea	3	(0.7)	3	(0.8)	10	(4.3)	36	(3.2)	131	(2.2)
General physical health deterioration	3	(0.7)	1	(0.3)	0	(0.0)	26	(2.3)	35	(0.6)
Hypercalcaemia	3	(0.7)	2	(0.5)	3	(1.3)	5	(0.4)	51	(0.9)
Hypotension	3	(0.7)	0	(0.0)	6	(2.6)	19	(1.7)	32	(0.5)
Myalgia	3	(0.7)	0	(0.0)	3	(1.3)	5	(0.4)	11	(0.2)
Pneumonitis	3	(0.7)	0	(0.0)	3	(1.3)	1	(0.1)	83	(1.4)
Back pain	2	(0.5)	0	(0.0)	6	(2.6)	15	(1.3)	64	(1.1)
Blood pressure increased	2	(0.5)	0	(0.0)	0	(0.0)	16	(1.4)	3	(0.1)
Electrocardiogram QT prolonged	2	(0.5)	0	(0.0)	4	(1.7)	10	(0.9)	1	(0.0)
Febrile neutropenia	2	(0.5)	22	(5.7)	0	(0.0)	1	(0.1)	7	(0.1)
Headache	2	(0.5)	1	(0.3)	5	(2.2)	24	(2.1)	18	(0.3)
Cancer pain	1	(0.2)	0	(0.0)	2	(0.9)	11	(1.0)	27	(0.5)
Dysphagia	1	(0.2)	0	(0.0)	2	(0.9)	12	(1.1)	30	(0.5)
Hypoxia	1	(0.2)	0	(0.0)	6	(2.6)	4	(0.4)	25	(0.4)
Muscular weakness	1	(0.2)	0	(0.0)	3	(1.3)	9	(0.8)	22	(0.4)
Myocardial infarction	1	(0.2)	0	(0.0)	4	(1.7)	7	(0.6)	19	(0.3)
Pleural effusion	1	(0.2)	1	(0.3)	5	(2.2)	9	(0.8)	68	(1.2)
Pneumonia aspiration	1	(0.2)	2	(0.5)	3	(1.3)	4	(0.4)	31	(0.5)
Syncope	1	(0.2)	4	(1.0)	0	(0.0)	13	(1.2)	34	(0.6)
Cardiac failure	0	(0.0)	3	(0.8)	3	(1.3)	6	(0.5)	11	(0.2)
Chronic obstructive pulmonary disease	0	(0.0)	0	(0.0)	3	(1.3)	1	(0.1)	29	(0.5)
Diverticulitis	0	(0.0)	0	(0.0)	4	(1.7)	6	(0.5)	7	(0.1)
Ejection fraction decreased	0	(0.0)	2	(0.5)	0	(0.0)	12	(1.1)	0	(0.0)
Leukopenia	0	(0.0)	31	(8.0)	0	(0.0)	1	(0.1)	7	(0.1)
Mental status changes	0	(0.0)	0	(0.0)	3	(1.3)	6	(0.5)	6	(0.1)
Metabolic encephalopathy	0	(0.0)	0	(0.0)	3	(1.3)	3	(0.3)	0	(0.0)
Oropharyngeal pain	0	(0.0)	0	(0.0)	5	(2.2)	3	(0.3)	3	(0.1)

Table 53: Exposure-Adjusted Grade 3-5 Adverse Events (Including Multiple Occurrences of Events) (Incidence ⩾ 5% in One or More Treatment Groups) in All-comer Participants (APaT Population)

	Event Count and Rate (Events/100 person-months)[a]	
	Lenvatinib + Pembrolizumab	TPC
Number of participants exposed	406	388
Total exposure[b] in person-months	3919.5	1765.2
Blood and lymphatic system disorders	**53 (1.4)**	**308 (17.4)**
Anaemia	28 (0.7)	68 (3.9)
Febrile neutropenia	2 (0.1)	23 (1.3)
Leukopenia	0 (0.0)	43 (2.4)
Neutropenia	7 (0.2)	147 (8.3)
Gastrointestinal disorders	**150 (3.8)**	**52 (2.9)**
Diarrhoea	35 (0.9)	8 (0.5)
General disorders and administration site conditions	**75 (1.9)**	**49 (2.8)**
Asthenia	25 (0.6)	15 (0.8)
Fatigue	21 (0.5)	18 (1.0)
Hepatobiliary disorders	**32 (0.8)**	**1 (0.1)**
Infections and infestations	**89 (2.3)**	**39 (2.2)**
Investigations	**214 (5.5)**	**281 (15.9)**
Lipase increased	32 (0.8)	5 (0.3)
Neutrophil count decreased	10 (0.3)	159 (9.0)
Weight decreased	42 (1.1)	1 (0.1)
White blood cell count decreased	6 (0.2)	68 (3.9)
Metabolism and nutrition disorders	**152 (3.9)**	**31 (1.8)**
Decreased appetite	32 (0.8)	2 (0.1)
Hypokalaemia	22 (0.6)	6 (0.3)
Musculoskeletal and connective tissue disorders	**34 (0.9)**	**5 (0.3)**
Renal and urinary disorders	**52 (1.3)**	**14 (0.8)**
Proteinuria	22 (0.6)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	**27 (0.7)**	**28 (1.6)**
Skin and subcutaneous tissue disorders	**36 (0.9)**	**3 (0.2)**
Vascular disorders	**221 (5.6)**	**16 (0.9)**
Hypertension	209 (5.3)	10 (0.6)

[a] Event rate per 100 person-months of exposure = event count *100/person-months of exposure.

[b] Drug exposure is defined as the interval between the first dose date + 1 day and the earlier of the last dose date + 30 or the database cutoff date.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 120 days of last dose are included.

MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

Grades are based on NCI CTCAE version 4.03

TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.

Database Cutoff Date: 26OCT2020

Source: [P775V01MK3475: adam-adsl; adae]

- ***Drug-related AEs (all and grade 3 -5)***

Table 54: Participants With Drug-Related Adverse Events by Decreasing Incidence (Incidence ⩾ 5% in One or More Treatment Groups) (APaT Population)

	KN775 Lenvatinib + Pembrolizumab		KN775 Treatment Physician's Choice		KN146 Lenvatinib + Pembrolizumab (Non-Endometrial Cancer)		Lenvatinib Monotherapy Safety Dataset[i]		Pembrolizumab Monotherapy Reference Safety Dataset[f]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	406		388		230		1,119		5,884	
with one or more adverse events	395	(97.3)	364	(93.8)	225	(97.8)	1,060	(94.7)	4,132	(70.2)
with no adverse events	11	(2.7)	24	(6.2)	5	(2.2)	59	(5.3)	1,752	(29.8)
Hypertension	248	(61.1)	4	(1.0)	90	(39.1)	643	(57.5)	32	(0.5)
Hypothyroidism	221	(54.4)	0	(0.0)	77	(33.5)	124	(11.1)	565	(9.6)
Diarrhoea	171	(42.1)	42	(10.8)	116	(50.4)	508	(45.4)	630	(10.7)
Nausea	158	(38.9)	157	(40.5)	76	(33.0)	394	(35.2)	535	(9.1)
Decreased appetite	149	(36.7)	64	(16.5)	85	(37.0)	452	(40.4)	461	(7.8)
Fatigue	113	(27.8)	92	(23.7)	125	(54.3)	487	(43.5)	1,170	(19.9)
Proteinuria	102	(25.1)	4	(1.0)	87	(37.8)	378	(33.8)	14	(0.2)
Vomiting	99	(24.4)	59	(15.2)	40	(17.4)	280	(25.0)	198	(3.4)
Weight decreased	90	(22.2)	7	(1.8)	48	(20.9)	331	(29.6)	137	(2.3)
Arthralgia	84	(20.7)	17	(4.4)	68	(29.6)	210	(18.8)	464	(7.9)
Palmar-plantar erythrodysaesthesia syndrome	84	(20.7)	3	(0.8)	51	(22.2)	230	(20.6)	15	(0.3)
Dysphonia	76	(18.7)	2	(0.5)	71	(30.9)	284	(25.4)	17	(0.3)
Asthenia	75	(18.5)	76	(19.6)	10	(4.3)	146	(13.0)	363	(6.2)
Stomatitis	70	(17.2)	46	(11.9)	68	(29.6)	295	(26.4)	71	(1.2)
Alanine aminotransferase increased	63	(15.5)	14	(3.6)	19	(8.3)	76	(6.8)	234	(4.0)
Anaemia	58	(14.3)	150	(38.7)	10	(4.3)	44	(3.9)	202	(3.4)
Aspartate aminotransferase increased	58	(14.3)	12	(3.1)	19	(8.3)	68	(6.1)	220	(3.7)
Myalgia	54	(13.3)	13	(3.4)	22	(9.6)	132	(11.8)	232	(3.9)
Headache	53	(13.1)	14	(3.6)	35	(15.2)	227	(20.3)	193	(3.3)
Rash	47	(11.6)	6	(1.5)	24	(10.4)	132	(11.8)	676	(11.5)
Mucosal inflammation	45	(11.1)	35	(9.0)	0	(0.0)	24	(2.1)	48	(0.8)
Platelet count decreased	43	(10.6)	20	(5.2)	9	(3.9)	50	(4.5)	32	(0.5)
Blood thyroid stimulating hormone increased	40	(9.9)	1	(0.3)	15	(6.5)	68	(6.1)	71	(1.2)
Hyperthyroidism	39	(9.6)	1	(0.3)	11	(4.8)	15	(1.3)	219	(3.7)
Hypomagnesaemia	38	(9.4)	12	(3.1)	16	(7.0)	28	(2.5)	32	(0.5)
Constipation	36	(8.9)	51	(13.1)	22	(9.6)	160	(14.3)	155	(2.6)
Dry mouth	33	(8.1)	9	(2.3)	25	(10.9)	124	(11.1)	143	(2.4)
Dysgeusia	32	(7.9)	26	(6.7)	21	(9.1)	73	(6.5)	60	(1.0)
Lipase increased	32	(7.9)	2	(0.5)	29	(12.6)	31	(2.8)	17	(0.3)
Thrombocytopenia	31	(7.6)	22	(5.7)	3	(1.3)	93	(8.3)	41	(0.7)
Abdominal pain	30	(7.4)	13	(3.4)	21	(9.1)	141	(12.6)	114	(1.9)
Abdominal pain upper	28	(6.9)	12	(3.1)	4	(1.7)	120	(10.7)	51	(0.9)

Pruritus	27	(6.7)	7	(1.8)	28	(12.2)	42	(3.8)	836	(14.2)
Blood alkaline phosphatase increased	26	(6.4)	5	(1.3)	14	(6.1)	33	(2.9)	85	(1.4)
Pyrexia	26	(6.4)	4	(1.0)	11	(4.8)	41	(3.7)	258	(4.4)
Epistaxis	25	(6.2)	7	(1.8)	17	(7.4)	100	(8.9)	6	(0.1)
Hypertriglyceridaemia	24	(5.9)	1	(0.3)	22	(9.6)	30	(2.7)	27	(0.5)
Neutropenia	22	(5.4)	127	(32.7)	2	(0.9)	27	(2.4)	30	(0.5)
Blood creatinine increased	21	(5.2)	2	(0.5)	17	(7.4)	32	(2.9)	68	(1.2)
Amylase increased	20	(4.9)	1	(0.3)	15	(6.5)	10	(0.9)	12	(0.2)
Leukopenia	20	(4.9)	47	(12.1)	0	(0.0)	27	(2.4)	29	(0.5)
Pain in extremity	20	(4.9)	9	(2.3)	17	(7.4)	96	(8.6)	65	(1.1)
Dry skin	19	(4.7)	7	(1.8)	25	(10.9)	98	(8.8)	174	(3.0)
Oedema peripheral	18	(4.4)	8	(2.1)	18	(7.8)	103	(9.2)	93	(1.6)
Alopecia	17	(4.2)	117	(30.2)	5	(2.2)	86	(7.7)	46	(0.8)
Dizziness	17	(4.2)	4	(1.0)	13	(5.7)	82	(7.3)	82	(1.4)
Dyspepsia	17	(4.2)	10	(2.6)	18	(7.8)	72	(6.4)	33	(0.6)
Neutrophil count decreased	17	(4.2)	93	(24.0)	2	(0.9)	18	(1.6)	26	(0.4)
Cough	16	(3.9)	7	(1.8)	34	(14.8)	80	(7.1)	193	(3.3)
Oral pain	16	(3.9)	2	(0.5)	16	(7.0)	74	(6.6)	10	(0.2)
Hyponatraemia	15	(3.7)	4	(1.0)	15	(6.5)	29	(2.6)	59	(1.0)
Lymphopenia	15	(3.7)	26	(6.7)	0	(0.0)	25	(2.2)	27	(0.5)
White blood cell count decreased	15	(3.7)	58	(14.9)	3	(1.3)	22	(2.0)	28	(0.5)
Dehydration	14	(3.4)	3	(0.8)	13	(5.7)	56	(5.0)	33	(0.6)
Dyspnoea	14	(3.4)	11	(2.8)	28	(12.2)	59	(5.3)	199	(3.4)
Rash maculo-papular	13	(3.2)	2	(0.5)	30	(13.0)	11	(1.0)	158	(2.7)
Lymphocyte count decreased	10	(2.5)	22	(5.7)	4	(1.7)	12	(1.1)	47	(0.8)
Muscle spasms	9	(2.2)	4	(1.0)	12	(5.2)	53	(4.7)	58	(1.0)
Neuropathy peripheral	8	(2.0)	21	(5.4)	0	(0.0)	1	(0.1)	41	(0.7)
Back pain	7	(1.7)	6	(1.5)	10	(4.3)	70	(6.3)	70	(1.2)
Taste disorder	6	(1.5)	5	(1.3)	0	(0.0)	67	(6.0)	29	(0.5)
Oropharyngeal pain	5	(1.2)	1	(0.3)	24	(10.4)	77	(6.9)	19	(0.3)
Adrenal insufficiency	4	(1.0)	0	(0.0)	16	(7.0)	0	(0.0)	32	(0.5)
Febrile neutropenia	1	(0.2)	21	(5.4)	0	(0.0)	0	(0.0)	0	(0.0)
Rhinorrhoea	1	(0.2)	0	(0.0)	17	(7.4)	10	(0.9)	12	(0.2)

Every participant is counted a single time for each applicable row and column.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

For KN775 dataset, non-serious adverse events up to 30 days of last dose and serious adverse events up to 120 days of last dose are included.

For KN146 dataset, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

For lenvatinib monotherapy safety dataset, both non-serious adverse events and serious adverse events up to 30 days of last dose are included.

For pembrolizumab monotherapy reference safety dataset, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

[i] Includes all subjects who received at least one dose of lenvatinib in E7080-G000-398, E7080-G000-303, E7080-G000-201, E7080-G000-204, E7080-G000-703, E7080-G000-203, E7080-G000-205, E7080-G000-206, E7080-J081-208, E7080-G000-209 and E7080-J081-105.

[j] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054:02OCT2017, E7080-G000-206: 01SEP2016)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, E7080-G000-703: 01SEP2016)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Thyroid (E7080-G000-398: 01SEP2016, E7080-G000-303: 01SEP2016, E7080-G000-201: 01SEP2016, E7080-J081-208: 01SEP2016)

Database cutoff date for Endometrial Cancer (KN775: 26OCT2020, E7080-G000-204: 01SEP2016)

Database cutoff date for Malignant Glioma (E7080-G000-203: 01SEP2016)

Database cutoff date for Renal Cell Carcinoma (E7080-G000-205: 15MAR2018)

Database cutoff date for Adenocarcinoma (E7080-G000-209: 01SEP2016)

Database cutoff date for Solid Tumor (KN146: 18AUG2020, E7080-J081-105: 01SEP2016)

Source: [ISS: adam-adsl; adae]

Table 55: Participants With Grade 3-5 Drug-Related Adverse Events by Decreasing Incidence (Incidence ⩾ 1% in One or More Treatment Groups) (APaT Population)

	KN775 Lenvatinib + Pembrolizumab		KN775 Treatment Physician's Choice		KN146 Lenvatinib + Pembrolizumab (Non-Endometrial Cancer)		Lenvatinib Monotherapy Safety Dataset[f]		Pembrolizumab Monotherapy Reference Safety Dataset[f]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	406		388		230		1,119		5,884	
with one or more adverse events	316	(77.8)	229	(59.0)	151	(65.7)	724	(64.7)	913	(15.5)
with no adverse events	90	(22.2)	159	(41.0)	79	(34.3)	395	(35.3)	4,971	(84.5)
Hypertension	146	(36.0)	1	(0.3)	46	(20.0)	331	(29.6)	10	(0.2)
Diarrhoea	25	(6.2)	3	(0.8)	19	(8.3)	69	(6.2)	55	(0.9)
Decreased appetite	24	(5.9)	0	(0.0)	5	(2.2)	34	(3.0)	21	(0.4)
Weight decreased	24	(5.9)	0	(0.0)	5	(2.2)	67	(6.0)	7	(0.1)
Lipase increased	18	(4.4)	1	(0.3)	18	(7.8)	12	(1.1)	11	(0.2)
Proteinuria	18	(4.4)	0	(0.0)	20	(8.7)	97	(8.7)	0	(0.0)
Asthenia	17	(4.2)	9	(2.3)	1	(0.4)	37	(3.3)	22	(0.4)
Fatigue	15	(3.7)	12	(3.1)	19	(8.3)	90	(8.0)	63	(1.1)
Alanine aminotransferase increased	13	(3.2)	2	(0.5)	3	(1.3)	10	(0.9)	35	(0.6)
Aspartate aminotransferase increased	13	(3.2)	2	(0.5)	3	(1.3)	3	(0.3)	35	(0.6)
Nausea	12	(3.0)	4	(1.0)	3	(1.3)	25	(2.2)	13	(0.2)
Palmar-plantar erythrodysaesthesia syndrome	11	(2.7)	0	(0.0)	1	(0.4)	22	(2.0)	1	(0.0)
Vomiting	10	(2.5)	6	(1.5)	1	(0.4)	20	(1.8)	10	(0.2)
Hyponatraemia	9	(2.2)	1	(0.3)	8	(3.5)	14	(1.3)	29	(0.5)
Anaemia	8	(2.0)	43	(11.1)	1	(0.4)	8	(0.7)	29	(0.5)
Stomatitis	8	(2.0)	2	(0.5)	1	(0.4)	24	(2.1)	5	(0.1)
Colitis	7	(1.7)	0	(0.0)	4	(1.7)	6	(0.5)	53	(0.9)
Hypokalaemia	7	(1.7)	3	(0.8)	0	(0.0)	7	(0.6)	10	(0.2)
Neutrophil count decreased	7	(1.7)	82	(21.1)	2	(0.9)	2	(0.2)	4	(0.1)
Platelet count decreased	7	(1.7)	3	(0.8)	2	(0.9)	5	(0.4)	2	(0.0)
Acute kidney injury	6	(1.5)	1	(0.3)	1	(0.4)	6	(0.5)	8	(0.1)
Mucosal inflammation	6	(1.5)	3	(0.8)	0	(0.0)	0	(0.0)	6	(0.1)
Amylase increased	5	(1.2)	0	(0.0)	4	(1.7)	5	(0.4)	6	(0.1)
Immune-mediated hepatitis	5	(1.2)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.0)
Pulmonary embolism	5	(1.2)	2	(0.5)	1	(0.4)	24	(2.1)	9	(0.2)
Abdominal pain	4	(1.0)	0	(0.0)	0	(0.0)	16	(1.4)	2	(0.0)
Arthralgia	4	(1.0)	0	(0.0)	4	(1.7)	5	(0.4)	17	(0.3)
Blood alkaline phosphatase increased	4	(1.0)	2	(0.5)	0	(0.0)	3	(0.3)	16	(0.3)
Blood creatine phosphokinase increased	4	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)	7	(0.1)
Dehydration	4	(1.0)	1	(0.3)	7	(3.0)	19	(1.7)	8	(0.1)
Hyperglycaemia	4	(1.0)	0	(0.0)	4	(1.7)	0	(0.0)	13	(0.2)
Hypothyroidism	4	(1.0)	0	(0.0)	0	(0.0)	8	(0.7)	7	(0.1)
Neutropenia	4	(1.0)	95	(24.5)	1	(0.4)	6	(0.5)	9	(0.2)
Pain in extremity	4	(1.0)	0	(0.0)	0	(0.0)	4	(0.4)	2	(0.0)
Thrombocytopenia	4	(1.0)	4	(1.0)	0	(0.0)	15	(1.3)	6	(0.1)
White blood cell count decreased	4	(1.0)	40	(10.3)	1	(0.4)	3	(0.3)	1	(0.0)
Hypertriglyceridaemia	3	(0.7)	0	(0.0)	7	(3.0)	6	(0.5)	6	(0.1)
Hypocalcaemia	3	(0.7)	1	(0.3)	1	(0.4)	11	(1.0)	2	(0.0)
Lymphocyte count decreased	3	(0.7)	13	(3.4)	0	(0.0)	3	(0.3)	7	(0.1)
Pneumonitis	3	(0.7)	0	(0.0)	3	(1.3)	0	(0.0)	78	(1.3)
Rash maculo-papular	3	(0.7)	0	(0.0)	3	(1.3)	0	(0.0)	16	(0.3)
Adrenal insufficiency	2	(0.5)	0	(0.0)	3	(1.3)	0	(0.0)	13	(0.2)
Blood pressure increased	2	(0.5)	0	(0.0)	0	(0.0)	15	(1.3)	0	(0.0)
Lymphopenia	2	(0.5)	11	(2.8)	0	(0.0)	2	(0.2)	5	(0.1)
Febrile neutropenia	1	(0.2)	21	(5.4)	0	(0.0)	0	(0.0)	0	(0.0)
Headache	1	(0.2)	0	(0.0)	0	(0.0)	14	(1.3)	3	(0.1)
Myocardial infarction	1	(0.2)	0	(0.0)	3	(1.3)	4	(0.4)	1	(0.0)
Pneumonia	1	(0.2)	2	(0.5)	1	(0.4)	12	(1.1)	13	(0.2)
Ejection fraction decreased	0	(0.0)	2	(0.5)	0	(0.0)	11	(1.0)	0	(0.0)
Leukopenia	0	(0.0)	27	(7.0)	0	(0.0)	1	(0.1)	3	(0.1)

Oropharyngeal pain	0	(0.0)	0	(0.0)	4	(1.7)	2	(0.2)	1	(0.0)

Every participant is counted a single time for each applicable row and column.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

For KN775 dataset, non-serious adverse events up to 30 days of last dose and serious adverse events up to 120 days of last dose are included.

For KN146 dataset, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

For lenvatinib monotherapy safety dataset, both non-serious adverse events and serious adverse events up to 30 days of last dose are included.

For pembrolizumab monotherapy reference safety dataset, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

[i] Includes all subjects who received at least one dose of lenvatinib in E7080-G000-398, E7080-G000-303, E7080-G000-201, E7080-G000-204, E7080-G000-703, E7080-G000-203, E7080-G000-205, E7080-G000-206, E7080-J081-208, E7080-G000-209 and E7080-J081-105.

[j] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054:02OCT2017, E7080-G000-206: 01SEP2016)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, E7080-G000-703: 01SEP2016)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Thyroid (E7080-G000-398: 01SEP2016, E7080-G000-303: 01SEP2016, E7080-G000-201: 01SEP2016, E7080-J081-208: 01SEP2016)

Database cutoff date for Endometrial Cancer (KN775: 26OCT2020, E7080-G000-204: 01SEP2016)

Database cutoff date for Malignant Glioma (E7080-G000-203: 01SEP2016)

Database cutoff date for Renal Cell Carcinoma (E7080-G000-205: 15MAR2018)

Database cutoff date for Adenocarcinoma (E7080-G000-209: 01SEP2016)

Database cutoff date for Solid Tumor (KN146: 18AUG2020, E7080-J081-105: 01SEP2016)

Source: [ISS: adam-adsl; adae]

- **Serious adverse event/deaths/other significant events**

  - ***Deaths due to adverse events***

The overall incidence of AEs resulting in death was comparable in the lenvatinib plus pembrolizumab EC group (5.7% - 23 deaths), the TPC EC group (4.9% - 19 deaths), and the pembrolizumab monotherapy RSD (5.3% - 312 deaths), and lower than in the lenvatinib plus pembrolizumab non-EC group (10.4% – 24 deaths) and the lenvatinib monotherapy group (8.7% - 97 deaths).

When comparing the exposure-adjusted fatal AEs, the overall rate was lower in the lenvatinib plus pembrolizumab EC group (0.15) compared to the TPC EC group (0.45).

The overall incidence of drug-related AEs resulting in death was comparable in all groups: lenvatinib plus pembrolizumab EC group (1.5% - 6 deaths), TPC EC group (2.1% - 8 deaths), lenvatinib plus pembrolizumab non-EC group (2.2% - 5 deaths), the lenvatinib monotherapy group (2.4% - 27 deaths) and the pembrolizumab monotherapy RSD (0.7% - 39 deaths).

Out of the 6 drug-related fatal AEs in the lenvatinib plus pembrolizumab EC group, 1 death due to multiorgan dysfunction syndrome was considered by the investigator as related to both lenvatinib and pembrolizumab. One death each due to cerebrovascular accident, right ventricular dysfunction, myelodysplastic syndrome, and death were considered by the investigator as related to lenvatinib, and 1 death due to colitis was considered by the investigator as related to pembrolizumab.

Table 56: Participants With Adverse Events Resulting in Death (Incidence > 0% in One or More Treatment Groups) in All-comer Participants (APaT Population)

	Lenvatinib + Pembrolizumab		TPC	
	n	(%)	n	(%)
Participants in population	406		388	
with one or more adverse events	23	(5.7)	19	(4.9)
with no adverse events	383	(94.3)	369	(95.1)
Cardiac disorders	**2**	**(0.5)**	**4**	**(1.0)**
Acute myocardial infarction	1	(0.2)	0	(0.0)
Cardiac failure	0	(0.0)	1	(0.3)
Cardiac failure congestive	0	(0.0)	1	(0.3)
Cardiogenic shock	0	(0.0)	1	(0.3)
Right ventricular dysfunction	1	(0.2)	0	(0.0)
Toxic cardiomyopathy	0	(0.0)	1	(0.3)
Gastrointestinal disorders	**5**	**(1.2)**	**0**	**(0.0)**
Colitis	1	(0.2)	0	(0.0)
Intestinal perforation	1	(0.2)	0	(0.0)
Large intestine perforation	1	(0.2)	0	(0.0)
Lower gastrointestinal haemorrhage	1	(0.2)	0	(0.0)
Malignant gastrointestinal obstruction	1	(0.2)	0	(0.0)
General disorders and administration site conditions	**6**	**(1.5)**	**5**	**(1.3)**
Death	5	(1.2)	3	(0.8)
Multiple organ dysfunction syndrome	1	(0.2)	2	(0.5)
Infections and infestations	**3**	**(0.7)**	**6**	**(1.5)**
Influenza	0	(0.0)	1	(0.3)
Pneumonia	2	(0.5)	2	(0.5)
Sepsis	0	(0.0)	3	(0.8)
Urosepsis	1	(0.2)	0	(0.0)
Injury, poisoning and procedural complications	**0**	**(0.0)**	**1**	**(0.3)**
Subdural haematoma	0	(0.0)	1	(0.3)
Metabolism and nutrition disorders	**1**	**(0.2)**	**0**	**(0.0)**
Decreased appetite	1	(0.2)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1**	**(0.2)**	**0**	**(0.0)**

Myelodysplastic syndrome	1	(0.2)	0	(0.0)
Nervous system disorders	**1**	**(0.2)**	**0**	**(0.0)**
Cerebrovascular accident	1	(0.2)	0	(0.0)
Psychiatric disorders	**1**	**(0.2)**	**0**	**(0.0)**
Assisted suicide	1	(0.2)	0	(0.0)
Renal and urinary disorders	**1**	**(0.2)**	**0**	**(0.0)**
Acute kidney injury	1	(0.2)	0	(0.0)
Reproductive system and breast disorders	**1**	**(0.2)**	**0**	**(0.0)**
Vaginal haemorrhage	1	(0.2)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**1**	**(0.2)**	**3**	**(0.8)**
Aspiration	0	(0.0)	1	(0.3)
Pulmonary embolism	1	(0.2)	1	(0.3)
Respiratory failure	0	(0.0)	1	(0.3)

Every participant is counted a single time for each applicable row and column.
Serious adverse events up to 120 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

Source: [P775V01MK3475: adam-adsl; adae]

- ***SAEs***

The overall incidence of SAEs was similar between the lenvatinib plus pembrolizumab EC group (52.7%), the lenvatinib plus pembrolizumab non-EC group (56.1%), the lenvatinib monotherapy group (54.8%), and higher than in the TPC EC group (30.4%) and the pembrolizumab monotherapy RSD (38.5%) (Table below). The most frequently reported SAEs (incidence ≥1%) were:

- Lenvatinib plus pembrolizumab: hypertension, UTI, diarrhoea, decreased appetite, vomiting, acute kidney injury, pyrexia, cholecystitis, colitis, pneumonia, death, dehydration, intestinal obstruction, sepsis, abdominal pain, ileus, and pulmonary embolism

- TPC: febrile neutropenia, anaemia, neutropenia, pulmonary embolism, and sepsis.

The most frequent exposure-adjusted SAEs in the lenvatinib plus pembrolizumab EC group (≥ 0.2 events / 100 person-months) were hypertension, UTI, diarrhoea, decreased appetite, vomiting, acute kidney injury, pyrexia, cholecystitis, colitis and pneumonia.

When comparing the exposure-adjusted SAEs, the overall rate was similar in the lenvatinib plus pembrolizumab EC group (10.15) compared to the TPC EC group (10.08). Exposure-adjusted rates of SAEs across the various SOCs were similar between the 2 groups. Only the 2 following SAEs were reported with an increased rate of at least 0.3 events / 100 person-months in the lenvatinib plus pembrolizumab EC group compared to the TPC EC group: hypertension and UTI. These 2 SAEs are identified very common ADRs in the SmPC section 4.8.

There was a marked higher incidence of the following SAEs in the lenvatinib plus pembrolizumab EC group (incidence ≥ 2%) compared with the lenvatinib monotherapy group and pembrolizumab monotherapy RSD: UTI and Diarrhoea. Of these SAEs, only UTI had a marked higher incidence in the lenvatinib plus pembrolizumab EC group compared with the lenvatinib plus pembrolizumab non-EC group.

Table 57: Participants With Serious Adverse Events by Decreasing Incidence (Incidence ⩾ 1% in One or More Treatment Groups) (APaT Population)

	KN775 Lenvatinib + Pembrolizumab		KN775 Treatment Physician´s Choice		KN146 Lenvatinib + Pembrolizumab (Non-Endometrial Cancer)		Lenvatinib Monotherapy Safety Dataset[1]		Pembrolizumab Monotherapy Reference Safety Dataset[1]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	406		388		230		1,119		5,884	
with one or more adverse events	214	(52.7)	118	(30.4)	129	(56.1)	613	(54.8)	2,266	(38.5)
with no adverse events	192	(47.3)	270	(69.6)	101	(43.9)	506	(45.2)	3,618	(61.5)
Hypertension	17	(4.2)	0	(0.0)	6	(2.6)	28	(2.5)	1	(0.0)
Urinary tract infection	13	(3.2)	2	(0.5)	3	(1.3)	8	(0.7)	59	(1.0)
Diarrhoea	10	(2.5)	3	(0.8)	4	(1.7)	13	(1.2)	59	(1.0)
Decreased appetite	9	(2.2)	0	(0.0)	0	(0.0)	15	(1.3)	18	(0.3)
Vomiting	9	(2.2)	3	(0.8)	3	(1.3)	23	(2.1)	28	(0.5)
Acute kidney injury	8	(2.0)	3	(0.8)	8	(3.5)	20	(1.8)	50	(0.8)
Pyrexia	8	(2.0)	3	(0.8)	4	(1.7)	8	(0.7)	67	(1.1)
Cholecystitis	7	(1.7)	0	(0.0)	3	(1.3)	12	(1.1)	7	(0.1)
Colitis	7	(1.7)	1	(0.3)	3	(1.3)	6	(0.5)	59	(1.0)
Pneumonia	6	(1.5)	3	(0.8)	7	(3.0)	47	(4.2)	246	(4.2)
Death	5	(1.2)	3	(0.8)	0	(0.0)	5	(0.4)	42	(0.7)
Dehydration	5	(1.2)	1	(0.3)	8	(3.5)	30	(2.7)	42	(0.7)
Intestinal obstruction	5	(1.2)	3	(0.8)	0	(0.0)	4	(0.4)	12	(0.2)
Sepsis	5	(1.2)	5	(1.3)	4	(1.7)	15	(1.3)	42	(0.7)
Abdominal pain	4	(1.0)	1	(0.3)	4	(1.7)	27	(2.4)	27	(0.5)
Ileus	4	(1.0)	0	(0.0)	0	(0.0)	2	(0.2)	10	(0.2)
Pulmonary embolism	4	(1.0)	5	(1.3)	3	(1.3)	29	(2.6)	71	(1.2)
Adrenal insufficiency	3	(0.7)	0	(0.0)	3	(1.3)	0	(0.0)	18	(0.3)
Asthenia	3	(0.7)	2	(0.5)	4	(1.7)	17	(1.5)	18	(0.3)
Constipation	3	(0.7)	0	(0.0)	3	(1.3)	6	(0.5)	21	(0.4)
General physical health deterioration	3	(0.7)	1	(0.3)	0	(0.0)	21	(1.9)	25	(0.4)
Nausea	3	(0.7)	1	(0.3)	4	(1.7)	17	(1.5)	28	(0.5)
Pneumonitis	3	(0.7)	0	(0.0)	4	(1.7)	2	(0.2)	117	(2.0)
Cerebrovascular accident	2	(0.5)	3	(0.8)	0	(0.0)	11	(1.0)	20	(0.3)
Dyspnoea	2	(0.5)	1	(0.3)	8	(3.5)	22	(2.0)	81	(1.4)
Febrile neutropenia	2	(0.5)	16	(4.1)	0	(0.0)	1	(0.1)	4	(0.1)
Headache	2	(0.5)	0	(0.0)	2	(0.9)	12	(1.1)	6	(0.1)
Hyponatraemia	2	(0.5)	2	(0.5)	5	(2.2)	10	(0.9)	39	(0.7)
Hypotension	2	(0.5)	0	(0.0)	3	(1.3)	17	(1.5)	13	(0.2)
Anaemia	1	(0.2)	9	(2.3)	0	(0.0)	5	(0.4)	59	(1.0)
Myocardial infarction	1	(0.2)	0	(0.0)	4	(1.7)	7	(0.6)	19	(0.3)
Neutropenia	1	(0.2)	7	(1.8)	0	(0.0)	2	(0.2)	3	(0.1)
Pleural effusion	1	(0.2)	1	(0.3)	1	(0.4)	9	(0.8)	83	(1.4)
Cancer pain	0	(0.0)	0	(0.0)	0	(0.0)	14	(1.3)	16	(0.3)
Chronic obstructive pulmonary disease	0	(0.0)	0	(0.0)	3	(1.3)	2	(0.2)	29	(0.5)
Diverticulitis	0	(0.0)	0	(0.0)	3	(1.3)	6	(0.5)	7	(0.1)
Hypoxia	0	(0.0)	0	(0.0)	3	(1.3)	2	(0.2)	17	(0.3)
Muscular weakness	0	(0.0)	0	(0.0)	3	(1.3)	3	(0.3)	9	(0.2)
Pneumonia aspiration	0	(0.0)	0	(0.0)	3	(1.3)	4	(0.4)	25	(0.4)
Seizure	0	(0.0)	2	(0.5)	2	(0.9)	12	(1.1)	15	(0.3)
Spinal compression fracture	0	(0.0)	0	(0.0)	3	(1.3)	2	(0.2)	1	(0.0)

Table 58: Exposure-Adjusted Serious Adverse Events (Including Multiple Occurrences of Events) (Incidence ⩾ 1% in One or More Treatment Groups) in All-comer Participants (APaT Population)

	Event Count and Rate (Events/100 person-months)[a]	
	Lenvatinib + Pembrolizumab	TPC
Number of participants exposed	406	388
Total exposure[b] in person-months	3919.5	1765.2
Blood and lymphatic system disorders	**7 (0.2)**	**39 (2.2)**
Anaemia	1 (0.0)	9 (0.5)
Febrile neutropenia	2 (0.1)	17 (1.0)
Neutropenia	1 (0.0)	7 (0.4)
Cardiac disorders	**14 (0.4)**	**14 (0.8)**
Endocrine disorders	**10 (0.3)**	**0 (0.0)**
Gastrointestinal disorders	**81 (2.1)**	**25 (1.4)**
Abdominal pain	4 (0.1)	1 (0.1)
Colitis	7 (0.2)	1 (0.1)
Diarrhoea	10 (0.3)	3 (0.2)
Ileus	5 (0.1)	0 (0.0)
Intestinal obstruction	5 (0.1)	3 (0.2)
Vomiting	9 (0.2)	4 (0.2)
General disorders and administration site conditions	**28 (0.7)**	**15 (0.8)**
Death	5 (0.1)	3 (0.2)
Pyrexia	8 (0.2)	3 (0.2)
Hepatobiliary disorders	**28 (0.7)**	**1 (0.1)**
Cholecystitis	9 (0.2)	0 (0.0)
Immune system disorders	**6 (0.2)**	**0 (0.0)**
Infections and infestations	**69 (1.8)**	**29 (1.6)**
Pneumonia	6 (0.2)	3 (0.2)
Sepsis	5 (0.1)	5 (0.3)
Urinary tract infection	14 (0.4)	2 (0.1)
Injury, poisoning and procedural complications	**5 (0.1)**	**3 (0.2)**
Investigations	**7 (0.2)**	**4 (0.2)**
Metabolism and nutrition disorders	**32 (0.8)**	**8 (0.5)**
Decreased appetite	9 (0.2)	0 (0.0)
Dehydration	5 (0.1)	1 (0.1)
Musculoskeletal and connective tissue disorders	**11 (0.3)**	**2 (0.1)**
Nervous system disorders	**18 (0.5)**	**8 (0.5)**
Psychiatric disorders	**5 (0.1)**	**2 (0.1)**
Renal and urinary disorders	**18 (0.5)**	**7 (0.4)**
Acute kidney injury	8 (0.2)	3 (0.2)
Reproductive system and breast disorders	**8 (0.2)**	**1 (0.1)**
Respiratory, thoracic and mediastinal disorders	**15 (0.4)**	**13 (0.7)**
Pulmonary embolism	4 (0.1)	5 (0.3)
Skin and subcutaneous tissue disorders	**9 (0.2)**	**1 (0.1)**
Vascular disorders	**24 (0.6)**	**3 (0.2)**
Hypertension	17 (0.4)	0 (0.0)

[a] Event rate per 100 person-months of exposure = event count *100/person-months of exposure.
[b] Drug exposure is defined as the interval between the first dose date + 1 day and the earlier of the last dose date + 30 or the database cutoff date.
Serious adverse events up to 120 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

Source: [P775V01MK3475: adam-adsl; adae]

The overall incidence of drug-related SAEs was similar between the lenvatinib plus pembrolizumab EC group (33.3%), the lenvatinib plus pembrolizumab non-EC group (25.7%), the lenvatinib monotherapy group (29.5%), and higher than in the TPC EC group (14.2%) and the pembrolizumab monotherapy RSD (11.1%) (Table below). The most frequently reported drug-related SAEs (incidence ⩾1%) were:

- TPC group: febrile neutropenia, neutropenia, and anaemia.

- Lenvatinib plus pembrolizumab group: hypertension, colitis, decreased appetite, vomiting, diarrhoea, pyrexia, and acute kidney injury. All these drug-related SAEs were more frequent with in the lenvatinib plus pembrolizumab EC group compared to the TPC EC group.

When comparing the exposure-adjusted drug-related SAEs, the overall rate was similar in the lenvatinib plus pembrolizumab EC group (5.15) compared to the TPC EC group (4.08). The details by drug-related SAEs were not provided.

Only the drug-related SAE pyrexia was reported with a marked higher incidence in the lenvatinib plus pembrolizumab EC group (incidence ≥ 1%) compared with the lenvatinib monotherapy group, pembrolizumab monotherapy RSD, and the lenvatinib plus pembrolizumab non-EC group.

Table 59: Participants With Drug-Related Serious Adverse Events by Decreasing Incidence (Incidence ⩾ 1% in One or More Treatment Groups) (APaT Population)

	KN775 Lenvatinib + Pembrolizumab		KN775 Treatment Physician´s Choice		KN146 Lenvatinib + Pembrolizumab (Non-Endometrial Cancer)		Lenvatinib Monotherapy Safety Dataset[i]		Pembrolizumab Monotherapy Reference Safety Dataset[j]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	406		388		230		1,119		5,884	
with one or more adverse events	135	(33.3)	55	(14.2)	59	(25.7)	330	(29.5)	656	(11.1)
with no adverse events	271	(66.7)	333	(85.8)	171	(74.3)	789	(70.5)	5,228	(88.9)
Hypertension	17	(4.2)	0	(0.0)	5	(2.2)	28	(2.5)	0	(0.0)
Colitis	7	(1.7)	0	(0.0)	3	(1.3)	5	(0.4)	51	(0.9)
Decreased appetite	7	(1.7)	0	(0.0)	0	(0.0)	10	(0.9)	5	(0.1)
Vomiting	7	(1.7)	2	(0.5)	0	(0.0)	14	(1.3)	9	(0.2)
Diarrhoea	6	(1.5)	2	(0.5)	3	(1.3)	10	(0.9)	38	(0.6)
Acute kidney injury	4	(1.0)	1	(0.3)	4	(1.7)	7	(0.6)	10	(0.2)
Pyrexia	4	(1.0)	0	(0.0)	1	(0.4)	3	(0.3)	17	(0.3)
Dehydration	3	(0.7)	1	(0.3)	6	(2.6)	14	(1.3)	4	(0.1)
Pneumonitis	3	(0.7)	0	(0.0)	4	(1.7)	0	(0.0)	111	(1.9)
Adrenal insufficiency	2	(0.5)	0	(0.0)	3	(1.3)	0	(0.0)	14	(0.2)
Nausea	2	(0.5)	1	(0.3)	1	(0.4)	13	(1.2)	8	(0.1)
Abdominal pain	1	(0.2)	0	(0.0)	0	(0.0)	13	(1.2)	2	(0.0)
Anaemia	1	(0.2)	7	(1.8)	0	(0.0)	0	(0.0)	5	(0.1)
Febrile neutropenia	1	(0.2)	15	(3.9)	0	(0.0)	0	(0.0)	0	(0.0)
Neutropenia	1	(0.2)	7	(1.8)	0	(0.0)	0	(0.0)	1	(0.0)
Pneumonia	1	(0.2)	2	(0.5)	1	(0.4)	13	(1.2)	14	(0.2)
Pulmonary embolism	1	(0.2)	1	(0.3)	0	(0.0)	19	(1.7)	7	(0.1)

Asthenia	0	(0.0)	1	(0.3)	1	(0.4)	11	(1.0)	6	(0.1)

Every participant is counted a single time for each applicable row and column.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

For KN775 dataset, non-serious adverse events up to 30 days of last dose and serious adverse events up to 120 days of last dose are included.

For KN146 dataset, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

For lenvatinib monotherapy safety dataset, both non-serious adverse events and serious adverse events up to 30 days of last dose are included.

For pembrolizumab monotherapy reference safety dataset, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

[i] Includes all subjects who received at least one dose of lenvatinib in E7080-G000-398, E7080-G000-303, E7080-G000-201, E7080-G000-204, E7080-G000-703, E7080-G000-203, E7080-G000-205, E7080-G000-206, E7080-J081-208, E7080-G000-209 and E7080-J081-105.

[j] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054:02OCT2017, E7080-G000-206: 01SEP2016)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, E7080-G000-703: 01SEP2016)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Thyroid (E7080-G000-398: 01SEP2016, E7080-G000-303: 01SEP2016, E7080-G000-201: 01SEP2016, E7080-J081-208: 01SEP2016)

Database cutoff date for Endometrial Cancer (KN775: 26OCT2020, E7080-G000-204: 01SEP2016)

Database cutoff date for Malignant Glioma (E7080-G000-203: 01SEP2016)

Database cutoff date for Renal Cell Carcinoma (E7080-G000-205: 15MAR2018)

Database cutoff date for Adenocarcinoma (E7080-G000-209: 01SEP2016)

Database cutoff date for Solid Tumor (KN146: 18AUG2020, E7080-J081-105: 01SEP2016)

Source: [ISS: adam-adsl; adae]

- ***Adverse Events of Special Interest for lenvatinib***

As expected, the incidence of Clinically Significant Adverse Events associated with Lenvatinib (CSAE) was higher in the lenvatinib plus pembrolizumab EC group (94.8%) compared with the TPC group (37.6%).

In the lenvatinib plus pembrolizumab EC group, the incidence of all reported CSAE, serious CSAE, Grade 3 to 5 CSAE, and CSAE leading to dose interruptions of any drug were generally consistent with those observed in the lenvatinib monotherapy and the lenvatinib plus pembrolizumab non-EC groups.

In the lenvatinib plus pembrolizumab EC group, the incidences of all reported drug-related CSAE, drug-related serious CSAE, drug-related Grade 3 to 5 CSAE, dose reduction of lenvatinib due to an AE, and discontinuations of any drug due to CSAE were slightly higher than in the lenvatinib monotherapy and the lenvatinib plus pembrolizumab non-EC groups.

In the lenvatinib plus pembrolizumab EC group, most CSAE were ≤Grade 3 (approximately 95%). Approximately 60% of CSAE were not resolved at the time of data cut-off; this was largely driven by hypothyroidism. The majority of the other CSAE were resolved or resolving at the time of the data cut-off.

The most common CSAE observed (incidence ≥ 15%) in the lenvatinib plus pembrolizumab EC group were hypertension (64%), hypothyroidism (57.4%), proteinuria (28.8%), PPES (21.2%), ALT increased (21.2%), and AST increased (19.7%).

The frequencies of CSAE in the lenvatinib plus pembrolizumab EC group were generally consistent with those in the lenvatinib monotherapy group, with the exception of the CSAE events of hepatotoxicity

(mainly ALT and AST increased, Grade 1 to 3), hypothyroidism (Grade 1 to 2), and renal events (mainly Blood creatinine increased, Grade 1 to 2) which were more reported with the combination.

All these CSAE are identified very common ADRs in the SmPC section 4.8.

ALT and AST increased and hypothyroidism were also more frequent in the lenvatinib plus pembrolizumab EC group compared to the lenvatinib plus pembrolizumab non-EC group (although the difference was less marked).

Eight participants (2.0%) in the lenvatinib plus pembrolizumab EC group died due to CSAE: arterial thromboembolic events [acute myocardial infarction, cerebral vascular accident], cardiac dysfunction [right ventricular dysfunction], GI perforation [intestinal perforation, large intestine perforation], haemorrhage [lower gastrointestinal haemorrhage, vaginal haemorrhage], and renal events [acute kidney injury]. Two of these deaths (cerebrovascular accident and right ventricular dysfunction) were considered by the investigator to be related to lenvatinib.

Table 60: Adverse Event Summary for CSAE (APaT Population)

	KN775 Lenvatinib + Pembrolizumab		KN775 Treatment Physician's Choice		KN146 Lenvatinib + Pembrolizumab (Non-Endometrial Cancer)		Lenvatinib Monotherapy Safety Dataset[f]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	406		388		230		1,119	
with one or more adverse events	385	(94.8)	146	(37.6)	206	(89.6)	972	(86.9)
with no adverse event	21	(5.2)	242	(62.4)	24	(10.4)	147	(13.1)
with drug-related[a] adverse events	369	(90.9)	69	(17.8)	189	(82.2)	907	(81.1)
with toxicity grade 3-5 adverse events	218	(53.7)	49	(12.6)	107	(46.5)	559	(50.0)
with toxicity grade 3-5 drug-related adverse events	195	(48.0)	16	(4.1)	81	(35.2)	482	(43.1)
with serious adverse events	80	(19.7)	27	(7.0)	47	(20.4)	202	(18.1)
with serious drug-related adverse events	60	(14.8)	11	(2.8)	25	(10.9)	126	(11.3)
with dose interruption of any drug due to an adverse event	138	(34.0)	11	(2.8)	87	(37.8)	376	(33.6)
interruption of Pembrolizumab	72	(17.7)	--		32	(13.9)	--	
interruption of Lenvatinib	109	(26.8)	--		82	(35.7)	376	(33.6)
interruption of both Pembrolizumab and Lenvatinib	34	(8.4)	--		19	(8.3)	--	
with dose reduction of Lenvatinib due to an adverse event	148	(36.5)	--		67	(29.1)	265	(23.7)
who died	8	(2.0)	5	(1.3)	7	(3.0)	29	(2.6)
who died due to a drug-related adverse event	2	(0.5)	3	(0.8)	3	(1.3)	9	(0.8)
discontinued any drug due to an adverse event	60	(14.8)	9	(2.3)	23	(10.0)	108	(9.7)
discontinued Pembrolizumab	27	(6.7)	--		17	(7.4)	--	
discontinued Lenvatinib	55	(13.5)	--		21	(9.1)	108	(9.7)
discontinued both Pembrolizumab and Lenvatinib	18	(4.4)	--		14	(6.1)	--	
discontinued any drug due to a drug-related adverse event	54	(13.3)	5	(1.3)	17	(7.4)	82	(7.3)
discontinued Pembrolizumab	17	(4.2)	--		--		--	
discontinued Lenvatinib	47	(11.6)	--		--		82	(7.3)
discontinued both Pembrolizumab and Lenvatinib	8	(2.0)	--		--		--	
discontinued any drug due to a serious adverse event	35	(8.6)	6	(1.5)	14	(6.1)	62	(5.5)
discontinued Pembrolizumab	18	(4.4)	--		10	(4.3)	--	
discontinued Lenvatinib	34	(8.4)	--		13	(5.7)	62	(5.5)
discontinued both Pembrolizumab and Lenvatinib	16	(3.9)	--		9	(3.9)	--	
discontinued any drug due to a serious drug-related adverse event	28	(6.9)	2	(0.5)	10	(4.3)	41	(3.7)
discontinued Pembrolizumab	8	(2.0)	--		--		--	
discontinued Lenvatinib	26	(6.4)	--		--		41	(3.7)
discontinued both Pembrolizumab and Lenvatinib	6	(1.5)	--		--		--	

[a] Determined by the investigator to be related to the drug.
Grades are based on NCI CTCAE version 4.0.
For KN775 dataset, non-serious adverse events up to 30 days of last dose and serious adverse events up to 120 days of last dose are included.
For KN146 dataset, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
For lenvatinib monotherapy safety dataset, both non-serious adverse events and serious adverse events up to 30 days of last dose are included.
[f] Includes all subjects who received at least one dose of lenvatinib in E7080-G000-398, E7080-G000-303, E7080-G000-201, E7080-G000-204, E7080-G000-703, E7080-G000-203, E7080-G000-205, E7080-G000-206, E7080-J081-208, E7080-G000-209 and E7080-J081-105.
Database cutoff date for Melanoma (E7080-G000-206: 01SEP2016)
Database cutoff date for Lung (E7080-G000-703: 01SEP2016)
Database cutoff date for Thyroid (E7080-G000-398: 01SEP2016, E7080-G000-303: 01SEP2016, E7080-G000-201: 01SEP2016, E7080-J081-208: 01SEP2016)
Database cutoff date for Endometrial Cancer (KN775: 26OCT2020, E7080-G000-204: 01SEP2016)
Database cutoff date for Malignant Glioma (E7080-G000-203: 01SEP2016)
Database cutoff date for Renal Cell Carcinoma (E7080-G000-205: 15MAR2018)
Database cutoff date for Adenocarcinoma (E7080-G000-209: 01SEP2016)
Database cutoff date for Solid Tumor (KN146: 18AUG2020, E7080-J081-105: 01SEP2016)

Source: [ISS: adam-adsl; adae]

Table 61: Participants With Clinically Significant Adverse Events by CSAE Category (Incidence > 0% in One or More Treatment Groups) (APaT Population)

	Study 309/KEYNOTE-775 Lenvatinib + Pembrolizumab		Study 309/KEYNOTE-775Treatment Physician´s Choice		KEYNOTE-146 Lenvatinib + Pembrolizumab (Non-Endometrial Cancer)		Lenvatinib Monotherapy Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	406		388		230		1,119	
with one or more AE	385	(94.8)	146	(37.6)	206	(89.6)	972	(86.9)
with no AE	21	(5.2)	242	(62.4)	24	(10.4)	147	(13.1)
Arterial Thromboembolic Events	15	(3.7)	3	(0.8)	15	(6.5)	64	(5.7)
Cardiac Dysfunction	4	(1.0)	12	(3.1)	14	(6.1)	62	(5.5)
Fistula Formation	10	(2.5)	4	(1.0)	3	(1.3)	23	(2.1)
GI Perforation	16	(3.9)	1	(0.3)	6	(2.6)	25	(2.2)
Hemorrhage	99	(24.4)	51	(13.1)	80	(34.8)	367	(32.8)
Hepatotoxicity	137	(33.7)	44	(11.3)	45	(19.6)	196	(17.5)
Hypertension	264	(65.0)	21	(5.4)	99	(43.0)	703	(62.8)
Hypocalcemia	16	(3.9)	14	(3.6)	8	(3.5)	98	(8.8)
Hypothyroidism	277	(68.2)	4	(1.0)	100	(43.5)	222	(19.8)
Palmar-plantar Erythrodysesthesia Syndrome	90	(22.2)	4	(1.0)	56	(24.3)	250	(22.3)
Posterior Reversible Encephalopathy Syndrome	1	(0.2)	0	(0.0)	1	(0.4)	3	(0.3)
Proteinuria	120	(29.6)	12	(3.1)	93	(40.4)	395	(35.3)
QT Prolongation	16	(3.9)	8	(2.1)	8	(3.5)	54	(4.8)
Renal Events	74	(18.2)	23	(5.9)	3	(18.7)	112	(10.0)

- ***Adverse Events of Special Interest for Pembrolizumab (AEOSI)***

Adverse Events of Special Interest for Pembrolizumab (AEOSI) are immune-mediated events and IRRs associated with pembrolizumab treatment.

As expected, the incidence of AEOSI was higher in the lenvatinib plus pembrolizumab EC group (67.2%) compared with the TPC group (4.4%) (Table below).

In the lenvatinib plus pembrolizumab EC group, the incidence of all reported AEOSI, and drug-related AEOSI were generally slightly higher than those observed in the lenvatinib plus pembrolizumab non-EC group, and much higher than those observed in the pembrolizumab monotherapy RSD group.

In the lenvatinib plus pembrolizumab EC group, the incidence of serious AEOSI and drug-related serious AEOSI were slightly higher compared to the lenvatinib plus pembrolizumab non-EC and pembrolizumab monotherapy RSD groups.

In the lenvatinib plus pembrolizumab EC group, the incidence of Grade 3 to 5 AEOSI, drug-related Grade 3 to 5 AEOSI, AEOSI leading to dose interruptions of any drug, and discontinuation of any drug due to an AEOSI, were generally similar than those observed in the lenvatinib plus pembrolizumab non-EC group, but higher than those observed in the pembrolizumab monotherapy RSD group.

In the lenvatinib plus pembrolizumab EC group, most AEOSI were ≤Grade 2 (approximately 81%). Most Grade 3 to 4 AEOSI were reported in ≤1% of participants in the lenvatinib plus pembrolizumab EC group, except for Grade 3 severe skin reactions (2.5%), Grade 3 colitis (1.5%), and Grade 3 hepatitis (1.5%).

Approximately 60% of AEOSI were not resolved at the time of data cut-off; this was largely driven by hypothyroidism. The majority of the other AEOSI were resolved or resolving at the time of the data cut-off.

The most common AEOSI observed (incidence ≥ 10%) in the lenvatinib plus pembrolizumab EC group were hypothyroidism (57.4%) and hyperthyroidism (11.6%).

The frequencies of AEOSI in the lenvatinib plus pembrolizumab EC group were generally consistent with those in the lenvatinib monotherapy group, with the exception of the AEOSI events of hypothyroidism (Grade 1 to 2), hyperthyroidism (Grade 1 to 3) and colitis (Grade 1 to 3) which were more reported with the combination.

Hyperthyroidism and hypothyroidism were also more frequent in the lenvatinib plus pembrolizumab EC group compared to the lenvatinib plus pembrolizumab non-EC group (although the difference was less marked for hypothyroidism).

There was 1 death in the lenvatinib plus pembrolizumab EC group due to an AEOSI of colitis, which was considered by the investigator to be related to pembrolizumab. One participant died of autoimmune encephalitis; however, as the death was beyond the 120-day post-treatment AE collection period it was not captured as a fatal event in tables or listings.

Table 62: Adverse Event Summary for AEOSI (APaT Population)

	KN775 Lenvatinib + Pembrolizumab		KN775 Treatment Physician's Choice		KN146 Lenvatinib + Pembrolizumab (Non-Endometrial Cancer)		Pembrolizumab Monotherapy Reference Safety Dataset[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	406		388		230		5,884	
with one or more adverse events	273	(67.2)	17	(4.4)	118	(51.3)	1,475	(25.1)
with no adverse event	133	(32.8)	371	(95.6)	112	(48.7)	4,409	(74.9)
with drug-related[a] adverse events	259	(63.8)	8	(2.1)	105	(45.7)	1,282	(21.8)
with toxicity grade 3-5 adverse events	53	(13.1)	1	(0.3)	26	(11.3)	381	(6.5)
with toxicity grade 3-5 drug-related adverse events	46	(11.3)	0	(0.0)	23	(10.0)	331	(5.6)
with serious adverse events	41	(10.1)	1	(0.3)	16	(7.0)	381	(6.5)
with serious drug-related adverse events	38	(9.4)	0	(0.0)	15	(6.5)	337	(5.7)
with dose interruption of any drug due to an adverse event	49	(12.1)	3	(0.8)	30	(13.0)	332	(5.6)
interruption of Pembrolizumab	40	(9.9)	--		19	(8.3)	332	(5.6)
interruption of Lenvatinib	30	(7.4)	--		20	(8.7)	--	
interruption of both Pembrolizumab and Lenvatinib	18	(4.4)	--		9	(3.9)	--	
with dose reduction of Lenvatinib due to an adverse event	12	(3.0)	--		7	(3.0)	--	
who died	1	(0.2)	0	(0.0)	0	(0.0)	11	(0.2)
who died due to a drug-related adverse event	1	(0.2)	0	(0.0)	0	(0.0)	11	(0.2)
discontinued any drug due to an adverse event	23	(5.7)	1	(0.3)	15	(6.5)	232	(3.9)
discontinued Pembrolizumab	20	(4.9)	--		14	(6.1)	232	(3.9)
discontinued Lenvatinib	16	(3.9)	--		6	(2.6)	--	
discontinued both Pembrolizumab and Lenvatinib	13	(3.2)	--		5	(2.2)	--	
discontinued any drug due to a drug-related adverse event	22	(5.4)	0	(0.0)	14	(6.1)	228	(3.9)
discontinued Pembrolizumab	19	(4.7)	--		--		228	(3.9)
discontinued Lenvatinib	9	(2.2)	--		--		--	
discontinued both Pembrolizumab and Lenvatinib	6	(1.5)	--		--		--	
discontinued any drug due to a serious adverse event	20	(4.9)	0	(0.0)	8	(3.5)	156	(2.7)
discontinued Pembrolizumab	17	(4.2)	--		7	(3.0)	156	(2.7)
discontinued Lenvatinib	16	(3.9)	--		3	(1.3)	--	
discontinued both Pembrolizumab and Lenvatinib	13	(3.2)	--		2	(0.9)	--	
discontinued any drug due to a serious drug-related adverse event	19	(4.7)	0	(0.0)	8	(3.5)	154	(2.6)
discontinued Pembrolizumab	16	(3.9)	--		--		154	(2.6)
discontinued Lenvatinib	9	(2.2)	--		--		--	
discontinued both Pembrolizumab and Lenvatinib	6	(1.5)	--		--		--	

[a] Determined by the investigator to be related to the drug.
Grades are based on NCI CTCAE version 4.0.
For KN775 dataset, non-serious adverse events up to 30 days of last dose and serious adverse events up to 120 days of last dose are included.
For KN146 dataset, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
For pembrolizumab monotherapy reference safety dataset, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
[j] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054:02OCT2017)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)
Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019)
Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)
Database cutoff date for Solid Tumor (KN146: 18AUG2020)
Database cutoff date for Endometrial Cancer (KN775: 26OCT2020)

Source: [ISS: adam-adsl; adae]

Table 63: Participants With Adverse Events of Special Interest by AEOSI Category (Incidence > 0% in One or More Treatment Groups) (APaT Population)

	Study 309/KEYNOTE-775 Lenvatinib + Pembrolizumab		Study 309/KEYNOTE-775 Treatment Physician´s Choice		KEYNOTE-146 Lenvatinib + Pembrolizumab (Non-Endometrial Cancer)		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants	406		388		230		5,884	
with one or more AE	273	(67.2)	17	(4.4)	118	(51.3)	1,475	(25.1)
with no AE	133	(32.8)	371	(95.6)	112	(48.7)	4,409	(74.9)
Adrenal Insufficiency	5	(1.2)	0	(0.0)	16	(7.0)	47	(0.8)
Colitis	19	(4.7)	1	(0.3)	13	(5.7)	110	(1.9)
Encephalitis	2	(0.5)	0	(0.0)	0	(0.0)	3	(0.1)
Guillain-Barre Syndrome	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Hepatitis	6	(1.5)	0	(0.0)	2	(0.9)	56	(1.0)
Hyperthyroidism	47	(11.6)	4	(1.0)	11	(4.8)	247	(4.2)
Hypophysitis	2	(0.5)	0	(0.0)	0	(0.0)	36	(0.6)
Hypothyroidism	234	(57.6)	3	(0.8)	87	(37.8)	652	(11.1)
Infusion Reactions	12	(3.0)	6	(1.5)	6	(2.6)	138	(2.3)
Myasthenic Syndrome	1	(0.2)	0	(0.0)	1	(0.4)	3	(0.1)
Myelitis	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Myocarditis	1	(0.2)	0	(0.0)	0	(0.0)	5	(0.1)
Myositis	2	(0.5)	0	(0.0)	2	(0.9)	19	(0.3)
Nephritis	2	(0.5)	0	(0.0)	2	(0.9)	23	(0.4)
Pancreatitis	5	(1.2)	0	(0.0)	6	(2.6)	18	(0.3)
Pneumonitis	5	(1.2)	1	(0.3)	5	(2.2)	264	(4.5)
Sarcoidosis	0	(0.0)	0	(0.0)	0	(0.0)	10	(0.2)
Severe Skin Reactions	13	(3.2)	1	(0.3)	10	(4.3)	97	(1.6)
Thyroiditis	8	(2.0)	0	(0.0)	2	(0.9)	58	(1.0)
Type 1 Diabetes Mellitus	4	(1.0)	0	(0.0)	0	(0.0)	20	(0.3)
Uveitis	3	(0.7)	0	(0.0)	0	(0.0)	21	(0.4)
Vasculitis	1	(0.2)	2	(0.5)	0	(0.0)	2	(0.0)

- **Laboratory findings**

Laboratory abnormalities of all grades with an incidence of ≥20% in the lenvatinib plus pembrolizumab EC group over the TPC group included: alkaline phosphatase increased, ALT increased, AST increased, cholesterol increased, lipase increased, magnesium decreased, platelets decreased, and triglycerides increased. Among these abnormalities, the largest clinically relevant difference between treatment groups was in laboratory parameters known to be associated with lenvatinib: ALT increased (lenvatinib plus pembrolizumab 53.4% vs TPC 20.7%) and AST increased (lenvatinib plus pembrolizumab 58.3% vs TPC 22.4%). The incidence of postbaseline Grade 3 or 4 laboratory abnormalities in the lenvatinib plus pembrolizumab EC group was similar to that of the TPC group.

Overall, the most frequently reported (≥30%) laboratory abnormalities (Grades 1 to 4) were similar in the lenvatinib plus pembrolizumab EC group and the lenvatinib monotherapy group, pembrolizumab monotherapy RSD, and lenvatinib plus pembrolizumab non-EC group, and the majority were Grade 1 to 2 toxicity: ALT increased, AST increased, Albumin Decreased, Alkaline Phosphatase Increased, Cholesterol Increased, Creatinine Increased, Haemoglobin Decreased, Lymphocytes Decreased, Magnesium Decreased, Potassium Decreased, Sodium Decreased and Triglycerides Increased. However, calcium Decreased, Leukocytes Decreased, Neutrophils Decreased, and Platelet count decreased (Grades 1 to 4) were more frequently reported with lenvatinib plus pembrolizumab EC group than in the other groups (around double incidence). And glucose Increased was more frequently reported with lenvatinib plus pembrolizumab EC group (57.1%) compared to lenvatinib plus pembrolizumab non-EC group (9.8%), but similarly to the pembrolizumab monotherapy RSD group (around 50.8%).

The percentages of participants in the lenvatinib plus pembrolizumab EC group with Grade 3 to 4 laboratory abnormalities were low and were generally consistent with the lenvatinib monotherapy group, pembrolizumab monotherapy RSD, and the lenvatinib plus pembrolizumab non-EC group. The most frequently reported (incidence ≥5%) Grade 3 to 4 laboratory abnormalities in the lenvatinib plus pembrolizumab EC group were: Lymphocyte decreased (16.9%), sodium decreased (14.4%), potassium decreased (10.7%), AST increased (8.5%), haemoglobin decreased (8.2%), phosphate decreased (8.2%), glucose increased (8.0%), ALT increased (7.7%), platelets decreased (7.2%), triglycerides increased (7.1%), magnesium decreased (6.9%), amylase increased (6.8%), and neutrophils decreased (5.9%).

Three participants in the lenvatinib plus pembrolizumab EC group met the prespecified drug-induced liver injury criteria of increase in ALT or AST ≥3 × ULN and bilirubin ≥1.5 × ULN and alkaline phosphatase <2 × ULN.

- **Safety in special populations**

  - ***MMR status***

- **Study 309/KEYNOTE-775**

Per the study protocol in Study 309/KEYNOTE-775, the safety was assessed separately depending on the tumor mismatch repair (MMR) status. In the lenvatinib plus pembrolizumab EC group and the TPC groups, there were fewer dMMR participants (n=64 and 63, respectively) as compared with pMMR participants (n=342 and 325).

Exposure by MMR status

There was a longer duration of exposure to lenvatinib plus pembrolizumab observed for dMMR participants (median: 335.5 days; range: 1 to 720 days) compared with pMMR participants (median:

219.5 days; range: 1 to 817 days). On the contrary, there was a shorter duration of exposure to TPC observed for dMMR participants (median: 86 days; range: 1 to 331 days) compared with pMMR participants (median: 106 days; range: 1 to 785 days).

Brief Summary of Adverse Events by MMR Status

The overall incidence of AEs in pMMR and dMMR participants was similar in the lenvatinib plus pembrolizumab and TPC groups (Table below), and was similar to that of the all-comer population.

Similar to the results of the all-comer population, in the lenvatinib plus pembrolizumab group, the pMMR and dMMR participants had a higher frequency of Grade 3 to 5 AEs, drug-related Grade 3 to 5 AEs, SAEs, drug-related SAEs, treatment discontinuation due to AE, and treatment interruption due to AEs compared with each TPC group. The incidence of drug-related deaths was similar in the 2 groups.

In the lenvatinib plus pembrolizumab group, there was a higher incidence of some AE categories (ie, Grade 3 to 5 AEs, drug-related Grade 3 to 5 AEs, SAEs, dose modifications due to AEs, discontinuation due to AEs, fatal AEs, fatal drug-related AEs) in the dMMR participants compared with the pMMR participants.

Table 64: Adverse Event Summary by MMR Status (pMMR, dMMR) in All-comer Participants (APaT Population)

	Lenvatinib + Pembrolizumab				TPC			
	pMMR		dMMR		pMMR		dMMR	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	342		64		325		63	
with one or more adverse events	341	(99.7)	64	(100.0)	324	(99.7)	62	(98.4)
with no adverse event	1	(0.3)	0	(0.0)	1	(0.3)	1	(1.6)
with drug-related[a] adverse events	333	(97.4)	62	(96.9)	308	(94.8)	56	(88.9)
with toxicity grade 3-5 adverse events	300	(87.7)	61	(95.3)	236	(72.6)	46	(73.0)
with toxicity grade 3-5 drug-related adverse events	261	(76.3)	55	(85.9)	193	(59.4)	36	(57.1)
with serious adverse events	170	(49.7)	44	(68.8)	94	(28.9)	24	(38.1)
with serious drug-related adverse events	106	(31.0)	29	(45.3)	44	(13.5)	11	(17.5)
with dose modification[b] due to an adverse event	316	(92.4)	64	(100.0)	137	(42.2)	24	(38.1)
with dose interruption[c] due to an adverse event	235	(68.7)	46	(71.9)	91	(28.0)	14	(22.2)
interruption of Pembrolizumab	165	(48.2)	38	(59.4)	0	(0.0)	0	(0.0)
interruption of Lenvatinib	199	(58.2)	39	(60.9)	0	(0.0)	0	(0.0)
interruption of both Pembrolizumab and Lenvatinib	100	(29.2)	25	(39.1)	0	(0.0)	0	(0.0)
with dose reduction[d] due to an adverse event	229	(67.0)	41	(64.1)	42	(12.9)	8	(12.7)
who died	16	(4.7)	7	(10.9)	15	(4.6)	4	(6.3)
who died due to a drug-related adverse event	4	(1.2)	2	(3.1)	6	(1.8)	2	(3.2)
discontinued[e] drug due to an adverse event	106	(31.0)	28	(43.8)	27	(8.3)	4	(6.3)
discontinued Pembrolizumab	60	(17.5)	16	(25.0)	0	(0.0)	0	(0.0)
discontinued Lenvatinib	97	(28.4)	28	(43.8)	0	(0.0)	0	(0.0)
discontinued both Pembrolizumab and Lenvatinib	43	(12.6)	14	(21.9)	0	(0.0)	0	(0.0)
discontinued drug due to a drug-related adverse event	87	(25.4)	21	(32.8)	20	(6.2)	2	(3.2)
discontinued Pembrolizumab	33	(9.6)	7	(10.9)	0	(0.0)	0	(0.0)
discontinued Lenvatinib	73	(21.3)	19	(29.7)	0	(0.0)	0	(0.0)
discontinued both Pembrolizumab and Lenvatinib	16	(4.7)	4	(6.3)	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	70	(20.5)	18	(28.1)	11	(3.4)	3	(4.8)
discontinued Pembrolizumab	47	(13.7)	13	(20.3)	0	(0.0)	0	(0.0)
discontinued Lenvatinib	64	(18.7)	17	(26.6)	0	(0.0)	0	(0.0)
discontinued both Pembrolizumab and Lenvatinib	38	(11.1)	12	(18.8)	0	(0.0)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	50	(14.6)	11	(17.2)	7	(2.2)	1	(1.6)
discontinued Pembrolizumab	24	(7.0)	4	(6.3)	0	(0.0)	0	(0.0)
discontinued Lenvatinib	41	(12.0)	9	(14.1)	0	(0.0)	0	(0.0)
discontinued both Pembrolizumab and Lenvatinib	15	(4.4)	2	(3.1)	0	(0.0)	0	(0.0)

[a] Determined by the investigator to be related to the drug.
[b] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
[c] For Lenvatinib + Pembrolizumab, the dose interruption of either Pembrolizumab or Lenvatinib.
[d] For Lenvatinib + Pembrolizumab, the dose reduction for only Lenvatinib.
[e] For Lenvatinib + Pembrolizumab, the discontinuation of either Pembrolizumab or Lenvatinib.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 120 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.03
TPC = Treatment Physician's Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

Source: [P775V01MK3475: adsm-adsl; adae]

When adjusted for exposure, in the lenvatinib plus pembrolizumab EC group, the overall toxicity profile was slightly worst for the pMMR group compared to the dMMR group with higher incidences of AEs (237.35 vs 208.93), drug-related AEs (138.43 vs 110.97), dose modification due to an AE (39.35 vs

31.8), dose interruption due to an AE (22.12 vs 17.18), and dose reduction due to an AE (15.94 vs 11.81) (table below).

Table 65: Exposure-Adjusted Adverse Event Summary (Including Multiple Occurrences of Events) (APaT Population)

	Event Count and Rate (Events/100 person-months)[a]			
	Lenvatinib + Pembrolizumab pMMR Participants		Lenvatinib + Pembrolizumab dMMR Participants	
Number of Participants exposed	342		64	
Total exposure[b] in person-months	3174.26		745.22	
Total events (rate)				
with one or more adverse events	7534	(237.35)	1557	(208.93)
with no adverse event	1	(0.03)	0	(0.00)
with drug-related[c] adverse events	4394	(138.43)	827	(110.97)
with toxicity grade 3-5 adverse events	992	(31.25)	224	(30.06)
with toxicity grade 3-5 drug-related adverse events	601	(18.93)	125	(16.77)
with serious adverse events	312	(9.83)	86	(11.54)
with serious drug-related adverse events	160	(5.04)	42	(5.64)
with dose modification[d] due to an adverse event	1249	(39.35)	237	(31.80)
with dose interruption[e] due to an adverse event	702	(22.12)	128	(17.18)
interruption of Pembrolizumab	372	(11.72)	70	(9.39)
interruption of Lenvatinib	523	(16.48)	93	(12.48)
interruption of both Pembrolizumab and Lenvatinib	193	(6.08)	35	(4.70)
with dose reduction[f] due to an adverse event	506	(15.94)	88	(11.81)
who died	16	(0.50)	7	(0.94)
who died due to a drug-related adverse event	4	(0.13)	2	(0.27)
discontinued[e] due to an adverse event	158	(4.98)	38	(5.10)
discontinued Pembrolizumab	81	(2.55)	20	(2.68)
discontinued Lenvatinib	128	(4.03)	36	(4.83)
discontinued both Pembrolizumab and Lenvatinib	51	(1.61)	18	(2.42)
discontinued due to a drug-related adverse event	130	(4.10)	26	(3.49)
discontinued Pembrolizumab	49	(1.54)	7	(0.94)
discontinued Lenvatinib	101	(3.18)	23	(3.09)
discontinued both Pembrolizumab and Lenvatinib	20	(0.63)	4	(0.54)
discontinued due to a serious adverse event	76	(2.39)	19	(2.55)
discontinued Pembrolizumab	48	(1.51)	13	(1.74)
discontinued Lenvatinib	67	(2.11)	18	(2.42)
discontinued both Pembrolizumab and Lenvatinib	39	(1.23)	12	(1.61)
discontinued due to a serious drug-related adverse event	53	(1.67)	11	(1.48)
discontinued Pembrolizumab	25	(0.79)	4	(0.54)
discontinued Lenvatinib	44	(1.39)	9	(1.21)
discontinued both Pembrolizumab and Lenvatinib	16	(0.50)	2	(0.27)

a. Event rate per 100 person-months of exposure = event count *100/person-months of exposure.

b. Drug exposure is defined as the between the first dose date + 1 day and the earlier of the last dose date + 30 or the database cutoff date.

c. Determined by the investigator to be related to the drug.

d. Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.

e. For Lenvatinib + Pembrolizumab, the dose interruption of either Pembrolizumab or Lenvatinib.

	Event Count and Rate (Events/100 person-months)[a]	
	Lenvatinib + Pembrolizumab pMMR Participants	Lenvatinib + Pembrolizumab dMMR Participants

f. For Lenvatinib + Pembrolizumab, the dose reduction for only Lenvatinib.

g. For Lenvatinib + Pembrolizumab, the discontinuation of either Pembrolizumab or Lenvatinib.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 120 days of last dose are included.

MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

Grades are based on Grades are based on NCI CTCAE version 4.03

TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.

Database Cutoff Date: 26OCT2020

Most Frequently Reported Adverse Events by MMR Status

The most frequently reported AEs (incidence ≥30%) for the pMMR participants were the same as the all-comer population:

- Lenvatinib plus pembrolizumab: hypertension, hypothyroidism, diarrhoea, nausea, decreased appetite, vomiting, weight decreased, fatigue, and arthralgia

- TPC: anaemia, nausea, neutropenia, and alopecia

Similar results were observed in the dMMR participants in the lenvatinib plus pembrolizumab group but with anaemia also occurring at an incidence ≥30% (35.9%), and arthralgia occurring at an incidence ≤ 30% (25%). Similar results were observed in the dMMR participants in the TPC group but with alopecia occurring at an incidence ≤30% (22.2%).

Grade 3 to 5 Adverse Events by MMR Status

Among pMMR participants, the incidence of Grade 3 to 5 AEs in the lenvatinib plus pembrolizumab group (87.7%) was higher compared with the TPC group (72.6%) and lower than the incidence of Grade 3 to 5 AEs for the all-comer population (88.9% lenvatinib plus pembrolizumab; 72.7% TPC).

The most frequently reported Grade 3 to 5 AEs (incidence ≥5%) for the pMMR participants were generally similar to the all-comer population, with the addition of ALT increased (5%) and removal of fatigue and hypokalemia for the lenvatinib plus pembrolizumab group:

- Lenvatinib plus pembrolizumab: hypertension, weight decreased, decreased appetite, diarrhoea, lipase increased, asthenia, proteinuria, anaemia, and ALT increased

- TPC: neutropenia, neutrophil count decreased, anaemia, white blood cell count decreased, febrile neutropenia, and leukopenia

The dMMR participants had a higher incidence of Grade 3 to 5 AEs than the pMMR participants (95.3% lenvatinib plus pembrolizumab; 73.0% TPC). The most frequently reported Grade 3 to 5 AEs (incidence ≥5%) for the dMMR participants were the following:

- Lenvatinib plus pembrolizumab: hypertension, weight decreased, decreased appetite, anaemia, diarrhoea, decreased appetite, fatigue, hypokalaemia, cholecystitis, hyponatraemia, mucosal inflammation and nausea

- TPC: neutropenia, neutrophil count decreased, anaemia, febrile neutropenia, and leukopenia

Deaths Due to Adverse Events by MMR Status

Among pMMR participants, the incidence of fatal AEs in the lenvatinib plus pembrolizumab group was low (4.7% including 4 drug-related fatal AE - 1.2%) and was similar compared with the TPC group (4.6% including 6 drug-related fatal AEs - 1.8%), and similar to the results of the all-comer population (5.7% including 6 drug-related fatal AEs - 1.5%; and 4.9% including 8 fatal AEs - 2.1%, respectively).

The incidence of AEs resulting in death for dMMR participants was higher compared to the pMMR participants and to the all-comer population: 10.9% in the lenvatinib plus pembrolizumab (including 2 drug-related fatal AEs - 3.1%) and 6.3% in the TPC group (including 2 drug-related fatal AEs - 3.2%).

Drug-related AEs resulting in death are further discussed below.

Other Serious Adverse Events by MMR Status

Among pMMR participants, the incidence of SAEs in the lenvatinib plus pembrolizumab group (49.7%) was higher compared with the TPC group (28.9%) and similar to the incidence of SAEs for the all-comer population (52.7% lenvatinib plus pembrolizumab; 30.4% TPC).

The most frequently reported SAEs (incidence ≥1%) for the pMMR participants were generally similar to the all-comer population, with the removal of sepsis, cholecystitis, pneumonia, death, and abdominal pain for the Lenvatinib plus pembrolizumab group, and with the removal of sepsis in the TPC group:

- Lenvatinib plus pembrolizumab: hypertension, UTI, diarrhoea, decreased appetite, vomiting, acute kidney injury, pyrexia, colitis, dehydration, intestinal obstruction, ileus, and pulmonary embolism

- TPC: febrile neutropenia, anaemia, neutropenia, and pulmonary embolism

The incidence of SAEs for dMMR participants was higher compared to the pMMR participants and to the all-comer population: 68.8% in the lenvatinib plus pembrolizumab group and 38.1% in the TPC group.

For the dMMR participants, the most frequently reported SAE (incidence ≥3%) were the following:

- Lenvatinib plus pembrolizumab: hypertension, UTI, diarrhoea, decreased appetite, vomiting, cholecystitis, pneumonia, death, sepsis, constipation, Female genital tract fistula, nausea, and Peritonitis

- TPC: febrile neutropenia, anaemia, and sepsis

Adverse Events of Special Interest and Clinically Significant Adverse Events

Clinically Significant Adverse Events by MMR Status – Lenvatinib

The incidence of pMMR participants with CSAE in each AE category was consistent with that of the all-comer population. As expected, incidence of pMMR participants with CSAE was higher in the lenvatinib plus pembrolizumab group (94.7%) compared with the TPC group (39.1%), and similar to the all-comer population (94.8% lenvatinib plus pembrolizumab; 37.6% TPC).

The most common CSAE (≥10%) in the lenvatinib plus pembrolizumab group were generally similar to those for the all-comer population: hypertension (65.5%), hypothyroidism (55.3%), proteinuria (28.9%), PPES (21.9%), ALT increased (21.6%), AST increased (21.1%), blood thyroid stimulating hormone increased (12.3%), and blood creatinine increased (10.5%).

The results were similar in the dMMR participants. Incidence of dMMR participants with CSAE was higher in the lenvatinib plus pembrolizumab group (95.3%) compared with the TPC group (30.2%) with the same most common CSAE (≥10%) observed in the pMMR participants.

Overview of Adverse Events of Special Interest by MMR Status – Pembrolizumab

The incidence of pMMR participants with AEOSI in each AE category was consistent with that of the all-comer population. As expected, incidence of pMMR participants with AEOSI was higher in the lenvatinib plus pembrolizumab group (66.1%) compared with the TPC group (4.9%), and similar to the all-comer population (67.2% lenvatinib plus pembrolizumab; 4.4% TPC).

The most common AEOSI (≥5%) in pMMR participants in the lenvatinib plus pembrolizumab group were consistent with those for the all-comer population: hypothyroidism (55.3%) and hyperthyroidism (10.8%).

The results were similar in the dMMR participants. Incidence of dMMR participants with AEOSI was higher in the lenvatinib plus pembrolizumab group (73.4%) compared with the TPC group (1.6%) with the same most common AEOSI (≥5%) observed in the pMMR participants.

When adjusted for exposure, in the lenvatinib plus pembrolizumab group, the observed event rates of AEOSI for dMMR participants were generally similar to the observed event rates for pMMR participants in the lenvatinib plus pembrolizumab group.

Discontinuation, Interruption and Dose Reduction Due to Adverse Events by MMR Status

Adverse Events Resulting in Treatment Discontinuation by MMR Status

The incidence of pMMR participants with AEs that led to discontinuation of both lenvatinib and pembrolizumab (12.6%) was similar to the results in the all-comers population (14.0%). The incidence of participants with AEs that led to discontinuation of lenvatinib (28.4%) was higher than for pembrolizumab (17.5%), similar to the results in the all-comers population (30.8% lenvatinib; 18.7% pembrolizumab).

In dMMR participants, there were an increased incidence of AEs that led to discontinuation of both lenvatinib and pembrolizumab (21.9%), lenvatinib (43.8%), and pembrolizumab (25.0%).

Hypertension, decreased appetite, asthenia, diarrhoea, proteinuria, and vomiting resulted in lenvatinib discontinuation in ≥1% of the pMMR participants. Only ALT increased resulted in pembrolizumab discontinuation in ≥1% of the pMMR participants. No AEs resulted in discontinuation of both lenvatinib and pembrolizumab in ≥1% of the pMMR participants.

Weight decrease, death, decreased appetite, and peritonitis resulted in lenvatinib discontinuation in ≥ 3% of the dMMR participants. Only death resulted in pembrolizumab discontinuation and in discontinuation of both lenvatinib and pembrolizumab in ≥3% of the dMMR participants

The incidence of pMMR participants with drug-related AEs that led to discontinuation of both lenvatinib and pembrolizumab (4.7%) was similar to the results in the all-comers population (4.9%). The incidence of participants with drug-related AEs that led to discontinuation of lenvatinib (21.3%) was higher than for pembrolizumab (9.6%), similar to the results in the all-comers population (22.7% lenvatinib; 9.9% pembrolizumab).

In dMMR participants, there were an increased incidence of drug-related AEs that led to discontinuation of both lenvatinib and pembrolizumab (6.3%), lenvatinib (29.7%), and pembrolizumab (10.9%).

Only hypertension resulted in lenvatinib discontinuation in ≥2% of the pMMR participants. No AEs resulted in discontinuation of pembrolizumab or both lenvatinib and pembrolizumab in ≥2% of the pMMR participant.

Only weight decreased and decreased appetite resulted in lenvatinib discontinuation in ≥2% of the dMMR participants. No AEs resulted in discontinuation of pembrolizumab or both lenvatinib and pembrolizumab in ≥2% of the dMMR participants.

Interruptions Due to Adverse Events by MMR Status

The incidence of pMMR participants with AEs that led to interruption of both lenvatinib and pembrolizumab (29.2%) was similar to the results in the all-comers population (30.8%). The incidence of pMMR participants with AEs that led to discontinuation of lenvatinib (58.2%) was higher than for pembrolizumab (48.2%), similar to the results in the all-comers population (58.6% lenvatinib; 50.0% pembrolizumab).

The dMMR participants had a higher incidence of AEs that led to interruption of both lenvatinib and pembrolizumab (39.1%), lenvatinib (60.9%), and pembrolizumab (59.4%).

Diarrhoea, hypertension, proteinuria, decreased appetite, and vomiting resulted in lenvatinib interruption in ≥5% of the pMMR participants. Only diarrhoea resulted in pembrolizumab interruption and in interruption of both lenvatinib and pembrolizumab in ≥5% of the pMMR participants.

Diarrhoea, hypertension, fatigue, and vomiting resulted in lenvatinib interruption in ≥5% of the dMMR participants. Only diarrhoea resulted in pembrolizumab interruption in ≥5% of the dMMR participants. No AE lead to interruption of both lenvatinib and pembrolizumab in ≥5% of the dMMR participants.

Dose Reductions Due to Adverse Events by MMR Status

The incidence of pMMR participants with AEs that led to dose reduction of lenvatinib (67%) was similar to the incidence in the dMMR participants (64.1%) and to the results in the all-comer population (66.5%).

Diarrhoea and hypertension resulted in lenvatinib reduction in ≥10% of the pMMR participants. Proteinuria and hypertension resulted in lenvatinib reduction in ≥10% of the dMMR participants.

Study KEYNOTE-158

AE summary and the AEOSI (Adverse Events of Special Interest for Pembrolizumab) summary were provided separately for non-MSI-H/pMMR and MSI-H/dMMR participants (in percentage and exposure-adjusted) for study KEYNOTE-158.

The median duration of exposure to pembrolizumab was more than double for those in the MSI-H/dMMR group compared with the non-MSI-H/pMMR group (9.3 months vs 3.42 months).

The overall incidence of AEs in participants in both groups was similar. The safety was generally consistent between the MSI-H and non-MSI-H groups except for a higher incidence of drug-related AEs in the MSI-H group (75.6% vs 63.3%) and of fatal AEs (3.3% vs 0%) (table below).

However, when adjusted for exposure, the overall toxicity profile was worst for the non-MSI-H/pMMR group compared to the MSI-H/dMMR group with higher incidences of AEs (142.73 vs 104.11), drug-related AEs (37.46 vs 30.46), Grade 3 to 5 AEs (19.88 vs 9.74), SAEs (11.36 vs 5.21), and of fatal AEs (0.53 vs 0) (table below).

For AEOSI, overall, the incidence of the Grade 3 to 5 AEs, dose modifications and deaths due to an AE, including drug-related AEs were similar between the 2 groups. However, a lower incidence was observed in the non-MSI-H/pMMR group compared with the MSI-H/dMMR group for the AEOSI (17.8% vs 27.8%), drug-related AEOSI (15.6% vs 25.6%) and SAEs (2.2% vs 4.4%). When adjusted for exposure, the incidence of Grade 3 to 5 AEOSI was higher in the non-MSI-H/pMMR group (1.24 vs 0.58) otherwise the safety was consistent between groups.

Table 66: Adverse Event Summary (Baseline MSI-High vs. non-MSI-High) (Cohorts D and K – Endometrial Carcinoma) (MK3475 200 mg Q3W) (ASaT Population)

	MSI-High		non-MSI-High	
	n	(%)	n	(%)
Participants in population	90		90	
with one or more adverse events	86	(95.6)	88	(97.8)
with no adverse event	4	(4.4)	2	(2.2)
with drug-related[a] adverse events	68	(75.6)	57	(63.3)
with toxicity grade 3-5 adverse events	47	(52.2)	50	(55.6)
with toxicity grade 3-5 drug-related adverse events	11	(12.2)	14	(15.6)
with serious adverse events	34	(37.8)	34	(37.8)
with serious drug-related adverse events	5	(5.6)	5	(5.6)
who died	0	(0.0)	3	(3.3)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	6	(6.7)	6	(6.7)
discontinued drug due to a drug-related adverse event	6	(6.7)	5	(5.6)
discontinued drug due to a serious adverse event	2	(2.2)	3	(3.3)
discontinued drug due to a serious drug-related adverse event	2	(2.2)	2	(2.2)

[a] Determined by the investigator to be related to the drug.

MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

Grades are based on NCI CTCAE version 4.03

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

(Database Cutoff Date: 05OCT2020).

Source: [P158V10MK3475: adam-adsl; adae]

Table 67: Exposure-Adjusted Adverse Event Summary (Including Multiple Occurrences of Events) (Baseline MSI-High vs. non-MSI-High) (Cohorts D and K – Endometrial Carcinoma) (MK3475 200 mg Q3W) (ASaT Population))

	Event Count and Rate (Events/100 person-months)[a]			
	MSI-High		non-MSI-High	
Number of Participants exposed	90		90	
Total exposure[b] in person-months	1037.37		563.30	
Total events (rate)				
adverse events	1,080	(104.11)	804	(142.73)
drug-related[c] adverse events	316	(30.46)	211	(37.46)
toxicity grade 3-5 adverse events	101	(9.74)	112	(19.88)
toxicity grade 3-5 drug-related adverse events	15	(1.45)	16	(2.84)
serious adverse events	54	(5.21)	64	(11.36)
serious drug-related adverse events	5	(0.48)	6	(1.07)
adverse events resulting in dose modification[d]	68	(6.56)	37	(6.57)
adverse events leading to death	0	(0.00)	3	(0.53)
drug-related adverse events leading to death	0	(0.00)	0	(0.00)
adverse events resulting in drug discontinuation	6	(0.58)	6	(1.07)
drug-related adverse events resulting in drug discontinuation	6	(0.58)	5	(0.89)
serious adverse events resulting in drug discontinuation	2	(0.19)	3	(0.53)
serious drug-related adverse events resulting in drug discontinuation	2	(0.19)	2	(0.36)

[a] Event rate per 100 person-months of exposure = event count *100/person-months of exposure.

[b] Drug exposure is defined as the earlier of the last dose date + 30 or the database cutoff date – the first dose date + 1.

[c] Determined by the investigator to be related to the drug.

[d] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.

Non-serious adverse events up to 30 days following the last dose and serious adverse events up to 90 days following the last dose are included.

MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

(Database Cutoff Date: 05OCT2020).

Source: [P158V10MK3475: adam-adsl; adae]

- ***Intrinsic and extrinsic factors***

Age

In the lenvatinib plus pembrolizumab EC group in Study 309/KEYNOTE-775, the AE profile was generally similar for participants <65 and ≥65 year-of-age (table below). However, the incidence of interruption of lenvatinib due to an AE, discontinuation of lenvatinib due to an AE or a drug-related AE, were higher in the older participants.

In the lenvatinib plus pembrolizumab non-EC group in KEYNOTE-146, the incidence of most categories were higher in the older participants: SAEs (all and drug-related), interruption (of pembrolizumab or lenvatinib or both) due to AE, fatal AEs and drug-related fatal AEs, discontinuation (of pembrolizumab or lenvatinib or both) due to AE or SAE.

In the lenvatinib monotherapy safety dataset, the incidence of most categories were also higher in the older participants: grade 3-5 (all and drug-related), SAEs (all and drug-related), interruption of lenvatinib due to AE, and discontinuation of lenvatinib due to AE or SAE.

In the pembrolizumab monotherapy safety dataset, the incidence of most categories were also higher in the older participants: grade 3-5 AEs (all and drug-related), SAEs (all and drug-related), interruption of pembrolizumab due to AE, and discontinuation of pembrolizumab due to AE or SAE.

In the lenvatinib plus pembrolizumab EC group in Study 309/KEYNOTE-775, the AE profile was generally similar for participants <65, 65-74 years, and ≥75 years. More participants in the ≥75 years of age group experienced drug-related SAEs, deaths, and discontinuation of lenvatinib, which was similar to the lenvatinib plus pembrolizumab non-EC group and lenvatinib monotherapy group.

In the lenvatinib plus pembrolizumab EC group in Study 309/KEYNOTE-775, central nervous system (confusion / extrapyramidal) AEs, AEs related to falling, cardiovascular events, and infections were generally similar amongst the <65, 65-74, and ≥75 age groups. However, cerebrovascular events increased considerably with age: <65 (2%), 65-74 (3.6%), and >75 (11.4%).

With regards AEs by grade and by age categories (<65, 65-74, and ≥75 age groups) for the 2 groups in Study 309/KEYNOTE-775, the most frequent AEs in the Lenvatinib plus pembrolizumab group in the oldest age group were (≥ 30% and with higher frequency in oldest group): anaemia (all grade: 27.3%, 22.9%, 34.3%; respectively), UTI (all grade: 22.0%, 28.3%, 34.4%), and hypertension (≥ Grade 3: 33.2%, 42.2%, 45.7%). The SmPC section 4.8 (special populations) has been adapted accordingly (for UTI and ≥ Grade 3 hypertension).

However, conclusions are limited due to the small number of participants in the ⩾75 years of age group (i.e. 35 in the lenvatinib plus pembrolizumab EC group in Study 309/KEYNOTE-775).

Table 68: Adverse Event Summary by Age Category (< 65, ⩾ 65 Years) (APaT Population)

	KN775 Lenvatinib + Pembrolizumab				KN775 Treatment Physician´s Choice				KN146 Lenvatinib + Pembrolizumab (Non-Endometrial Cancer)			
	<65		>=65		<65		>=65		<65		>=65	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	205		201		192		196		127		103	
with one or more adverse events	204	(99.5)	201	(100.0)	191	(99.5)	195	(99.5)	127	(100.0)	103	(100.0)
with no adverse event	1	(0.5)	0	(0.0)	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)
with drug-related[a]adverse events	198	(96.6)	197	(98.0)	181	(94.3)	183	(93.4)	126	(99.2)	99	(96.1)
with toxicity grade 3-5 adverse events	178	(86.8)	183	(91.0)	137	(71.4)	145	(74.0)	110	(86.6)	93	(90.3)
with toxicity grade 3-5 drug-related adverse events	153	(74.6)	163	(81.1)	106	(55.2)	123	(62.8)	79	(62.2)	72	(69.9)
with serious adverse events	109	(53.2)	105	(52.2)	55	(28.6)	63	(32.1)	64	(50.4)	65	(63.1)
with serious drug-related adverse events	64	(31.2)	71	(35.3)	25	(13.0)	30	(15.3)	27	(21.3)	32	(31.1)
with dose interruption of any drug due to an adverse event	134	(65.4)	147	(73.1)	52	(27.1)	53	(27.0)	104	(81.9)	91	(88.3)
interruption of Pembrolizumab	103	(50.2)	100	(49.8)	--		--		63	(49.6)	59	(57.3)
interruption of Lenvatinib	111	(54.1)	127	(63.2)	--		--		99	(78.0)	88	(85.4)
interruption of both Pembrolizumab and Lenvatinib	65	(31.7)	60	(29.9)	--		--		44	(34.6)	45	(43.7)
with dose reduction of Lenvatinib due to an adverse event	130	(63.4)	140	(69.7)	--		--		80	(63.0)	72	(69.9)
who died	12	(5.9)	11	(5.5)	9	(4.7)	10	(5.1)	9	(7.1)	15	(14.6)
who died due to a drug-related adverse event	4	(2.0)	2	(1.0)	5	(2.6)	3	(1.5)	0	(0.0)	5	(4.9)
discontinued any drug due to an adverse event	61	(29.8)	73	(36.3)	11	(5.7)	20	(10.2)	25	(19.7)	40	(38.8)
discontinued Pembrolizumab	36	(17.6)	40	(19.9)	--		--		21	(16.5)	34	(33.0)
discontinued Lenvatinib	56	(27.3)	69	(34.3)	--		--		21	(16.5)	36	(35.0)
discontinued both Pembrolizumab and Lenvatinib	27	(13.2)	30	(14.9)	--		--		16	(12.6)	26	(25.2)
discontinued any drug due to a drug-related adverse event	47	(22.9)	61	(30.3)	10	(5.2)	12	(6.1)	13	(10.2)	27	(26.2)
discontinued Pembrolizumab	19	(9.3)	21	(10.4)	--		--		--		--	
discontinued Lenvatinib	39	(19.0)	53	(26.4)	--		--		--		--	
discontinued both Pembrolizumab and Lenvatinib	8	(3.9)	12	(6.0)	--		--		--		--	
discontinued any drug due to a serious adverse event	40	(19.5)	48	(23.9)	5	(2.6)	9	(4.6)	15	(11.8)	26	(25.2)
discontinued Pembrolizumab	27	(13.2)	33	(16.4)	--		--		12	(9.4)	23	(22.3)
discontinued Lenvatinib	37	(18.0)	44	(21.9)	--		--		14	(11.0)	22	(21.4)
discontinued both Pembrolizumab and Lenvatinib	24	(11.7)	26	(12.9)	--		--		11	(8.7)	19	(18.4)
discontinued any drug due to a serious drug-related adverse event	26	(12.7)	35	(17.4)	4	(2.1)	4	(2.0)	6	(4.7)	15	(14.6)
discontinued Pembrolizumab	11	(5.4)	17	(8.5)	--		--		--		--	
discontinued Lenvatinib	21	(10.2)	29	(14.4)	--		--		--		--	
discontinued both Pembrolizumab and Lenvatinib	6	(2.9)	11	(5.5)	--		--		--		--	

	Lenvatinib Monotherapy Safety Dataset[i]				Pembrolizumab Monotherapy Reference Safety Dataset[j]			
	<65		>=65		<65		>=65	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	700		419		3,385		2,499	
with one or more adverse events	692	(98.9)	416	(99.3)	3,268	(96.5)	2,422	(96.9)
with no adverse event	8	(1.1)	3	(0.7)	117	(3.5)	77	(3.1)
with drug-related[a]adverse events	660	(94.3)	400	(95.5)	2,366	(69.9)	1,766	(70.7)
with toxicity grade 3-5 adverse events	542	(77.4)	357	(85.2)	1,505	(44.5)	1,324	(53.0)
with toxicity grade 3-5 drug-related adverse events	418	(59.7)	306	(73.0)	456	(13.5)	457	(18.3)
with serious adverse events	370	(52.9)	243	(58.0)	1,182	(34.9)	1,084	(43.4)
with serious drug-related adverse events	193	(27.6)	137	(32.7)	346	(10.2)	310	(12.4)
with dose interruption of any drug due to an adverse event	445	(63.6)	312	(74.5)	799	(23.6)	693	(27.7)
interruption of Pembrolizumab	--		--		799	(23.6)	693	(27.7)
interruption of Lenvatinib	445	(63.6)	312	(74.5)	--		--	
interruption of both Pembrolizumab and Lenvatinib	--		--		--		--	
with dose reduction of Lenvatinib due to an adverse event	303	(43.3)	228	(54.4)	--		--	
who died	57	(8.1)	40	(9.5)	144	(4.3)	168	(6.7)
who died due to a drug-related adverse event	13	(1.9)	14	(3.3)	21	(0.6)	18	(0.7)
discontinued any drug due to an adverse event	172	(24.6)	127	(30.3)	399	(11.8)	391	(15.6)
discontinued Pembrolizumab	--		--		399	(11.8)	391	(15.6)
discontinued Lenvatinib	172	(24.6)	127	(30.3)	--		--	
discontinued both Pembrolizumab and Lenvatinib	--		--		--		--	
discontinued any drug due to a drug-related adverse event	115	(16.4)	93	(22.2)	207	(6.1)	203	(8.1)
discontinued Pembrolizumab	--		--		207	(6.1)	203	(8.1)
discontinued Lenvatinib	115	(16.4)	93	(22.2)	--		--	
discontinued both Pembrolizumab and Lenvatinib	--		--		--		--	
discontinued any drug due to a serious adverse event	100	(14.3)	79	(18.9)	287	(8.5)	285	(11.4)
discontinued Pembrolizumab	--		--		287	(8.5)	285	(11.4)
discontinued Lenvatinib	100	(14.3)	79	(18.9)	--		--	
discontinued both Pembrolizumab and Lenvatinib	--		--		--		--	
discontinued any drug due to a serious drug-related adverse event	53	(7.6)	52	(12.4)	123	(3.6)	122	(4.9)
discontinued Pembrolizumab	--		--		123	(3.6)	122	(4.9)
discontinued Lenvatinib	53	(7.6)	52	(12.4)	--		--	
discontinued both Pembrolizumab and Lenvatinib	--		--		--		--	

[a] Determined by the investigator to be related to the drug.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
For KN775 dataset, non-serious adverse events up to 30 days of last dose and serious adverse events up to 120 days of last dose are included.
For KN146 dataset, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
For lenvatinib monotherapy safety dataset, both non-serious adverse events and serious adverse events up to 30 days of last dose are included.
For pembrolizumab monotherapy reference safety dataset, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
[i] Includes all subjects who received at least one dose of lenvatinib in E7080-G000-398, E7080-G000-303, E7080-G000-201, E7080-G000-204, E7080-G000-703, E7080-G000-203, E7080-G000-205, E7080-G000-206, E7080-J081-208, E7080-G000-209 and E7080-J081-105.
[j] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054:02OCT2017, E7080-G000-206: 01SEP2016)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, E7080-G000-703: 01SEP2016)
Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019)
Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)
Database cutoff date for Thyroid (E7080-G000-398: 01SEP2016, E7080-G000-303: 01SEP2016, E7080-G000-201: 01SEP2016, E7080-J081-208: 01SEP2016)
Database cutoff date for Endometrial Cancer (KN775: 26OCT2020, E7080-G000-204: 01SEP2016)
Database cutoff date for Malignant Glioma (E7080-G000-203: 01SEP2016)
Database cutoff date for Renal Cell Carcinoma (E7080-G000-205: 15MAR2018)
Database cutoff date for Adenocarcinoma (E7080-G000-209: 01SEP2016)
Database cutoff date for Solid Tumor (KN146: 18AUG2020, E7080-J081-105: 01SEP2016)

Source: [ISS: adam-adsl; adae]

Table 69: Adverse Event Summary for Elderly Participants by Age in All-comer Participants (APaT Population)

	Age (Years)											
	Lenvatinib + Pembrolizumab						TPC					
	< 65		65-74		>= 75		< 65		65-74		>= 75	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in Population	205		166		35		192		157		39	
with one or more adverse events	204	(99.5)	166	(100.0)	35	(100.0)	191	(99.5)	156	(99.4)	39	(100.0)
who died	12	(5.9)	5	(3.0)	6	(17.1)	9	(4.7)	8	(5.1)	2	(5.1)
with serious adverse events	109	(53.2)	86	(51.8)	19	(54.3)	55	(28.6)	49	(31.2)	14	(35.9)
discontinued due to an adverse event	61	(29.8)	59	(35.5)	14	(40.0)	11	(5.7)	15	(9.6)	5	(12.8)
CNS (confusion/extrapyramidal)	56	(27.3)	60	(36.1)	13	(37.1)	7	(3.6)	9	(5.7)	2	(5.1)
AE related to falling	13	(6.3)	17	(10.2)	5	(14.3)	4	(2.1)	6	(3.8)	3	(7.7)
CV events	140	(68.3)	124	(74.7)	22	(62.9)	51	(26.6)	41	(26.1)	10	(25.6)
Cerebrovascular events	4	(2.0)	6	(3.6)	4	(11.4)	2	(1.0)	3	(1.9)	0	(0.0)
Infections	124	(60.5)	101	(60.8)	20	(57.1)	70	(36.5)	58	(36.9)	19	(48.7)

AEs were followed 30 days after last dose of study treatment; SAEs were followed 120 days after last dose of study treatment.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020.

Source: [P775V01MK3475: adam-adsl; adae]

The AE summary was provided by age categories (i.e. <75 and ≥75 years) for the following datasets: Study 309/KEYNOTE-775 lenvatinib plus pembrolizumab EC group and the TPC EC group; Study 309/KEYNOTE-775 + KEYNOTE-146 + KEYNOTE-581 Lenvatinib + Pembrolizumab across indications; Lenvatinib monotherapy safety dataset; and Pembrolizumab Monotherapy RSD. As there is a limited number of participants ≥75 years of age in the pembrolizumab + lenvatinib group (n=35) and TPC group (n=39) from Study 309/KEYNOTE-775 and the pooled Study 309/KEYNOTE-775 + KEYNOTE-146 + KEYNOTE-581 pembrolizumab + lenvatinib group (n=115), the data should be interpreted with caution.

Table 70: Adverse Event Summary by Age (<75 Years, >=75 Years) (APaT Population)

	KN775 Lenvatinib + Pembrolizumab (Age<75 Years)		KN775 Lenvatinib + Pembrolizumab (Age>=75 Years)		KN775 Treatment Physician´s Choice (Age<75 Years)		KN775 Treatment Physician´s Choice (Age>=75 Years)		KN775 + KN146 + KN581 Lenvatinib + Pembrolizumab (Age<75 Years)		KN775 + KN146 + KN581 Lenvatinib + Pembrolizumab (Age>=75 Years)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	371		35		349		39		997		115	
with one or more adverse events	370	(99.7)	35	(100.0)	347	(99.4)	39	(100.0)	996	(99.9)	114	(99.1)
with no adverse event	1	(0.3)	0	(0.0)	2	(0.6)	0	(0.0)	1	(0.1)	1	(0.9)
with drug-related[a] adverse events	361	(97.3)	34	(97.1)	325	(93.1)	39	(100.0)	970	(97.3)	110	(95.7)
with toxicity grade 3-5 adverse events	330	(88.9)	31	(88.6)	253	(72.5)	29	(74.4)	860	(86.3)	104	(90.4)
with toxicity grade 3-5 drug-related adverse events	288	(77.6)	28	(80.0)	204	(58.5)	25	(64.1)	718	(72.0)	89	(77.4)
with serious adverse events	195	(52.6)	19	(54.3)	104	(29.8)	14	(35.9)	523	(52.5)	70	(60.9)
with serious drug-related adverse events	120	(32.3)	15	(42.9)	47	(13.5)	8	(20.5)	306	(30.7)	46	(40.0)
with dose interruption of any drug due to an adverse event	257	(69.3)	24	(68.6)	91	(26.1)	14	(35.9)	755	(75.7)	96	(83.5)
interruption of Pembrolizumab	185	(49.9)	18	(51.4)	--		--		515	(51.7)	72	(62.6)
interruption of Lenvatinib	218	(58.8)	20	(57.1)	--		--		690	(69.2)	89	(77.4)
interruption of both Pembrolizumab and Lenvatinib	114	(30.7)	11	(31.4)	--		--		355	(35.6)	54	(47.0)
with dose reduction of Lenvatinib due to an adverse event	254	(68.5)	16	(45.7)	--		--		684	(68.6)	65	(56.5)
who died	17	(4.6)	6	(17.1)	17	(4.9)	2	(5.1)	56	(5.6)	15	(13.0)
who died due to a drug-related adverse event	4	(1.1)	2	(5.7)	7	(2.0)	1	(2.6)	12	(1.2)	5	(4.3)
discontinued any drug due to an adverse event	120	(32.3)	14	(40.0)	26	(7.4)	5	(12.8)	319	(32.0)	53	(46.1)
discontinued Pembrolizumab	69	(18.6)	7	(20.0)	--		--		224	(22.5)	41	(35.7)
discontinued Lenvatinib	111	(29.9)	14	(40.0)	--		--		261	(26.2)	48	(41.7)
discontinued both Pembrolizumab and Lenvatinib	52	(14.0)	5	(14.3)	--		--		141	(14.1)	29	(25.2)
discontinued any drug due to a drug-related adverse event	97	(26.1)	11	(31.4)	18	(5.2)	4	(10.3)	243	(24.4)	41	(35.7)
discontinued Pembrolizumab	38	(10.2)	2	(5.7)	--		--		--		--	
discontinued Lenvatinib	82	(22.1)	10	(28.6)	--		--		--		--	
discontinued both Pembrolizumab and Lenvatinib	20	(5.4)	0	(0.0)	--		--		--		--	
discontinued any drug due to a serious adverse event	79	(21.3)	9	(25.7)	12	(3.4)	2	(5.1)	195	(19.6)	29	(25.2)
discontinued Pembrolizumab	54	(14.6)	6	(17.1)	--		--		145	(14.5)	24	(20.9)
discontinued Lenvatinib	73	(19.7)	8	(22.9)	--		--		166	(16.6)	28	(24.3)
discontinued both Pembrolizumab and Lenvatinib	46	(12.4)	4	(11.4)	--		--		111	(11.1)	20	(17.4)
discontinued any drug due to a serious drug-related adverse event	54	(14.6)	7	(20.0)	7	(2.0)	1	(2.6)	127	(12.7)	19	(16.5)
discontinued Pembrolizumab	26	(7.0)	2	(5.7)	--		--		--		--	
discontinued Lenvatinib	45	(12.1)	5	(14.3)	--		--		--		--	

discontinued both Pembrolizumab and Lenvatinib	17	(4.6)	0	(0.0)	--	--	--	--

	Lenvatinib Monotherapy Safety Dataset[i] (Age<75 Years)		Lenvatinib Monotherapy Safety Dataset[i] (Age>=75 Years)		Pembrolizumab Monotherapy Reference Safety Dataset[j] (Age<75 Years)		Pembrolizumab Monotherapy Reference Safety Dataset[j] (Age>=75 Years)	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	1,021		98		5,122		762	
with one or more adverse events	1,011	(99.0)	97	(99.0)	4,946	(96.6)	744	(97.6)
with no adverse event	10	(1.0)	1	(1.0)	176	(3.4)	18	(2.4)
with drug-related[a] adverse events	963	(94.3)	97	(99.0)	3,590	(70.1)	542	(71.1)
with toxicity grade 3-5 adverse events	815	(79.8)	84	(85.7)	2,396	(46.8)	433	(56.8)
with toxicity grade 3-5 drug-related adverse events	648	(63.5)	76	(77.6)	767	(15.0)	146	(19.2)
with serious adverse events	553	(54.2)	60	(61.2)	1,901	(37.1)	365	(47.9)
with serious drug-related adverse events	297	(29.1)	33	(33.7)	559	(10.9)	97	(12.7)
with dose interruption of any drug due to an adverse event	674	(66.0)	83	(84.7)	1,272	(24.8)	220	(28.9)
interruption of Pembrolizumab	--		--		1,272	(24.8)	220	(28.9)
interruption of Lenvatinib	674	(66.0)	83	(84.7)	--		--	
interruption of both Pembrolizumab and Lenvatinib	--		--		--		--	
with dose reduction of Lenvatinib due to an adverse event	478	(46.8)	53	(54.1)	--		--	
who died	85	(8.3)	12	(12.2)	247	(4.8)	65	(8.5)
who died due to a drug-related adverse event	21	(2.1)	6	(6.1)	33	(0.6)	6	(0.8)
discontinued any drug due to an adverse event	265	(26.0)	34	(34.7)	645	(12.6)	145	(19.0)
discontinued Pembrolizumab	--		--		645	(12.6)	145	(19.0)
discontinued Lenvatinib	265	(26.0)	34	(34.7)	--		--	
discontinued both Pembrolizumab and Lenvatinib	--		--		--		--	
discontinued any drug due to a drug-related adverse event	183	(17.9)	25	(25.5)	342	(6.7)	68	(8.9)
discontinued Pembrolizumab	--		--		342	(6.7)	68	(8.9)
discontinued Lenvatinib	183	(17.9)	25	(25.5)	--		--	
discontinued both Pembrolizumab and Lenvatinib	--		--		--		--	
discontinued any drug due to a serious adverse event	157	(15.4)	22	(22.4)	461	(9.0)	111	(14.6)
discontinued Pembrolizumab	--		--		461	(9.0)	111	(14.6)
discontinued Lenvatinib	157	(15.4)	22	(22.4)	--		--	
discontinued both Pembrolizumab and Lenvatinib	--		--		--		--	
discontinued any drug due to a serious drug-related adverse event	91	(8.9)	14	(14.3)	204	(4.0)	41	(5.4)
discontinued Pembrolizumab	--		--		204	(4.0)	41	(5.4)
discontinued Lenvatinib	91	(8.9)	14	(14.3)	--		--	
discontinued both Pembrolizumab and Lenvatinib	--		--		--		--	

[a] Determined by the investigator to be related to the drug.
For KN581 and KN775, non-serious adverse events up to 30 days of last dose and serious adverse events up to 120 days of last dose are included.
For KN146 dataset, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
For lenvatinib monotherapy safety dataset, both non-serious adverse events and serious adverse events up to 30 days of last dose are included.
For pembrolizumab monotherapy reference safety dataset, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
[i] Includes all subjects who received at least one dose of lenvatinib in E7080-G000-398, E7080-G000-303, E7080-G000-201, E7080-G000-204, E7080-G000-703, E7080-G000-203, E7080-G000-205, E7080-G000-206, E7080-J081-208, E7080-G000-209 and E7080-J081-105.
[j] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054:02OCT2017, E7080-G000-206: 01SEP2016)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, E7080-G000-703: 01SEP2016)
Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019)
Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)
Database cutoff date for Thyroid (E7080-G000-398: 01SEP2016, E7080-G000-303: 01SEP2016, E7080-G000-201: 01SEP2016, E7080-J081-208: 01SEP2016)
Database cutoff date for Endometrial Cancer (KN775: 26OCT2020, E7080-G000-204: 01SEP2016)
Database cutoff date for Malignant Glioma (E7080-G000-203: 01SEP2016)
Database cutoff date for Renal Cell Carcinoma (E7080-G000-205: 15MAR2018, KN426: 24AUG2018, KN581: 28AUG2020)
Database cutoff date for Adenocarcinoma (E7080-G000-209: 01SEP2016)
Database cutoff date for Solid Tumor (KN146: 18AUG2020, E7080-J081-105: 01SEP2016)
Source: [ISS: adam-adsl; adae]

The observed incidence rates of the AE categories of the Study 309/KEYNOTE-775 pembrolizumab + lenvatinib group were generally similar in the <75 and ≥75 age groups, however higher rate were observed for the elderly for: drug-related SAEs, deaths, deaths due to a drug-related AE, and discontinuations due to AE. However, as a similar pattern was generally observed between the age groups in all datasets, this does not suggest a new safety concern for pembrolizumab + lenvatinib across age groups.

Of note, the 6 fatal events observed in the participants ≥75 years of age were: 2 "death", 1 urosepsis, 1 myelodysplatic syndrome, 1 cerebrovascular event and 1 assisted suicide.

Sex

All participants in the lenvatinib plus pembrolizumab EC group were female. The AE profile based on gender in the lenvatinib plus pembrolizumab EC group was generally consistent with the safety profiles of females treated with lenvatinib or pembrolizumab monotherapy.

ECOG performance status

In the lenvatinib plus pembrolizumab EC group in Study 309/KEYNOTE-775, there were 60.1% of participants with ECOG of 0 and 39.9% participants with ECOG of 1.

In each group (lenvatinib plus pembrolizumab EC group in Study 309/KEYNOTE-775, lenvatinib monotherapy safety data set, pembrolizumab monotherapy RSD, and lenvatinib plus pembrolizumab non-EC group in KEYNOTE-146), the safety profiles were in generally consistent between participants with ECOG of 0 or 1. However, the incidence of SAEs, fatal AEs, and drug-related fatal AEs were increased in the participants with ECOG of 1.

Geographical region

In the lenvatinib plus pembrolizumab EC group in Study 309/KEYNOTE-775, there were 28.1% of participants from EU regions and 71.9% participants not from EU regions.

In each group (lenvatinib plus pembrolizumab EC group in Study 309/KEYNOTE-775, lenvatinib monotherapy safety data set, pembrolizumab monotherapy RSD, and lenvatinib plus pembrolizumab non-EC group in KEYNOTE-146), the safety profiles were in generally consistent between participants from EU or not. However, lenvatinib plus pembrolizumab EC group and lenvatinib plus pembrolizumab non-EC group presented higher incidence of dose reduction of lenvatinib due to AEs in the participants not from EU (difference not observed in the lenvatinib monotherapy group).

Ethnicity

Frequencies of AEs by grade and by ethnicity for the 2 groups in Study 309/KEYNOTE-775 were provided. There was a limited number of participants in the lenvatinib plus pembrolizumab and TPC treatment groups who were Asian (n=85 and n=86, respectively) or from other ethnicity (n=29 and n=34, respectively); therefore, the data should be interpreted with caution.

The incidences and severity of the most frequently reported AEs (incidence ≥15%) in the lenvatinib plus pembrolizumab group were generally similar between the different categories with the following differences (≥10% difference) noted:

- AEs higher in Whites than Asians: mucosal inflammation (14.1% vs 1.2%), abdominal pain (23.0% vs 8.2%), UTI (29.7% vs 12.9%), diarrhoea (57.4% vs 47.1%; Grade ≥3: 7.4% vs 10.6%), weight decreased (37.1% vs 27.1%), hypomagnesaemia (21.5% vs 4.7%), dizziness (13.7% vs 1.2%), asthenia (27.3% vs 3.5%; Grade ≥3: 7.4% vs 0%), and fatigue (39.1% vs 17.6%)
- AEs higher in Asians than Whites: anaemia (34.1% vs 23.4%; Grade ≥3: 10.6 % vs 4.3%), malaise (23.5% vs 0.8%), oedema (12.9% vs 2.3%), neutrophil count decrease (16.5% vs 2%; Grade ≥3: 9.4% vs 0.4%), stomatitis (37.6% vs 14.1%), platelet count decreased (32.9% vs 7.0%, Grade ≥3: 10.6% vs 0.8%), proteinuria (51.8% vs 22.3%; Grade ≥3: 10.6% vs 3.9%), PPE (40.0% vs 13.3%; Grade ≥3: 5.9% vs 2.0%), and pyrexia (31.8% vs 10.5%)

- ***Use in Pregnancy and Lactation***

As of the data cut off, there were no reports of pregnancy in the lenvatinib plus pembrolizumab EC group.

- **Safety related to drug-drug interactions and other interactions**

As pembrolizumab is an IgG antibody that is administered parenterally and cleared by catabolism, food and DDI are not anticipated to influence exposure. Drugs that affect the CYP enzymes, and other metabolizing enzymes, are not expected to interfere with the metabolism of an IgG antibody. The IgG antibodies, in general, do not directly regulate the expression of CYP enzymes, other enzymes, or transporters involved in drug elimination. Therefore, no dedicated DDI studies have been performed. In addition, in vitro experiments and studies conducted in preclinical species have been shown to have limited value in predicting DDI potential in humans [Ref. 5.4: 03JJPS]. Therefore, no preclinical PK studies were conducted to assess the propensity of pembrolizumab to be a victim or perpetrator of PK DDIs.

The main metabolic pathways for lenvatinib in humans were identified as enzymatic (CYP3A and aldehyde oxidase) and non-enzymatic processes. The IC50 values for the 9 main CYP isoforms, the 5 main UGT isoforms, AO, and the 11 transporters tested were more than 4 µM, suggesting lenvatinib is not a perpetrator of DDI at the maximum dose of 24 mg QD. Lenvatinib is a substrate of P-gp and BCRP but was not a substrate any of the other transporters evaluated. No formal PK drug interaction studies have been conducted with pembrolizumab. Since pembrolizumab is a mAb; PK interactions with lenvatinib are not expected.

Studies evaluating pharmacodynamic drug interactions with pembrolizumab have not been conducted. However, as systemic corticosteroids may be used in combination with pembrolizumab to ameliorate potential side effects, the potential for a pharmacokinetic DDI with pembrolizumab as a victim was assessed as part of the population pharmacokinetic analysis. No relationship was observed between prolonged use of systemic corticosteroids and pembrolizumab exposure. Nevertheless, the use of systemic corticosteroids or other immunosuppressants before the start of pembrolizumab treatment should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of pembrolizumab. However, systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab treatment to treat immune-mediated adverse reactions.

- **Discontinuation due to adverse events**

  - ***Adverse Events Leading to Treatment Discontinuation***

Adverse Events Leading to Treatment Discontinuation

The incidence of participants with AEs that led to discontinuation of any study intervention was higher in the lenvatinib and pembrolizumab EC group (33%) compared with the TPC group (8%). The incidence of participants with AEs that led to discontinuation of both lenvatinib and pembrolizumab was 14.0%, with discontinuation of lenvatinib (30.8%) higher than for pembrolizumab (18.7%).

The incidence of AEs resulting in lenvatinib discontinuation was generally consistent between the lenvatinib plus pembrolizumab EC group (30.8%) and the lenvatinib monotherapy group (26.7%). Hypertension, decreased appetite, asthenia, weight decreased, diarrhoea, proteinuria, intestinal obstruction, and vomiting resulted in lenvatinib discontinuation in ≥1% of participants in the lenvatinib plus pembrolizumab EC group. Hypertension, asthenia, proteinuria, and fatigue resulted in lenvatinib discontinuation in ≥1% of participants in the lenvatinib monotherapy group.

The incidence of AEs resulting in pembrolizumab discontinuation was similar for the lenvatinib plus pembrolizumab EC group (18.7%) compared to the pembrolizumab monotherapy RSD group (13.4%). Diarrhoea, intestinal obstruction, and ALT increased resulted in pembrolizumab discontinuation in ≥1%

of participants in the lenvatinib plus pembrolizumab EC group. No individual AEs in the pembrolizumab monotherapy group resulted in pembrolizumab discontinuation in >1% of participants.

The overall incidence of AEs resulting in discontinuation of both lenvatinib and pembrolizumab was consistent between the lenvatinib plus pembrolizumab EC group (14.0%) and lenvatinib plus pembrolizumab non-EC group (18.3%). Intestinal obstruction was the only AE resulting in discontinuation of lenvatinib and pembrolizumab with an incidence of ≥1% in the lenvatinib plus pembrolizumab EC group; no individual AEs ≥1% resulted in discontinuation of lenvatinib and pembrolizumab in the lenvatinib plus pembrolizumab non-EC group.

From all these AEs resulting in discontinuation of lenvatinib, pembrolizumab, or both in the lenvatinib plus pembrolizumab EC group, only intestinal obstruction is not an identified ADR in the SmPC.

Drug-related Adverse Events Leading to Treatment Discontinuation

The incidence of participants with drug-related AEs that led to discontinuation of any study intervention was higher in the lenvatinib and pembrolizumab EC group (26.6%) compared with the TPC group (5.7%). The incidence of participants with drug-related AEs that led to discontinuation of both lenvatinib and pembrolizumab was 4.9%, with discontinuation of lenvatinib (22.7%) higher than for pembrolizumab (9.9%).

The incidence of drug-related AEs resulting in lenvatinib discontinuation was generally consistent between the lenvatinib plus pembrolizumab EC group (22.7%) and the lenvatinib monotherapy group (18.6%). Drug-related AEs in the lenvatinib plus pembrolizumab EC group resulting in lenvatinib discontinuation (regardless of action taken for pembrolizumab) in ≥1% of participants included hypertension, asthenia, weight decreased, decreased appetite, proteinuria, diarrhoea, and vomiting. Hypertension, asthenia, proteinuria, and fatigue resulted in lenvatinib discontinuation in ≥1% of participants in the lenvatinib monotherapy group.

The incidence of drug-related AEs resulting in pembrolizumab discontinuation was similar for the lenvatinib plus pembrolizumab EC group (9.9%) and the pembrolizumab monotherapy group (7.0%). ALT increased was the only drug-related AE in the lenvatinib plus pembrolizumab EC group resulting in pembrolizumab discontinuation in ⩾1% of participants. No individual AEs in the pembrolizumab monotherapy group resulted in pembrolizumab discontinuation in >1% of participants.

- ***Adverse Events Leading to Treatment interruption***

Adverse Events Leading to Treatment interruption

The incidence of participants with AEs that led to interruption of any study intervention was higher in the lenvatinib and pembrolizumab EC group (69.2%) compared with the TPC group (27.1%). The incidence of participants AEs that led to interruption of both lenvatinib and pembrolizumab was 30.8%, with interruption of lenvatinib (58.6%) higher than for pembrolizumab (50.0%).

The incidence of AEs resulting in lenvatinib interruption was similar in the lenvatinib plus pembrolizumab EC group (58.6%) and the lenvatinib monotherapy group (67.6%). AEs in the lenvatinib plus pembrolizumab EC group resulting in lenvatinib discontinuation in ≥5% of participants included hypertension, diarrhoea, proteinuria, and vomiting. Hypertension, diarrhoea, proteinuria, and vomiting, nausea, asthenia, fatigue, PPES and decreased appetite resulted in lenvatinib interruption in ≥5% of participants in the lenvatinib monotherapy group.

The incidence of AEs resulting in pembrolizumab interruption was higher in the lenvatinib plus pembrolizumab group (50.0%) than in the pembrolizumab monotherapy RSD group (25.4%). Diarrhoea was the only AE in the lenvatinib plus pembrolizumab group resulting in pembrolizumab discontinuation in ≥5% of participants. No individual AEs in the pembrolizumab monotherapy group resulted in pembrolizumab interruption in >5% of participants.

The overall incidence of AEs resulting in interruption of both lenvatinib and pembrolizumab was similar in the lenvatinib plus pembrolizumab group (30.8%) and the lenvatinib plus pembrolizumab non-EC group (38.7%). In the Lenvatinib plus pembrolizumab group, the most common AEs resulting in treatment interruption of both drugs (>1%) were: diarrhoea, ALT increased, AST increased, UTI, hypertension, cholecystitis, blood creatinine increased, hyperthyroidism, and vomiting. Diarrhoea, colitis, nausea, fatigue, pneumonia, URTI, Decreased appetite, Dehydration, Arthralgia, Acute kidney injury, Proteinuria, Dyspnoea, and Pleural effusion resulted in interruption of both lenvatinib and pembrolizumab in the lenvatinib plus pembrolizumab non-EC group.

Drug-related Adverse Events Leading to Treatment interruption

The incidence of drug-related AEs resulting in lenvatinib interruption was lower in the lenvatinib plus pembrolizumab EC group (45.8%) than in the lenvatinib monotherapy group (61.3%). Drug-related AEs in the lenvatinib plus pembrolizumab EC group resulting in lenvatinib interruption in ≥2% of participants included hypertension, diarrhoea, proteinuria, decreased appetite, vomiting, fatigue, nausea, and weight decreased [Table 5.3.5.3.3-endometrial1: 34]. The same drug-related AES plus abdominal pain, abdominal pain upper, stomatitis, and asthenia resulted in lenvatinib interruption in ≥2% of participants in the lenvatinib monotherapy group.

The incidence of AEs resulting in pembrolizumab interruption was higher in the lenvatinib plus pembrolizumab EC group (25.6%) than in the pembrolizumab monotherapy RSD group (14.2%). Drug-related AEs in the lenvatinib plus pembrolizumab EC group resulting in pembrolizumab interruption in ≥ 2% of participants included diarrhoea and ALT increased [Table 5.3.5.3.3-endometrial1: 35]. No individual AEs in the pembrolizumab monotherapy group resulted in pembrolizumab interruption in >5% of participants.

- ***Adverse Events Leading to dose reduction of lenvatinib***

Adverse Events Leading to dose reduction of lenvatinib

In Study 309/KEYNOTE-775, the pembrolizumab dose was fixed at 200 mg Q3W and dose reduction was not allowed.

The starting dose for lenvatinib was 20 mg QD, however dose modifications were allowed according to the approved label and standard practice. The overall incidence of AEs resulting in dose reduction of lenvatinib was higher in the lenvatinib plus pembrolizumab EC group (66.5%) than in the lenvatinib monotherapy group (47.5%).

In the lenvatinib and pembrolizumab EC group, the AEs that most frequently led to lenvatinib dose reduction (incidence >5%) were hypertension, diarrhoea, PPES, proteinuria, decreased appetite, fatigue, and weight decreased, all of which are known to be associated with lenvatinib. From those, hypertension, diarrhoea, proteinuria, decreased appetite, and fatigue, resulted in lenvatinib dose reduction in >5% of participants in the lenvatinib monotherapy group. All these AEs resulting in dose reduction of lenvatinib in the lenvatinib plus pembrolizumab EC group are identified ADRs in the SmPC.

The overall incidence of AEs resulting in a dose reduction of lenvatinib in the lenvatinib plus pembrolizumab EC group (66.5%) was consistent with the lenvatinib plus pembrolizumab non-EC group (66.1%) [Table 5.3.5.3.3-endometrial1: 36].

Drug-related Adverse Events Leading to dose reduction of lenvatinib

The overall incidence of AEs resulting in dose reduction of lenvatinib was higher in the lenvatinib plus pembrolizumab EC group (65.0%) than in the lenvatinib monotherapy group (46.2%). The most frequently reported (incidence ≥5%) drug-related AEs leading to lenvatinib dose reduction were hypertension, diarrhoea, PPES, proteinuria, fatigue, decreased appetite, and weight decreased in the lenvatinib plus pembrolizumab group (similar in both groups).

- **Post marketing experience**

The safety profile of lenvatinib was summarized in the Periodic Safety Update Report covering the period 13-FEB-2019 through 12-FEB-2020, specifically Appendix 2B (Cumulative and Interval Summary Tabulations of Serious and Non-serious Adverse Reactions from Post-marketing Data Sources) [Ref. 5.3.6: 7902-psur-13feb19-12feb20]. The safety profile of pembrolizumab was summarized in the Periodic Safety Update Report covering the period 04-SEP-2019 through 03-SEP-2020, specifically Appendix 20.3.1 (Numbers of Adverse Drug Reactions by Preferred Term from Post-authorization Sources) [Ref. 5.3.6: 3475-psur-04sep19-03sep20].

No revocation or withdrawal of lenvatinib or pembrolizumab or registration for safety reasons has occurred in any country.

2.5.1. Discussion on clinical safety

Overall population

Demographic and other baseline characteristics

Demographic and other baseline characteristics in Study 309/KEYNOTE-775 were generally well balanced between the lenvatinib plus pembrolizumab EC group and the TPC EC group. In the lenvatinib plus pembrolizumab EC group, all participants were female, and most were white (63.1%) or Asian (20.9%), with an ECOG performance status of 0 (60.1%), and a minority were based in the EU (28.1%). Half of them were under 65 year-of-age, and half of them over 65 year-of-age. Some differences were noted with the other groups (more participants ≥65 years of age, less white people, more Hispanic or Latino people, more participants with ECOG performance status of 0), but they are not expected to affect the interpretation of the safety results.

Median duration

The median duration of treatment was longer in the lenvatinib plus pembrolizumab non-EC group (9.79 months) compared to the lenvatinib plus pembrolizumab EC group (7.59 months), which was longer

compared to the TPC EC group (3.43 months), the lenvatinib monotherapy safety dataset (5.55 months) and the pembrolizumab monotherapy RSD (4.86 months).

Adverse events

The summary of AEs, despite showing similar proportions of overall AEs in the two arms, displayed a worse safety profile for the combination treatment group when compared to controls (TPC EC group), as shown by higher proportions of subjects with drug-related AEs (97.3% vs 93.8%, respectively), Grade 3-5 drug-related AEs (77.8% vs 59%), drug-related SAEs (33.3% vs 14.2%), who had dose interruption of any drug due to an AE (69.2% vs 27.1%) or who discontinued any drug due to an AE (33% vs 8%). Proportions of fatal events and drug-related fatal events were comparable across study arms. However, when evaluating exposure-adjusted incidence rates, a partially reversed safety picture is found showing lower incidence rates per 100 person-months, respectively, in the lenvatinib+pembrolizumab group when compared to TPC group for AEs (232 vs 256, respectively), drug-related AEs (133 vs 153), Grade 3-5 AEs (31.02 vs 48.78), drug-related Grade 3-5 AEs (18.52 vs 34.5), fatal events (0.59 vs 1.08), with comparable rates for SAEs, drug-related SAEs, and deaths due to drug-related AE. On the contrary, rates of dose modification (37.9 vs 18.6), dose interruption (21.18 vs 11.5), dose reduction (15.16 vs 4.76), and discontinuation due to AE (5 vs 2.32), to a drug-related AEs (3.98 vs. 1.76), to a SAEs (2.42 vs. 0.85), or to a drug-related SAEs (1.63 vs. 0.45), remained higher in the study group of interest.

Overall, the safety profile was similar between the lenvatinib plus pembrolizumab EC group and non-EC group. Only the incidence of drug-related Grade 3 to 5 AEs was higher in the lenvatinib plus pembrolizumab EC group compared with the lenvatinib plus pembrolizumab non-EC group (77.8% vs. 65.7%). Enhanced toxicity was observed with the combination compared to the monotherapies for the following: Grade 3 to 5 AEs (88.9% lenvatinib plus pembrolizumab EC group vs. 80.3% lenvatinib monotherapy vs. 48.1% pembrolizumab monotherapy RSD), drug-related Grade 3 to 5 AEs (77.8% vs. 64.7% vs. 15.5%, respectively), lenvatinib dose reduction due to an AE (66.5% combination vs. 47.5% monotherapy), and pembrolizumab dose interruption due to AEs (50% combination vs. 25.4% monotherapy).

When comparing exposure-adjusted rate, the overall AE summary profile of the lenvatinib plus pembrolizumab EC group was generally consistent with the lenvatinib plus pembrolizumab non-EC group, except for lower rate of dose interruption of any drugs due to AEs (21.18 vs. 26.74), and lenvatinib interruption due to AEs (15.72 vs. 23.33); and higher rate in the lenvatinib plus pembrolizumab EC group compared with the lenvatinib plus pembrolizumab non-EC group observed for Grade 3 to 5 AEs (31.02 vs. 25.73), drug-related Grade 3 to 5 AEs (18.52 vs. 12.24), drug-related SAEs (5.15 vs. 2.85); discontinuation due to AEs (5 vs. 3.1), to drug-related AEs (3.98 vs. 1.91), to a SAEs (2.42 vs. 1.74), or to a drug-related SAEs (1.63 vs. 0.87).

The most common AEs (all and drug-related) with the combination therapy in EC are in general consistent with the known safety profiles of the respective monotherapies and the combination therapy in non-EC.

The most frequent exposure-adjusted AEs in the lenvatinib plus pembrolizumab EC group (> 4 events / 100 person-months) were diarrhoea, hypertension, nausea, vomiting, hypothyroidism, decreased appetite, proteinuria, arthralgia, fatigue, and weight decreased. All these AEs are identified very common ADRs in section 4.8 of the SmPC. Hypertension, nausea, vomiting, decreased appetite, proteinuria, arthralgia, fatigue, and weight decreased are known AEs associated with lenvatinib; hypothyroidism and diarrhoea have been described for both lenvatinib and pembrolizumab.

The criteria used to select the ADRs for the ADR table for the combination with pembrolizumab for EC in section 4.8 of the SmPC were as follows (meeting at least one of the criteria):

- Lenvima ADR terms in the monotherapy column carried over for all subsequent columns when observed for the combination and adjusted to the appropriate frequency category based on the pooled data

- Agency mandated terms

- AEs occurring at an incidence higher than the respective monotherapy safety profiles were assessed for additive or potentiated effect and clinical relevance.

In addition, a paragraph similar to the Keytruda SmPC was added prior to the section 4.8 ADR table reading as follows :

"Adverse reactions known to occur with lenvatinib or combination therapy components given alone may occur during treatment with these medicinal products in combination, even if these reactions were not reported in clinical studies with combination therapy.

For additional safety information when lenvatinib is administered in combination, refer to the SmPC for the respective combination therapy component (pembrolizumab)."

Of note, differences will remain with the Keytruda (pembrolizumab) SmPC as the ADR table has been updated to show the ADR with the combination of pembrolizumab with axitinib or Lenvatinib.

The most frequently reported drug-related AEs (incidence ≥30%) in the lenvatinib plus pembrolizumab EC group were hypertension, hypothyroidism, diarrhoea, nausea, and decreased appetite. All these drug-related AEs are identified as very common ADRs in the SmPC section 4.8. Hypertension, nausea, and decreased appetite are known AEs associated with lenvatinib; hypothyroidism and diarrhoea have been described for both lenvatinib and pembrolizumab.

In the lenvatinib plus pembrolizumab EC group compared with the lenvatinib monotherapy group, the pembrolizumab monotherapy RSD, and the lenvatinib plus pembrolizumab non-EC group, there was a marked higher incidence (in %) of the following AEs (all and drug-related): hypothyroidism, anaemia, UTI, ALT increased, AST increased, hypomagnesemia, mucosal inflammation, hyperthyroidism, Blood thyroid stimulating hormone increased, platelet count decreased, neutropenia, leukopenia, and neutrophil count decreased.

Thrombocytopenia (including decreased platelet count), neutropenia (including decreased neutrophil count), leukopenia (including decreased white blood cell count), oral inflammation (including mucosal inflammation), hypothyroidism, UTI, ALT increased, AST increased, hypomagnesemia, and increased blood thyroid stimulating hormone are listed in the ADR table of section 4.8 of the SmPC for Lenvatinib monotherapy and for the combination.

The most common Grade 3-5 AEs (all and drug-related) with the combination therapy in EC are in general consistent with the known safety profiles of the respective monotherapies and the combination therapy in non-EC.

The most frequent exposure-adjusted Grade 3 to 5 AEs in the lenvatinib plus pembrolizumab EC group (≥ 0.5 events / 100 person-months) were hypertension, weight decreased, decreased appetite, diarrhoea, lipase increased, anaemia, asthenia, proteinuria, fatigue, and hypokalemia. All these Grade 3 to 5 AEs are identified very common ADRs in section 4.8 of the SmPC. All these AEs are known AEs associated with lenvatinib or pembrolizumab or both.

The most frequently reported drug-related grade 3 to 5 AEs (incidence ≥4%) in the lenvatinib plus pembrolizumab EC group were hypertension, diarrhoea, decreased appetite, weight decreased, lipase increased, proteinuria, and asthenia. All these drug-related AEs are identified very common ADRs in the SmPC section 4.8.

The overall incidence of fatal AEs was comparable in the lenvatinib plus pembrolizumab EC group (5.7% - 23 deaths), the TPC EC group (4.9% - 19 deaths), and the pembrolizumab monotherapy RSD (5.3% - 312 deaths), and lower than in the lenvatinib plus pembrolizumab non-EC group (10.4% – 24 deaths) and the lenvatinib monotherapy group (8.7% - 97 deaths). The overall incidence of drug-related fatal AEs was comparable in all groups: lenvatinib plus pembrolizumab EC group (1.5% - 6 deaths), TPC EC group (2.1% - 8 deaths), lenvatinib plus pembrolizumab non-EC group (2.2% - 5 deaths), the lenvatinib monotherapy group (2.4% - 27 deaths) and the pembrolizumab monotherapy RSD (0.7% - 39 deaths). Out of the 6 drug-related fatal AEs in the lenvatinib plus pembrolizumab EC group, 1 death due to multiorgan dysfunction syndrome was considered by the investigator as related to both lenvatinib and pembrolizumab. One death each due to cerebrovascular accident, right ventricular dysfunction, myelodysplastic syndrome, and death were considered by the investigator as related to lenvatinib, and 1 death due to colitis was considered by the investigator as related to pembrolizumab.

The frequency, type, and severity of SAEs (all and drug-related) reported in the lenvatinib plus pembrolizumab EC group reflect the established individual safety profiles of lenvatinib and pembrolizumab monotherapy and is generally consistent with the safety profile when used in combination in non-EC.

The most frequent exposure-adjusted SAEs in the lenvatinib plus pembrolizumab EC group (≥ 0.2 events / 100 person-months) were hypertension, UTI, diarrhoea, decreased appetite, vomiting, acute kidney injury, pyrexia, cholecystitis, colitis and pneumonia. The most frequently reported drug-related SAEs in the lenvatinib plus pembrolizumab EC group (incidence ≥1%) were hypertension, colitis, decreased appetite, vomiting, diarrhoea, pyrexia, and acute kidney injury. Of these, only pneumonia, colitis and pyrexia are not identified ADRs in the SmPC section 4.8. All these SAEs are known AEs associated with lenvatinib or pembrolizumab or both.

The types, incidence, severity and outcome of Clinically Significant Adverse Events associated with Lenvatinib (CSAE) reported in the lenvatinib plus pembrolizumab EC group were generally consistent with the established safety profile of lenvatinib when used as monotherapy, with the exception of an increased frequency of hepatotoxicity (mainly ALT and AST increased, Grade 1 to 3), hypothyroidism (Grade 1 to 2), and renal events (mainly Blood creatinine increased, Grade 1 to 2). All these CSAE are identified as very common ADRs in the SmPC section 4.8.

The types, incidence, severity and outcome of Adverse Events of Special Interest for Pembrolizumab (AEOSI) reported in the lenvatinib plus pembrolizumab EC group were generally consistent with the established safety profile of pembrolizumab when used as monotherapy, with the exception of increased frequencies of hypothyroidism (Grade 1 to 2), hyperthyroidism (Grade 1 to 3) and colitis (Grade 1 to 3). Only hypothyroidism and hyperthyroidism are identified as very common ADRs in the SmPC section 4.8. Colitis have not been identified. There was 1 death in the lenvatinib plus pembrolizumab EC group due to an AEOSI of colitis, which was considered by the investigator to be related to pembrolizumab.

No new safety concerns based on laboratory abnormalities were reported in the lenvatinib plus pembrolizumab EC group. Overall, the most frequently reported (≥30%) laboratory abnormalities (Grades 1 to 4) were similar in the lenvatinib plus pembrolizumab EC group and the lenvatinib monotherapy group, pembrolizumab monotherapy RSD, and lenvatinib plus pembrolizumab non-EC group, and the majority were Grade 1 to 2 toxicity: ALT increased, AST increased, Albumin Decreased, alkaline Phosphatase Increased, Cholesterol Increased, Creatinine Increased, Haemoglobin Decreased, Lymphocytes Decreased, Magnesium Decreased, Potassium Decreased, Sodium Decreased and Triglycerides Increased. *The frequencies based on laboratory values for the applicable ADRs* in the ADR table in section 4.8 of the SmPC were reflected in line with the Guideline on the evaluation of anticancer medicinal products in man, EMA/CHMP/205/95 Rev.5 - Section 8.9,

The percentages of participants in the lenvatinib plus pembrolizumab EC group with Grade 3 to 4 laboratory abnormalities were low and were generally consistent with the lenvatinib monotherapy group, pembrolizumab monotherapy RSD, and the lenvatinib plus pembrolizumab non-EC group. The most frequently reported (incidence ≥5%) Grade 3 to 4 laboratory abnormalities in the lenvatinib plus pembrolizumab EC group were: Lymphocyte decreased (16.9%), sodium decreased (14.4%), potassium decreased (10.7%), AST increased (8.5%), haemoglobin decreased (8.2%), phosphate decreased (8.2%), glucose increased (8.0%), ALT increased (7.7%), platelets decreased (7.2%), triglycerides increased (7.1%), magnesium decreased (6.9%), amylase increased (6.8%), and neutrophils decreased (5.9%).

Three participants in the lenvatinib plus pembrolizumab EC group met the prespecified drug-induced liver injury (DILI) criteria of increase in ALT or AST ≥3 × ULN and bilirubin ≥1.5 × ULN and alkaline phosphatase <2 × ULN. DILI is an identified ADR of lenvatinib, pembrolizumab and the combination (under the name hepatitis).

In the lenvatinib plus pembrolizumab EC group, the incidence of participants with AEs that led to discontinuation of both lenvatinib and pembrolizumab was 14.0%, with discontinuation of lenvatinib (30.8%) higher than for pembrolizumab (18.7%). The types and incidences of AEs (all and drug-related) resulting in treatment discontinuation or interruption of both drugs were generally consistent with the safety profile of the combination in non-EC. The AEs (all and drug-related) that led to discontinuation or interruption of either lenvatinib or pembrolizumab were generally consistent with the known safety profiles of pembrolizumab monotherapy or lenvatinib monotherapy (no suggestion of new safety concern).

In the lenvatinib plus pembrolizumab EC group, intestinal obstruction is the only ADR not identified in the SmPC that had led to lenvatinib and/or pembrolizumab discontinuation (led also to lenvatinib discontinuation in lenvatinib monotherapy). Intestinal obstruction is a common complication of EC due to intra-abdominal tumor adhesions [Tuca et al., 2012].

In Study 309/KEYNOTE-775, the pembrolizumab dose was fixed at 200 mg Q3W and dose reduction was not allowed. The types and incidences of AEs (all and drug-related) resulting in a dose reduction of lenvatinib in the lenvatinib plus pembrolizumab EC group were generally consistent with the lenvatinib monotherapy.

Overall, several differences between the safety profiles of the different groups were justified as a result of the longer duration of treatment in the lenvatinib plus pembrolizumab EC and non-EC groups compared to the other groups (increasing the time during which AEs could be collected).

MMR status

Per the study protocol in Study 309/KEYNOTE-775, the safety was assessed separately depending on the tumor mismatch repair (MMR) status. In the lenvatinib plus pembrolizumab EC group and the TPC groups, there were fewer dMMR participants (n=64 and 63, respectively) as compared with pMMR participants (n=342 and 325). However, because of the limited number of dMMR participants, definitive conclusions cannot be drawn.

There was a longer duration of exposure to lenvatinib plus pembrolizumab observed for dMMR participants (median: 335.5 days; range: 1 to 720 days) compared with pMMR participants (median: 219.5 days; range: 1 to 817 days). On the contrary, there was a shorter duration of exposure to TPC observed for dMMR participants (median: 86 days; range: 1 to 331 days) compared with pMMR participants (median: 106 days; range: 1 to 785 days).

Although the safety profile was overall the same by MMR status, in the dMMR participants compared with the pMMR participants in the lenvatinib plus pembrolizumab EC group, there were higher incidence of:

Grade 3 to 5 AEs (95.3% vs. 87.7%, respectively), drug-related Grade 3 to 5 AEs (85.9% vs. 76.3%), SAEs (68.8% vs. 49.7%), dose modifications due to AEs (100% vs. 92.4%), discontinuations due to AEs (43.8% vs. 31%), fatal AEs (10.9% vs. 4.7%), and fatal drug-related AEs (3.1% vs. 1.2%)

In the pMMR and dMMR participants, the AEs (all and drug-related) that led to discontinuation and the AEs that led to interruption of both drugs or of either lenvatinib or pembrolizumab were generally consistent with the results in the all-comers population. The AEs that most frequently led to lenvatinib dose reduction in pMMR and dMMR participants were generally consistent with those for the all-comer participants.

When adjusted for exposure, in the lenvatinib plus pembrolizumab EC group, the overall toxicity profile was slightly worst for the pMMR group compared to the dMMR group with higher incidences of AEs (237.35 vs 208.93), drug-related AEs (138.43 vs 110.97), dose modification due to an AE (39.35 vs 31.8), dose interruption due to an AE (22.12 vs 17.18), and dose reduction due to an AE (15.94 vs 11.81). When adjusted for exposure, the observed event rates of AEOSI for dMMR participants were generally similar to the observed event rates for pMMR participants.

In study KEYNOTE-158, the median duration of exposure to pembrolizumab was more than double for those in the MSI-H/dMMR group compared with the non-MSI-H/pMMR group (9.3 months vs 3.42 months). The overall incidence of AEs in participants in both groups was similar. The safety was generally consistent between the MSI-H and non-MSI-H groups except for a higher incidence of drug-related AEs in the MSI-H group (75.6% vs 63.3%) and of fatal AEs (3.3% vs 0%). However, when adjusted for exposure, the overall toxicity profile was worst for the non-MSI-H/pMMR group compared to the MSI-H/dMMR group with higher incidences of AEs (142.73 vs 104.11), drug-related AEs (37.46 vs 30.46), Grade 3 to 5 AEs (19.88 vs 9.74), SAEs (11.36 vs 5.21), and of fatal AEs (0.53 vs 0). For AEOSI, overall, the incidence of the Grade 3 to 5 AEs, dose modifications and deaths due to an AE, including drug-related AEs were similar between the 2 groups. However, a lower incidence was observed in the non-MSI-H/pMMR group compared with the MSI-H/dMMR group for the AEOSI (17.8% vs 27.8%), drug-related AEOSI (15.6% vs 25.6%) and SAEs (2.2% vs 4.4%). When adjusted for exposure, the incidence of Grade 3 to 5 AEOSI was higher in the non-MSI-H/pMMR group (1.24 vs 0.58) otherwise the safety was consistent between groups. There was a limited number of participants in both groups (90 each); therefore, the data should be interpreted with caution. The observed differences in the safety profile of lenvatinib plus pembrolizumab between dMMR and pMMR participants might not be clinically meaningful.

Intrinsic and extrinsic factors

The safety findings in the lenvatinib plus pembrolizumab EC group based on age, gender, ECOG performance status, and region were generally consistent with the established safety profiles of lenvatinib and pembrolizumab monotherapy.

In the lenvatinib plus pembrolizumab EC group in Study 309/KEYNOTE-775, the safety profile was generally similar for participants <65 and ≥65 year-of-age. However, the incidence of interruption of lenvatinib due to an AE, discontinuation of lenvatinib due to an AE or a drug-related AE, were higher in the older participants (similarly to the lenvatinib plus pembrolizumab non-EC group and lenvatinib monotherapy group). Moreover, the safety profile was generally similar for participants <65, 65-74 years, and ≥75 years. More participants in the ≥75 years of age group experienced drug-related SAEs, deaths, and discontinuation of lenvatinib (which was similar to the lenvatinib plus pembrolizumab non-EC group and lenvatinib monotherapy group). However, conclusions are limited due to the small number of participants in the ≥75 years of age group (i.e. 35 in the lenvatinib plus pembrolizumab EC group in Study 309/KEYNOTE-775).

In the lenvatinib plus pembrolizumab EC group in Study 309/KEYNOTE-775, central nervous system (confusion / extrapyramidal) AEs, AEs related to falling, cardiovascular events, and infections were

generally similar amongst the <65, 65-74, and ≥75 age groups. However, cerebrovascular events increased considerably with age: <65 (2%), 65-74 (3.6%), and >75 (11.4%). Arterial thromboembolic events (ATEs) (including cerebrovascular events) is a risk identified in section 4.4 of the SmPC and an important identified risk in the RMP where it is mentioned that risk factors associated with thromboembolic events in addition to the underlying malignant disease include age ≥65 years.

Table of AEs by grade and by age categories (<65, 65-74, and ≥75 age groups) for the 2 groups in Study 309/KEYNOTE-775 was provided. The most frequent AEs in the Lenvatinib plus pembrolizumab group in the oldest age group were (≥ 30% and with higher frequency in oldest group): anaemia (all grade: 27.3%, 22.9%, 34.3%; respectively), UTI (all grade: 22.0%, 28.3%, 34.4%), and hypertension (≥ Grade 3: 33.2%, 42.2%, 45.7%). The SmPC section 4.8 (special populations) has been adapted accordingly (for UTI and ≥ Grade 3 hypertension).

The AE summary has also been provided by age categories (i.e. <75 and ≥75 years) for the following datasets: Study 309/KEYNOTE-775 lenvatinib plus pembrolizumab EC group and the TPC EC group; Study 309/KEYNOTE-775 + KEYNOTE-146 + KEYNOTE-581 Lenvatinib + Pembrolizumab across indications; Lenvatinib monotherapy safety dataset; and Pembrolizumab Monotherapy RSD. As there is a limited number of participants ≥75 years of age in the pembrolizumab + lenvatinib group (n=35) and TPC group (n=39) from Study 309/KEYNOTE-775 and the pooled Study 309/KEYNOTE-775 + KEYNOTE-146 + KEYNOTE-581 pembrolizumab + lenvatinib group (n=115), the data should be interpreted with caution. The observed incidence rates of the AE categories of the Study 309/KEYNOTE-775 lenvatinib+pembrolizumab group were generally similar in the <75 and ≥75 age groups, however higher rate were observed for the elderly for: drug-related SAEs, deaths, deaths due to a drug-related AE, and discontinuations due to AE. However, as a similar pattern was generally observed between the age groups in all datasets, this does not suggest a new safety concern for pembrolizumab + lenvatinib across age groups.

All participants in the lenvatinib plus pembrolizumab EC group were female. The AE profile based on gender in the lenvatinib plus pembrolizumab EC group was generally consistent with the safety profiles of females treated with lenvatinib or pembrolizumab monotherapy.

In the lenvatinib plus pembrolizumab EC group in Study 309/KEYNOTE-775, there were 60.1% of participants with ECOG performance status of 0 and 39.9% participants with ECOG of 1. In each group, the safety profiles were in generally consistent between participants with ECOG of 0 or 1. However, the incidence of SAEs, fatal AEs, and drug-related fatal AEs were increased in the participants with ECOG of 1.

In the lenvatinib plus pembrolizumab EC group in Study 309/KEYNOTE-775, there were 28.1% of participants from EU regions and 71.9% participants not from EU regions. In each group, the safety profiles were in generally consistent between participants from EU or not. However, lenvatinib plus pembrolizumab EC group and lenvatinib plus pembrolizumab non-EC group presented higher incidence of dose reduction of lenvatinib due to AEs in the participants not from EU (difference not observed in the lenvatinib monotherapy group).

Table of the frequencies of AEs by grade and by ethnicity for the 2 groups in Study 309/KEYNOTE-775 was provided. There was a limited number of participants in the lenvatinib plus pembrolizumab and TPC treatment groups who were Asian (n=85 and n=86, respectively) or from other ethnicity (n=29 and n=34, respectively); therefore, the data should be interpreted with caution. The incidences and severity of the most frequently reported AEs (incidence ≥15%) in the lenvatinib plus pembrolizumab group were generally similar between the different categories with the following differences (≥10% difference) noted:

- AEs higher in Whites than Asians: mucosal inflammation (14.1% vs 1.2%), abdominal pain (23.0% vs 8.2%), UTI (29.7% vs 12.9%), diarrhoea (57.4% vs 47.1%; Grade ≥3: 7.4% vs 10.6%), weight decreased (37.1% vs 27.1%), hypomagnesaemia (21.5% vs 4.7%), dizziness (13.7% vs 1.2%), asthenia (27.3% vs 3.5%; Grade ≥3: 7.4% vs 0%), and fatigue (39.1% vs 17.6%)
- AEs higher in Asians than Whites: anaemia (34.1% vs 23.4%; Grade ≥3: 10.6 % vs 4.3%), malaise (23.5% vs 0.8%), oedema (12.9% vs 2.3%), neutrophil count decrease (16.5% vs 2%; Grade ≥3: 9.4% vs 0.4%), stomatitis (37.6% vs 14.1%), platelet count decreased (32.9% vs 7.0%, Grade ≥3: 10.6% vs 0.8%), proteinuria (51.8% vs 22.3%; Grade ≥3: 10.6% vs 3.9%), PPE (40.0% vs 13.3%; Grade ≥3: 5.9% vs 2.0%), and pyrexia (31.8% vs 10.5%)

All AEs are ADRs for the combination with the exception of pyrexia and oedema (as shown in ADR table in section 4.8 of the SmPC), which were reported as primarily Grade 1 or 2 events. The SmPC section 4.8 (ethnic origin) has been adapted accordingly**.**

As of the data cut-off, there were no reports of pregnancy in the lenvatinib plus pembrolizumab EC group.

Data received after initial assessment

Fifty-two AEs for 6 clinical study participants enrolled at a single study center started prior to the data cut-off for interim analysis 1 (IA1) (data cut-off 26 October 2020) of Study 309/KEYNOTE-775, but were not entered into the database at the time of the database lock (20 November 2020) that was used to support the CSR and eCTD summary modules in the extension of indication submission.

These AEs were identified by site monitors and entered retrospectively into the database prior to the next database lock performed to provide data for the 90-day Safety Update Report (SUR). This 90-day SUR includes additional safety data reported between the IA1 data cutoff of 26-Oct-2020 and the SUR data cutoff of 08 February 2021 (database lock on 22 March 2021), representing an additional 3.5 months of safety data from Study 309/KEYNOTE-775 (SUR not submitted).

The main contributing factors for this GCP deviation were incomplete documentation with subsequent late entry of safety data by the site and insufficient oversight by the Principal Investigator (enhanced by the COVID-19 pandemic). Corrective / preventive actions have been implemented.

None of these AEs were fatal AEs or SAEs. Out of these 52 AEs, there were:

- 31 AEs in 2 subjects in the combination group: mainly grade 1 or 2, with 1 Grade 3 hypertension and 1 Grade 4 lipase elevation, both assessed per investigator as related to Lenvatinib.
- 21 AEs in 4 subjects in the chemotherapy group: mainly grade 1 or 2, with 1 Grade 3 vomiting related to doxorubicin.

No new safety signals were identified and safety was consistent with that reported in the initial CSR. These additional 52 AEs are not impacting the previous benefit/risk assessment (+0.34% in the combination arm vs +0.46% in the TPC arm), and the additional 3.5 months data (after IA1) will be submitted after marketing authorisation during the pharmacovigilance follow-up.

2.5.2. Conclusions on clinical safety

The safety profile of lenvatinib+pembrolizumab combination for treatment of advanced EC in patients who have disease progression following prior platinum-based systemic therapy in any setting and are not candidates for curative surgery or radiation was not substantially different from that of standard

chemotherapy based on physician's choice, although with different types of AEs as expected from the different class of drugs.

The apparent worse safety profile of lenvatinib+pembrolizumab for most AEs and drug-related AEs was partially reverted at exposure-adjusted incidence analysis showing slightly lower rates with the treatment of interest as compared to chemotherapy, while SAEs and deaths did not differ between groups. Dose interruptions and treatment discontinuations (mostly related to lenvatinib) occurred however more frequently in the lenvatinib+pembrolizumab arm than in controls, also when adjusted for exposure.

Well-known safety concerns associated with lenvatinib (CSAEs) and with pembrolizumab (AEOSIs) (especially the latter) were more common with the combination treatment than with the single-drug regimens, which is in line with the safety pattern found for non-EC indications of lenvatinib+pembrolizumab treatment. Most of these AEs presented with the expected severity and were managed following consolidated indications.

No new safety concerns were identified.

Overall, IV pembrolizumab 200 mg Q3W in combination with oral lenvatinib 20 mg QD showed a manageable safety profile in the advanced endometrial carcinoma population that is generally consistent with the established safety profiles of the individual pembrolizumab and lenvatinib monotherapies, and the safety profile of the combination in non-EC.

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 CHMP endorsed the Risk Management Plan version 14.1 with the following content:

Safety concerns

Table 71: Summary of the safety concerns

Important identified risks	• Proteinuria and nephrotic syndrome • Renal failure or impairment • Cardiac failure • Posterior reversible encephalopathy syndrome (PRES) • Hepatotoxicity • Haemorrhagic events • Arterial thromboembolic events (ATEs) • QTc prolongation • Hypothyroidism • Gastrointestinal perforation and fistula formation

	• Non-gastrointestinal fistula formation (any fistula which does not involve the stomach or intestine) and pneumothorax
Important potential risks	• Venous thromboembolic events (VTEs) • Abnormal pregnancy outcome, excretion of lenvatinib in milk • Male and female fertility • Bone and teeth abnormalities in the paediatric population • Impaired wound healing • Interstitial Lung Disease (ILD)-like conditions • Overdose (concomitant everolimus) (RCC)
Missing information	• Use in severe hepatic impairment • Use in severe renal impairment • Long-term use

No new safety concerns were identified as part of this extension of indication in advanced endometrial cancer.

Pharmacovigilance plan

Table 72: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones** (required by regulators)	**Due dates**
Category 3 - **Required additional pharmacovigilance activities**				
RCC				
Study 307 Ongoing	Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in combination with Everolimus or Pembrolizumab Versus Sunitinib Alone in First-Line Treatment of Subjects with Advanced Unresectable RCC.	- all important identified and potential risks - continue to characterise/confirm the current safety profile of lenvatinib in combination with everolimus in advanced RCC	The protocol and the data analysis plan for PK/PD should be submitted: Updated protocol: Final report submission:	30 Nov 2016 10 Sep 2019 13 Aug 2021

Table 72: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones (required by regulators)	Due dates
HCC				
Study E7080-M000-508 (Observational Clinical Study: Category 3)	To characterise hepatic-related toxicity and overall safety profile (SAEs, Grade 3-5 AEs, dose modifications, and discontinuations due to AEs) in real-life conditions in the EU (Western population) in HCC patients, including patients with Child-Pugh B. Overall survival data and detailed baseline characteristics will also be collected.	Hepatotoxicity in HCC patients	Protocol submitted on: Final report submission:	22 Apr 2020 Dec 2029

No new additional pharmacovigilance activities were identified as a result of this extension of indication in advanced endometrial cancer

Risk minimisation measures

Table 73: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Identified Risks		
Proteinuria and Nephrotic Syndrome	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC sections 4.2 and 4.4 where advice on monitoring urine protein and managing proteinuria or nephrotic syndrome is provided. • PL section 4	Additional pharmacovigilance activities: Study 307.
Renal failure or impairment	Routine risk minimisation measures: • SmPC Section 4.8	Additional pharmacovigilance activities: Study 307.

Table 73: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• SmPC Sections 4.2 and 4.4 where advice on managing risk factors and managing renal failure or impairment is provided • PL section 4	
Cardiac failure	Routine risk minimisation measures: • SmPC section 4.8 • SmPC Sections 4.2 and 4.4 where advice on monitoring patients and managing cardiac failure is provided. • PL section 4	Additional pharmacovigilance activities: Study 307.
Posterior reversible encephalopathy syndrome (PRES)	Routine risk minimisation measures: • SmPC Section 4.4 and 4.8 • PL section 4	Additional pharmacovigilance activities: Study 307.
Hepatotoxicity	Routine risk minimisation measures: • SmPC section 4.8 • SmPC Sections 4.2 and 4.4 where advice on monitoring liver function and managing hepatotoxicity is provided. • PL section 4	Additional pharmacovigilance activities: Studies 307, 508.
Haemorrhagic events	Routine risk minimisation measures: • SmPC Sections 4.4 and 4.8 • PL section 4	Additional pharmacovigilance activities: Study 307.
Arterial thromboembolic events (ATEs)	Routine risk minimisation measures: • SmPC section 4.8 • SmPC section 4.4 where advice to discontinue in case of ATE is given • PL section 4	Additional pharmacovigilance activities: Study 307.
QTc prolongation	Routine risk minimisation measures: • SmPC section 4.8	Additional pharmacovigilance activities: Study 307.

Table 73: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• SmPC Sections 4.2 and 4.4 where advice on monitoring electrolytes and managing QT interval prolongation is provided • PL section 4	
Hypothyroidism	Routine risk minimisation measures: • SmPC section 4.8 • SmPC section 4.4 where advice on monitoring thyroid function is given • PL section 4	Additional pharmacovigilance activities: Study 307.
Gastrointestinal perforation and fistula formation	Routine risk minimisation measures: • SmPC sections 4.4 and 4.8 • Sections 4.2 where recommendations for dose modifications/ withdrawal are provided • PL section 4	Additional pharmacovigilance activities: Study 307.
Non-gastrointestinal fistula formation and Pneumothorax	Routine risk minimisation measures: • SmPC section 4.8 • SmPC section 4.4 where advice that lenvatinib should not be started in patients with fistulae and when to permanently discontinue lenvatinib is given • PL section 4	Additional pharmacovigilance activities: Study 307.
Potential Risks		
Venous thromboembolic events (VTEs)	Routine risk minimisation measures: • SmPC section 4.8 • PL section 4	Additional pharmacovigilance activities: Study 307.
Abnormal pregnancy outcome, excretion in breast milk	Routine risk minimisation measures: • SmPC section 4.6 • PL section 2	Additional pharmacovigilance activities: None
Male and female fertility	Routine risk minimisation measures: • SmPC section 4.6	Additional pharmacovigilance activities:

Table 73: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		None
Bone and teeth abnormalities in the paediatric population	Routine risk minimisation measures: • SmPC section 5.3	Additional pharmacovigilance activities: Study 207
Impaired wound healing	No risk minimization measures are recommended at present as there is insufficient clinical evidence to establish this as an identified risk. The need for risk minimization measures will be revisited on review of pharmacovigilance data. Prescription only medicine.	Additional pharmacovigilance activities: Study 307.
Interstitial lung disease (ILD)¬like conditions	Not applicable	Additional pharmacovigilance activities: Study 307.
Overdose (concomitant everolimus)	Routine risk minimisation measures: • SmPC section 4.2 • PL section 2	Additional pharmacovigilance activities: None
Missing information		
Use in severe hepatic impairment	Routine risk minimisation measures: • SmPC section 4.2 • PL section 2	None
Use in severe renal impairment	Routine risk minimisation measures: • SmPC section 4.2 • PL section 2	None
Long-term use	Not applicable	Additional pharmacovigilance activities: None

No new additional risk minimisations activities were identified as a result of this extension of indication in advanced endometrial cancer.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s), which were reviewed and accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative(s) of Bulgaria, Estonia, Croatia, Latvia, Lithuania, Hungary, Malta, Poland, Romania, Slovenia, United Kingdom (Northern Ireland).

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 applicant and has been found acceptable for the following reasons: The proposed changes in the context of this extension of indication do not involve a relevant impact on the PIL.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The MAH applied for an extension of indication for lenvatinib in combination with pembrolizumab in second line endometrial carcinoma patients:

"LENVIMA in combination with pembrolizumab is indicated for the treatment of adult patients with advanced endometrial carcinoma (EC) who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation (see section 5.1)".

During the procedure, the indication was updated as follows:

- LENVIMA, in combination with lenvatinib, is indicated for the treatment of advanced **or recurrent** endometrial carcinoma in adults who have disease progression **on or** following prior **treatment with a platinum-containing** ~~systemic~~ therapy in any setting and who are not candidates for curative surgery or radiation ~~(see section 5.1).~~

3.1.1. Disease or condition

Endometrial cancer is the sixth most common cancer among women worldwide[1] and the most common gynaecological cancer in developed countries, with a median age at diagnosis of 63 years. Adenocarcinoma of the endometrium is typically divided in type I (70-80%) which include the less aggressive endometrioid histology, and type II (20-30%) comprising non-endometrioid histologies, having poorer prognosis[2]. Microsatellite unstable tumours (MSI-H) is one of the four clinically significant molecular subtypes of endometrial cancer with different clinical prognoses[3].

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394-424.
[2] Tran AQ, Gehrig P. Recent advances in endometrial cancer. F1000Res. 2017 Jan 27;6(F1000 Faculty Rev):81.
[3] The Cancer Genome Atlas (TCGA) Research Network; Kandoth C, Schultz N, Cherniack AD, et al. Integrated genomic characterization of endometrial carcinoma. Nature 2013;497:67-73.

Most of endometrial cancer patients are diagnosed when disease is localized, and the prognosis for EC is significantly influenced by disease stage. Patients with regional and distant metastatic disease have 5-year survival rates of 69% and 16.8%, respectively[4]. Approximately 20% of EC cases recur with poor prognosis[5]. In general, the median survival of patients with recurrent or advanced disease is 12 months[6].

3.1.2. Available therapies and unmet medical need

Currently, the mainstay of treatment of EC is surgery with hysterectomy and bilateral salpingo-oophorectomy; based on the risk stratification, adjuvant treatment radiotherapy and/or chemotherapy are used[7]. Hormonal therapy can be used as systemic treatment for front-line hormone receptor-positive grade 1 or 2 tumours in the absence of rapidly progressive disease[37]. Endometrial cancer is a relatively chemo-sensitive disease, with anthracyclines, platinum-based drugs and taxanes shown to be the most active agents. For patients with advanced disease not amenable to radical treatment, according to ESMO guidelines, the standard of care is carboplatin and paclitaxel as first line treatment[37]. Cytotoxic chemotherapy as second-line treatment after platinum-containing therapy is supported by limited evidence, especially with treatment-free interval following first-line chemotherapy <6–12 months, and it is generally associated with low response rates (≤ 15%), limited PFS (4 months), and toxicity[8].

In the EU, the anti-PD1 antibody Jemperli (dostarlimab) has been approved in 2021 for the treatment of adult patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen.

Reported median PFS of <4 months reflects the rapid disease progression of advanced EC, and the need for therapeutics to control disease soon after treatment initiation. Advanced EC patients often have substantial morbidity from prior therapy (surgery, radiation, platinum-based chemotherapy) or their disease, which often includes intraabdominal involvement that can lead to debilitating ascites, bowel obstruction, fistula, and perforation. Therefore, rapid disease control of advanced EC is essential to both maintain QoL and prolong survival in these patients.

3.1.3. Main clinical studies

Study-309/KEYNOTE-775 is a multicenter, open-label, randomized 1:1, Phase 3 trial to compare the efficacy and safety of lenvatinib in combination with pembrolizumab versus treatment of physician's choice (paclitaxel or doxorubicin) in participants with advanced endometrial cancer (EC) progressed after prior platinum-based therapy. The results of the Interim Analysis 1 (i.e. final for PFS, interim for OS) with data cut-off date 26 October 2020 have been submitted. The median duration of follow up in the overall population is 11.4 months (range 0.3, 26.9).

[4] National Cancer Institute. Bethesda (MD): National Cancer Institute. 2019. SEER cancer stat facts: uterine cancer. Available from: https://seer.cancer.gov/statfacts/html/corp.html.
[5] Suhaimi SS, Ab Mutalib NS, Jamal R. Understanding molecular landscape of endometrial cancer through next generation sequencing: what we have learned so far? Front Pharmacol. 2016 Nov 1;7:409.
[6]Makker V, Green AK, Wenham RM, Mutch D, Davidson B, Miller DS. New therapies for advanced, recurrent, and metastatic endometrial cancers. Gynecol Oncol Res Pract. 2017 Dec 2;4:19.
[7] N. Colombo, C. Creutzberg, F. Amant, T. Bosse, et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer. Ann Oncol 2016; 27: 16-41.

[8] McMeekin S, Dizon D, Barter J, Scambia G, Lisyanskaya A, OaKEYNOTEin A, et al. Phase III randomized trial of second-line ixabepilone versus paclitaxel or doxorubicin in women with advanced endometrial cancer. Gynecol Oncol. 2015 Jul;138(1):18-23.

3.2. Favourable effects

- Study-309/KEYNOTE-755 showed a statistically significant and clinically relevant PFS benefit of lenvatinib+pembrolizumab versus standard chemotherapy in all comers (HR 0.56, 95%CI 0.47, 0.66, p>0.0001 one-sided, median PFS 7.2 vs 3.8 months) and in pMMR primary populations (HR 0.60, 95%CI 0.50, 0.72, p<0.0001 one-sided, median PFS 6.6 vs 3.8 months) at the final PFS analysis.
- A statistically significant and clinically relevant benefit of lenvatinib+pembrolizumab versus chemotherapy was shown in OS in all comers (HR 0.62, 95%CI 0.51, 0.75, p<0.0001 one-sided, median OS 18.3 versus 11.4 months) and in pMMR (HR 0.68, 95%CI 0.56, 0.84, p=0.0001 one-sided, median OS from 17.4 versus 12 month) at the interim OS analysis, with about 50% of patients with a death event. OS curves overlap up to month 3 and remained consistently separated throughout the duration of the evaluation period. All p-values are one sided.
- ORR improvement was seen for lenvatinib+pembrolizumab versus chemotherapy in all comers [31.9% (27.4, 36.6), versus 14.7% (11.4, 18.4)] as well as in pMMR population [30.3% (25.5, 35.5) versus 15.1% (11.5, 19.3)]. CR rates were also higher for the combination.
- In the all comers, the median DOR was longer in the experimental arm (14.4 vs 5.7 months), with higher number of durable responses (71.9% versus 42.6% of responding subjects for ≥6 months). The same trend was observed in the pMMR subgroup (median DOR 9.2 versus 5.7 months, durable responses lasting ≥6 months 65.6% versus 42.1%).
- Consistent treatment effect across all main subgroups analysed.
- The benefit of the combination is also observed in the smaller dMMR subgroup (not formally tested), where efficacy of the combination appears higher compared to what observed in the pMMR population (PFS HR 0.36, OS HR 0.37, ORR 40% versus 12.3%, CR 13.8% versus 3.1%, median DOR NR versus 4.1 months).

3.3. Uncertainties and limitations about favourable effects

- The population of Study 309/ KEYNOTE-775 possibly reflects a fitter subgroup of subjects with advanced endometrial carcinoma in terms of ECOG and comorbidities, and it might not be fully representative of an endometrial cancer population with generally dismal prognosis. The exclusion of patients with ECOG ≥2 from clinical studies is mentioned in section 4.4 of the SmPC and also reflected in the description of Study 309- KEYNOTE-775 study in section 5.1 of the SmPC.

- Lack of direct comparison of the combination with each monotherapy, especially with pembrolizumab monotherapy relative to the dMMR subgroup. Results by MMR subgroup have been reflected in section 5.1 of the SmPC. Data on indirect comparison in the dMMR population are reflected in this assessment report.

- No data on PD-L1 status have been collected in Study 309/KEYNOTE-775 and consequently no subgroup analyses by PD-L1 expression have been conducted.

- OS data is not fully mature yet and this limits the efficacy estimation at this moment. The MAH is recommended to submit the results from the final OS analysis in the overall population and by MMR biomarker by Q4 2022.

3.4. Unfavourable effects

Compared to standard chemotherapy, lenvatinib+pembrolizumab displayed a worse safety profile, as shown by higher proportions of subjects with drug-related AEs (97.3% versus 93.8%, respectively), Grade 3-5 drug-related AEs (77.8% versus 59%), drug-related SAEs (33.3% versus 14.2%), who had dose interruption of any drug due to an AE (69.2% versus 27.1%) or who discontinued any drug due to an AE (33% versus 8%). Proportions of fatal events and drug-related fatal events were comparable across study arms.

When evaluating exposure-adjusted incidence rates per 100 person-months, a partially reversed safety picture is found: AEs 232 versus 256, drug-related AEs 133 versus 153, Grade 3-5 AEs 31.02 versus 48.78, drug-related Grade 3-5 AEs 18.52 versus 34.5, and fatal events 0.59 versus 1.08. For SAEs (10.15 and 10.08 per 100 person-months in the combination arm and controls, respectively), drug-related SAEs (5.15 and 4.08), and deaths due to drug-related AE (0.15 and 0.45) the incidence rate of events was comparable across study arms. However, the proportion of subjects with dose modification (37.9 versus 18.6 per 100 person-months), dose interruption (21.18 versus 11.5), dose reduction (15.16 versus 4.76), and discontinuation due to AE (5 versus 2.32), to a drug-related AEs (3.98 versus. 1.76), to a SAEs (2.42 versus 0.85), or to a drug-related SAEs (1.63 versus 0.45), all remained higher in the study group of interest.

The most common AEs in the Study 309/KEYNOTE-775 lenvatinib+pembrolizumab group were: hypertension (64%), hypothyroidism (57.4%), diarrhoea (54.2%), nausea (49.5%), decreased appetite (44.8%), vomiting (36.7%), weight decreased (34%), fatigue (33%), arthralgia (30.5%).

The well-known safety concerns associated with pembrolizumab (AEOSIs) were reported in 67.2% of Study 309/KEYNOTE-775 combination arm participants, and in 25.1% pembrolizumab monotherapy RSD subjects. Most often reported AEOSIs were hypothyroidism (57.6%), hyperthyroidism (11.6%), and colitis (4.7%).

The frequency and severity of CSAEs in the Study 309/KEYNOTE-775 lenvatinib+pembrolizumab group was generally consistent with those found in the non-EC lenvatinib plus pembrolizumab group and the lenvatinib monotherapy SD, with the exception of the CSAEs of hepatotoxicity (33.7% versus 17.5% and 19.6%, respectively), hypothyroidism (68.2% versus 19.8% and 43.5%), and renal events (18.2% versus 10.0% and 18.7%). Most CSAEs resolved, and only few resulted in treatment discontinuation.

3.5. Uncertainties and limitations about unfavourable effects

More participants in the ≥75 years of age group experienced drug-related SAEs, deaths, and discontinuation of lenvatinib compared to the other age categories (which was similar to the lenvatinib plus pembrolizumab non-EC group and lenvatinib monotherapy group). However, conclusions are limited due to the small number of participants in the ≥75 years of age group (i.e. 35 in the lenvatinib plus pembrolizumab EC group in Study 309/KEYNOTE775). Section 4.8 of the SmPC was updated to reflect that patients of age ≥75 years were more likely to experience some adverse reactions. Furthermore, reduced tolerability of lenvatinib in elderly patients is also mentioned in section 4.4 of the SmPC.

The use in patients with severe hepatic impairment or with severe renal impairment, and long-term use safety remain a missing information as listed in the RMP and will continue to be mitigated by routine pharmacovigilance activities and routine risk minimisations measures.

3.6. Effects Table

Table 74: Effects Table for Lenvima in combination with pembrolizumab in advanced, recurrrent or metastatic Endometrial cancer adult patients progressed after platinum-based therapy (Study 309/KEYNOTE-775, data cut-off 26 Oct 2020, IA1)

Effect	Short description	Unit	Pembro+lenva (all comers n=411, pMMR n=346)	TPC (all comers n=416, pMMR n=351)	Uncertainties / Strength of evidence	Ref
Favourable Effects						
PFS (by BICR per RECIST 1.1)	Time from date of randomization to date of first documentation of disease progression, as determined by BICR per RECIST 1.1, or death from any cause (whichever occurred first)	*All comers*			PFS results statistically significant and clinically relevant in ITT and pMMR population / study subjects not fully representative of the target population; lack of direct comparison with monotherapy; similar activity in combo and pembrolizumab mono in dMMR population based on indirect comparison	CSR KEY NO TE-755
		months (95% CI)	7.2 (5.7, 7.6)	3.8 (3.6, 4.2)		
		HR 0.56 (0.47, 0.66) p<0.0001*				
		pMMR				
		months (95% CI)	6.6 (5.6, 7.4)	3.8 (3.6, 5)		
		HR 0.60 (0.5, 0.72) p<0.0001*				
OS	Time from date of randomization to date of death from any cause	*All comers*			OS results statistically significant and clinically relevant in ITT and pMMR population	CSR KEY NO TE-755
		months (95% CI)	18.3 (15.2, 20.5)	11.4 (10.5, 12.9)		
		HR 0.62 (0.51, 0.75) p<0.0001*				
		pMMR				
		months (95% CI)	17.4 (14.2, 19.9)	12 (10.8, 13.3)		
		HR 0.68 (0.56, 0.84) p=0.0001*				
ORR	Proportion of participants who have best overall response of either CR or PR, as determined by BICR per RECIST 1.1	*All comers*			ORR of the combination not outstanding but doubled compared to chemotherapy	CSR KEY NO TE-755
		% (95% CI)	31.9 (27.4, 36.6)	14.7 (11.4, 18.4)		
		pMMR				
		% (95% CI)	30.3 (25.5, 35.5)	15.1 (11.5, 19.3)		
Unfavourable Effects						
AE			**Lenvatinib+ pembro**	**TPC (n=388)**		CSR KEY

Effect	Short description	Unit	Pembro+lenva (all comers n=411, pMMR n=346)	TPC (all comers n=416, pMMR n=351)	Uncertainties / Strength of evidence	Ref
summary			**(n=406)**			NOTE-755
	Proportion					
	Drug-related AEs	%	97.3	93.8	The safety profile of lenvatinib+pembro resulted worse compared to standard chemotherapy	
	Drug-related Grade 3-5 AEs	%	77.8	59.0		
	Drug-related SAEs	%	33.3	14.2		
	Fatal AEs	%	5.7	4.7		
	Discontinuation of any drug due to AE	%	33.0	8.0		
	Exposure-adj. incidence					
	Drug-related AEs	X 100 p-m	133	153	Exposure-adjusted incidence rates only partially revert the safety findings	
	Drug-related Grade 3-5 AEs	X 100 p-m	18.52	34.5		
	Drug-related SAEs	X 100 p-m	5.15	4.08		
	Fatal AEs	X 100 p-m	0.59	1.08		
	Discontinuation of any drug due to AE	X 100 p-m	5.0	2.32		
			Lenvatinib+pembro (n=406)			
ADR			All Grades	Grade ≥3		
	Hypertension	%	63	37.2		
	diarrhoea	%	57	8.1		
	Hypothyroidism	%	56			

Notes: p-values are one-sided

3.7. Benefit-risk assessment and discussion

3.8. Importance of favourable and unfavourable effects

In Study-309/KEYNOTE-775 a statistically significant and clinically meaningful advantage was shown on PFS and OS outcomes for the combination pembrolizumab + lenvatinib as compared to standard chemotherapy (doxorubicin or paclitaxel, TPC) in the setting with dismal prognosis of advanced endometrial cancer patients progressed to at least one prior platinum-based therapy not amenable for curative treatment. ORR for the combination was not outstanding but was doubled compared to the

standard treatment. These results were however obtained in a trial population apparently more fit and with less comorbidities compared to the target population, restricted to patients with ECOG 0-1. The benefit of the combination over TPC was shown in the all comers as well as in the pMMR population (populations for the primary analyses) and was evident also in the dMMR subgroup. However, the design of the study lacking monotherapy arms hampers the assessment of the contribution of each component to the combination, which has been supported with indirect comparison with pembrolizumab and lenvatinib single arm trials. Noting the limitations of cross trial comparison, added to some baseline differences in populations enrolled in these studies, it can be suggested that both pembrolizumab and lenvatinib, each having a limited activity in this setting separately, are contributing to the treatment effect in the combination regimen in pMMR EC population. On the contrary, in the dMMR subgroup the activity of the pembrolizumab + lenvatinib does not appear significantly different as compared to pembrolizumab alone, whilst lenvatinib adds toxicity. Overall, the combination appears indeed not particularly well tolerated, with higher rate of discontinuations due to adverse event compared to the chemotherapy arm. The safety profile of lenvatinib+pembrolizumab is different compared to chemotherapy, as expected, and consistent with the known safety profile of both drugs, with no new safety concern identified. In elderly individuals, for pembrolizumab an increased toxicity for several AE categories (drug-related grade 3-5 AEs, drug-related SAE, death due to AE, discontinuation due to AE) is noted when the drug is administered in combination with lenvatinib as compared to pembrolizumab monotherapy.

3.8.1. Balance of benefits and risks

The combination of lenvatinib plus pembrolizumab represents an effective treatment with a manageable safety profile and is a valuable treatment option for the population of patients with second line recurrent or advanced EC as compared to standard chemotherapy. A clinical benefit of lenvatinib in combination with pembrolizumab was shown over the chemotherapy options for participants with advanced EC in the overall population. The safety profile of lenvatinib+pembrolizumab combination is different compared to chemotherapy, as expected, and consistent with the known safety profile of both drugs, with no new safety concern identified, although the combination overall appears not to be particularly well tolerated.

3.8.2. Additional considerations on the benefit-risk balance

None.

3.9. Conclusions

The overall B/R of lenvatinib in combination with pembrolizumab after treatment with platinum-based therapy is positive.

The following measure is considered necessary to address issues to address issues related to efficacy:

Final OS data of 309/KEYNOTE-775 in overall population and by MMR biomarker should be submitted as a recommendation (expected in 4Q2022).

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, II and IIIB

Extension of indication to include lenvatinib in combination with pembrolizumab for the treatment of adult patients with advanced endometrial carcinoma (EC) who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 14.1 of the RMP has also been agreed. In addition, the MAH took the opportunity to make minor editorial changes to the SmPC, Annex II and to update the list of local representatives in the Package Leaflet in line with the latest QRD template version 10.2.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II and IIIB and to the Risk Management Plan are recommended.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.

5. 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 'Lenvima H/C/003727/II/0042'