14 October 2021
EMA/617606/2021
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Keytruda

International non-proprietary name: pembrolizumab

Procedure No. EMEA/H/C/003820/II/0105

## Note

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

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# List of abbreviations

| Abbreviation | Definition |
|---|---|
| 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 |

| Abbreviation | Definition |
|---|---|
| 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/MSD Study number KEYNOTE-146 |
| Study 309/KEYNOTE-775 | Eisai study number E7080-G000-309/MSD 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, Merck Sharp & Dohme B.V. 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 pembrolizumab in combination with lenvatinib for the treatment of advanced endometrial carcinoma in adults who have disease progression following prior systemic therapy in any setting and who 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 33.1 of the RMP has also been submitted.

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

## *Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0043/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0043/2018 was completed.

The PDCO issued an opinion on compliance for the PIP P/0043/2018.

## *Information relating to orphan market exclusivity*

## Similarity

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

## *Scientific advice*

The MAH did not seek Scientific Advice at the CHMP. CHMP scientific advice was obtained by Eisai Limited on the study design of the pivotal Study 309/KEYNOTE-775 on 09-NOV-2017.

### *1.2. Steps taken for the assessment of the product*

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

Rapporteur: Armando Genazzani

| Timetable | Actual dates |
|---|---|
| Submission date | 10 March 2021 |
| Start of procedure: | 27 March 2021 |
| CHMP Rapporteur Assessment Report | 28 May 2021 |
| PRAC Rapporteur Assessment Report | 31 May 2021 |
| PRAC Outcome | 10 June 2021 |
| CHMP members comments | 14 June 2021 |
| Updated CHMP Rapporteur(s) (Joint) Assessment Report | 17 June 2021 |
| Request for supplementary information (RSI) | 24 June 2021 |
| CHMP Rapporteur Assessment Report | 23 Aug 2021 |
| CHMP members comments | 06 Sept 2021 |
| Updated CHMP Rapporteur Assessment Report | 10 Sept 2021 |
| RSI | 16 Sept 2021 |
| Rapporteur's preliminary assessment report circulated on: | 29 Sept 2021 |
| CHMP members comments | 04 Oct 2021 |
| Updated CHMP Rapporteur(s) (Joint) Assessment Report | 08 Oct 2021 |
| CHMP opinion: | 14 Oct 2021 |

# 2. Scientific discussion

### *2.1. Introduction*

The MAH is requesting an extension of indication for KEYTRUDA, in combination with lenvatinib, for the treatment of advanced endometrial carcinoma (EC) in adults following prior systemic therapy based on the pivotal phase III Study 309/KEYNOTE-775, supported by results of the Phase 1b/2 trial Study 111/KEYNOTE-146, and 3 additional Phase 2/1b trials (Study 204, KEYNOTE-158 and KEYNOTE-028) to provide context for understanding the contribution of components lenvatinib and pembrolizumab to the efficacy and safety of the combination.

## 2.1.1. Problem statement

### *Disease or condition*

Advanced endometrial carcinoma following progression to platinum-based chemotherapy.

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

"Keytruda in combination with lenvatinib 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 is as follows:

Endometrial carcinoma (EC)
Keytruda, 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 therapy in any setting and who are not candidates for curative surgery or radiation.

### *Epidemiology and risk factors*

Endometrial cancer is the sixth most common cancer among women worldwide[1] and the most common gynaecological cancer in developed countries. The estimated number of new cases and deaths from EC in 2018 were 121,600 and 26,000, respectively[2]. More than 90% of cases of endometrial cancer occur in women >50 years, with a median age at diagnosis of 63 years.

### *Biologic features, aetiology and pathogenesis*

Adenocarcinoma of the endometrium is the most common histologic type of uterine cancer, historically classified into two main clinico-pathological and molecular types: type I is more common (70-80%) and less aggressive composed by endometrioid histology, and type II comprises non-endometrioid subtypes (serous, clear-cell and undifferentiated carcinomas, carcinosarcoma/malignant-mixed Müllerian tumour), typically with poorer prognosis and not clearly associated with estrogen stimulation[3].

Four clinically significant molecular subtypes with differing clinical prognoses have been identified: (i) POLE (ultra-mutated)tumours, (ii) microsatellite unstable tumours (MSI-H), (iii) copy-number low (iv) copy number high[4].

EC is one of the cancers with a high observed rate of dMMR/MSI-H (average of approximately 34%). Microsatellite instability is a result of the inability of DNA mismatch repair enzymes to repair random mutations leading to tumorigenesis. Approximately 15% patients with previously treated EC have tumors that are MSI-H or dMMR[5].

Most patients with endometrial cancer have an identifiable source of excess oestrogen and typically display a characteristic clinical profile comprising a high body mass index, often with other components of metabolic

[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] Ferlay J, Colombet M, Soerjomataram I, Dyba T, Randi G, Bettio M, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries and 25 major cancers in 2018. Eur J Cancer. 2018;103:356-87.
[3] Tran AQ, Gehrig P. Recent advances in endometrial cancer. F1000Res. 2017 Jan 27;6(F1000 Faculty Rev):81.
[4] 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.
[5] Prendergast EN, Holman LL, Liu AY, Lai TS, Campos MP, Fahey JN, et al. Comprehensive genomic profiling of recurrent endometrial cancer: implications for selection of systemic therapy. Gynecol Oncol. 2019;154:461-6.

syndrome (e.g. hypertension, diabetes), correlating with good prognostic features of endometrial cancer, including low tumour grade, endometrioid histology and presentation at early stage[6]. Tumours associated with mismatch repair abnormalities and Lynch Syndrome appear to be distinct, with worse prognostic factors and worse clinical outcome[7]. Other risk factors for endometrial cancer include unopposed oestrogen therapy, oestrogen-producing tumours and early menarche/late menopause.

## *Clinical presentation, diagnosis and stage/prognosis*

Most of endometrial cancer patients have localized disease (67%), while 21% have regional disease, and approximately 9% have distant metastases. The prognosis for EC is significantly influenced by disease stage. 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[8]. Approximately 20% of EC cases recur with poor prognosis[9]. The population of patients with recurrent EC is heterogeneous in terms of histological subtypes and grades, stages at initial diagnosis, prior therapy, duration of recurrence-free intervals and sites of recurrence (distal or local)[10]. In general, the median survival of patients with recurrent or advanced disease is 12 months[11].

## *Management*

Treatment of EC may vary depending on the grade, histology, stage of the disease, and MSI/MMR status.

Currently, the mainstay of treatment of EC is surgery with hysterectomy and bilateral salpingo-oophorectomy; based on the risk stratification, adjuvant treatment including brachyterapy, external beam pelvic RT, and/or chemotherapy are used[12].

Patients with advanced disease (defined as bulky FIGO stage IIIA-IV), or recurrent disease should only be considered for surgery if it is anticipated that cytoreduction with no macroscopic residual disease can be achieved. RT can be used as a primary treatment in patients with unresectable disease, or where there are medical contraindications to surgery[14].

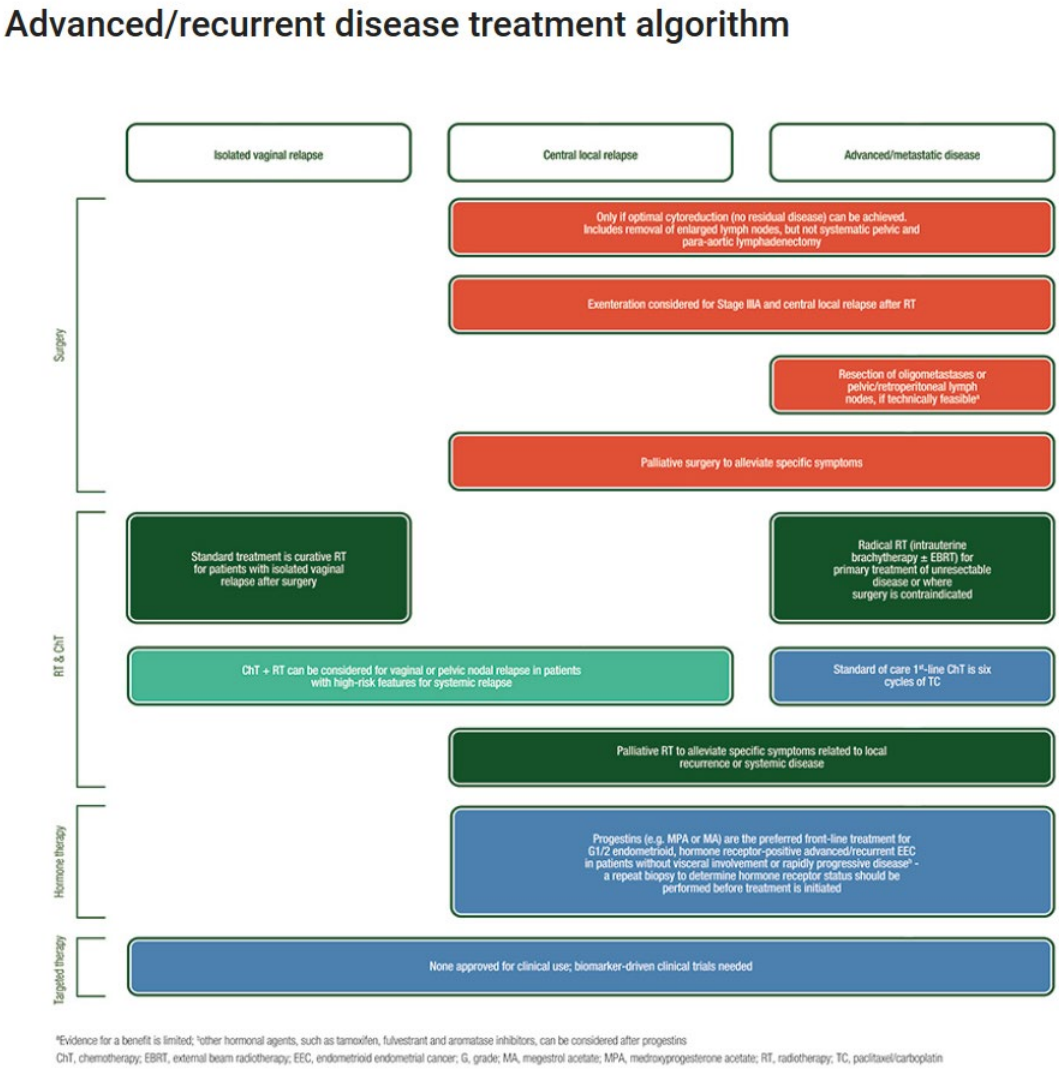
Hormonal therapy is indicated for patients with advanced or recurrent endometrial cancer and endometrioid histology. Response to hormonal therapy is quite variable, according to e.g. pathological factors, for example, hormonal therapy is more likely to be effective in grade 1 or 2 endometrioid tumours. Positivity of ER and/or PgR could be a predictive factor of response to endocrine therapy. Hormone therapy (progestogens are generally recommended) is the preferred 1L systemic treatment for front-line hormone receptor-positive grade 1 or 2 tumours in the absence of rapidly progressive disease[14].

Endometrial cancer is a relatively chemo-sensitive disease, with anthracyclines, platinum-based drugs and taxanes shown to be the most active agents. According to ESMO guidelines, the standard of care is carboplatin and paclitaxel as first line treatment[14]. Per NCCN guidelines, platinum-based chemotherapy is the standard first-line systemic therapy for patients with metastatic, recurrent, or high-risk disease[13].

[6] World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Report. Food, Nutrition, Physical Activity, and the Prevention of Endometrial Cancer. 2013;http://www.dietandcancerreport.org (2 April 2015, date last accessed).
[7] Garg K, Soslow RA. Endometrial carcinoma in women aged 40 years and younger. Arch Pathol Lab Med 2014; 138: 335–342.
[8] 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.
[9] 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.
[10] Obel JC, Friberg G, Fleming GF. Chemotherapy in endometrial cancer. Clin Adv Hematol Oncol. 2006 Jun;4(6):459-68.
[11]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.
[12] N. Colombo, C. Creutzberg, F. Amant, T. Bosse, et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer. Ann Oncol 2016; 27: 16-41.
[13] NCCN guidelines, Uterine neoplasm, v 3.2021

Evidence supporting the use of second-line chemotherapy after platinum-containing therapy in patients with endometrial cancer is limited, especially when the treatment-free interval following first-line chemotherapy is <6–12 months, and no specific regimen can be recommended as a 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[14].

Cytotoxic chemotherapy as second-line treatment for advanced EC is associated with low response rates ( $\leqslant$ 15%), limited PFS (4 months), and toxicity[14].




*(Table from eUpdate – Endometrial Cancer Algorithms Published: 8 June 2017. Authors: Colombo N, Creutzberg C, Querleu D, Barahona M and Sessa C, on behalf of the ESMO Guidelines Committee)*

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. In countries other than EU, pembrolizumab as monotherapy is approved for a selected subset of patients with MSI-H or dMMR solid tumors including those with EC.

[14] McMeekin S, Dizon D, Barter J, Scambia G, Lisyanskaya A, Oaknin 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.

Lenvatinib in combination with pembrolizumab received accelerated, conditional, or provisional approval in the US, Canada, and Australia for the treatment of patients with advanced EC that is not MSI-H or dMMR who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation, based on the results of the single-arm phase 1b/2 Study 111/KEYNOTE-146. On July 2021, FDA granted regular approval to pembrolizumab and lenvatinib for the above indication in patients that is not MSI-H or dMMR who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation, based on Study 309/KEYNOTE-775.

## 2.1.2. About the product

**Pembrolizumab** is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Keytruda potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment. Keytruda is approved in EU as monotherapy in melanoma, NSCLC, HNSCC, cHL, urothelial carcinoma, and colorectal cancer MSI-H. It is approved in combination with chemotherapy in NSCLC, HNSCC, oesophageal carcinoma and triple negative breast cancer. It is also approved in combination with a TKI (axitinib) in RCC.

**Lenvatinib** is a TKI active against both VEGFR (1,2,3,4) and FGFR (1,2,3,4). It 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 is known as LENVIMA, which is currently authorised as monotherapy for differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma and for hepatocellular carcinoma, and as KISPLYX, indicated in combination with everolimus for renal cell carcinoma.

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

The clinical development plan for the combination lenvatinib plus pembrolizumab advanced EC is summarized in the table below:

| Study | Design | Participant Population | Primary Endpoint(s) | Status |
|---|---|---|---|---|
| Study E7080-A001-111/<br>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.<br>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.<br>**Phase 2-Expansion:** ORR($Week_{24}$) | Ongoing |
| Study E7080-G000-309/<br>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<br>OS | Fully Enrolled Ongoing |
| Study E7080-G000-313/<br>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<br>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.

Scientific Advice was given by CHMP to Eisai Limited (MAH of lenvatinib) on the design of the pivotal Study 309/KEYNOTE-775 (EMEA/H/SA/1375/6/2017/II SA). CHMP generally agreed with the proposed study design. Main comments were the following:

- 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 Study 309/KEYNOTE-775 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 endpoints. Within this submission, both PFS and OS reached statistical significance at IA1.

- With regard to contribution of 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.

A presubmission meeting was held with the EMA and EU (Co)Rapporteurs for both lenvatinib and pembrolizumab on 03-FEB-2021, where results from Study 309/KEYNOTE-775 were presented and discussed in view of the planned Type II variation applications.

### 2.1.4. General comments on compliance with GCP

The MAH claimed that clinical trials were performed in accordance with GCP, and that trials carried out outside of the European Union meet the ethical requirements of Directive 2001/20/EC. The assessment of Study 309/KEYNOTE-775 data did not raise concern over GCP compliance leading to request for GCP inspection.

## *2.2. Non-clinical aspects*

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP (please refer to the EPAR for Keytruda procedure number EMA/H/C/003820/II/0104).

### 2.2.1. Ecotoxicity/environmental risk assessment

According to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00) proteins are exempted from the submission of ERA studies because they are unlikely to result in significant risk to the environment. Pembrolizumab is a protein, therefore an ERA has not been submitted. This is considered acceptable.

### 2.2.2. Conclusion on the non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP (please refer to the EPAR for Keytruda procedure number EMA/H/C/003820/II/0104).

## *2.3. Clinical aspects*

### 2.3.1. Introduction

### GCP

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

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

| Study ID | Phase | Country/Region | Study Title | Study Design | Dosing Regimen | Study Population | Participant Exposure |
|---|---|---|---|---|---|---|---|
| E7080-G000-309/ KEYNOTE-775 [Ref. 5.3.5.1: P775V01MK3475] | 3 | Argentina, Australia, Brazil, Canada, Colombia, France, Germany, Ireland, Israel, Italy, Japan, Mexico, New Zealand, Poland, Republic of Korea, Russian Federation, Spain, Taiwan, Turkey, United Kingdom US | 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 | Multicenter, randomized, open-label, active-controlled | Pembrolizumab 200 mg Q3W IV plus lenvatinib 20 mg daily oral versus Treatment of Physician's choice: Doxorubicin 60 mg/m$^2$ Q3W IV or Paclitaxel 80 mg/m$^2$ QW IV, 3 weeks on/1 week off<br>Duration: Pembrolizumab: up to 35 cycles<br>Doxorubicin: cumulative lifetime dosage of 500 mg/m$^2$ or lower consistent with site standard of care.<br>Lenvatinib: no maximum duration | Females ≥18 years participants with advanced endometrial carcinoma | Lenvatinib plus pembrolizumab: N = 406;<br>doxorubicin or paclitaxel: N = 388 |
| E7080-A001-111/ KEYNOTE-146 [Ref. 5.3.5.2: P146V01MK3475] | 1b/2 | Spain US | A Multicenter, Open-Label Phase 1b/2 Trial of Lenvatinib (E7080) Plus Pembrolizumab in Subjects With Selected Solid Tumors | Multicenter, single-arm, open-label | Lenvatinib 20 mg daily oral plus pembrolizumab 200 mg IV Q3W<br>Pembrolizumab: up to 35 cycles<br>Lenvatinib: no maximum duration | Females ≥18 years participants with advanced endometrial carcinoma | 79 in advanced endometrial carcinoma cohort |
| E7080-G000-204 [Ref. 5.3.5.2: PE204V01] | 2 | Europe, Russia, Ukraine, US | An Open-Label, Single-Arm, Multicenter Phase 2 Study of E7080 [Lenvatinib] in Subjects with Advanced Endometrial Cancer and Disease Progression Following First-Line Chemotherapy | Multicenter, single-arm, open-label | Lenvatinib 24 mg daily oral No maximum duration | Females ≥18 years participants with advanced endometrial carcinoma | 133 |
| KEYNOTE-028 [Ref. 5.3.5.2: P028V06MK3475] | 1b | Canada, France, Korea Spain United Kingdom, US | A Phase 1b Study of Pembrolizumab (MK-3475) in Subjects with Select Advanced Solid Tumors | Multicenter, open-label | Pembrolizumab 10 mg/kg IV every 2 weeks | Males/females; Age ≥18 years;<br>Female Participants with endometrial carcinoma (Cohort B3) | 10 mg/kg Q2W; 24 participants (Cohort B3) |
| KEYNOTE-158-08 [Ref. 5.3.5.2: P158V05MK3475] | 2 | Australia, Brazil, Canada, Denmark, France, Israel, Italy, Japan, Norway, Russia, South Korea, Spain, Taiwan, USA | A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predictive Biomarkers in Subjects with Advanced Solid Tumors (KEYNOTE-158) | Open-label, multicenter, non-randomized, multigroup study of pembrolizumab in participants with various types of advanced (unresectable and/or metastatic) rare cancers | Pembrolizumab 200 mg IV Q3W | Female participants with endometrial carcinoma aged 41 to 86 were enrolled in Cohort D endometrial carcinoma, and MSI-H endometrial carcinoma in Cohort K | 107 participants in Cohort D endometrial carcinoma, and 38 participants with MSI-H endometrial carcinoma in Cohort K were enrolled and treated. |

## 2.3.2. Pharmacokinetics

Clinical pharmacology results for the combination therapy of Pembrolizumab together with Lenvatinib, specific to support approval for second line treatment of EC, are available from the Phase 3 Study 309/KEYNOTE-775.

**The clinical pharmacology package** includes 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.

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

The MAH submitted only the lenvatinib method validation as well as the bioanalytical report (MK-3475-775).

## *Analytical methods*

*Lenvatinib (MK-7902) Quantification Method Validation*

In phase 3 clinical Study 309/KEYNOTE-775, lenvatinib (MK-7902) concentrations in human sodium heparinized plasma have been determined by a HPLC-MS/MS method, validated at Syneos Health Clinique, Québec, Canada.

| | |
|---|---|
| **Reference Standard(s)** | E7080 (MK-7902), Lot Numbers: 164H0501 and 191H1702<br>MK-7902-13C6 (Internal Standard), Lot Number: L-005416795-002H001 |
| **Matrix and anti-coagulant** | Human plasma and sodium heparin |
| **Sample Aliquot Volume (HPLC-MS/MS)** | 0.100 mL |
| **Calibration Range** | 0.25 to 250.00 ng/mL |
| **Quality Control (QC) Concentrations** | 0.75, 12.50, 125.00 and 187.50 ng/mL |
| **Highest Dilution QC Concentration** | In validation: 2500.00 ng/mL |
| **Demonstrated Storage Stability** | 675 days at -20ºC |
| **Maximum Sample Storage Duration From Collection to Analysis** | 927 days at -20ºC |

*Lenvatinib (MK-7902) Bionanalytical report (MK-3475-775)*

Analysis started on 14-Aug-2019 and ended on 26-Nov-2020.

Frozen samples with dry ice still present, were shipped to the bioanalytical laboratory; then, were stored at approximately -20ºC until analyzed. As declared in the BA report, 4423 samples were received and 2452 were analysed.

The same analytical methodology was used across all lenvatinib assay validation and sample analysis, as shown in the table below.

| | LC MS MS 4000-01 | LC MS MS 4000-13 | LC MS MS 4000-17 |
|---|---|---|---|
| Instrument platform | AB Sciex API 4000 | AB Sciex API 4000 | AB Sciex API 4000 |
| Ionization Source | Turbo IonSpray | Turbo IonSpray | Turbo IonSpray |
| LC System | Acquity UPLC | Acquity UPLC | Acquity UPLC |

Prior to each run, the suitability of the instrument was demonstrated through the injection of a system suitability test. Furthermore, to verify that the performance of each instrument was comparable during sample analysis, the QC results from each run were grouped by instrument and examined. Results confirm that each instrument generated comparable data during the course of study sample analysis.

**Pharmacokinetic in target population**

An overview of the lenvatinib clinical pharmacology study for this extension of indication in EC patients is presented below:

**Table 1 - Clinical Pharmacology Studies : Definitive Pharmacokinetics in Patients**

**Study KN-775/E7080-G000-309**

| 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<br><br>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.

Blood samples from all participants in the lenvatinib plus pembrolizumab group (Arm A) were collected as specified in the protocol of Study 309/KEYNOTE-775 at Cycle 1 Day1, Cycle 1 Day 15 and Cycle 2 Day 1 (see scheme here below).

**Table 2 - Schedule of Activities –Treatment Period**

| Trial Period | Screening[a] | Treatment Period Arm A: 21-Day Cycles Arm B: 21-Day or 28-Day Cycles | | | | | | | | | EOT | Post Treatment | | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment Cycle | | Cycle 1 | | | Cycle 2 | | | Cycle 3 - last | | | | | | | |
| Cycle Day | | 1 | 8 | 15 | 1 | 8 | 15 | 1 | 8 | 15 | | Safety FU[b] | FU Visits | Survival FU | |
| **Administration of Study Treatment** | | | | | | | | | | | | | | | |
| Lenvatinib plus pembrolizumab | | X | | | X | | | X | | | | | | | Lenvatinib 20 mg QD plus pembrolizumab 200 mg Q3W; 21-day cycle. |
| Doxorubicin | | X | | | X | | | X | | | | | | | 60 mg/m$^2$ Q3W; 21-day cycle. |
| Paclitaxel | | X | X | X | X | X | X | X | X | X | | | | | 80 mg/m$^2$ QW; 3 weeks on, 1 week off of each 28-day cycle. |

| Trial Period | Screening[a] | Treatment Period Arm A: 21-Day Cycles Arm B: 21-Day or 28-Day Cycles | | | | | | | | | EOT | Post Treatment | | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment Cycle | | Cycle 1 | | | Cycle 2 | | | Cycle 3 - last | | | | | | | |
| Cycle Day | | 1 | 8 | 15 | 1 | 8 | 15 | 1 | 8 | 15 | | Safety FU[b] | FU Visits | Survival FU | |
| Lenvatinib PK blood sample (Arm A only) | | X | | X | X | | | | | | | | | | C1D1: 0.5-4 h and 6-10 h postdose.<br>C1D15: predose and 2-12 h postdose.<br>C2D1: predose, 0.5-4 h, and 6-10 h postdose.<br>Note: all predose samples should be collected within 30 minutes of lenvatinib dosing.<br>Note: postdose samples not needed if lenvatinib administration is skipped. |

Plasma concentrations of lenvatinib were measured. Lenvatinib was analyzed using a population PK approach.
Lenvatinib was quantified by use of validated High-Performance Liquid Chromatography tandem mass spectroscopy method.
Plasma concentrations of Pembrolizumab were not measured within this study.
Results of the PK evaluation for lenvatinib are provided in a standalone report (Population Analysis CPMS-E7080-015P-v1).

## *Population PK Analysis*

Report CPMS-E7080-015R-v1 describes objectives, methods and results of the population PK analysis of lenvatinib using data pooled across several studies, including Study KN-775/309. This report also includes PK/safety analyses (Study KN-775/309/Arm A) in subjects with EC.

The objective of the population pharmacokinetics (PK) analysis of lenvatinib is:

• Compare the PK of lenvatinib in subjects with advanced EC (Study KN-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.

The objective of the PK/safety analysis of combination therapy of lenvatinib and pembrolizumab in subjects with EC is:

• Explore the relationship of lenvatinib exposure vs the occurrence of TEAEs related/specific to only lenvatinib in subjects with EC and which were previously specified to include hypertension, proteinuria, weight decreased, vomiting, and hypothyroidism.

The updated Population PK analysis was performed using data from Study KN775/309 in subjects with EC pooled with data from Phase 1 studies in healthy volunteers and Phase 1, 2 and/or 3 studies in subjects with other solid tumors, for a total of 22 studies. Exposure-response analysis for adverse events related to lenvatinib only was performed using data from Study 309/Arm A in subjects with EC.
To simplify PK model development, and focus on therapeutically relevant exposures, only PK data following lenvatinib doses of 3.2 mg and above were included in the analysis.
A brief description of the studies included in the popPK analysis is presented below.

**Table 3 – Brief description of Studies with PK sampling included in population PK analyses of Lenvatinib**

| Study Number | Lenvatinib Dose Range and Regimen | N | Formulation | Subject | Pharmacokinetic sampling |
|---|---|---|---|---|---|
| MK-3475-775/E7080-G000-309 | Arm A: lenvatinib 20 mg (orally, QD) plus pembrolizumab 200 mg (IV Q3W) | 403 | Capsule | EC | C1D1: 0.5-4 h and 6-10 h post-dose.<br>C1D15: pre-dose and 2-12 h post-dose<br>C2D1: predose, 0.5-4 h, and 6-10 h post-dose |
| E7080-G000-307 | **Arm A:** lenvatinib 18 mg QD plus everolimus 5 mg QD<br>**Arm B:** lenvatinib 20 mg QD plus pembrolizumab (200 mg IV, every 3 weeks)<br>**Arm C:** sunitinib 50 mg QD on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2) | 697 | Capsule | RCC | Lenvatinib (Arms A and B) and everolimus (Arm A):<br>Day 1/Cycle 1: 0.5- 4 and 6- 10 h post-dose<br>Day 15/Cycle 1: pre-dose and 2 – 12 h post-dose<br>Day 1/Cycle 2: pre-dose and 0.5-4 and 6-10 h post-dose<br>Day 1/Cycles 3, 4, 5 and 6: pre-dose<br>Pembrolizumab and antidrug antibodies (ADA) – Arm B:<br>Day 1 of Cycles 1, 2, 3, 5: pre-dose and during the off-treatment visit after pembrolizumab discontinuation for subjects<br>Day 1/Cycles 1 and 2: 30 minutes following the end of the pembrolizumab infusion |
| E7080-G000-205 | Phase 1b: lenvatinib 12, 18 and 24 mg QD + everolimus 5 mg QD<br>Phase 2: lenvatinib 18 mg QD + everolimus 5 mg QD<br>or lenvatinib 24 mg QD or everolimus 10 mg QD | 116 | Capsule | RCC | Subjects for Sparse PK sampling for lenvatinib and everolimus:<br>Day 1/Cycles 1-3: pre-dose and 2-8 h post-dose<br>Subjects for Intensive PK sampling for lenvatinib and everolimus:<br>Day 15/Cycle 1: Pre-dose and at 0.5, 1, 2, 3, 4, 8, 12 and 24 h post-dose |

| | | | | | |
|---|---|---|---|---|---|
| E7080-G000-218 | **Arm A:** lenvatinib 18 mg without up-titration plus everolimus 5 mg (both orally, once daily)<br>**Arm B:** lenvatinib 14 mg with up-titration plus everolimus 5 mg (both orally, once daily) | 337 | Capsule | RCC | Day 1/Cycle 1: 0.5-4 h and 6-10 h post-dose<br>Day 15/Cycle 1: pre-dose and 0.5-4 h and 6-10 h post-dose on C1D15, and<br>Day 1/Cycle 2: pre-dose and 2-12 h post-dose |
| E7080-M001-221 | lenvatinib 18 mg plus everolimus 5 mg (both orally, once daily) | 31 | Capsule | RCC | Day 1/Cycle 1: 2-8 h post-dose<br>Day 15/Cycle 1: pre-dose<br>Day 1/Cycle 2 and 3: pre-dose and 2-8 h post-dose |
| E7080-J081-112 | lenvatinib 18 mg QD + everolimus 5 mg QD | 7 | Capsule | RCC | Day 1 and 15 of Cycle 1: 1, 2, 4, 8, and 24 h post dose/ $C_{trough}$: Day 15 of Cycle 1 |
| E7080-J081-115 | lenvatinib 20 mg QD plus pembrolizumab (200 mg IV, every 3 weeks) | 6 | Capsule | Solid Tumors | Day 1 and 15 of Cycle 1: 1, 2, 4, 8, and 24 h post dose/ $C_{trough}$: Day 15 of Cycle 1 |
| E7080-G000-304 | 12 mg (body weight ≥ 60 kg) or 8 mg (body weight < 60 kg) QD | 468 | Capsule | HCC | Day 1 of Cycle 1 and 2: Pre-dose, and post-dose on 0.5-4 h and 6-10 h, Cycle 1 Day 15: Pre-dose and 2-12 h post dose<br>$C_{trough}$: Cycle 3-Cycle 6/Day1 |
| E7080-J081-202 | Phase 1: 8 - 16 mg QD<br>Phase 2: 12 mg QD | 20<br>46 | Tablet | HCC | Days 1 and 15 of Cycle 1 :0.5, 1, 2, 4, 6, 8 and 24 h post dose<br>$C_{trough}$: Days 1, 8, 15 and 22 of Cycle 1<br>$C_{trough}$: Days 1, 8, 15 and 22 of Cycle 1<br>Days 1 of Cycle 2 and 3 |
| E7080-G000-303 | 24 mg QD | 260 | Capsule | DTC | Day 1 and 15 of Cycle 1: Pre-dose, and post-dose on 0.5-4 h and 6-10 h, Cycle 2 Day 1: Pre-dose and 2-12 h post dose<br>$C_{trough}$: Cycle 3-Cycle 6/Day1 |
| E7080-G000-201 | 10 mg BID and 24 mg QD | 98 | Tablet | DTC and MTC | Day 1/Cycles 1 and 2: pre-dose, 0.5and 2 h post-dose<br>Day 8/Cycle 1: pre-dose<br>Day 1/Cycle 3: pre-dose and 2h post-dose |
| E7080-G000-211 | 18 and 24 mg QD continuous | 184 | Capsule | DTC | Day 1 and 15 of Cycle 1: Pre-dose, and post-dose on 0.5-4 h and 6-10 h, Cycle 2 Day 1: Pre-dose and 2-12 h post dose |
| E7080-E044-101 | 0.2 – 32 mg QD | 66 | Tablet | Solid Tumors | Day 1 of Cycle 1 and Cycle 2: 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 24 h post dose<br>$C_{trough}$: Days 8, 15 and 22 of Cycle 1 |
| E7080-A001-102 | Schedule 1: 0.1 – 3.2 mg BID x 7d/14d | 62 | Tablet | Solid Tumors | |

| | | | | | |
|---|---|---|---|---|---|
| | Schedule 2: 3.2 – 12 mg BID | | | Melanoma | Day 1 of Cycle 1 and Cycle 2: 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 24 h post dose<br>$C_{trough}$: Days 8, 15 and 22 of Cycle 1 |
| E7080-J081-103 | 0.5 – 20 mg BID x 14d/21d | 18 | Tablet | Solid Tumors | 1, 2, 3, 5, 6, 8, 12, 24, 48, 96, and 168 h post dose on Day1 of Cycle 0 and Day 14 of Cycle1/ $C_{trough}$: Days 5, 8 and 11 of Cycle 1, Day 8 of Cycle 2 |
| E7080-J081-105 | 20 and 24 mg QD | 9 | Capsule | Solid Tumors | Day 1 and 15 of Cycle 1: 1, 2, 4, 8, and 24 h post dose/ $C_{trough}$: Days 8, 15 of Cycle 1, Day 15 of Cycle 2 |
| E7080-A001-001 | 10 mg | 20 | Tablet/ capsule | HV | Pre-dose and 1, 2, 3, 4, 8, 16, 24, 48, 72, 96, 120, 144, and 168 h post-dose |
| E7080-A001-002 | 32 mg | 51 | Capsule | HV | Pre-dose and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, and 96 h post-dose |
| E7080-A001-003 | 10 mg | 15 | Capsule | HV | Pre-dose and 1, 2, 3, 4, 8, 12, 16, 24, 48, 72, 96, 120, 144, and 168 h post-dose |
| E7080-A001-005 | 24 mg | 26 | Capsule | HV/RI | Pre-dose and 0.5, 1, 2, 3, 4, 8, 12, 16, 24, 48, 72, 96, 120, 144, and 168 h post-dose |
| E7080-A001-006 | 5 and 10 mg | 26 | Capsule | HV/HI | Pre-dose and 0.5, 1, 2, 3, 4, 8, 12, 16, 24, 48, 72, 96, 120, 144, 168, 240, 288, and 336 h post-dose |
| E7080-A001-008 | 10 mg | 59 | Capsule | HV | Pre-dose and 1, 2, 3, 4, 8, 12, 16, 24, 48, 72, 96, and 120 h post-dose |
| EC: endometrial cancer, RCC: renal cell carcinoma, HCC: hepatocellular carcinoma, DTC: differentiated thyroid cancer, MTC: medullary thyroid cancer, ATC: anaplastic thyroid cancer, HV: healthy volunteers, RI: renal impairment, HI: hepatic impairment<br>Subjects who received a starting dose of 3.2 mg and higher were included in PK dataset | | | | | |

For lenvatinib population PK analysis, data were included if subjects received at least 1 dose of lenvatinib and had at least one adequately documented and quantifiable plasma concentration.
The final pooled lenvatinib PK dataset included 25738 observations from a total of 3025 subjects. For Study KN775/309 EC subjects, there were 2178 lenvatinib concentrations available from 403 subjects, with all 403 EC subjects receiving concomitant pembrolizumab.

For PK/safety analyses of AEs, 403 subjects with EC from the lenvatinib + pembrolizumab combination arm (Arm A) from Study KN775/309 with PK information and who have at least one post-baseline safety evaluation were included in the analysis.

***Pharmacokinetic Model Development***

The analysis of lenvatinib total plasma concentration data from Study KN775/309 (Arm A) was pooled with existing PK dataset consisting of pooled data from several Phase 1 studies in healthy volunteers and Phase 1, 2 and 3 studies in subjects with solid tumors, which was previously described in report CPMS-E7080-013R). This popPK model included 21 studies: E7080-A001-001 to 008, E7080-E044-101, E7080-A001-102, E7080- J081-103&105, E7080-J081-112, E7080-G000-201, E7080-J081-202, E7080-G000-205, E7080-G000-303, E7080-G000-304, E7080-G000- 211, E7080-M000-221, and E7080-G000-218

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 apparent plasma clearance of drug after oral administration (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).

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, CYP3A4 inhibitors on CL/F, and capsule formulation on relative bioavailability. 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 tumor 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 population PK model was used to derive individual PK parameters and lenvatinib exposure in subjects from Study KN775/309. These data were then merged with safety dataset for AEs. Lenvatinib AUC at steady state based on the starting dose was derived as follows:

$$AUC\ (ng.\frac{h}{mL}) = \frac{\mathrm{F1} \cdot \text{Starting dose (mg)} \cdot 1000}{\text{Individual apparent clearance } (\frac{\mathrm{L}}{\mathrm{h}})}$$

Individual clearance is the model predicted individual apparent clearance and F1 is relative bioavailability of capsule to tablet formulation

**PK Model Acceptability Criteria**

The following criteria were considered when assessing the acceptability of a model:

- ✓ A "minimization successful" statement by the NONMEM program.
- ✓ Covariance step terminates without any warning message.
- ✓ The number of significant digits should be ≥ 3 for all estimated θ values.
- ✓ Final estimates of θ values should not be close to the initial estimate boundaries.
- ✓ The standard error of θ estimates should be less than 20% and the standard error of
- ✓ η estimates should be less than 50% of the estimate itself.
- ✓ Correlation between parameters less than 0.95.

In addition, the following goodness-of-fit-plots were used to evaluate the ability of the model to describe the available data which demonstrate no systematic trends:

- ✓ Population and individual predictions *versus* observations
- ✓ Conditional weighted residuals (CWRES) *versus* population predictions (PRED) and *versus* time

**Covariate PK Model Development**

In the current PK analysis of lenvatinib, a full covariate model was fitted to the pooled PK dataset which included known fixed covariate effects (formulation on F1 and of CYP3A inhibitors and healthy subjects on CL/F), and effects of sex, ALP, albumin, tumor type and co-medication with pembrolizumab (categorical) on CL/F. No backwards deletion was carried out.

**Final PK Model Evaluation**

VISUAL PREDICTIVE CHECK: The final PK of lenvatinib model was evaluated using pcVPC constructed using PSN (Bergstrand, et al, 2011). Using parameters from the final PK model, lenvatinib concentrations were

simulated over (N = 250) dataset using original dosing history and covariate information. The median and 5th and 95th simulated percentiles (90% prediction interval [PI]) of were calculated and plotted with observed lenvatinib concentration data.
BOOTSTRAP METHODS: The final PK model for lenvatinib was evaluated using bootstrap re-sampling to construct nonparametric parameter summaries including confidence intervals (Yafune and Ishiguro, 1999)

***PK/Safety Model Development***

The relationship of event probabilities corresponding to grades of treatment emergent adverse events (TEAEs) and lenvatinib exposure were evaluated using a proportional odds model. Lenvatinib exposures corresponded to lenvatinib and pembrolizumab combination arm (Study KN775/309 Arm A) with starting dose Auks lenvatinib exposure used for analysis.
For each AE, probabilities of having no AE and a Grade 1, 2 or 3 AE was estimated as a function of lenvatinib exposure. The following TEAEs were analyzed: hypertension, proteinuria, weight decreased, vomiting and hypothyroidism
For these TEAEs, lenvatinib AUC (AUCLEN) was tested as drug effect. These exposure effects were modeled as log-transformed values. The effects of the following covariates were tested in this multivariate TEAE analysis; age category (⩾65 years vs < 65 years), ECOG-PS (1 vs 0), and a parameter for Japanese study participants vs. others (PTSeth). The full (prespecified) model approach was considered for all TEAEs. This proportional-odds cumulative logit model employed logit-transformation to constrain estimated probabilities between 0 and 1, using:

$$P(Y \geq i) = \frac{e^{f_i}}{1 + e^{f_i}} \ , \ i = 1, 2, 3$$

where *fi* represents logit functions of the cumulative probability that CTC grade is ≥ *i* = 1, 2, or 3 and effects of predictors:

$$f_1 = B_1 + f\,(predictors)$$

$$f_2 = B_1 + B_2 + f\,(predictors)$$

$$f_3 = B_1 + B_2 + B_3 + f\,(predictors)$$

where Bi representing the baseline probabilities for the different CTC grades (on a logit scale). The function *f* (predictors) is function of log-linear lenvatinib exposure and the effect of covariates with the structural form below:

$$f\,(predictors) = \alpha_1 \cdot AUC_{LEN} + \alpha_2 \cdot PTSeth + \alpha_3 \cdot AGE + \alpha_4 \cdot ECOG$$

## RESULTS

**Datasets**: 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 KN775/309. All 403 EC subjects received concomitant pembrolizumab. Additional data from another 5 subjects were excluded from the analysis as these data were causing numerical difficulties.

PK/safety dataset for AEs included 403 data records of each adverse event from 403 subjects with EC from the lenvatinib + pembrolizumab combination arm (Arm A) from Study KN775/309.

**Subject Disposition:** the following two tables present the subject demographic and baseline characteristics for the pooled lenvatinib PK population (N=3025) and the subject demographic and baseline characteristics for the pooled lenvatinib PK population for EC subjects in Study KN775/309, respectively.

**Table 4 – Summary of demographics and covariates included in the Population PK analysis of Lenvatinib from all studies (N=3025)**

| Demographic (unit) | Mean (SD) | Median | Range (Min-Max) |
|---|---|---|---|
| Age (years) | 60.2 (12.3) | 62.0 | 18 - 92 |
| Weight (kg) | 76.2 (19.0) | 74.0 | 32.6 - 190 |
| Albumin (g/L) | 40.9 (5.0) | 41.0 | 19 - 67 |
| ALP (IU/L) | 116.1 (94.3) | 87.0 | 19 - 1135 |
| ALT (IU/L) | 25.1 (23.5) | 19.0 | 3 - 660 |
| AST (IU/L) | 28.7 (29.6) | 21.0 | 4 - 930 |
| Bilirubin (umbel/L) | 11.1 (110.9) | 7.9 | 2 – 6100 |
| Creatinine clearance (mL/min) | 88.1 (33.8) | 83.0 | 17 – 304.5 |
| Gender | Male=1816, Female=1209 | | |
| Race | White=1943, Black/African American=98, Asian other than Japanese or Chinese=274, Japanese=349, Chinese=174, American Indian or Alaskan Native=8, Native Hawaiian or Other Pacific Islander=8, Other or mixed race=77, Missing/Unknown=94 | | |
| ECOG performance status | 0=1846, 1=889, 2=24, 3=1, Missing=265 | | |
| Tumor type | EC=403, HCC=534, Thyroid=542, RCC=1188, Other solid tumor=161, Healthy subjects=197 | | |
| Concomitant CYP3A4 inducers [a)] | Yes=9, No=3016 | | |
| Concomitant CYP3A4 inhibitors [a)] | Yes=50, No=2975 | | |
| Concomitant everolimus[a)] | Yes=795, No=2230 | | |
| Concomitant pembrolizumab[a)] | Yes=754, No=2271 | | |
| Formulation | Capsule=2705, Tablet=320 | | |

a)Yes or No was decided based on during study data
EC=endometrial cancer; HCC=hepatic cell carcinoma; RCC=renal cell carcinoma

**Table 5 – Summary of Demographics and Covariates for EC subjects included in the population PK Analysis of Lenvatinib from Study KN775/309 (Arm A) (N=403)**

| Demographic (unit) | Mean (SD) | Median | Range (Min-Max) |
|---|---|---|---|
| Age (years) | 63.2 (9.1) | 64.0 | 30 - 82 |
| Weight (kg) | 72.0 (19.7) | 68.5 | 35.4 – 165.3 |
| Albumin (g/L) | 39.8 (4.9) | 40.4 | 20.2 – 67 |
| ALP (IU/L) | 124.5 (92.4) | 91.0 | 21 - 640 |
| ALT (IU/L) | 19.7 (13.4) | 16.0 | 4 - 103 |
| AST (IU/L) | 23.2 (12.8) | 20.0 | 6 - 145 |
| Bilirubin (umol/L) | 23.0 (303) | 7.0 | 2.1 - 6100 |
| Creatinine clearance (mL/min) | 87.4 (31.0) | 81.9 | 29 - 256 |
| Gender | Female=403 | | |
| Race | White=254, Black/African American=16, Asian other than Japanese or Chinese=31, Japanese=52, Chinese=2, American Indian or Alaskan Native=4, Native Hawaiian or Other Pacific Islander=1, Other or mixed race=7, Missing=36 | | |
| ECOG performance status | 0=244, 1=159 | | |
| Concomitant CYP3A4 inducers[a)] | Yes=1, No=402 | | |
| Concomitant CYP3A4 inhibitors[a)] | Yes=4, No=399 | | |
| Concomitant pembrolizumab[a)] | Yes=403 No=0 | | |
| Formulation | Capsule=403 | | |

a)Yes or No was decided based on during study visit
EC=endometrial cancer

The PK/safety dataset for AEs consisted of 403 female subjects with EC from the lenvatinib + pembrolizumab combination arm from Study KN775/309. The baseline demographics for this population are summarized in the table below:

**Table 6 - Summary of Demographics and Covariates included in the PK/Safety Analysis Study KN775/309 (N=403)**

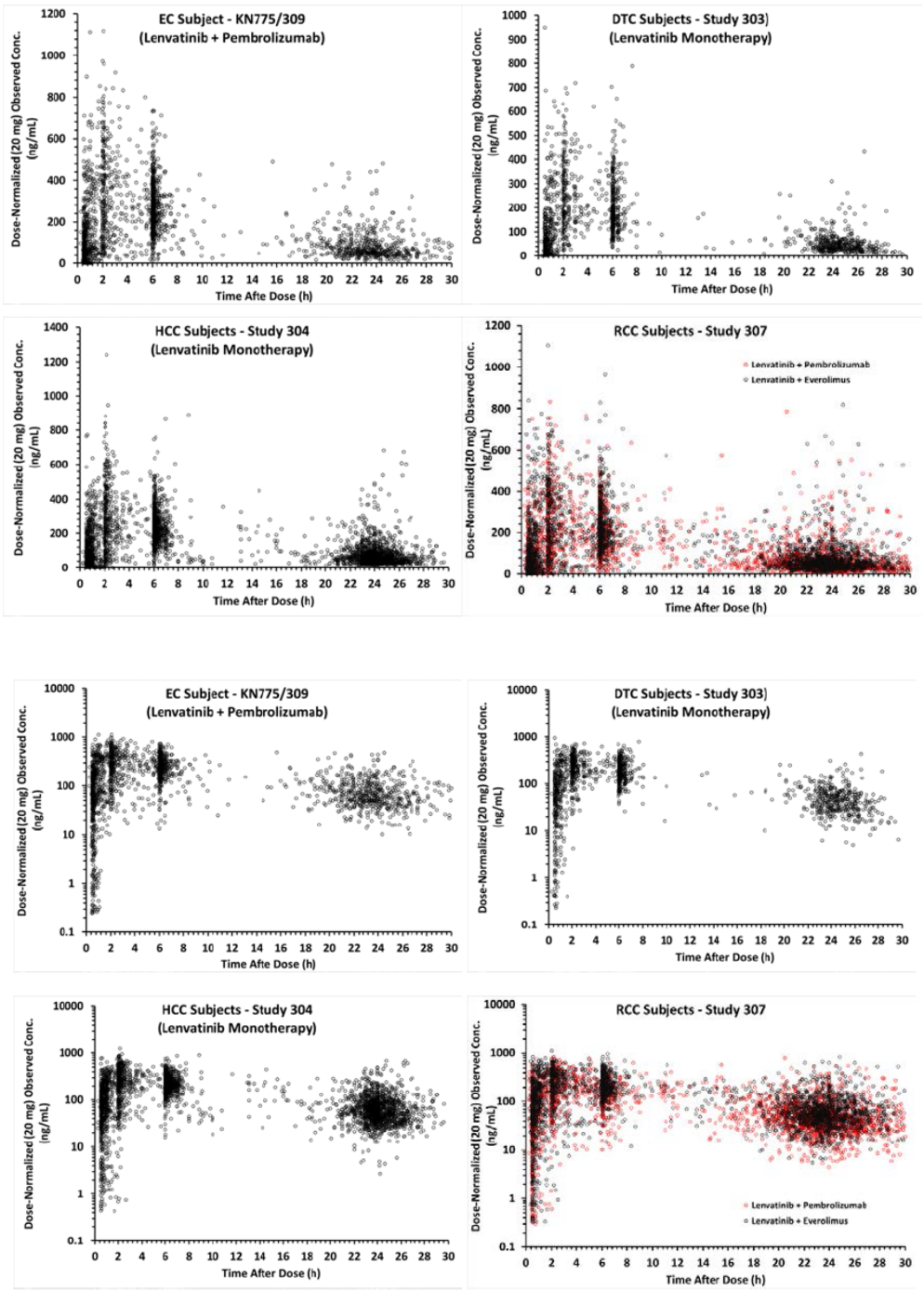
| Demographic (unit) | Number of Subjects |
|---|---|
| Age | < 65 years=202, >= 65 years=201 |
| Gender | Female=403 |
| ECOG performance status | 0=244, 1=159 |
| Japanese Study Participants | Non-Japanese=351, Japanese=52 |

**Lenvatinib Pharmacokinetic Analysis**

Linear and semi-log scatter plots of the observed lenvatinib plasma concentrations versus time after dose (for 30 hours post dose) at steady state following lenvatinib + pembrolizumab combination in EC subjects from Study KN775/309 are presented in linear and semi-log plots in the figure reported below. Concentration data are dose-normalized to 20 mg lenvatinib in DTC subjects from Study 303 following lenvatinib monotherapy, in HCC subjects from Study 304 following lenvatinib monotherapy, and in RCC subjects from Study 307 following lenvatinib + pembrolizumab combination and following lenvatinib + everolumus combination.

**Figure 1:**

**Linear and Semi-Log Plots of Dose-Normalized observed Lenvatinib Plasma Concentration versus Time after Dose at Steady State in EC Subjects (Study KN775/309), DTC Subjects (Study 303), HCC Subjects (Study 304) and RCC Subjects (Study 307)**




Figures above show a major overlap in observed lenvatinib plasma concentrations in EC subjects receiving concomitant pembrolizumab, in HCC subjects receiving lenvatinib monotherapy and RCC subjects receiving lenvatinib in combination with either pembrolizumab or everolimus with slightly lower exposure to lenvatinib in DTC subjects receiving lenvatinib monotherapy. Additionally, the figure shows a major overlap in

exposure to lenvatinib in RCC subjects following lenvatinib + pembrolizumab combination and following lenvatinib + everolumus combination.

**PK Model results for Lenvatinib**

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. The parameter estimates, precision of the estimate and 95% confidence intervals for the final lenvatinib PK model are presented in the following table:

## Table 7 – Population pharmacokinetic parameter estimates of Lenvatinib final model

| Parameter | NONMEM Estimates | | |
|---|---|---|---|
| | Point Estimate | %RSE | 95% Confidence Interval |
| $CL/F\ [L/h] = \Theta_{CL} * (WGT/74)^{0.75} * \Theta_{INHIB}^{INHIB} * \Theta_{ALP}^{ALP} * \Theta_{ALB}^{ALB} * \Theta_{HV}^{HV} * \Theta_{DTC}^{DTC} * \Theta_{HCC}^{HCC} * \Theta_{RCC}^{RCC} * \Theta_{EC}^{EC} * \Theta_{Pembro}^{Pembro} * \Theta_{SEX}^{SEX}$ | | | |
| Basal CL/F for subjects with other type of solid tumor in L/h [$\Theta_{CL}$] | 6.65 | 2.06 | 6.38 – 6.92 |
| Effect of CYP3A4 inhibitors on CL/F [$\Theta_{INHIB}$] | 0.896 Fixed | – | – |
| Effect of ALP (>ULN) on CL/F [$\Theta_{ALP}$] | 0.939 | 0.724 | 0.926 – 0.952 |
| Effect of ALB (<30 g/L) on CL/F [$\Theta_{ALB}$] | 0.856 | 1.92 | 0.824 – 0.888 |
| Effect of healthy subjects on CL/F [$\Theta_{HV}$] | 1.19 Fixed | – | – |
| Effect of DTC population on CL/F [$\Theta_{DTC}$] | 0.970 | 2.74 | 0.918 – 1.02 |
| Effect of HCC population on CL/F [$\Theta_{HCC}$] | 0.824 | 2.71 | 0.780 – 0.868 |
| Effect of RCC population on CL/F [$\Theta_{RCC}$] | 0.802 | 2.31 | 0.766 – 0.838 |
| Effect of EC population on CL/F [$\Theta_{EC}$] | 0.751 | 3.64 | 0.697 – 0.805 |

| Parameter | NONMEM Estimates | | |
|---|---|---|---|
| | Point Estimate | %RSE | 95% Confidence Interval |
| Effect on concomitant pembrolizumab on CL/F [$\Theta_{Pembro}$] | 1.07 | 2.20 | 1.02 – 1.12 |
| Effect on females on CL/F [$\Theta_{SEX}$] | 0.886 | 1.64 | 0.858 – 0.914 |
| V1/F [L] = $\Theta_{V1}$*WGT/74 | | | |
| Basal V1/F in L [$\Theta_{V1}$] | 45.1 | 1.49 | 43.8 – 46.4 |
| V2/F [L] = $\Theta_{V2}$*WGT/74 | | | |
| Basal V2/F in L [$\Theta_{V2}$] | 21.7 | 3.76 | 20.1 – 23.3 |
| V3/F [L] = $\Theta_{V3}$*WGT/74 | | | |
| Basal V3/F in L [$\Theta_{V3}$] | 30.9 Fixed | – | – |
| Q1/F [L/h] = $\Theta_{Q1}$*(WGT/74)$^{0.75}$ | | | |
| Basal Q1/F in L/h [$\Theta_{Q1}$] | 3.61 | 2.55 | 3.43 – 3.79 |
| Q2/F [L/h] = $\Theta_{Q2}$*(WGT/74)$^{0.75}$ | | | |
| Basal Q2/F in L/h [$\Theta_{Q2}$] | 0.847 | 2.73 | 0.802 – 0.892 |
| Ka [1/h] = $\Theta_{Ka}$ | | | |
| Basal Ka in 1/h [$\Theta_{Ka}$] | 0.803 Fixed | – | – |
| D1 [h] = $\Theta_{D1}$ | | | |
| Basal D1 in h [$\Theta_{D1}$] | 1.27 Fixed | – | – |
| F1 = $\Theta_{F1}$ | | | |
| Relative bioavailability of capsule vs tablet formulation [$\Theta_{F1}$] | 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

| Parameter | NONMEM Estimates | | |
|---|---|---|---|
| | Point Estimate | %RSE | 95% Confidence Interval |

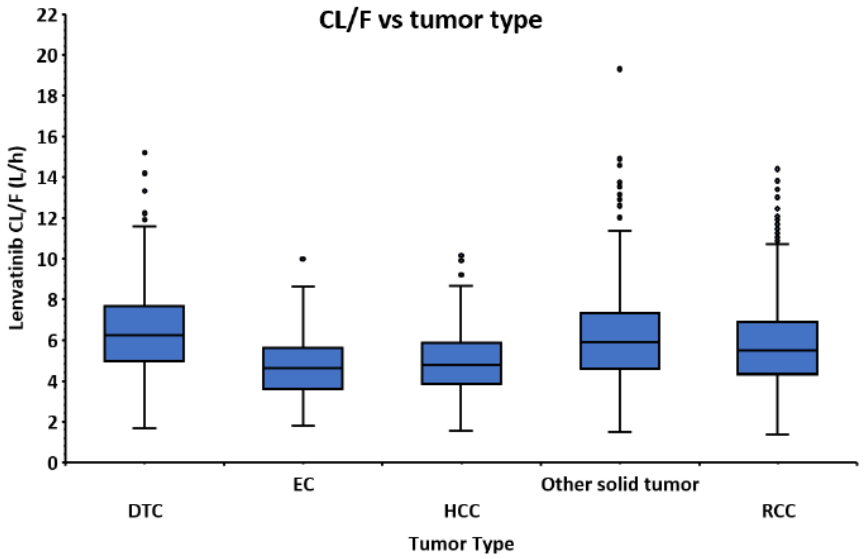
bioavailability of capsule to tablet formulation; TAD = Time after dose; CI = confidence interval; WGT = weight (kg); INHIB = CYP3A4 inhibitors; ALB =albumin, 0 (≥ ALB 30 g/L) or 1 (< ALB 30 g/L); ALP = Alkaline phosphatase measurement (IU/L) 0 (ALP ≤ upper limit of normal) or 1 (ALP > upper limit of 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

All the parameters of the structural model were estimated with a %RSE ≤ 3.76%. Lenvatinib CL/F increased with increasing body weight (power = 0.75), decreased by 14.4% with albumin levels below 30 g/L and decreased by 6.1% with ALP above upper limit of normal (ULN).
The EC population was estimated with a 24.9% lower lenvatinib CL/F compared with other solid tumor types excluding DTC, RCC and HCC. The DTC population was noted to have similar lenvatinib CL/F to that in patients with other solid tumor types (0.970; 95% CI: 0.918 – 1.02) excluding EC, RCC and HCC. The RCC population was found to have a 19.8% lower lenvatinib CL/F compared with other solid tumor types excluding EC, DTC and HCC.
The HCC population was found to have a 17.6% lower lenvatinib CL/F compared with other solid tumor types excluding EC, DTC and RCC. The effects of DTC, RCC and HCC on CL/F are comparable with those from a recent PK analyses (CPMS-E7080-013R and CPMSE7080- 012R-LP-v1). Lenvatinib CL/F was found to be 7% higher with concomitant pembrolizumab and to be 11.4% lower in females compared to males. The magnitude of each effect is within the inter-subject variability for CL/F (33.5 %) and hence of no clinical relevance.
Inter-individual variability (IIV) in the model parameters was moderate to high ranging between 33.5% for CL/F and 104% for D1. IIV was well estimated with good precision for all the parameters (%RSE ≤ 12.5%). The proportional residual variability in lenvatinib concentrations for TAD ≤ 2 h was moderate (%CV=48.5), moderate for cancer patient studies (%CV=40.2), and low for Phase 1 studies with full profiles (%CV=16.6).

**Summary of Individual Derived Pharmacokinetic Parameters of Lenvatinib in Subjects with EC**

Boxplot in the following figure shows the predicted CL/F among the different tumor types.

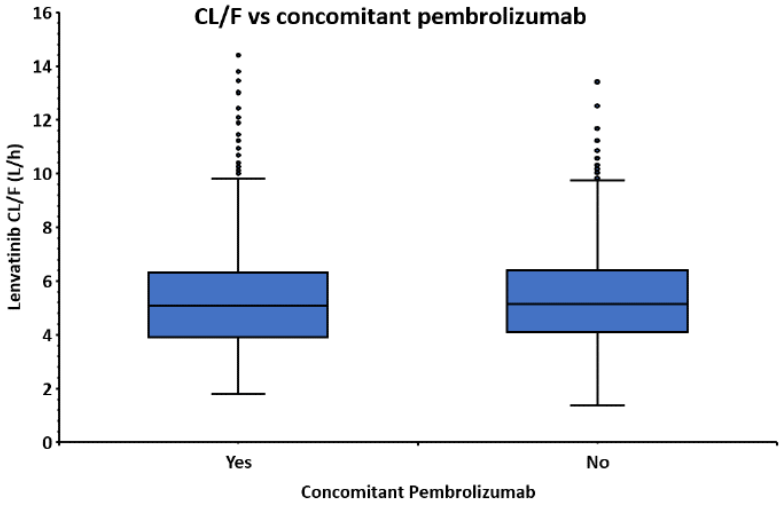
**Figure 2 – Relationship between individual Model-Predicted Lenvatinib CL/F and Tumour type**




DTC=thyroid; EC=endometrial cancer, HCC=hepatic cell carcinoma; RCC=renal cell carcinoma

While the effect of concomitant pembrolizumab on lenvatinib PK was found to be statistically significantly higher (by 7%), this effect is small and of no clinical relevance, as demonstrated graphically in the figure reported below. The figure depicts a major overlap in lenvatinib CL/F with and without concomitant pembrolizumab. The effect of concomitant pembrolizumab depicted below is based on comparisons of data from EC subjects from Studies KN775/309 and RCC subjects from Study 307/Arm B receiving lenvatinib + pembrolizumab with data from HCC subjects from Studies 202 and 304 receiving lenvatinib monotherapy and RCC subjects from Study 307/Arm A receiving lenvatinib + everolimus.

**Figure 3 – Relationship between individual Model-Predicted Lenvatinib CL/F and concomitant pembrolizumab**




Individual lenvatinib CL/F and AUC for EC subjects receiving lenvatinib 20 mg in combination with pembrolizumab in Study KN775/309 are summarized in the following table.

**Table 8 – Summary of individual mode-predicted lenvatinib pharmacokinetic parameters in EC subjects from lenvatinib + Pembrolizumab arm in study KN775/309**

| 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 |

The median and range of parameters are comparable with CL/F and AUC dose-normalized to 20 mg in subjects with RCC and other tumor types received lenvatinib monotherapy or with concomitant everolimus in the pooled PK dataset (table below), confirming the absence of an effect of pembrolizumab co-administration on lenvatinib exposure in EC subjects.

**Table 9 – Summary of individual mode-predicted lenvatinib CL/F and AUC dose-normalised to 20mg by Tumor type in subjects receiving lenvatinib monotherapy or concomitantly with pembrolizumab or Everolumus 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 |
| Thyroid | 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 |

RCC: Studies 112, 205, 218, 221 & 307 (Arms A & B); Thyroid: Studies 201, 211 and 303; HCC: Studies 202 and 304; other solid tumors: Studies 101, 102, 103, 105 & 115.

Study KN775/309 individual lenvatinib CL/F and AUC for Asian (Japanese + Chinese + other Asian), and Japanese and White/other populations receiving lenvatinib 20 mg in combination with pembrolizumab are summarized in the following two tables:

**Table 10 – Summary of individual model-predicted Lenvatinib pharmacokinetic parameters in EC subjects of lenvatinib+ pembrolizumab in Study KN775/309 (Asian vs White/Others)**

| Race | Parameter (unit) | N | Mean | SD | Median | Min | Max |
|---|---|---|---|---|---|---|---|
| White/Others | CL/F (L/h) | 318 | 4.86 | 1.42 | 4.90 | 1.78 | 10.15 |
| White/Others | AUC (ng•h/mL) | 318 | 3979 | 1313 | 3597 | 1738 | 9932 |
| Asian | CL/F (L/h) | 85 | 4.02 | 1.06 | 4.00 | 1.84 | 6.72 |
| Asian | AUC (ng•h/mL) | 85 | 4710 | 1340 | 4411 | 2626 | 9568 |

Asian = Japanese (N=52) + Chinese (N=2) + other Asian (N=31)

**Table 11 – Summary of individual model-predicted Lenvatinib pharmacokinetic parameters in EC subjects of lenvatinib+ pembrolizumab in Study KN775/309 (Japanese vs White/Others)**

| Race | Parameter (unit) | N | Mean | SD | Median | Min | Max |
|---|---|---|---|---|---|---|---|
| White/Others | CL/F (L/h) | 351 | 4.79 | 1.42 | 4.80 | 1.78 | 10.15 |
| White/Others | AUC (ng•h/mL) | 351 | 4047 | 1350 | 3672 | 1738 | 9932 |
| Japanese | CL/F (L/h) | 52 | 3.96 | 0.94 | 3.92 | 1.84 | 6.42 |
| Japanese | AUC (ng•h/mL) | 52 | 4721 | 1208 | 4505 | 2747 | 9568 |

The dataset contained 52 Japanese, 2 Chinese and 31 Asians other than Chinese or Japanese. The median and range of parameter values for these populations are comparable with White/Others receiving lenvatinib 20 mg in combination with pembrolizumab in Study KN775/309. Additionally, the results are depicted as boxplots in figures below, and demonstrated a major overlap for both CL/F and AUC (20 mg) between Asian or Japanese subjects and White/Others.

**Figure 4 -**

**Boxplot of CL/F and 20 mg AUC for Asian (Japanese + Chinese + other Asian) vs White/Other Subjects in EC subjects Treated with Lenvatinib + Pembrolizumab in Study KN775/309**

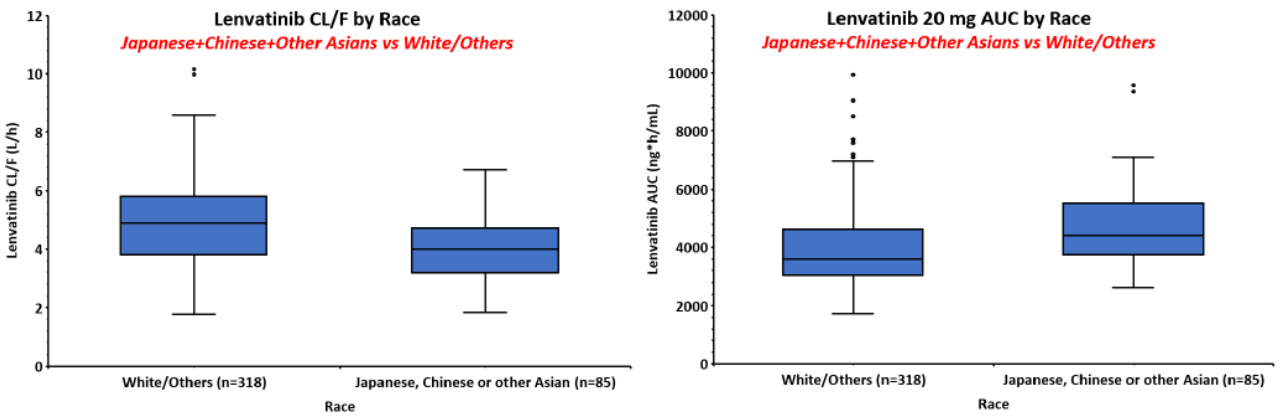
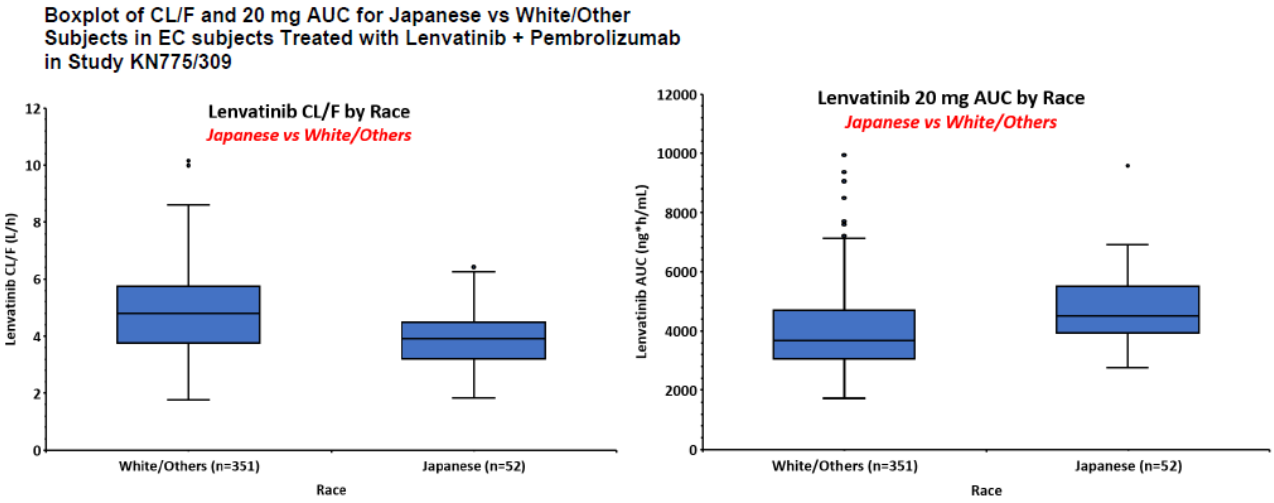
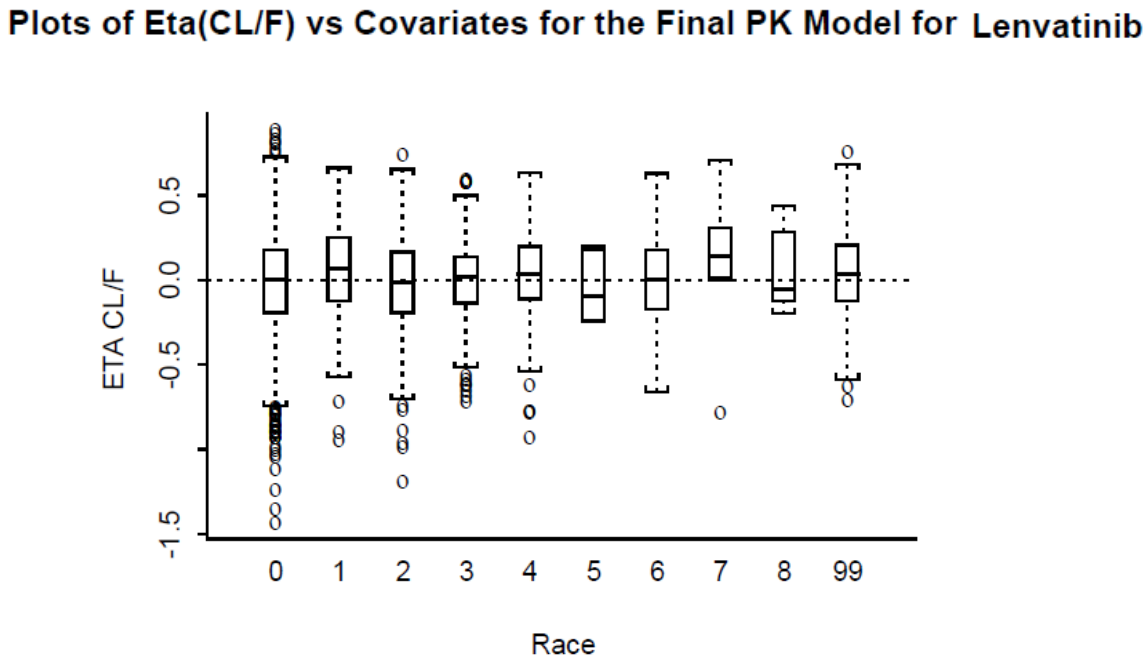


**Figure 5-**




This is also supported by the absence of an apparent relationship between eta (CL/F) and race, as depicted in the following figure.

**Figure 6 -**



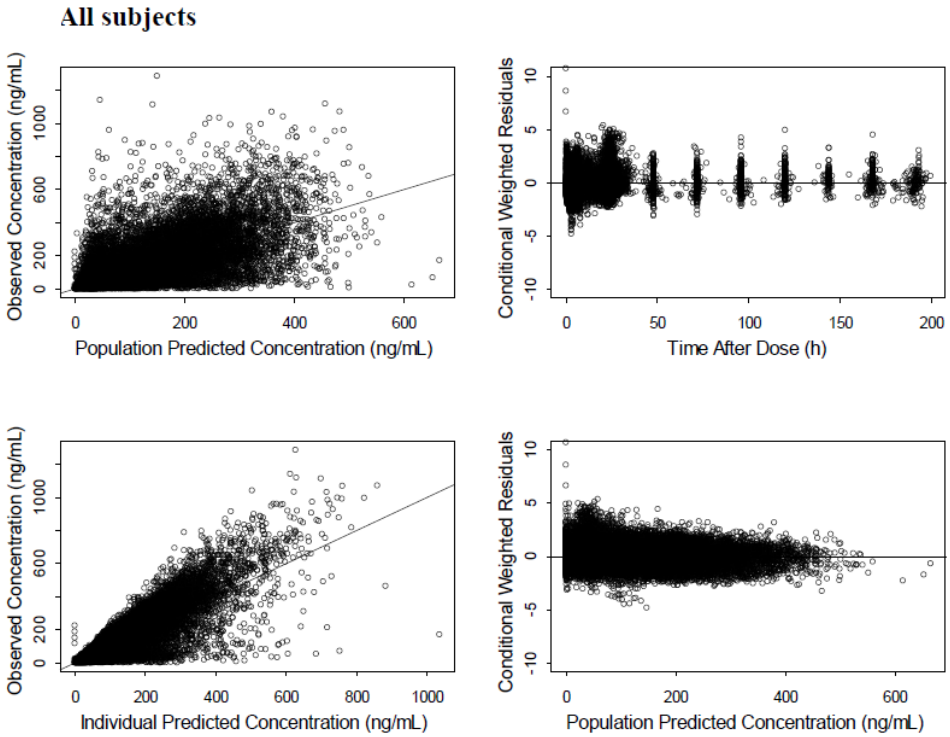

0 = White; 1 = Black or African American; 2 = Asian excluding Japanese or Chinese; 3 = Japanese; 4 = Chinese; 5 = Unknown; 6 = other or mixed race; 7 = American Indian or Alaskan Native; 8 = Native Hawaiian or other Pacific Islander; 99 = missing.

**Goodness of Fit Plots for the Final PK Model for Lenvatinib in the overall population ad EC patients.**

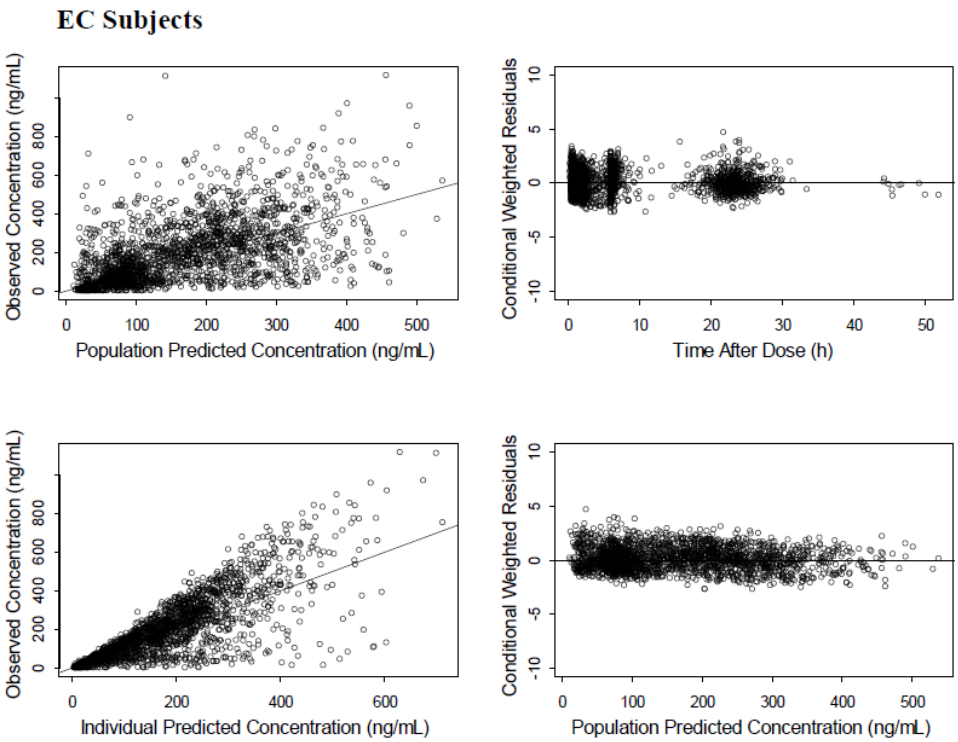
Goodness-of-fit-plots for the final PK model for lenvatinib based on the pooled dataset are presented in the figure reported below, overall and stratified by tumor type. The scatter plots of population model-predicted

and individual model-predicted concentrations versus observed concentrations showed even distribution around the line of unity. The scatter plots of CWRES vs. population predicted concentrations and vs. time showed the CWRES to be evenly distributed around zero, supporting the current PK model.

**Figures 7 -**

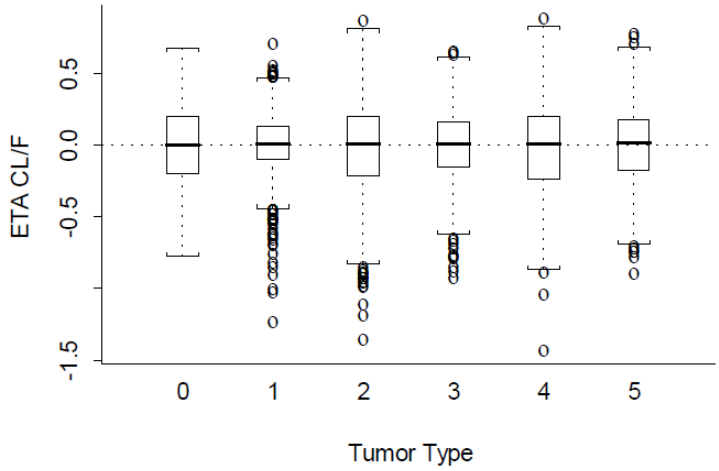



**Figures 8 -**



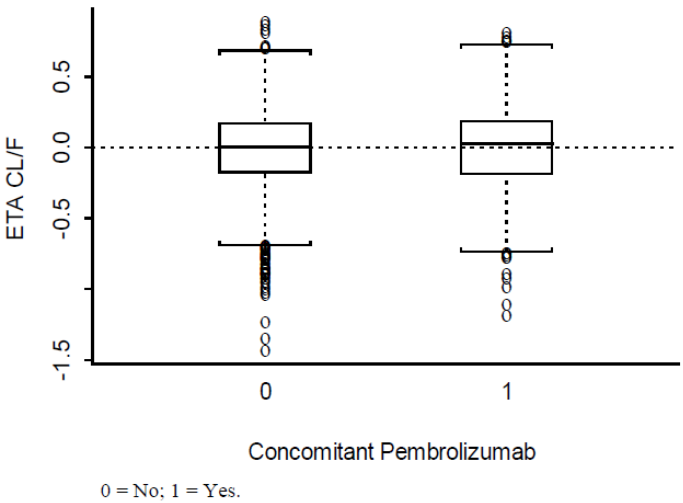
Plots of ETA (CL/F) vs covariates (tumor type and concomitant pembrolizumab) are presented in the following figures, which show that in the presence of established model covariates additional trends do not persist between CL/F and any of the other covariates, such as concomitant pembrolizumab and tumor type:

**Figure 9 -**




0=healthy subjects; 1 = DTC; 2 = RCC; 3 = HCC; 4 = other type of cancer; 5 = EC.

**Figure 10 -**

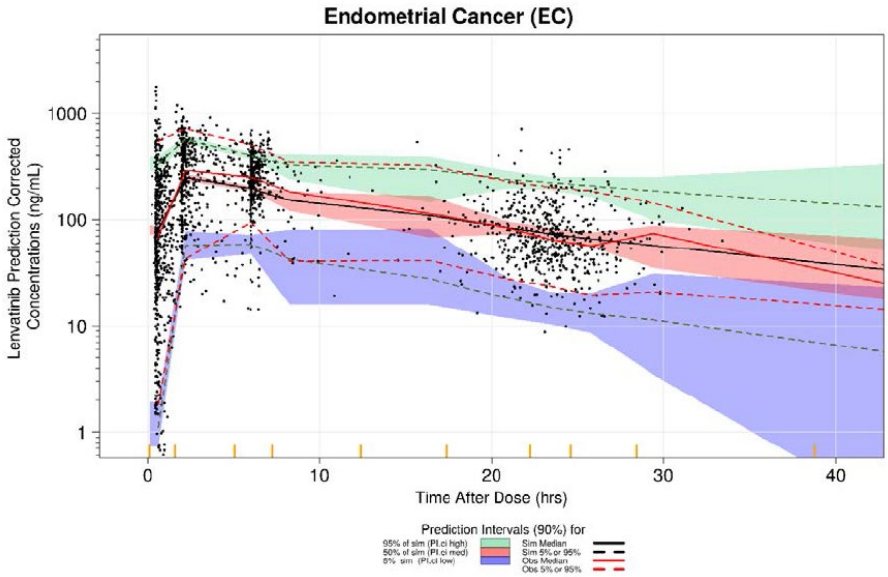



0 = No; 1 = Yes.

**Visual Predictive Check**

Final PK model was also evaluated using pcVPC (N=250). Figure 6 below shows lenvatinib PK profile up to 40 h post-doing in EC subjects of lenvatinib + pembrolizumab arm in Study KN775/309 and pcVPC plots by tumor type, see figure below:

**Figure 11 – Prediction-corrected visual predictive check observed and predicted lenvatinib concentrations in EC subjects treated with Lenvatinib + Pembrolizumab in Study KN775/309**




The 90% prediction intervals were constructed for the 5th, 50th and 95th percentiles of simulated and observed data. Plot display a good agreement of simulated and observed data across time, across all quantiles of data. The final PK model displays good predictive performance for the lenvatinib concentration time course in EC subjects from Study KN775/309 and other tumor types.

**Bootstrap**

Bootstrap results (N=250) for the lenvatinib population PK model are presented in Table below. The bootstrap median estimates and 95% CI include the NONMEM point estimates and standard errors based on asymptotic standard errors. This demonstrates the lenvatinib population PK model to be well supported by the observed data.

**Table 12 - Bootstrap results for final pharmacokinetic model for lenvatinib**

| Parameter | NONMEM Estimate | Bootstrap Median (95% CI) |
|---|---|---|
| $CL/F\ [L/h] = \Theta_{CL}*(WGT/74)^{0.75}*\Theta_{INHIB}^{INHIB}*\Theta_{ALP}^{ALP}*\Theta_{ALB}^{ALB}*\Theta_{HV}^{HV}*\Theta_{DTC}^{DTC}*\Theta_{HCC}^{HCC}*\Theta_{RCC}^{RCC}*\Theta_{EC}^{EC}*\Theta_{Pembro}^{Pembro}*\Theta_{SEX}^{SEX}$ | | |
| Basal CL/F in L/h [$\Theta_{CL}$] | 6.65 | 6.63 (6.42 – 6.87) |
| Effect of inhibitors on CL/F [$\Theta_{INHIB}$] | 0.896 Fixed | – |
| Effect of ALP (>ULN) on CL/F [$\Theta_{ALP}$] | 0.939 | 0.942 (0.918 – 0.963) |
| Effect of ALB (<30 g/L) on CL/F [$\Theta_{ALB}$] | 0.856 | 0.862 (0.804 – 0.906) |
| Effect of healthy subjects on CL/F [$\Theta_{HV}$] | 1.19 Fixed | – |
| Effect of DTC population on CL/F [$\Theta_{DTC}$] | 0.970 | 0.971 (0.932 – 1.01) |
| Effect of HCC population on CL/F [$\Theta_{HCC}$] | 0.824 | 0.824 (0.793 – 0.856) |
| Effect of RCC population on CL/F [$\Theta_{RCC}$] | 0.802 | 0.803 (0.774 – 0.832) |
| Effect of EC population on CL/F [$\Theta_{EC}$] | 0.751 | 0.746 (0.707 – 0.791) |
| Effect on concomitant pembrolizumab on CL/F [$\Theta_{Pembro}$] | 1.07 | 1.08 (1.04 – 1.12) |
| Effect on females on CL/F [$\Theta_{SEX}$] | 0.886 | 0.886 (0.861 – 0.912) |
| $V1/F\ [L] = \Theta_{V1}*WGT/74$ | | |
| Basal V1/F in L [$\Theta_{V1}$] | 45.1 | 45.2 (44.1 – 46.3) |
| $V2/F\ [L] = \Theta_{V2}*WGT/74$ | | |
| Basal V2/F in L [$\Theta_{V2}$] | 21.7 | 21.7 (20.1 – 23.2) |
| $V3/F\ [L] = \Theta_{V3}*WGT/74$ | | |
| Basal V3/F in L [$\Theta_{V3}$] | 30.9 Fixed | – |
| $Q1/F\ [L/h] = \Theta_{Q1}*(WGT/74)^{0.75}$ | | |
| Basal Q1/F in L/h [$\Theta_{Q1}$] | 3.61 | 3.61 (3.33 – 3.85) |
| $Q2/F\ [L/h] = \Theta_{Q2}*(WGT/74)^{0.75}$ | | |
| Basal Q2/F in L/h [$\Theta_{Q2}$] | 0.847 | 0.846 (0.798 – 0.893) |
| $Ka\ [1/h] = \Theta_{Ka}$ | | |
| Basal Ka in 1/h [$\Theta_{Ka}$] | 0.803 Fixed | – |
| $D1\ [h] = \Theta_{D1}$ | | |
| Basal D1 in h [$\Theta_{D1}$] | 1.27 Fixed | – |
| $F1 = \Theta_{F1}$ | | |
| Relative bioavailability of capsule vs tablet formulation [$\Theta_{F1}$] | 0.882 Fixed | – |
| **Inter-individual variability (%CV)** | | |
| CL/F | 33.5 | 33.4 (32.4 – 34.5) |

| Parameter | NONMEM Estimate | Bootstrap Median (95% CI) |
|---|---|---|
| V1/F | 43.6 | 43.3 (40.1 – 46.2) |
| V2/F | 65.0 | 65.6 (59.9 – 70.5) |
| V3/F | 33.9 | 33.5 (27.9 – 39.4) |
| Ka | 52.0 | 53.8 (42.2 – 64.6) |
| D1 | 104 | 103 (99.6 – 108) |
| **Residual variability** | | |
| Proportional (%CV) (Clin pharm studies) | 16.6 | 16.6 (15.2 – 17.8) |
| Proportional (%CV) (Patients studies) | 40.2 | 40.3 (39.5 – 41.1) |
| Proportional (%CV) (TAD ≤ 2 h) | 48.5 | 48.4 (46.2 – 50.4) |
| Additional (ng/mL) (TAD ≤ 2 h) | 17.5 | 17.5 (12.3 – 21.2) |

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

**PK/Safety Analyses**

Lenvatinib population PK model was used to derive individual PK parameters and resulting lenvatinib exposure (AUC) in subjects from Study KN775/309. This lenvatinib exposure measure was based on the starting treatment dose and individual-level predictions of pharmacokinetic parameters. Exposure data were merged with the PK/TEAEs analysis dataset. The PK/safety analysis for TEAEs included 403 subjects with EC from Study KN775/309. The subject quartiles of lenvatinib AUC (Q1 - Q4 group) are presented in the table below:

**Table 13 - Lenvatinib AUC group for PK/safety analysis for TEAEs for Study KN775/309**

| | AUC Q1 group | AUC Q2 group | AUC Q3 group | AUC Q4 group |
|---|---|---|---|---|
| N | 101 | 101 | 101 | 100 |
| AUC range (ng·h/mL) | 1740-3140 | 3160-3840 | 4870-4280 | 4870-9930 |
| Median AUC (ng·h/mL) | 2860 | 3470 | 4280 | 5770 |

Q: Quartile

Results from each TEAE analysis: hypertension, proteinuria, weight decrease, vomiting and hypothyroidism is presented below, from Figure 7 to Figure 11, respectively. Left figure panels display the observed proportion of TEAE CTC grades across four quartiles of lenvatinib AUC (stacked barplots). Right panels illustrate the central tendency of the relationship between lenvatinib AUC and the model predicted probability across each of the 3 grades of common terminology criteria for adverse events.

**Figure 12 – Lenvatinib AUC vs. Proportion of Hypertension CTC grades**

[Left] Observed proportion of hypertension CTC grades by quartile of lenvatinib exposure
[Right] Predicted proportion of hypertension CTC grades, solid line

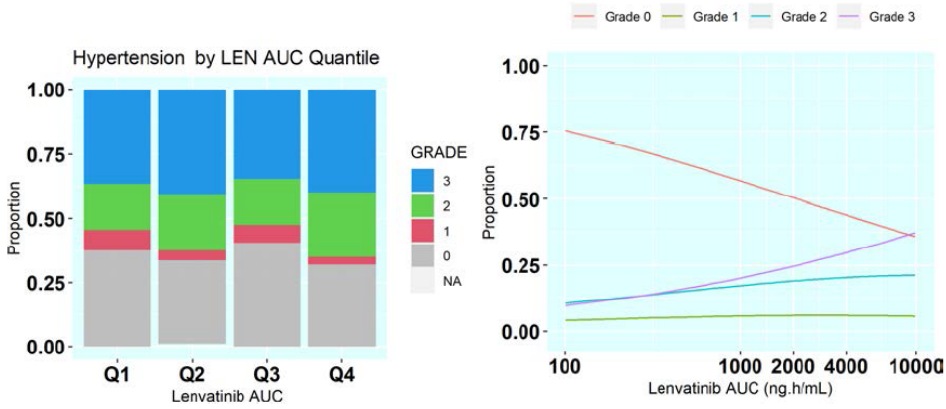



**Figure 13 – Lenvatinib AUC vs. Proportion of Proteinuria CTC grades**

[Left] Observed proportion of proteinuria CTC grades by quartile of lenvatinib exposure
[Right] Predicted proportion of proteinuria CTC grades, solid line

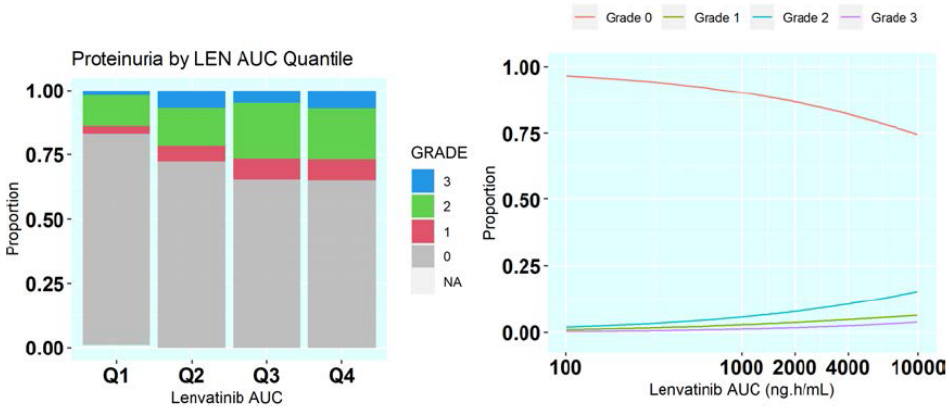



**Figure 14 – Lenvatinib AUC vs. Proportion of weight decrease CTC grades**

[Left] Observed proportion of weight decreased CTC grades by quartile of lenvatinib exposure
[Right] Predicted proportion of weight decreased CTC grades, solid line

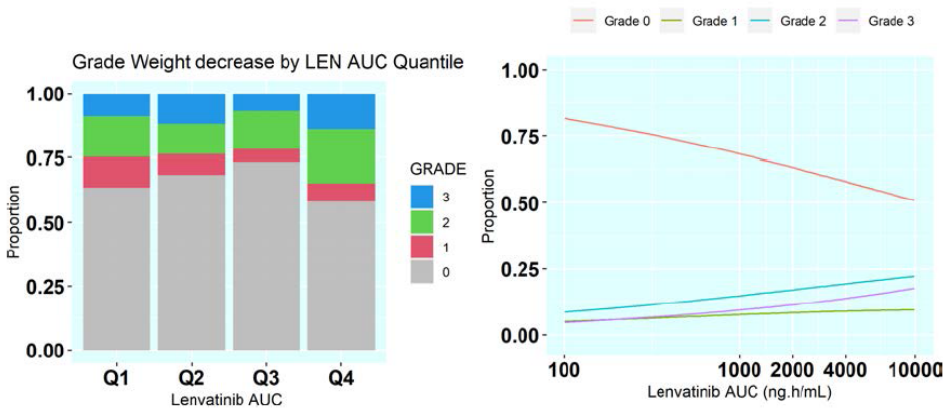


**Figure 15 - Lenvatinib AUC vs. Proportion of vomiting CTC grades**

[Left] Observed proportion of vomiting CTC grades by quartile of lenvatinib exposure
[Right] Predicted proportion of vomiting CTC grades, solid line

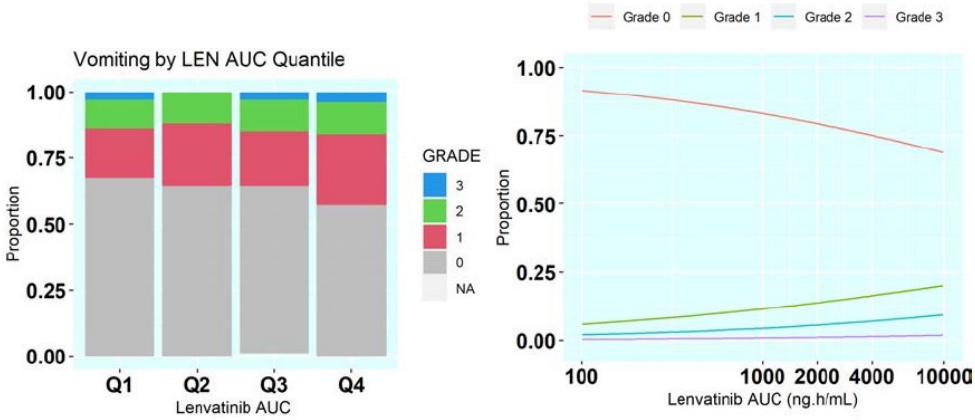
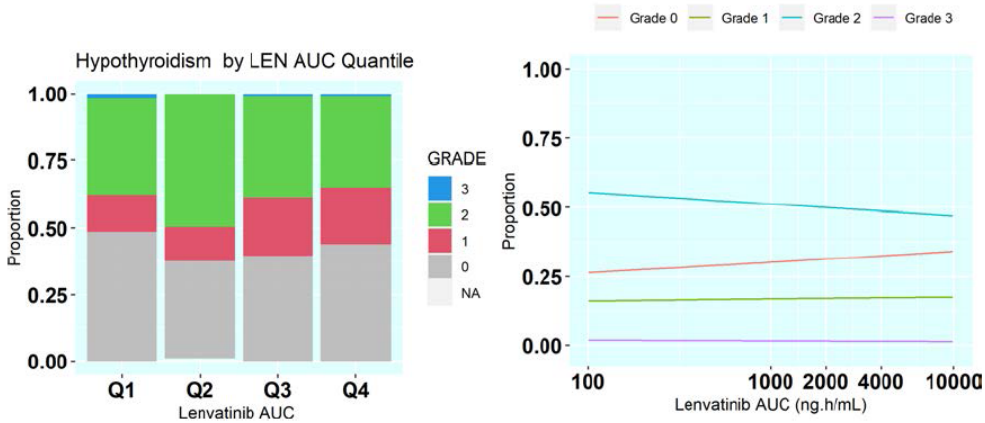



**Figure 16 – Lenvatinib AUC vs. Proportion of Hypothyroidism CTC grades**

[Left] Observed proportion of hypothyroidism CTC grades by quartile of lenvatinib exposure
[Right] Predicted proportion of hypothyroidism CTC grades, solid line




There was a weak, generally positive relationship of TEAEs and lenvatinib AUC, for all TEAE categories except for hypothyroidism, where the relationship was essentially flat over the AUC range. The 95% CIs for the exposure logit parameter included 0 across all TEAE categories. For hypertension, proteinuria, weight decreased and vomiting, probability of any AE (GRADE >0 ) increased on average up to 7% across the range of Q1-Q4 exposures corresponding to 12.5%-87.5% of the distribution, as represented in Table 14.

**Table 14 Point Estimate of Probability of Grade 1 to 3 TEAEs at Median Lenvatinib Concentration Quantiles**

| Lenvatinib AUC Quartile Median | Hypertension | Proteinuria | Weight decreased | Vomiting | Hypothyroidism |
|---|---|---|---|---|---|
| [a]Q1 (2860 ng·h/mL) | 0.531 | 0.155 | 0.396 | 0.208 | 0.680 |
| Q2 (3470 ng·h/mL) | 0.548 | 0.168 | 0.410 | 0.223 | 0.677 |
| Q3 (4280 ng·h/mL) | 0.567 | 0.183 | 0.426 | 0.239 | 0.673 |
| Q4 (5770 ng·h/mL) | 0.597 | 0.207 | 0.449 | 0.263 | 0.668 |

## 2.3.3. Pharmacodynamics

### *Mechanism of action*

KEYTRUDA is an antibody that binds to the programmed death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. KEYTRUDA potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.

## 2.3.4. PK/PD modelling

Data from Arm A of the study were used to explore the relationship between exposure to lenvatinib and safety events related to lenvatinib (**Population Analysis** CPMS-E7080-015P-v1), see section above.

No new information regarding PK/PD modelling for pembrolizumab is available within this extension of indication.

## 2.3.5. Discussion on clinical pharmacology

Clinical pharmacology results for the combination therapy of Pembrolizumab together with Lenvatinib, specific to support approval for second line treatment of advanced endometrial carcinoma (EC), are available from the Phase 3 Study 309/KEYNOTE-775.

*Analytical methods*
The lenvatinib method validation (Project n. 187184AUWZ) as well as the bioanalytical report (MK-3475-775) were submitted.
The method for the determination of lenvatinib (MK-7902) was proven to be precise, accurate, sensitive and selective over the validated range from 0.25 to 250 ng/mL. Dilution integrity has been demonstrated using QC samples at 2500 ng/mL, diluted 20 folds and showed that it does not affect precision and accuracy. The method is reliable and reproducible and the analyte and the internal standard are 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.

The long-Term stability validation of lenvatinib in matrix (human sodium heparinized plasma) has been evaluated and demonstrated for a period up to 675 days at -20°C and -80°C.

Calibration standard and QC acceptance criteria for each analytical run were set according to the EMA "Guideline on bioanalytical method validation" (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**). Intra-run and between-run precision and accuracy were suitably demonstrated. Linearity of calibration curve was set applying a weighted (1/x2) linear least-squares regression of the peak area ratios (analyte to internal standard) of the calibration standards. The selectivity of the assay was confirmed by processing control (analyte-free) human sodium heparinized plasma samples in each run to demonstrate that no interfering

compounds elute at the same retention times than that of the analyte and internal standard. Interfering medications investigated, at therapeutic concentrations, were: acetaminophen, acetylsalicylic acid, caffeine, cotinine, dimenhydrinate, dextromethorphan, diphenhydramine, ethinyl estradiol, ibuprofen, levonorgestrel, nicotine, pseudoephedrine, and salicylic acid. The results met the pre-established acceptance criteria.
The MAH stated that during assay development and validation, multiple LC MS/MS systems (LC MS MS 4000 01, LC MS MS 4000 13 and LC MS MS 4000 17) were used and found to be equivalent. System performances such as calibration curves, Y intercept and slope were found to be comparable across systems, therefore no cross or partial validation has been considered necessary across systems.

A total of 461 re-assayed analyses (18.80%) corresponding to 425 re-analyzed study samples were performed. Main reason for re-analysis (18.07% of the total) was concentrations measured above the upper limit of quantitation of the calibration curve. A total of 173 study samples were successfully analyzed for the incurred sample reproducibility analysis fulfilling the acceptance criteria as set by relevant EMA guideline.

*Pharmacokinetic data*
The clinical pharmacology package for this Application includes 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.

Plasma concentrations of Pembrolizumab and ADA were not collected in Study 309/KEYNOTE-775.

Pembrolizumab PK and ADA data were not collected in Study 309/KEYNOTE-775, and so no new information is provided for pembrolizumab in alignment with the agreement reached with the Rapporteurs in 2017. Although it is understood that the potential of DDI between biologics and small molecules, such as lenvatinib, is negligible, considering divergent metabolic pathways for both compounds sparse samples should have been collected for pembrolizumab to check if the observed concentrations in EC patients treated with pembrolizumab in combination with lenvatinib fall within the range of predicted concentrations (using the reference model), both after first dose and at steady state.
It was also clarified that PK data of pembrolizumab have been collected in a number of other studies investigating the same combination therapy (pembrolizumab and lenvatinib) in another indication where PK results confirmed no impact to the exposures of pembrolizumab and lenvatinib in presence of each other in the combination setting.

Although this was understood, the dossier of this procedure lacked a clear reference to tables and figures that demonstrate this consistency in exposures.

An updated lenvatinib population PK analysis was provided that describes objectives, methods and results of the population PK analysis of lenvatinib using data pooled across several studies, including Study KN-775/309. This report also includes PK/safety analyses (Study KN-775/309/Arm A) in subjects with EC.
The updated Population PK analysis was performed using data from Study KN775/309 in subjects with EC pooled with data from Phase 1 studies in healthy volunteers and Phase 1, 2 and/or 3 studies in subjects with other solid tumors, for a total of 22 studies. Exposure-response analysis for adverse events related to lenvatinib only was performed using data from Study 309/Arm A in subjects with EC.

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 KN775/309.

A lot of Lenvatinib Observations were excluded from PK Dataset as "outlier, inconsistent with PK profile". In total 79 PK observations of 2408 (3.3% of total) from Study 309/KEYNOTE-775 were excluded from the PK analyses. Most of the excluded PK observations were inconsistent with the PK profile of lenvatinib with the majority of those with TAD >60 hours having concentrations close to the limit of quantification of 0.25 ng/mL. These excluded observations were causing numerical difficulties during estimation resulting in model termination or termination with errors. When these observations were excluded the PK model terminated successfully.

Regarding excluded BLQ observations from Study 309/KEYNOTE-775, 97 observations (1.4% of total observations) were associated with TAD $\leqslant$200 hours, and the majority (>79%) of those were TAD $\leqslant$1 hour.

Linear and semi-log plots of dose-normalized lenvatinib plasma concentration versus time after dose at steady state in EC patients, showed that median lenvatinib plasma concentration-time profiles were comparable when lenvatinib was administered alone and with pembrolizumab. As already stated no data are available for pembrolizumab plasma concentration in combination with lenvatinib.

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.

All the parameters of the final model seem to be well estimated with a %RSE $\leqslant$ 3.76%.

The EC population was estimated with a 24.9% lower lenvatinib CL/F compared with other solid tumor types excluding DTC, RCC and HCC. Moreover, Lenvatinib CL/F was found to be 7% higher with concomitant pembrolizumab. Individual Derived Pharmacokinetic Parameters, CL/F and AUC, for EC subjects receiving lenvatinib 20 mg in combination with pembrolizumab in Study KN775/309 were compared with CL/F and AUC dose-normalized to 20 mg in subjects with RCC and other tumor types received lenvatinib monotherapy or with concomitant everolimus in the pooled PK dataset.

The CL of lenvatinib in EC patients is lower and hence the AUC higher than both the values of lenvatinib in monotherapy and the values of lenvatinib in combination with everolimus in RCC.

However, the CL of lenvatinib 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. No hypothesis on the cause of the observed difference in CL in EC patients, with the argument that the magnitude of this effect in EC patients (24.9%) is within the inter-subject variability for CL (33.5%) and hence of no apparent clinical relevance.

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 (tumor type and concomitant pembrolizumab) seems to be normally distributed with a mean of 0.

The Final PK model was also evaluated using pcVPC. The prediction corrected VPCs which includes and excludes Study 309/KEYNOTE-775 were provioded. Plots indicates good predictive performance of the final PK model for the lenvatinib concentration time course in the overall population considered in the final model (popPK analysis of lenvatinib from all studies) both including and excluding Study 309/KEYNOTE-775.

Lenvatinib population PK model was used to derive individual PK parameters and resulting lenvatinib exposure (AUC) in subjects from Study KN775/309, and exposure data were merged with the PK/TEAEs analysis dataset.

There was a weak, generally positive relationship of TEAEs and lenvatinib AUC, for all TEAE categories (hypertension, proteinuria weight decrease and vomiting) except for hypothyroidism, where the relationship was essentially flat over the AUC range.

Pembrolizumab Dose: The MAH stated that as the 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 would 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.

## 2.3.6. Conclusions on clinical pharmacology

The Pharmacokinetics of Pembrolizumab was not evaluated in Study 309/KEYNOTE-775.

# *2.4. Clinical efficacy*

## 2.4.1. 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. Since then, this dosage has been implemented across the lenvatinib plus pembrolizumab clinical programme.

**KEYNOTE-146: A Multicenter, Open-Label Phase 1b/2 Trial of Lenvatinib (E7080) Plus Pembrolizumab in Subjects With Selected Solid Tumors**

E7080-A001-111/KEYNOTE-146 is an ongoing, multicenter, open-label, Phase 1b/2 study of the combination of lenvatinib plus pembrolizumab in subjects with 1 of the following confirmed metastatic tumor types: EC, renal cell carcinoma (RCC), non-small-cell lung cancer (NSCLC), squamous cell carcinoma of the head and neck (HNSCC), urothelial carcinoma (UC), or melanoma.

The study was conducted in 2 phases, Phase 1b and Phase 2.

- In **Phase 1b (dose finding)**, the primary objective was to determine and confirm the maximum tolerated dose (MTD) for lenvatinib once daily (QD) in combination with pembrolizumab 200 mg Q3W in subjects with selected solid tumors.

The MTD was investigated using a dose de-escalation strategy with a 3 + 3 design.

The lenvatinib doses selected were 24, 20, and 14 mg QD all in combination with pembrolizumab 200 mg Q3W given IV. Lenvatinib 24 mg was selected as the starting dose based on the recommended dose for lenvatinib monotherapy in locally differentiated thyroid cancer (see Lenvima SmPC). Lenvatinib 20 mg and 14 mg were the first and second doses in lenvatinib's dose reduction scheme for all tumors (except hepatocellular carcinoma) for which data were available.

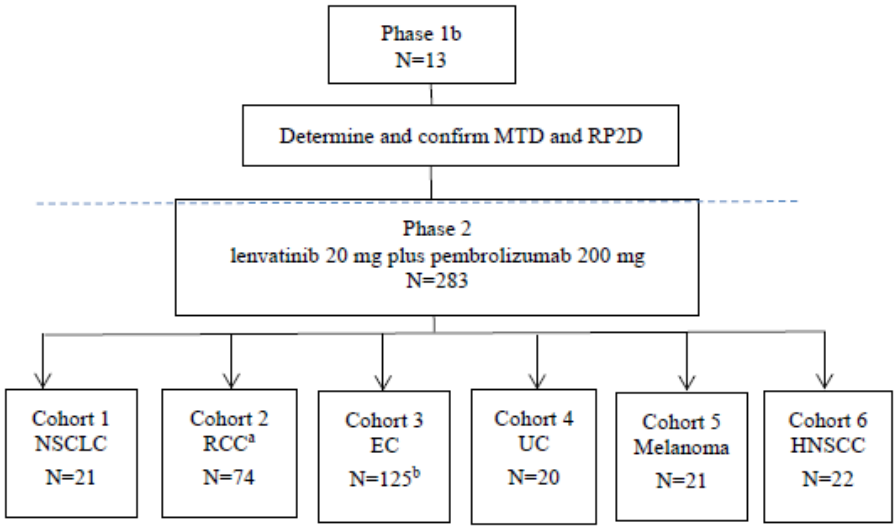
For determination of the MTD, only dose-limiting toxicities (DLTs) during the first 21 days (Cycle 1) of treatment were assessed. Once the MTD was determined, the recommended Phase 2 dose (RP2D) for lenvatinib to be used in combination with pembrolizumab was chosen and enrollment in Phase 2 began, where RP2D was used.

A total of **13 subjects** were enrolled in phase 1b. The first 3 subjects, including 2 subjects with RCC and 1 with NSCLC, received lenvatinib at **24 mg** QD in combination with pembrolizumab 200 mg Q3W (Dose

Level 1). Two of the 3 subjects experienced a DLT during the first cycle of treatment (Grade 3 arthralgia and Grade 3 fatigue, respectively). In both cases, the dose of lenvatinib was reduced and the subjects continued to receive study treatment. Subsequently, the combination of lenvatinib **20 mg** plus pembrolizumab 200 mg (Dose Level 2) was investigated in 3 subjects, including 2 subjects with EC. No DLTs were observed and the cohort was expanded to a total of 10 subjects to confirm the MTD. No other DLTs were observed, and the MTD was determined to be lenvatinib 20 mg plus pembrolizumab 200 mg, which was the RP2D for the Phase 2 Extension.

- In **Phase 2 (extension)**, subjects were assigned by tumor type to 1 of 6 cohorts (EC, RCC, NSCLC, HNSCC, UC, or melanoma) and received the RP2D of lenvatinib 20 mg QD orally plus pembrolizumab 200 mg IV Q3W. Primary objective was to evaluate ORR as of Week 24 in each of the cohorts, using immune-related (ir) RECIST per investigator assessment. A total of 273 subjects were enrolled in Phase 2 and received the RP2D of the combination.

**Figure 17: Study 111/KEYNOTE-146 Phase 2 design schematic – cohort expansion in selected tumours**

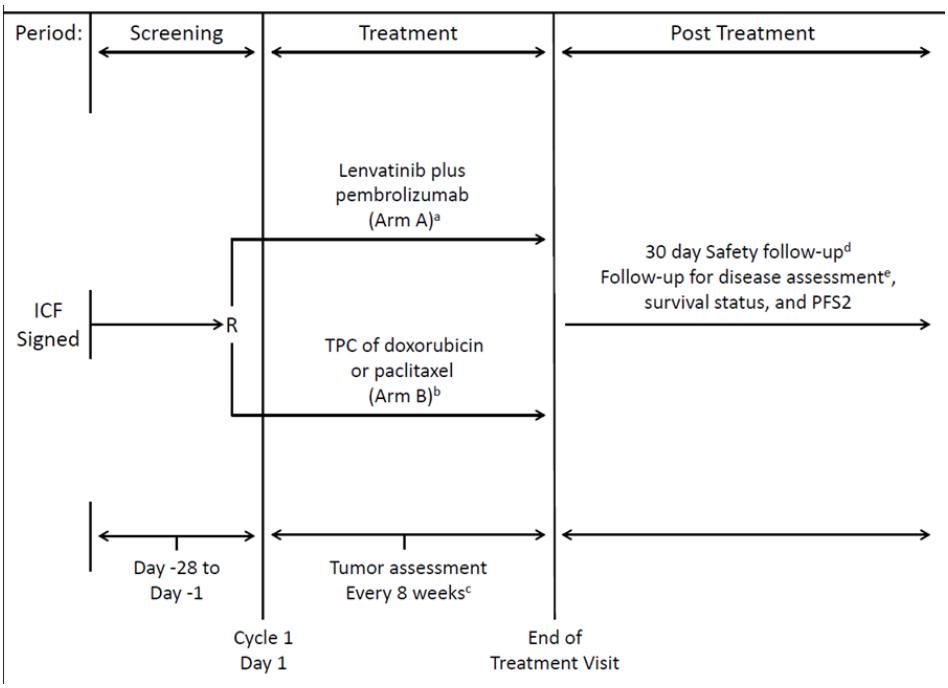



## 2.4.2. Main study

## Title of Study

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

**Figure 18 : Study 309/KEYNOTE-775 study design**




Abbreviations: AEs = adverse events; BICR = blinded independent central review; ICF = informed consent form; PD = progressive disease; PFS2 = progression-free survival on next line of therapy; Q8W = every 8 weeks; Q12W = every 12 weeks; R = randomization; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; TPC = Treatment of Physician's Choice.

[a] Lenvatinib 20 mg orally once daily plus pembrolizumab 200 mg intravenously every 3 weeks.

[b] Doxorubicin 60 mg/m2 (by intravenous bolus, 1-hour infusion, or per institutional guidelines) every 3 weeks or paclitaxel 80 mg/m2 (by 1-hour infusion or per institutional guidelines) given weekly, 3 weeks on/1 week off. Maximum doses of study drugs: doxorubicin (cumulative lifetime dosage of 500 mg/m2 or lower as consistent with site's standard of care); paclitaxel (per site standard of care).

[c] Imaging to be performed Q8W from the date of randomization, or sooner if clinically indicated, until BICR-confirmation of disease progression per RECIST 1.1.

[d] If End of Treatment visit occurs ≥30 days from last dose of study treatment, a safety follow-up visit is not required.

[e] For participants discontinuing for reasons other than BICR-confirmed PD, starting another anticancer therapy, tumor imaging should be performed Q8W from the date of randomization, or more frequently if clinically indicated, until BICR-confirmed PD during Efficacy Follow-up. Following the primary analysis for the study, follow-up visits and tumor assessments should be performed Q12W or more frequently if required by local standard of care. Serious AEs that occur within 120 days of the end of treatment or before initiation of a new anticancer treatment should also be followed and recorded.

## *Methods*

## Study participants

Key Inclusion Criteria:

- Histologically confirmed EC.
- 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.
- Provided a fresh or archival tumor sample for determination of MMR status.

- Had at least 1 measurable target lesion according to RECIST 1.1, including a non-nodal target lesion ≥1 cm in the longest diameter and LN lesion that measured ≥1.5 cm in the short axis.
- Female participants of at least 18 years of age, if she is not pregnant not breastfeeding and not a WOCBP or a WOCBP who agrees to follow contraceptive guidelines as per protocol.
- Written informed consent.
- Had an ECOG Performance Status of 0 or 1.
- Adequately controlled blood pressure 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.
- Adequate organ function (as defined in the protocol)

Key Exclusion Criteria:

- Had carcinosarcoma (malignant mixed Műllerian tumor), endometrial leiomyosarcoma and endometrial stromal sarcomas.
- Had CNS metastases, unless they have completed local therapy and have discontinued the use of corticosteroids for this indication for at least 4 weeks before starting treatment in this study.
- Had gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of lenvatinib.
- Had a pre-existing Grade ≥3 gastrointestinal or non-gastrointestinal fistula.
- Radiographic evidence of major blood vessel invasion/infiltration.
- Clinically significant hemoptysis or tumor bleeding within 2 weeks prior to the first dose of study drug.
- Had significant cardiovascular impairment within 12 months of the first dose of study drug (such as history of congestive heart failure greater than NYHA Class II, unstable angina, myocardial infarction or cerebrovascular accident, stroke, or cardiac arrhythmia associated with hemodynamic instability.
- Active infection (any infection requiring systemic treatment).
- Known positivity for HIV, known active HBV or HCV.
- Has a history of (non-infectious) pneumonitis that required treatment with steroids, or has current pneumonitis.
- Had a diagnosis of immunodeficiency or was 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.
- Had an active autoimmune disease (with the exception of psoriasis) that required systemic treatment in the past 2 years. Replacement therapy is not considered a form of systemic treatment.
- Had received greater than 1 prior systemic chemotherapy regimen (other than adjuvant or neoadjuvant) for EC. Participants may have received up to 2 regimens of platinum-based chemotherapy in total, as long as one was given in the neoadjuvant or adjuvant treatment setting.
- Prior treatment with any treatment targeting VEGF-directed angiogenesis, any anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
- Had urine protein ≥1 g/24 h.
- Had prolongation of QTc interval to >480 ms.

- Had LVEF below the institutional (or local laboratory) normal range as determined by MUGA or ECHO.

**Biomarker assessment**

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.

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

POLE mutation was not assessed.

## Treatments

**Table 15: study interventions**

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

Abbreviations: IV = intravenous; Q3W = every 3 weeks; QD = once daily; QW = every week.
a. 4 mg capsules provided for successive dose reduction of lenvatinib.
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.
Maximum doses of study drugs: pembrolizumab (35 cycles); doxorubicin (cumulative lifetime dosage of 500 mg/m$^2$ or lower as consistent with site's standard of care); paclitaxel (per site standard of care); no maximum number of doses for lenvatinib.

Prior to randomization, investigators selected and recorded the TPC option to be used in the event the participant was assigned to that arm.

Cross-over was not permitted.

Imaging to be performed Q8W from the date of randomization, or sooner if clinically indicated, until BICR-confirmation of disease progression per RECIST 1.1.

## Objectives and endpoints

PFS and OS were dual primary efficacy endpoints, evaluated in pMMR participants and all-comer participants.

ORR was key secondary endpoint (i.e. hypothesis tested within the multiplicity testing strategy with alpha control) evaluated in pMMR participants and all-comer participants.

**Table 16 -**

| 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).<br><br>*Hypothesis (H1):* The combination of lenvatinib and pembrolizumab is superior to TPC as assessed by PFS in pMMR participants.<br><br>*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).<br><br>*Hypothesis (H2):* The combination of lenvatinib and pembrolizumab is superior to TPC as assessed by OS in pMMR participants.<br><br>*Hypothesis (H5):* The combination of lenvatinib and pembrolizumab is superior to TPC as assessed by OS in all-comer participants. | **OS**, defined as the time from date of randomization to date of death from any cause. |
| **Secondary** | |
| *Objective:* To compare the objective response rate (ORR) of participants treated with lenvatinib in combination with pembrolizumab versus TPC by BICR.<br><br>*Hypothesis (H3):* The combination of lenvatinib and pembrolizumab is superior to TPC as assessed by ORR in pMMR participants.<br><br>*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 | Incidence of treatment-emergent adverse events (TEAEs), serious AEs (SAEs), and immune-related AEs. |

| | |
|---|---|
| pembrolizumab versus TPC in pMMR participants and in all-comer participants. | Proportion of participants discontinuing study treatment due to TEAEs.<br><br>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. |
| **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.<br><br>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 | 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 |

| | |
|---|---|
| versus TPC by investigator assessment in pMMR participants and in all-comer participants. | 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 pembrolizumab in pMMR participants and in all-comer participants. | Molecular (genomic, metabolic, and/or proteomic) determinants of response or resistance to treatments, using blood and/or tumor tissue. |

## Sample size

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

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

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

Sample size and power calculations based on pMMR participants: the study had 90% power to detect a statistically significant difference in **OS** at one-sided α=0.0245 and as a result, 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 43 months after the first participant is randomized (19 months enrollment plus 24 months follow-up period), required to detect a statistically significant difference in **OS** at 0.0245 level with 90% power, under the following assumptions that: 1) HR 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 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 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 alpha 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 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), required to detect a statistically significant difference in **OS** at 0.02205 level with 93.5% power, under the following assumptions: 1) HR 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

Patients were randomized in a 1:1 ratio to the combination of lenvatinib and pembrolizumab or to TPC (doxorubicin or paclitaxel). Treatment allocation/randomization will occur centrally using an interactive response technology (IRT) system, based on the following stratification factors:

- MMR status (pMMR or dMMR)

- ECOG performance status (0 or 1)

- geographic region (Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel or Region 2: rest of the world)

- prior history of pelvic radiation (yes or no).

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

## Blinding (masking)

This was an open-label study.

All images obtained were submitted to a blinded independent central review (BICR) to assess objective response and progression-free survival.

## Statistical methods

**Populations for efficacy analysis:** The Intention-to-Treat (ITT) population served as the population for the primary efficacy analyses, which included all randomized participants, analyzed in the treatment group to which they were randomized.

The HRQoL analyses are based on the HRQoL full analysis set (FAS) population, defined as participants who have received treatment and have at least one HRQoL assessment available.

**Statistical methods:** Analyses were performed in two subsets of subjects: All-comer participants and pMMR participants.

For the primary analysis of PFS and OS, the non-parametric Kaplan-Meier method was used to estimate the PFS curve in each treatment group. The treatment difference in PFS was assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (ie, the HR) between the treatment arms. The stratification factors used for randomization (MMR status, ECOG, geographic region, and prior history of pelvic radiation) were applied to both the stratified log-rank test and the stratified Cox model.

For ORR, stratified Miettinen and Nurminen's method was used for comparison of the ORR between two treatment groups. The stratification factors used for randomization were applied to the analysis. The point estimate of ORR and 95% CI using exact binomial method proposed by Clopper and Pearson (1934) were to be provided.

**Censoring rules:**

**Table 17: 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 |
| PD or death documented immediately after ≥2 consecutive missed disease assessments or after new anti-cancer therapy, if any | 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 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. | | | |

**Table 18: Censoring Rules for DOR**

| Situation | Date of Progression or Censoring | Outcome |
|---|---|---|
| No progression nor death, no new anti-cancer therapy initiated | Last adequate disease assessment | Censor (non-event) |
| No progression nor death, new anti-cancer therapy initiated | Last adequate disease assessment before new anti-cancer therapy initiated | Censor (non-event) |
| Death or progression immediately after ≥ 2 consecutive missed disease assessments or after new anti-cancer therapy, if any | Earlier date of last adequate disease assessment prior to ≥ 2 missed adequate disease assessments and new anti-cancer therapy, if any | Censor (non-event) |
| Death or progression after ≤ 1 missed disease assessments and before new anti-cancer therapy, if any | PD or death | End of response (Event) |
| A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response. | | |

**Interim analyses:** efficacy interim analyses (IA) were conducted by the external DMC. Two OS IA and one OS final analysis (FA) were planned. The PFS FA was performed at the time of first IA for OS. Since the timing of the first interim analysis is driven by the required number of OS event, the observed number of PFS events may be different from the expected counts. The Lan-DeMets spending function with O'Brien-Fleming boundary were used for alpha allocation among IA and FA for OS.

**Table 19: 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<br>OS | Both ~368 OS events and at least 6 months after last participant randomized | ~27 months | Final PFS analysis<br>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; OS = overall survival; PFS = progression-free survival; pMMR = mismatch repair proficient.

† 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).

**Multiplicity:** The total family-wise error rate (Type-I error) among the dual-primary PFS and OS and the secondary ORR endpoints was strongly controlled at one-sided 0.025 level. The multiplicity strategy followed the graphical approach of Maurer and Bretz.

**Figure 19: Multiplicity Graph for Type I Error Control of Study Hypotheses**

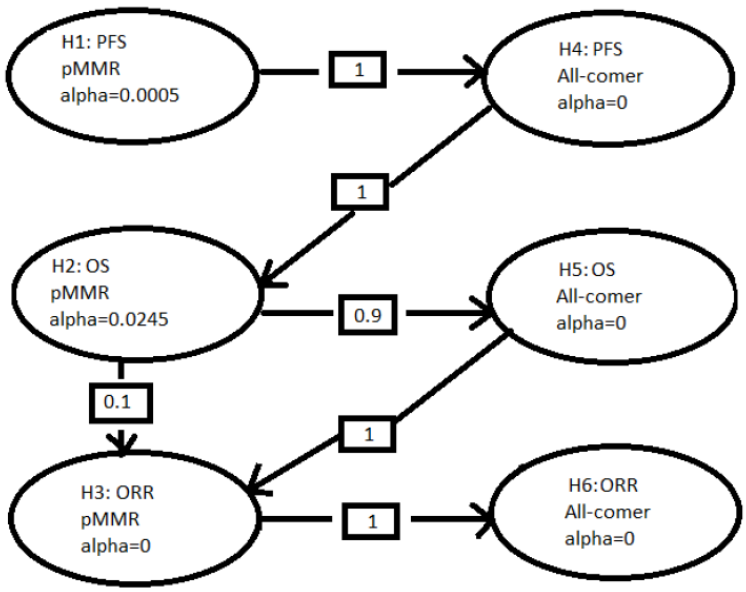


**Table 20: Boundary Properties for Planned Analyses of OS Based on Potential Alpha-Levels to be Used for Testing in the pMMR Participants**

| Analysis | Value | α =0.0245 | α =0.025 |
|---|---|---|---|
| IA1<br>N: 660<br>OS events: 368 (70%*)<br>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<br>N: 660<br>OS Events: 463 (88%*)<br>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<br>N: 660<br>OS Events: 526<br>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.

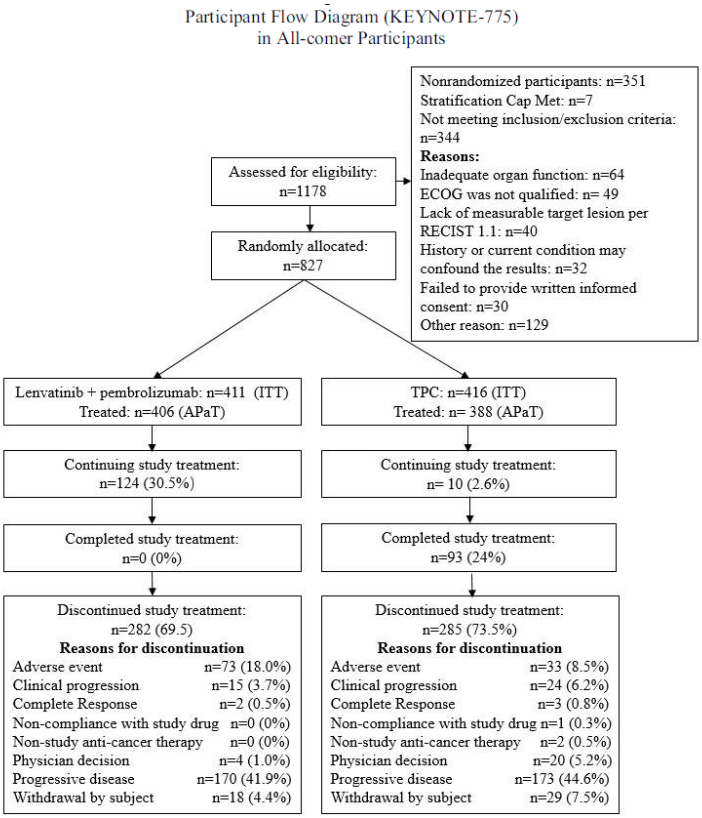
**Table 21: Boundary Properties for Planned Analyses of OS Based on Potential Alpha-Levels to be Used for Testing in the All-comer Participants at pMMR Participant Analysis Time Points**

| Analysis | Value | α =0.02205 | α =0.0225 |
|---|---|---|---|
| IA1<br>N: 780<br>OS events: 433 (70%*)<br>Month: 27 | Z | 2.5000 | 2.4901 |
| | *p* (1-sided) † | 0.0062 | 0.0064 |
| | HR at bound ‡ | 0.7862 | 0.7870 |
| | P(Cross) if HR=1 § | 0.0062 | 0.0064 |
| | P(Cross) if HR=0.75 ¦ | 0.6890 | 0.6927 |
| | | | |
| IA2<br>N: 780<br>OS Events: 544 (88%*)<br>Month: 35 | Z | 2.2318 | 2.2222 |
| | *p* (1-sided) † | 0.0128 | 0.0131 |
| | HR at bound ‡ | 0.8257 | 0.8263 |
| | P(Cross) if HR=1 § | 0.0147 | 0.0150 |
| | P(Cross) if HR=0.75 ¦ | 0.8750 | 0.8769 |
| | | | |
| FA<br>N: 780<br>OS Events: 618<br>Month: 43 | Z | 2.1109 | 2.1030 |
| | *p* (1-sided) † | 0.0174 | 0.0177 |
| | HR at bound ‡ | 0.8437 | 0.8443 |
| | P(Cross) if HR=1 § | 0.0221 | 0.0225 |
| | P(Cross) if HR=0.75 ¦ | 0.9354 | 0.9365 |

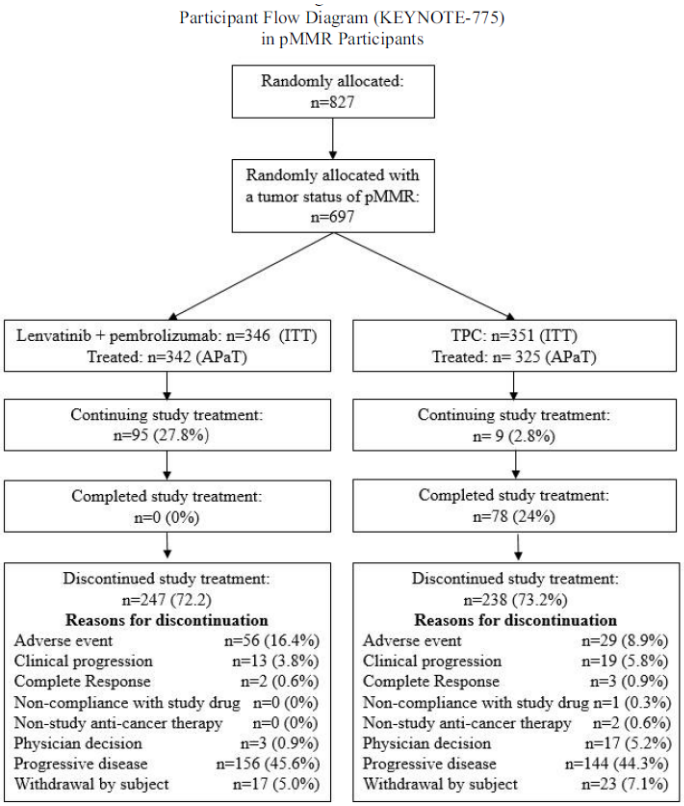
Abbreviation: HR = hazard ratio; IA= interim analysis; FA= final analysis.
The number of events and timings are estimated.
* Percentage of total planned events at the interim analysis.
† *p* (1-sided) is the nominal α for group sequential testing.
‡ HR at bound is the approximate observed HR required 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*

### Figure 20 - Participant flow




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




Abbreviations: APaT=All patient as treated; ITT=intent to treat.
Source:[Table 10-2] [Table 10-4]

Disposition of Participants
in All-comer Participants
(ITT Population)

| | Lenvatinib + Pembrolizumab | | TPC | | Total | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Participants in population | 411 | | 416 | | 827 | |
| **Status for Trial** | | | | | | |
| Discontinued | 191 | (46.5) | 264 | (63.5) | 455 | (55.0) |
| Death | 184 | (44.8) | 236 | (56.7) | 420 | (50.8) |
| Lost To Follow-Up | 0 | (0.0) | 2 | (0.5) | 2 | (0.2) |
| Withdrawal By Subject | 7 | (1.7) | 26 | (6.3) | 33 | (4.0) |
| Participants Ongoing | 220 | (53.5) | 152 | (36.5) | 372 | (45.0) |
| **Status for Study medication in Trial** | | | | | | |
| Started | 406 | | 388 | | 794 | |
| Completed | 0 | (0.0) | 93 | (24.0) | 93 | (11.7) |
| Discontinued | 282 | (69.5) | 285 | (73.5) | 567 | (71.4) |
| Adverse Event | 73 | (18.0) | 33 | (8.5) | 106 | (13.4) |
| Clinical Progression | 15 | (3.7) | 24 | (6.2) | 39 | (4.9) |
| Complete Response | 2 | (0.5) | 3 | (0.8) | 5 | (0.6) |
| Non-Compliance With Study Drug | 0 | (0.0) | 1 | (0.3) | 1 | (0.1) |
| Non-Study Anti-Cancer Therapy | 0 | (0.0) | 2 | (0.5) | 2 | (0.3) |
| Physician Decision | 4 | (1.0) | 20 | (5.2) | 24 | (3.0) |
| Progressive Disease | 170 | (41.9) | 173 | (44.6) | 343 | (43.2) |
| Withdrawal By Subject | 18 | (4.4) | 29 | (7.5) | 47 | (5.9) |
| Participants Ongoing | 124 | (30.5) | 10 | (2.6) | 134 | (16.9) |

If the overall count of participants is calculated and displayed within a section in the first row, then it is used as the denominator for the percentage calculation. Otherwise, participants in population is used as the denominator for the percentage calculation.
Completed study medication: For Lenvatinib + Pembrolizumab, completed 35 infusions of pembrolizumab. For TPC of doxorubicin, received a lifetime maximum cumulative dose of doxorubicin or for TPC of paclitaxel, a maximum tolerable dose was reached per investigator.
TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

Disposition of Participants
in pMMR Participants
(ITT Population)

| | Lenvatinib + Pembrolizumab | | TPC | | Total | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Participants in population | 346 | | 351 | | 697 | |
| **Status for Trial** | | | | | | |
| Discontinued | 168 | (48.6) | 219 | (62.4) | 387 | (55.5) |
| Death | 161 | (46.5) | 196 | (55.8) | 357 | (51.2) |
| Lost To Follow-Up | 0 | (0.0) | 2 | (0.6) | 2 | (0.3) |
| Withdrawal By Subject | 7 | (2.0) | 21 | (6.0) | 28 | (4.0) |
| Participants Ongoing | 178 | (51.4) | 132 | (37.6) | 310 | (44.5) |
| **Status for Study medication in Trial** | | | | | | |
| Started | 342 | | 325 | | 667 | |
| Completed | 0 | (0.0) | 78 | (24.0) | 78 | (11.7) |
| Discontinued | 247 | (72.2) | 238 | (73.2) | 485 | (72.7) |
| Adverse Event | 56 | (16.4) | 29 | (8.9) | 85 | (12.7) |
| Clinical Progression | 13 | (3.8) | 19 | (5.8) | 32 | (4.8) |
| Complete Response | 2 | (0.6) | 3 | (0.9) | 5 | (0.7) |
| Non-Compliance With Study Drug | 0 | (0.0) | 1 | (0.3) | 1 | (0.1) |
| Non-Study Anti-Cancer Therapy | 0 | (0.0) | 2 | (0.6) | 2 | (0.3) |
| Physician Decision | 3 | (0.9) | 17 | (5.2) | 20 | (3.0) |
| Progressive Disease | 156 | (45.6) | 144 | (44.3) | 300 | (45.0) |
| Withdrawal By Subject | 17 | (5.0) | 23 | (7.1) | 40 | (6.0) |
| Participants Ongoing | 95 | (27.8) | 9 | (2.8) | 104 | (15.6) |

If the overall count of participants is calculated and displayed within a section in the first row, then it is used as the denominator for the percentage calculation. Otherwise, participants in population is used as the denominator for the percentage calculation.
Completed study medication: For Lenvatinib + Pembrolizumab, completed 35 infusions of pembrolizumab. For TPC of doxorubicin, received a lifetime maximum cumulative dose of doxorubicin or for TPC of paclitaxel, a maximum tolerable dose was reached per investigator.
TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

## Recruitment

Participants were enrolled from 11-JUN-2018 to 03-FEB-2020 across 167 global sites in 21 countries worldwide.

## Conduct of the study

### 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 reported for 51 participants in this study, 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 (deviations that may compromise critical data analyses pertaining to primary efficacy and/or safety endpoints or the participant's safety) (2.4%), 11 vs 9 subjects in the combination vs control arm, respectively.

**Table 22: 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]

### Protocol amendment

Two general protocol amendment and 5 country-specific protocol amendment were issued (see table below):

**Table 23: Protocol amendments of study 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. |

## Baseline data

**Table 24: 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) |
| **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 25: Prior Therapies for Endometrial Cancer (ITT Population)**

| | Lenvatinib + Pembro | | TPC | | Total | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Participants in population | 411 | | 416 | | 827 | |
| **Prior Lines of Systemic Therapy** | | | | | | |
| 1 | 297 | (72.3) | 277 | (66.6) | 574 | (69.4) |
| 2 | 103 | (25.1) | 126 | (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) | 315 | (75.7) | 641 | (77.5) |
| 2 | 83 | (20.2) | 101 | (24.3) | 184 | (22.2) |
| >=3 | 1 | (0.2) | 0 | (0.0) | 1 | (0.1) |
| **Neo-adjuvant/Adjuvant** | | | | | | |
| Yes | 224 | (54.5) | 251 | (60.3) | 475 | (57.4) |
| No | 187 | (45.5) | 165 | (39.7) | 352 | (42.6) |
| **Primary Therapy** | | | | | | |
| Yes | 74 | (18.0) | 48 | (11.5) | 122 | (14.8) |
| No | 337 | (82.0) | 368 | (88.5) | 705 | (85.2) |
| **Progressive Disease/Relapse** | | | | | | |
| Yes | 197 | (47.9) | 214 | (51.4) | 411 | (49.7) |
| No | 214 | (52.1) | 202 | (48.6) | 416 | (50.3) |
| **Palliative Hormonal Therapy** | | | | | | |
| Yes | 36 | (8.8) | 44 | (10.6) | 80 | (9.7) |
| No | 375 | (91.2) | 372 | (89.4) | 747 | (90.3) |
| **Prior Systemic Therapies Received by Setting [a]** | | | | | | |
| Neo-adjuvant/adjuvant only | 144 | (35.0) | 159 | (38.2) | 303 | (36.6) |
| Primary therapy | 69 | (16.8) | 43 | (10.3) | 112 | (13.5) |
| Progressive disease/relapse only | 114 | (27.7) | 117 | (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) | 329 | (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) | 199 | (47.8) | 388 | (46.9) |
| No | 222 | (54.0) | 217 | (52.2) | 439 | (53.1) |
| **History of Prior Brachytherapy** | | | | | | |
| Yes | 103 | (25.1) | 122 | (29.3) | 225 | (27.2) |
| No | 308 | (74.9) | 294 | (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]

**Table 26: Adminstration of Pembrolizumab, Doxorubicin and Paclitaxel in All-comer participants (APaT population)**

| | Lenvatinib + Pembrolizumab | TPC | |
|---|---|---|---|
| | Pembrolizumab | Doxorubicin | Paclitaxel |
| Participants in population | 406 | 289 | 99 |
| Number of Cycles Received | | | |
| N | 406 | 289 | 99 |
| Mean (SD) | 12.1 (8.7) | 4.8 (2.5) | 6.7 (4.3) |
| Median | 10.0 | 5.0 | 6.0 |
| Range | 1 to 35 | 1 to 10 | 1 to 27 |

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

Source: [P775V01MK3475: adam-adsl; adamsum]

Of 99 participants treated with paclitaxel in the all-comer population, 81 (81.8%) received paclitaxel before study with 53 (53.5%) receiving paclitaxel in the neoadjuvant/adjuvant setting.

**Table 27: 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 | 5 | (1.4) | 6 | (1.7) | 11 | (1.6) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Differentiation | | | | | | |
| 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 28 : Prior Therapies for Endometrial Cancer in pMMR Participants (ITT Population)**

| | Lenvatinib + Pembrolizumab | | TPC | | Total | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Participants in population | 346 | | 351 | | 697 | |
| **Prior Lines of Systemic Therapy** | | | | | | |
| 1 | 244 | (70.5) | 226 | (64.4) | 470 | (67.4) |
| 2 | 92 | (26.6) | 114 | (32.5) | 206 | (29.6) |
| >=3 | 10 | (2.9) | 11 | (3.1) | 21 | (3.0) |
| **Prior Lines of Platinum Based Therapy** | | | | | | |
| 0 | 1 | (0.3) | 0 | (0.0) | 1 | (0.1) |
| 1 | 269 | (77.7) | 257 | (73.2) | 526 | (75.5) |
| 2 | 75 | (21.7) | 94 | (26.8) | 169 | (24.2) |
| >=3 | 1 | (0.3) | 0 | (0.0) | 1 | (0.1) |
| **Neo-adjuvant/Adjuvant** | | | | | | |
| Yes | 197 | (56.9) | 219 | (62.4) | 416 | (59.7) |
| No | 149 | (43.1) | 132 | (37.6) | 281 | (40.3) |
| **Primary Therapy** | | | | | | |
| Yes | 60 | (17.3) | 40 | (11.4) | 100 | (14.3) |
| No | 286 | (82.7) | 311 | (88.6) | 597 | (85.7) |
| **Progressive Disease/Relapse** | | | | | | |
| Yes | 165 | (47.7) | 183 | (52.1) | 348 | (49.9) |
| No | 181 | (52.3) | 168 | (47.9) | 349 | (50.1) |
| **Palliative Hormonal Therapy** | | | | | | |
| Yes | 30 | (8.7) | 35 | (10.0) | 65 | (9.3) |
| No | 316 | (91.3) | 316 | (90.0) | 632 | (90.7) |
| **Prior Systemic Therapies Received by Setting [a]** | | | | | | |
| Neo-adjuvant/adjuvant only | 125 | (36.1) | 133 | (37.9) | 258 | (37.0) |
| Primary therapy | 55 | (15.9) | 35 | (10.0) | 90 | (12.9) |
| Progressive disease/relapse only | 90 | (26.0) | 92 | (26.2) | 182 | (26.1) |
| Treatment in both neo-adjuvant/adjuvant and PD/relapse setting | 71 | (20.5) | 86 | (24.5) | 157 | (22.5) |
| Not Applicable | 5 | (1.4) | 5 | (1.4) | 10 | (1.4) |
| **Interval from End of Most Recent Therapy to First Dose (mos)** | | | | | | |
| Participants with data | 342 | | 325 | | 667 | |
| Mean | 7.8 | | 8.6 | | 8.2 | |
| SD | 9.2 | | 11.9 | | 10.6 | |
| Median | 4.8 | | 5.5 | | 5.1 | |
| Range | 0 to 74 | | 0 to 100 | | 0 to 100 | |
| **History of Prior Hysterectomy** | | | | | | |
| Yes | 252 | (72.8) | 279 | (79.5) | 531 | (76.2) |
| No | 94 | (27.2) | 72 | (20.5) | 166 | (23.8) |
| **History of Prior External Beam Radiotherapy** | | | | | | |
| Yes | 155 | (44.8) | 159 | (45.3) | 314 | (45.1) |
| No | 191 | (55.2) | 192 | (54.7) | 383 | (54.9) |
| **History of Prior Brachytherapy** | | | | | | |
| Yes | 88 | (25.4) | 97 | (27.6) | 185 | (26.5) |
| No | 258 | (74.6) | 254 | (72.4) | 512 | (73.5) |

[a] Does not include the therapeutic setting of palliative hormonal therapy.

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

**Table 29: Study Population Lenvatinib + Pembrolizumab, Doxorubicin, and Paclitaxel in pMMR Participants**

| | Lenvatinib + Pembrolizumab | Doxorubicin | Paclitaxel | Total |
|---|---|---|---|---|
| Number of Participants Randomized (ITT) | 346 | 254 | 97 | 697 |
| Number of Participants Received Treatment (Actual Treatment) (APaT) [a] | 342 | 239 | 86 | 667 |
| Number of Participants Randomized and Did not Receive Treatment | 4 | 16 | 10 | 30 |

[a] Includes one participant in the Doxorubicin column for whom the investigator site selected paclitaxel prior to randomization, but was actually treated with doxorubicin.
Database Cutoff Date: 26OCT2020

Medical History and Concurrent Illnesses: In all-comer participants, the 2 treatment groups were generally comparable for medical history conditions and concurrent illnesses. More than 50% of participants reported prior medical history of gastrointestinal disorders or vascular disorders. Approximately 13% of participants had hypothyroidism in each group. About 10% had hepatobiliary disorders including 4.0% with cholelithiasis (similar incidence in both groups) and 4.3% with hepatic steatosis (6.7% in the lenvatinib plus pembrolizumab group and 1.8% in the TPC group). About 50% of participants had metabolism and nutrition disorders including diabetes mellitus (9.3%), type 2 diabetes mellitus (9.1%), hypercholesterolemia (10.1%) and obesity (5.5%). More than half of the patients had vascular disorders including 44.7% with hypertension in both arms.

## Numbers analysed

A total of 827 patients were included in the ITT population (411 in the pembrolizumab + lenvatinib arm vs 416 in the chemotherapy arm). Of those, 697 (84.3%) were pMMR (346 in the pembrolizumab + lenvatinib arm vs 351 in the chemotherapy arm).

**Table 30 : 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

**Table 31 : 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

## Outcomes and estimation

Results of IA1 analysis were provided (i.e. final for PFS, interim for OS). As of the data cut-off date of 26-OCT-2020 for IA1, the median duration of follow up in the overall population (all comers and pMMR populations) was 11.4 months (range 0.3, 26.9).

**Table 32 : Efficacy Summary at IA1 (primary analysis populations all comers and pMMR; dMMR population is <u>not</u> included in the multiplicity strategy)**

| | **pMMR Endometrial Carcinoma** | | **All-Comer Participants** | | ***dMMR endometrial carcinoma*** | |
|---|---|---|---|---|---|---|
| **Endpoint** | **Lenvatinib + Pembrolizumab (N=346)** | **TPC (Chemotherapy) (N=351)** | **Lenvatinib + Pembrolizumab (N=411)** | **TPC (Chemotherapy) (N=416)** | ***Lenvatinib + Pembrolizumab (N=65)*** | ***TPC (Chemotherapy) (N=65)*** |
| **PFS (BICR Assessment per RECIST 1.1)** | | | | | | |
| Nb of events (%) | 247 (71.4) | 238 (67.8) | 281 (68.4) | 286 (68.8) | *34 (52.3)* | *48 (73.8)* |
| Median PFS[a], months (95% CI) | 6.6 (5.6, 7.4) | 3.8 (3.6, 5.0) | 7.2 (5.7, 7.6) | 3.8 (3.6, 4.2) | *10.7 (5.6, NR)* | *3.7 (3.1, 4.4)* |
| HR (95% CI)[b] p-value[c] | 0.60 (0.50, 0.72), <0.0001 | | 0.56 (0.47, 0.66), <0.0001 | | *0.36 (0.23, 0.57)* | |
| **OS** | | | | | | |
| Nb of events (%) | 165 (47.7) | 203 (57.8) | 188 (45.7) | 245 (58.9) | *23 (35.4)* | *42 (64.6)* |
| Median OS[a], months (95% CI) | 17.4 (14.2, 19.9) | 12.0 (10.8, 13.3) | 18.3 (15.2, 20.5) | 11.4 (10.5, 12.9) | *NR (NR, NR)* | *8.6 (5.5, 12.9)* |
| HR (95% CI)[b] p-value[c] | 0.68 (0.56, 0.84), 0.0001 | | 0.62 (0.51, 0.75), <0.0001 | | *0.37 (0.22, 0.62)* | |
| **ORR % (95% CI) (BICR Assessment per RECIST 1.1)** | 30.3 (25.5, 35.5) | 15.1 (11.5, 19.3) | 31.9 (27.4, 36.6) | 14.7 (11.4, 18.4) | *40 (28.0, 52.9)* | *12.3 (5.5, 22.8)* |
| CR, n (%) (95% CI) | 18 (5.2) (3.1, 8.1) | 9 (2.6) (1.2, 4.8) | 27 (6.6) (4.4, 9.4) | 11 (2.6) (1.3, 4.7) | *9 (13.8)* | *2 (3.1)* |
| ORR Difference % (95% CI)[d], p-value[e] | 15.2 (9.1, 21.4), <0.0001 | | 17.2 (11.5, 22.9), <0.0001 | | *27.7 (12.9, 41.7)* | |
| **Median Duration of Response** months (range) | N=105 9.2 (1.6+ - 23.7+) | N=53 5.7 (0.0+ - 24.2+) | N=131 14.4 (1.6+ - 23.7+) | N=61 5.7 (0.0+ - 24.2+) | *N=26 NR (2.1+ - 20.4+)* | *N=8 4.1 (1.9+ - 15.6+)* |

Abbreviations: BICR: blinded independent central review; CI = confidence interval; CR = complete response; dMMR = mismatch repair deficient; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; pMMR = mismatch repair proficient; TPC = treatment of physician's choice.

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, MMR status (all-comer only) and prior history of pelvic radiation.

c: One-sided p-value based on log-rank test stratified by ECOG performance status, MMR status (all-comer only), geographic region, and prior history of pelvic radiation.

d: Based on Miettinen & Nurminen method stratified by ECOG performance status, geographic region, MMR status (all-comer only), and prior history of pelvic radiation.

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

Data cutoff: 26-OCT-2020

**Primary Endpoints**

- **Progression-Free Survival**

At the IA1 (corresponding to final analysis for PFS), the combination of lenvatinib plus pembrolizumab was statistical significantly superior to TPC with respect to PFS in both pMMR participants and all-comer participants.

***All comers***

**Table 33- Analysis of progression free survival on BICR 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 | 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.
BICR= Blinded Independent Central Review.
TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

**Table 34 – Summary of event and censoring description for progression free survival based on BICR assessment per RECIST 1.1 (Primary censoring rule) in all-comer participants (ITT population)**

| | Lenvatinib + Pembrolizumab (N=411) | TPC (N=416) |
|---|---|---|
| Number of Events (%) | 281 (68.4) | 286 (68.8) |
| Death | 40 (9.7) | 39 (9.4) |
| Documented Progression | 241 (58.6) | 247 (59.4) |
| Number of Censored (%) | 130 (31.6) | 130 (31.3) |
| New Anti-Cancer Therapy | 24 (5.8) | 77 (18.5) |
| No Pd/Death As Of The Data Cutoff Date | 101 (24.6) | 35 (8.4) |
| No Adequate Post-Baseline Disease Assessment | 5 (1.2) | 18 (4.3) |
| Kaplan-Meier Estimates (months)[a] | | |
| Median (95% CI) | 7.2 (5.7, 7.6) | 3.8 (3.6, 4.2) |
| [Q1, Q3] | [3.7, 18.2] | [1.9, 7.4] |

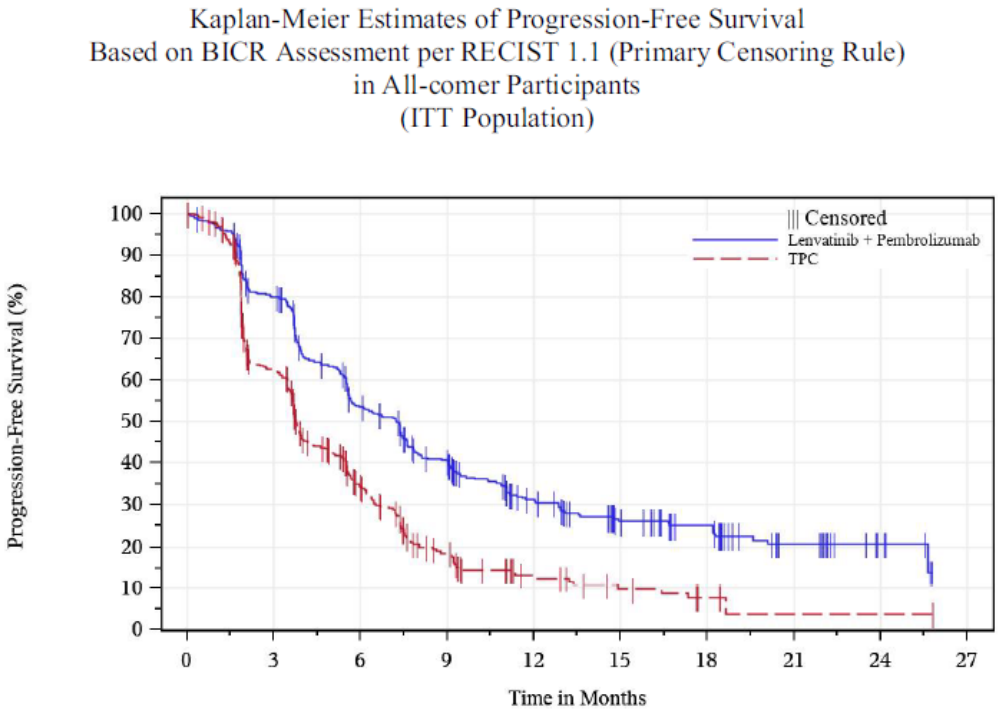
a From product-limit (Kaplan-Meier) method for censored data.
BICR = Blinded independent central review.
TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

**Table 35 – Summary of progression free survival rate over time based on BICR assessment per RECIST 1.1 (Primary censoring rule) in all-comer participants (ITT population)**

| | 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

**Figure 21 -**



***pMMR participants***

**Table 36- Analysis of progression free survival on BICR assessment per RECIST 1.1 (Primary censoring rule) in pMMR 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 | 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 37 – Summary of event and censoring description for progression free survival based on BICR assessment per RECIST 1.1 (Primary censoring rule) in pMMR participants (ITT population)**

| | Lenvatinib + Pembrolizumab (N=346) | TPC (N=351) |
|---|---|---|
| Number of Events (%) | 247 (71.4) | 238 (67.8) |
| Death | 32 (9.2) | 26 (7.4) |
| Documented Progression | 215 (62.1) | 212 (60.4) |
| Number of Censored (%) | 99 (28.6) | 113 (32.2) |
| New Anti-Cancer Therapy | 20 (5.8) | 70 (19.9) |
| No Pd/Death As Of The Data Cutoff Date | 74 (21.4) | 28 (8.0) |
| No Adequate Post-Baseline Disease Assessment | 5 (1.4) | 15 (4.3) |
| Kaplan-Meier Estimates (months)[a] | | |
| Median (95% CI) | 6.6 (5.6, 7.4) | 3.8 (3.6, 5.0) |
| [Q1, Q3] | [3.7, 12.9] | [1.9, 7.5] |

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

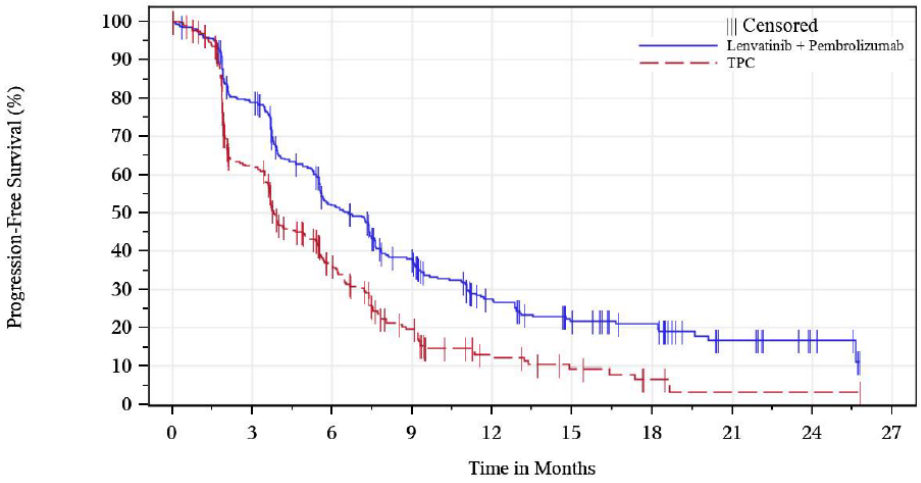
**Table 38 – Summary of progression free survival rate over time based on BICR assessment per RECIST 1.1 (Primary censoring rule) in pMMR participants (ITT population)**

| | 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

**Figure 22-**

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




**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 |

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

- **Overall Survival**

At IA1, KEYNOTE-775 met the success criteria for the hypothesis of OS in pMMR and all-comer participants.

***All comers***

**Table 39 – Analysis of overall survival in all-comer participants (ITT population)**

| 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] |

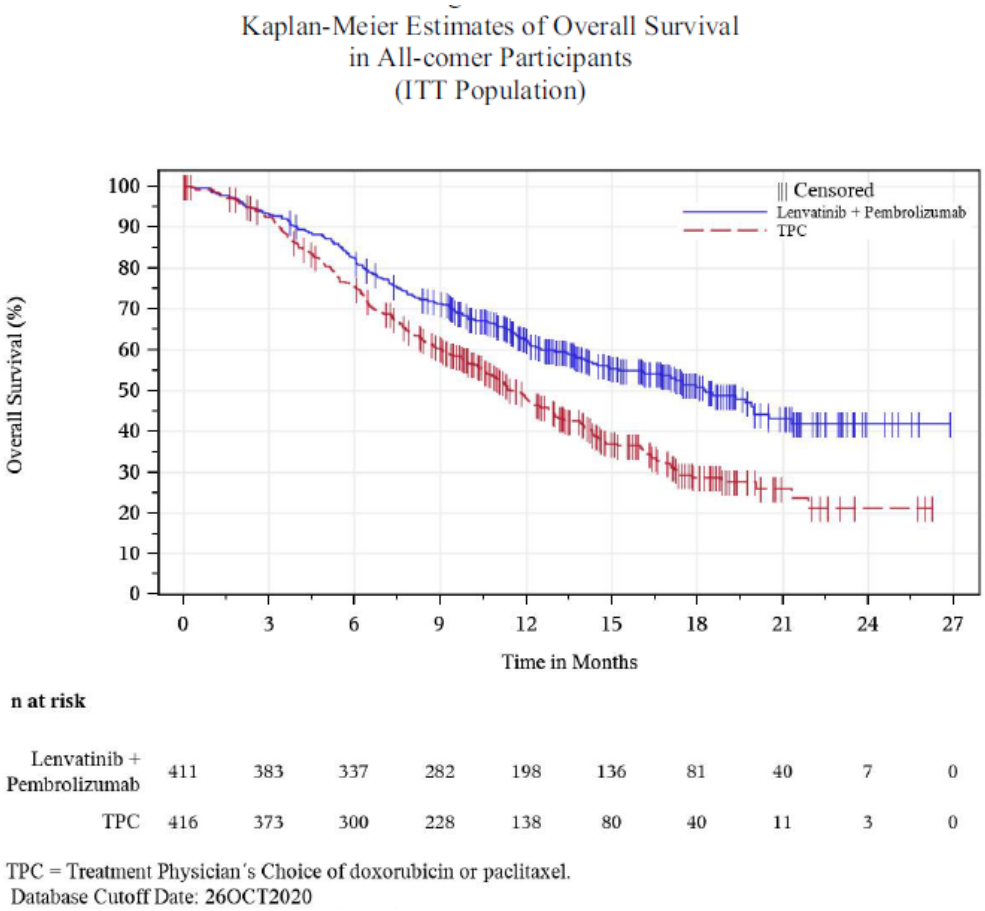
[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation.
[c] One-sided p-value based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

**Table 40 – Summary of overall survival rate over time in all-comer participants (ITT population)**

| | Lenvatinib + Pembrolizumab (N=411) % (95% CI)[a] | TPC (N=416) % (95% CI)[a] |
|---|---|---|
| **Summary of Overall Survival rate at time point** | | |
| 6 months | 82.4 (78.4, 85.8) | 75.4 (70.9, 79.3) |
| 12 months | 62.5 (57.5, 67.1) | 47.9 (42.7, 53.0) |
| 18 months | 50.9 (45.2, 56.3) | 28.6 (23.2, 34.3) |
| 24 months | 42.0 (35.1, 48.8) | 21.4 (14.2, 29.6) |

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

**Figure 23 -**




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

***pMMR participants***

**Table 41 – Analysis of overall survival in pMMR participants (ITT population)**

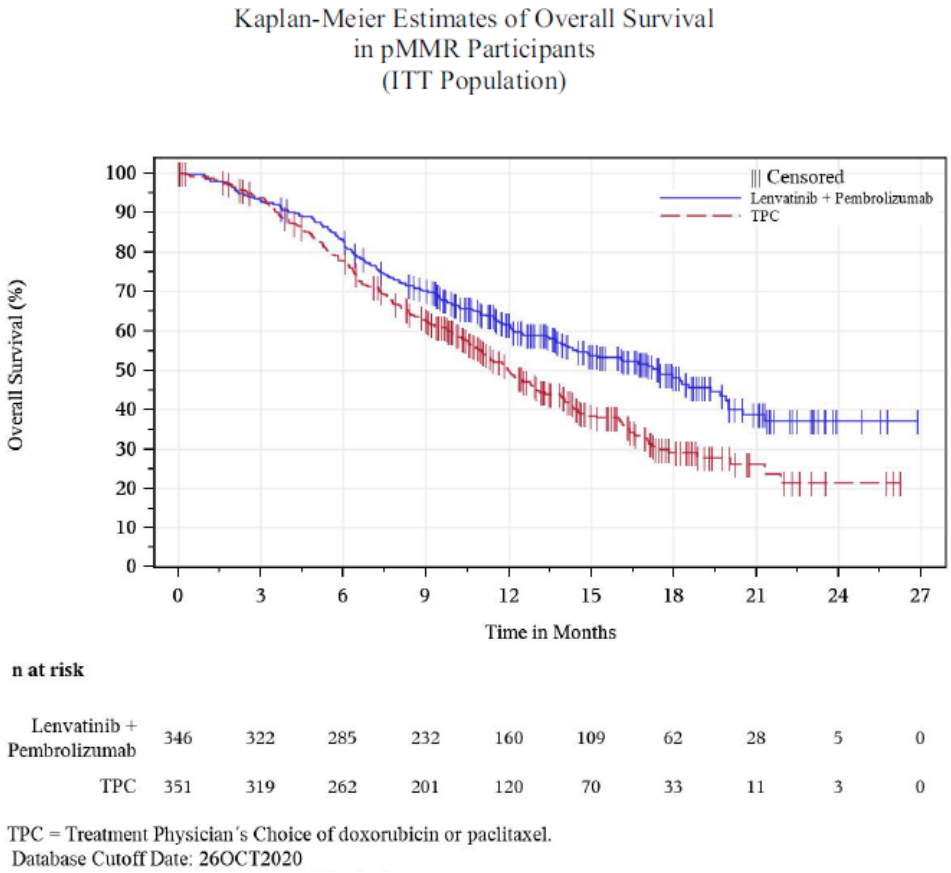
| Treatment | N | Number of Events (%) | Person-month | Event Rate/ 100 Person-months | Median OS [a] (months) (95% CI) | OS Rate at 12 months in % [a] (95% CI) |
|---|---|---|---|---|---|---|
| Lenvatinib + Pembrolizumab | 346 | 165 (47.7) | 4128.6 | 4.0 | 17.4 (14.2, 19.9) | 61.6 (56.1, 66.6) |
| TPC | 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.
TPC = Treatment Physician's Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

**Table 42 – Summary of overall survival rate over time in pMMR participants (ITT population)**

| | Lenvatinib + Pembrolizumab (N=346) % (95% CI)[a] | TPC (N=351) % (95% CI)[a] |
|---|---|---|
| **Summary of Overall Survival rate at time point** | | |
| 6 months | 82.9 (78.5, 86.5) | 77.9 (73.1, 81.9) |
| 12 months | 61.6 (56.1, 66.6) | 49.5 (43.8, 55.0) |
| 18 months | 48.2 (41.9, 54.3) | 29.2 (23.1, 35.5) |
| 24 months | 37.2 (29.5, 45.0) | 21.5 (13.9, 30.1) |
| [a] From product-limit (Kaplan-Meier) method for censored data.<br>TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.<br>Database Cutoff Date: 26OCT2020 | | |

**Figure 24 -**




**<u>Secondary Endpoints</u>**

- **ORR**

***All comers***

**Table 43 -Analysis of confirmed objective response based on BICR assessment per RECIST 1.1 in all-comer participants (ITT population)**

| Treatment | N | Number of Responses | Response Rate (%) (95% CI) | Difference in % vs. TPC | |
|---|---|---|---|---|---|
| | | | | Estimate (95% CI)[a] | p-Value[b] |
| Lenvatinib + Pembrolizumab | 411 | 131 | 31.9 (27.4, 36.6) | 17.2 (11.5, 22.9) | <0.0001 |
| TPC | 416 | 61 | 14.7 (11.4, 18.4) | | |

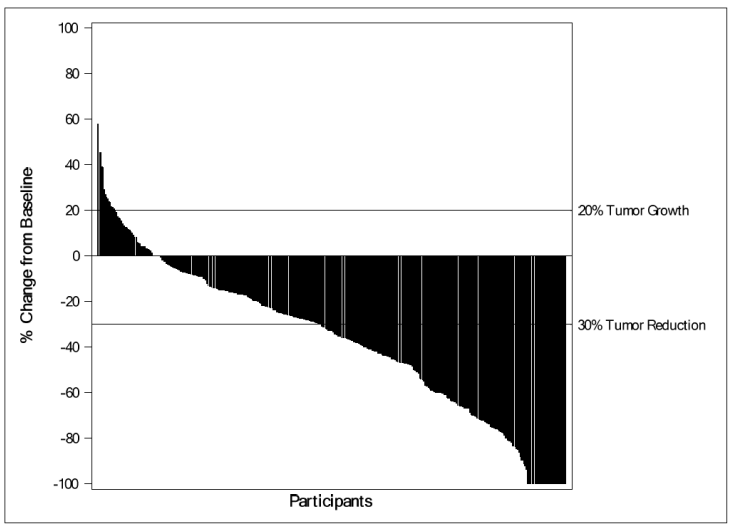
[a] Based on Miettinen & Nurminen method stratified by MMR Status, ECOG performance status, geographic region, and prior history of pelvic radiation.
[b] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
BICR = Blinded Independent Central Review.
TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.
Database cutoff date: 26OCT2020

**Table 44 -Summary of best overall response based on BICR assessment per RECIST 1.1 in all-comer participants (ITT population)**

| Response Evaluation | Lenvatinib + Pembrolizumab | | | TPC | | |
|---|---|---|---|---|---|---|
| | N | % | 95% CI[a] | N | % | 95% CI[a] |
| **Participants in population** | **411** | | | **416** | | |
| Complete Response (CR) | 27 | 6.6 | (4.4, 9.4) | 11 | 2.6 | (1.3, 4.7) |
| Partial Response (PR) | 104 | 25.3 | (21.2, 29.8) | 50 | 12.0 | (9.1, 15.5) |
| **Objective Response (CR+PR)** | **131** | **31.9** | **(27.4, 36.6)** | **61** | **14.7** | **(11.4, 18.4)** |
| Stable Disease (SD) | 193 | 47.0 | (42.0, 51.9) | 167 | 40.1 | (35.4, 45.0) |
| **Disease Control [CR+PR+(SD ≥ 7 Weeks)]** | **296** | **72.0** | **(67.4, 76.3)** | **194** | **46.6** | **(41.8, 51.6)** |
| **Clinical Benefit [CR+PR+(SD ≥ 23 Weeks)]** | **201** | **48.9** | **(44.0, 53.9)** | **99** | **23.8** | **(19.8, 28.2)** |
| Progressive Disease (PD) | 61 | 14.8 | (11.5, 18.7) | 123 | 29.6 | (25.2, 34.2) |
| Not Evaluable (NE) | 5 | 1.2 | (0.4, 2.8) | 8 | 1.9 | (0.8, 3.8) |
| No Assessment (NA) | 21 | 5.1 | (3.2, 7.7) | 57 | 13.7 | (10.5, 17.4) |

[a]Based on binomial exact confidence interval method.
NE: Post-baseline assessment(s) available, but not evaluable.
No Assessment: No post-baseline assessment available for response evaluation.
For best overall response of CR and PR, only confirmed responses are included.
BICR = Blinded independent central review.
TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

**Figure 25 – Waterfall Plot of best percentage change from baseline for target lesions based on BICR assessment per RECIST 1.1 in all-comer participants with measurable disease (lenvatinib + Pembrolizumab arm)**




Database cutoff date: 26OCT2020

***pMMR participants***

**Table 45 -Analysis of confirmed objective response based on BICR assessment per RECIST 1.1 in pMMR participants (ITT population)**

| Treatment | N | Number of Responses | Response Rate (%) (95% CI) | Difference in % vs. TPC | |
|---|---|---|---|---|---|
| | | | | Estimate (95% CI)[a] | p-Value[b] |
| Lenvatinib + Pembrolizumab | 346 | 105 | 30.3 (25.5, 35.5) | 15.2 (9.1, 21.4) | <0.0001 |
| TPC | 351 | 53 | 15.1 (11.5, 19.3) | | |

[a] Based on Miettinen & Numminen method stratified by ECOG performance status, geographic region, and prior history of pelvic radiation.
[b] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
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

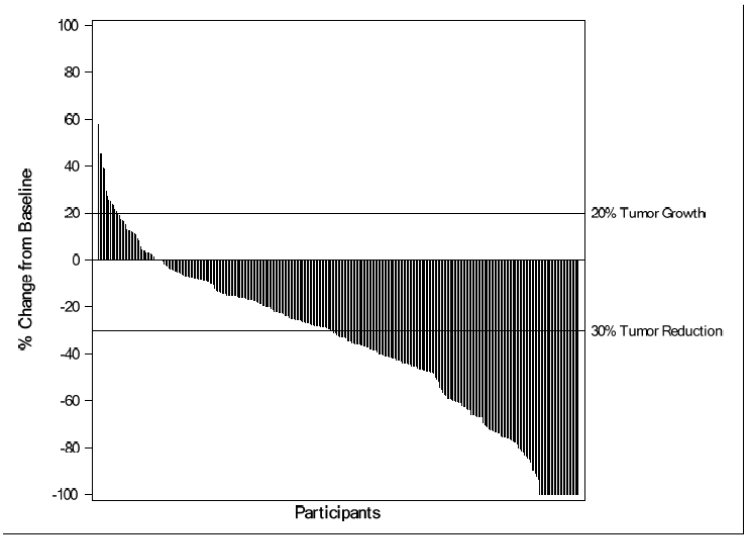
**Table 46 -Summary of best overall response based on BICR assessment per RECIST 1.1 in pMMR participants (ITT population)**

| Response Evaluation | Lenvatinib + Pembrolizumab | | | TPC | | |
|---|---|---|---|---|---|---|
| | N | % | 95% CI[a] | N | % | 95% CI[a] |
| **Participants in population** | **346** | | | **351** | | |
| Complete Response (CR) | 18 | 5.2 | (3.1, 8.1) | 9 | 2.6 | (1.2, 4.8) |
| Partial Response (PR) | 87 | 25.1 | (20.7, 30.1) | 44 | 12.5 | (9.3, 16.5) |
| **Objective Response (CR+PR)** | **105** | **30.3** | **(25.5, 35.5)** | **53** | **15.1** | **(11.5, 19.3)** |
| Stable Disease (SD) | 168 | 48.6 | (43.2, 54.0) | 139 | 39.6 | (34.4, 44.9) |
| **Disease Control [CR+PR+(SD ≥ 7 Weeks)]** | **248** | **71.7** | **(66.6, 76.4)** | **163** | **46.4** | **(41.1, 51.8)** |
| **Clinical Benefit [CR+PR+(SD ≥ 23 Weeks)]** | **165** | **47.7** | **(42.3, 53.1)** | **85** | **24.2** | **(19.8, 29.0)** |
| Progressive Disease (PD) | 54 | 15.6 | (11.9, 19.9) | 108 | 30.8 | (26.0, 35.9) |
| Not Evaluable (NE) | 2 | 0.6 | (0.1, 2.1) | 7 | 2.0 | (0.8, 4.1) |
| No Assessment (NA) | 17 | 4.9 | (2.9, 7.8) | 44 | 12.5 | (9.3, 16.5) |

[a]Based on binomial exact confidence interval method.
NE: Post-baseline assessment(s) available, but not evaluable.
No Assessment: No post-baseline assessment available for response evaluation.
For best overall response of CR and PR, only confirmed responses are included.
BICR = Blinded independent central review.
TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

**Figure 26 – Waterfall Plot of best percentage change from baseline for target lesions based on BICR assessment per RECIST 1.1 in pMMR participants with measurable disease (lenvatinib + Pembrolizumab arm)**

Waterfall Plot of Best Percentage Change From Baseline for Target Lesions Based on BICR Assessment per RECIST 1.1 in pMMR Participants with Measurable Disease (Lenvatinib + Pembrolizumab Arm)




Database cutoff date: 26OCT2020
Source: [P775V01MK3475: adam-adsl; adtl]

- **Quality of life (EORTC QLQ-30)**

Health-related Quality of Life (HRQoL) was assessed for both pMMR and all-comers population using the PRO instruments EORTC QLQ-C30, EORTC QLQ-EN24, and EuroQoL EQ-5D-5L.

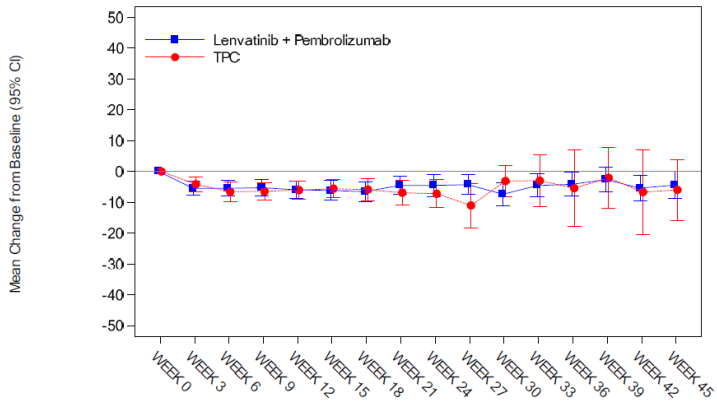
Baseline GHS/QoL scores were similar between the lenvatinib plus pembrolizumab group and TPC group. The GHS/QoL scores decreased similarly in both treatment groups.

**Table 47 – Analysis of change from baseline in EORTC QLQ-C30 global health status to week (all-comer full analysis set)**

| Treatment | Baseline | | Week 12 | | Change from Baseline to Week 12 | |
|---|---|---|---|---|---|---|
| | 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

Empirical Mean Change from Baseline and 95% CI for the EORTC QLQ-C30 Global Health Status/QoL Over Time by Treatment Group (All-comer Full Analysis Set)



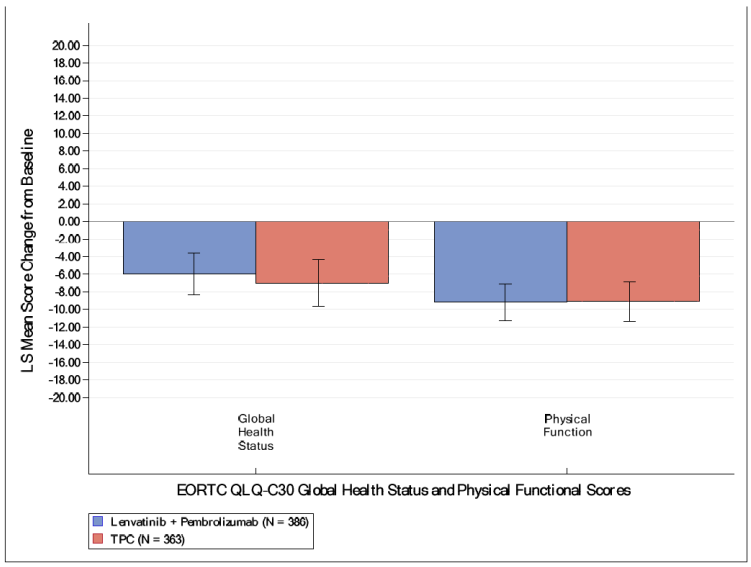

Number of Participants

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lenvatinib + Pembrolizumab | 370 | 341 | 325 | 319 | 298 | 273 | 266 | 247 | 226 | 216 | 208 | 185 | 180 | 169 | 148 | 131 |
| TPC | 351 | 317 | 233 | 282 | 221 | 172 | 138 | 132 | 88 | 59 | 27 | 28 | 17 | 16 | 10 | 14 |

**Figure 27 -** Database Cutoff Date: 26OCT2020

**Figure 28 -**

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)




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

Baseline PRO scores were generally similar between lenvatinib plus pembrolizumab group and TPC group as measured by EORTC QLQ-30 physical functioning score, EORTC QLQ-EN24 urological symptoms score, and EQ-5D-5L VAS score.

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, while EORTC QLQ-EN24 urological symptoms scores were maintained over time in both groups.

**Exploratory Endpoints**

- **Duration of Response and Time to Response**

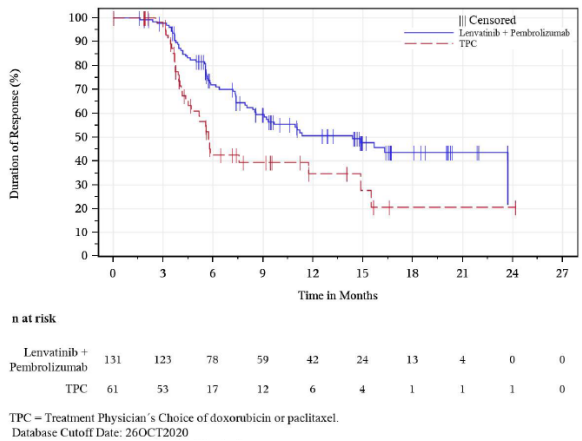
***All comers***

***Table 48 – Summary of time to response and duration of response 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+) |
| **Number (%[b]) of Participants with Extended Response Duration:** | | |
| ≥6 months | 78 (71.9) | 17 (42.6) |
| ≥12 months | 42 (50.6) | 6 (34.6) |
| ≥18 months | 13 (43.6) | 1 (20.8) |
| ≥24 months | 0 (NR) | 1 (20.8) |

[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.
NR = Not Reached.
TPC = Treatment Physician's Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

**Figure 29 - Kaplan-Meier estimates of duration of response in subjects with confirmed response *based on BICR assessment per RECIST 1.1 in all comer-participants (ITT population)***




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

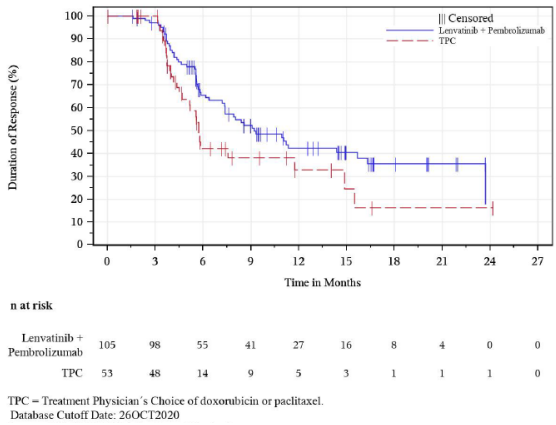
***pMMR participants***

***Table 49 – Summary of time to response and duration of response 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+) |
| **Number (%[b]) of Participants with Extended Response Duration:** | | |
| ≥6 months | 55 (65.6) | 14 (42.1) |
| ≥12 months | 27 (42.3) | 5 (32.8) |
| ≥18 months | 8 (35.5) | 1 (16.4) |
| ≥24 months | 0 (NR) | 1 (16.4) |

[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.
NR = Not Reached.
TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

**Figure 30 - Kaplan-Meier estimates of duration of response in subjects with confirmed response *based on BICR assessment per RECIST 1.1 in pMMR participants (ITT population)***




- **Progression-Free Survival on Next-Line Therapy (PFS2)**

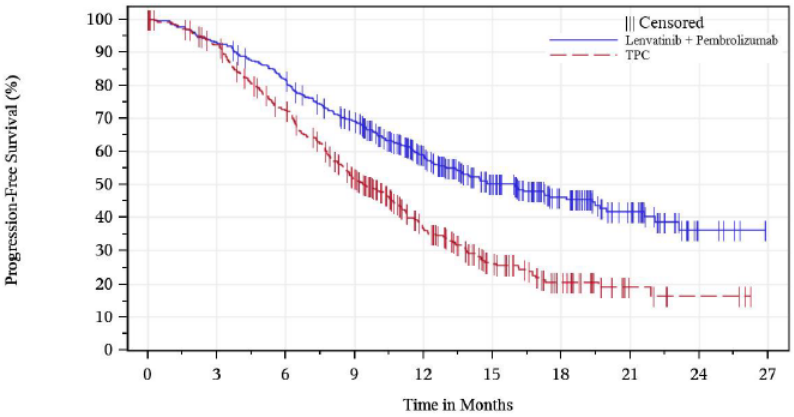
***All comers***

**Table 50 – Analysis of progression free survival on next line therapy (PFS2) 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 | 203 (49.4) | 4821.7 | 4.2 | 16.0 (13.0, 19.5) | 81.7 (77.6, 85.1) |
| TPC | 416 | 272 (65.4) | 3706.5 | 7.3 | 9.5 (8.6, 10.7) | 72.5 (67.9, 76.6) |
| **Pairwise Comparisons** | | | | | Hazard Ratiob (95% CI)[b] | p-Value |
| Lenvatinib + Pembrolizumab vs. TPC | | | | | 0.56 (0.46, 0.67) | <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

**Figure 31 - Kaplan-Meier estimates of progression free survival on next line therapy (PFS2) based on investigator assessment per RECIST 1.1 (Primary censoring rule) in all-comer participants (ITT Population)**




**n at risk**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Lenvatinib + Pembrolizumab | 411 | 382 | 333 | 274 | 183 | 120 | 69 | 38 | 6 | 0 |
| TPC | 416 | 372 | 285 | 191 | 100 | 52 | 26 | 7 | 3 | 0 |

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

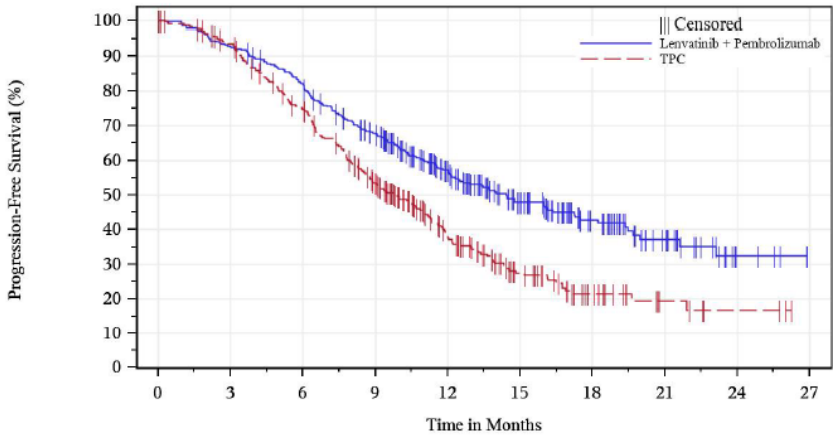
***pMMR participants***

**Table 51 – Analysis of progression free survival on next line therapy (PFS2) based on investigator assessment per RECIST 1.1 (Primary censoring rule) in pMMR 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 | 346 | 178 (51.4) | 3945.9 | 4.5 | 14.4 (12.1, 17.3) | 82.0 (77.5, 85.7) |
| TPC | 351 | 225 (64.1) | 3182.4 | 7.1 | 9.8 (8.7, 11.1) | 74.8 (69.8, 79.1) |
| **Pairwise Comparisons** | | | | | Hazard Ratiob (95% CI)[b] | p-Value |
| Lenvatinib + Pembrolizumab vs. TPC | | | | | 0.62 (0.50, 0.75) | <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 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.
TPC = Treatment Physician's Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

**Figure 31 - Kaplan-Meier estimates of progression free survival on next line therapy (PFS2) based on investigator assessment per RECIST 1.1 (Primary censoring rule) in pMMR participants (ITT Population*)***




n at risk

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Lenvatinib + Pembrolizumab | 346 | 321 | 281 | 224 | 145 | 93 | 50 | 26 | 5 | 0 |
| TPC | 351 | 318 | 248 | 166 | 86 | 44 | 20 | 7 | 3 | 0 |

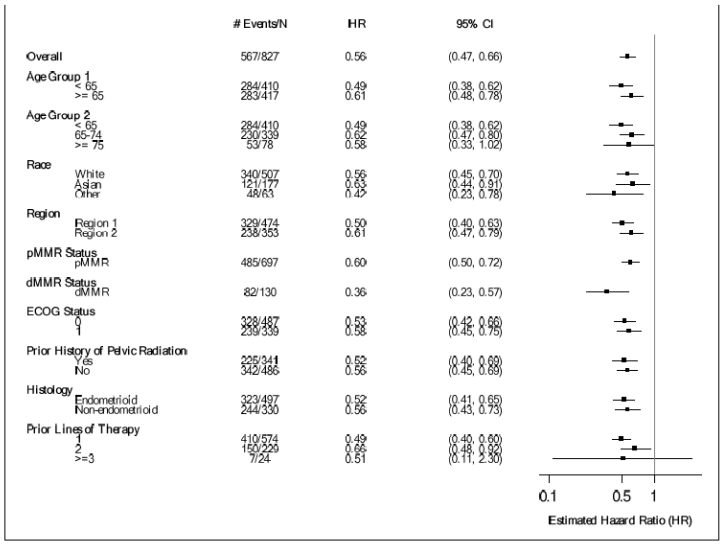
TPC = Treatment Physician's Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

## Ancillary analyses

- **Subgroup analyses**

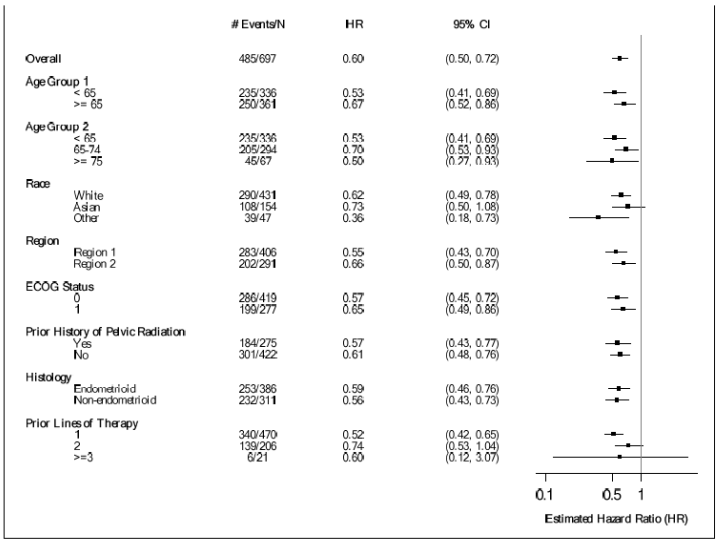
### *Progression free survival*

**Table 52 -Progression free survival by subgroups 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

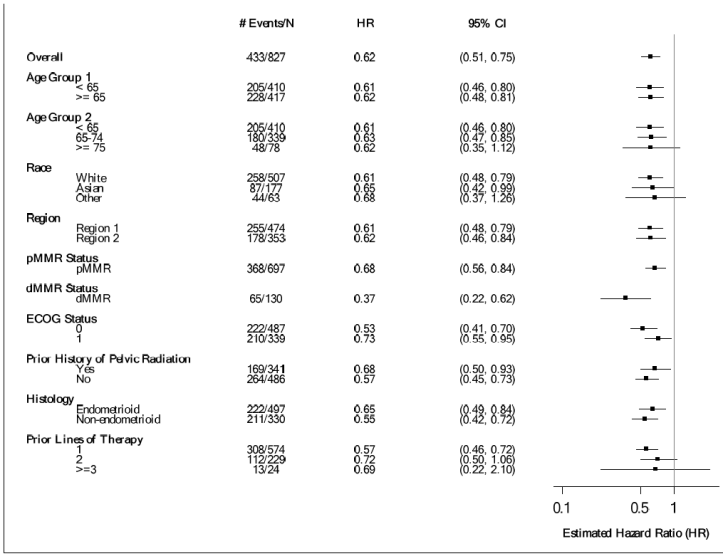
**Table 53 -Progression free survival by subgroups factors based on BICR assessment per RECIST 1.1 (primary censoring rule) in pMMR participants (ITT population)**




Note: Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel or Region 2: rest of the world
Database Cutoff Date: 26OCT2020

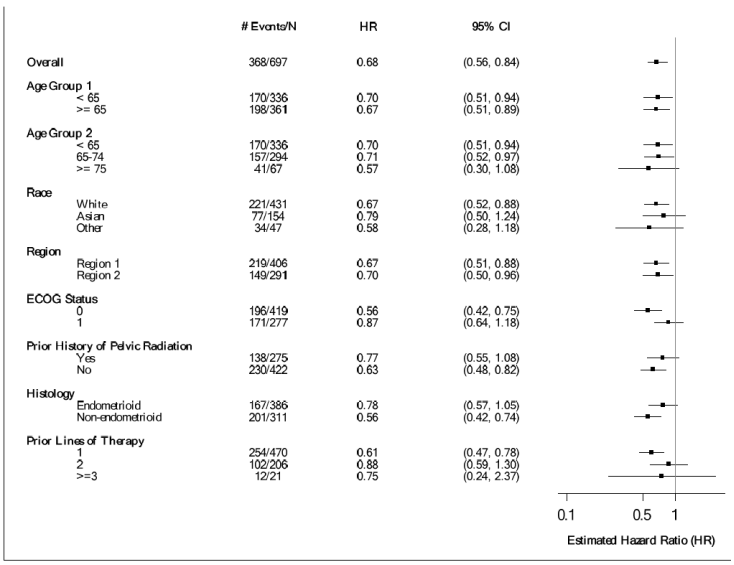
***Overall survival***

**Table 54 -Overall survival y subgroups factors 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

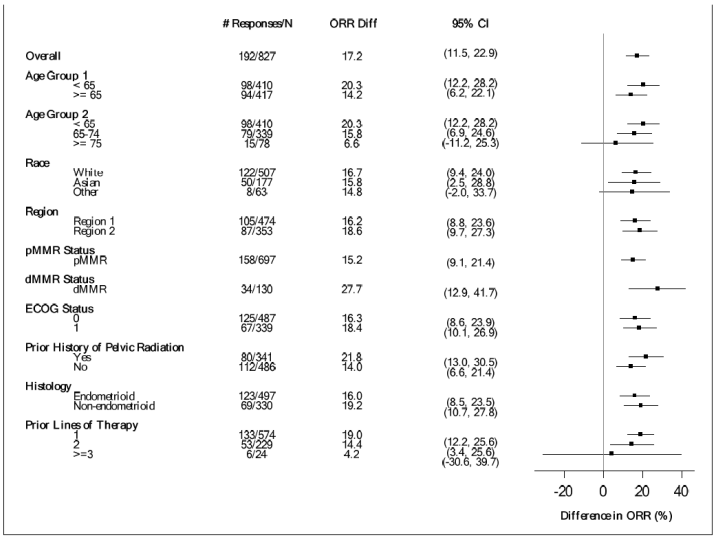
**Table 55 -Overall survival y subgroups factors in pMMR participants (ITT population)**




Note: Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel or Region 2: rest of the world
Database Cutoff Date: 26OCT2020

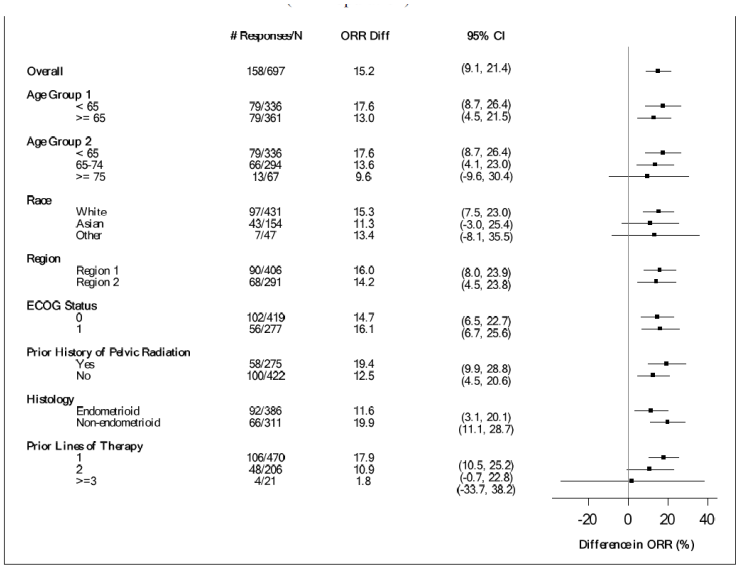
### *Overall response rate*

**Table 56 -Objective response rate (confirmed) by subgroups 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

**Table 57 -Progression free survival by subgroups factors based on BICR assessment per RECIST 1.1 (primary censoring rule) in pMMR participants (ITT population*)***




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

The dMMR subgroup was not prespecified in the multiplicity strategy for Type I error control, so only nominal p-values have been provided for the efficacy endpoints.

**Table 58 – Disposition of participants in dMMR participants (ITT population)**

| | Lenvatinib + Pembrolizumab | | TPC | | Total | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Participants in population | 65 | | 65 | | 130 | |
| **Status for Trial** | | | | | | |
| Discontinued | 23 | (35.4) | 45 | (69.2) | 68 | (52.3) |
| Death | 23 | (35.4) | 40 | (61.5) | 63 | (48.5) |
| Withdrawal By Subject | 0 | (0.0) | 5 | (7.7) | 5 | (3.8) |
| Participants Ongoing | 42 | (64.6) | 20 | (30.8) | 62 | (47.7) |
| **Status for Study medication in Trial** | | | | | | |
| Started | 64 | | 63 | | 127 | |
| Completed | 0 | (0.0) | 15 | (23.8) | 15 | (11.8) |
| Discontinued | 35 | (54.7) | 47 | (74.6) | 82 | (64.6) |
| Adverse Event | 17 | (26.6) | 4 | (6.3) | 21 | (16.5) |
| Clinical Progression | 2 | (3.1) | 5 | (7.9) | 7 | (5.5) |
| Physician Decision | 1 | (1.6) | 3 | (4.8) | 4 | (3.1) |
| Progressive Disease | 14 | (21.9) | 29 | (46.0) | 43 | (33.9) |
| Withdrawal By Subject | 1 | (1.6) | 6 | (9.5) | 7 | (5.5) |
| Participants Ongoing | 29 | (45.3) | 1 | (1.6) | 30 | (23.6) |

If the overall count of participants is calculated and displayed within a section in the first row, then it is used as the denominator for the percentage calculation. Otherwise, participants in population is used as the denominator for the percentage calculation.
Completed study medication: For Lenvatinib + Pembrolizumab, completed 35 infusions of pembrolizumab. For TPC of doxorubicin, received a lifetime maximum cumulative dose of doxorubicin or for TPC of paclitaxel, a maximum tolerable dose was reached per investigator.
TPC = Treatment Physician's Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

**Table 59: Disease characteristics in dMMR participants (ITT population)**

| | Lenvatinib + Pembrolizumab | | 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 Differentiation | 2 | (3.1) | 1 | (1.5) | 3 | (2.3) |
| 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.

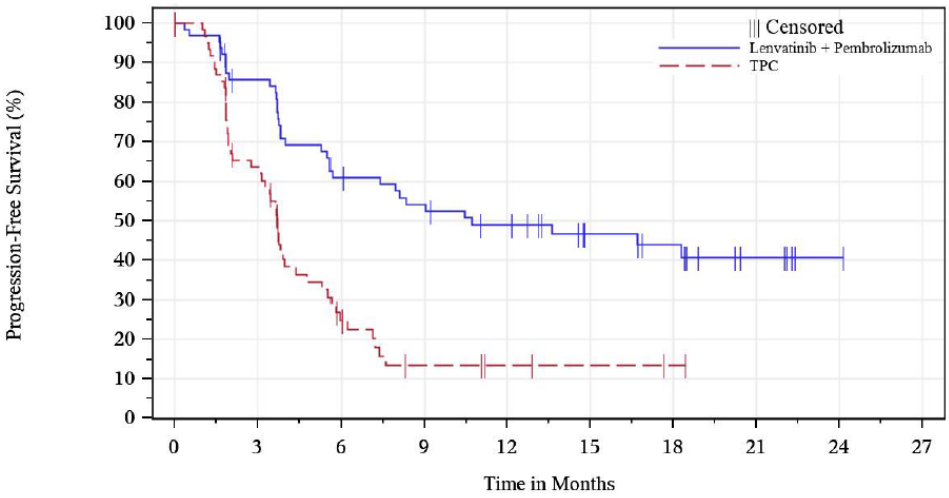
Database Cutoff Date: 26OCT2020

**Table 60 – Analysis of Progression free survival based on BICR assessment per RECIST 1.1 (primary censoring rule) in dMMR 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 | 65 | 34 (52.3) | 640.9 | 5.3 | 10.7 (5.6, NR) | 61.0 (47.6, 71.9) |
| TPC | 65 | 48 (73.8) | 267.7 | 17.9 | 3.7 (3.1, 4.4) | 24.8 (14.3, 36.8) |
| **Pairwise Comparisons** | | | | | Hazard Ratio[b] (95% CI)[b] | p-Value |
| Lenvatinib + Pembrolizumab vs. TPC | | | | | 0.36 (0.23, 0.57) | <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.
[c] One-sided p-value based on log-rank test.
NR = Not reached.
BICR= Blinded Independent Central Review.
TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

**Figure 31 - Kaplan-Meier estimates of progression free survival based on BICR assessment per RECIST 1.1 (Primary censoring rule) in dMMR participants (ITT Population)**




**n at risk**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Lenvatinib + Pembrolizumab | 65 | 52 | 37 | 32 | 26 | 17 | 13 | 5 | 1 | 0 |
| TPC | 65 | 37 | 12 | 5 | 3 | 2 | 1 | 0 | 0 | 0 |

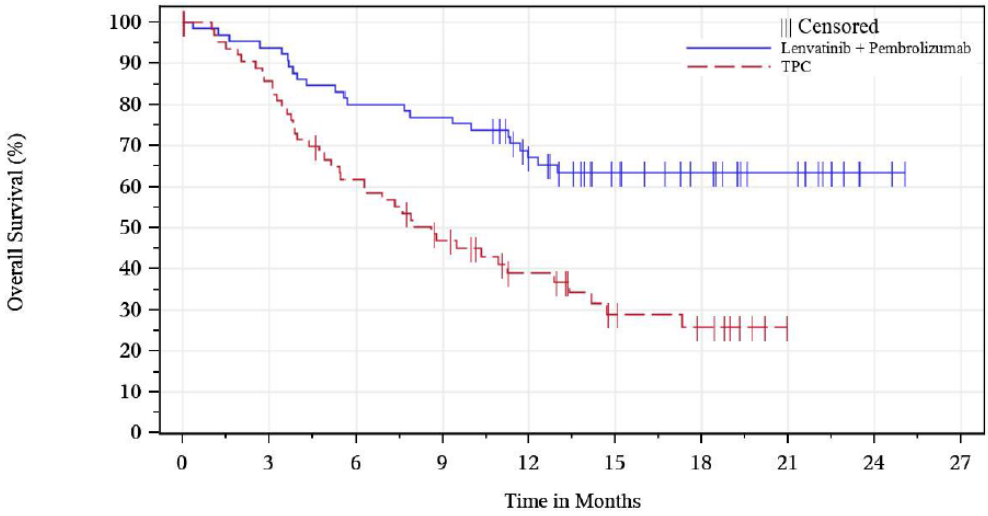
TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

**Table 61 – Analysis of overall survival in dMMR participants (ITT population)**

| 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 | 65 | 23 (35.4) | 880.6 | 2.6 | NR (NR, NR) | 67.2 (54.2, 77.2) |
| TPC | 65 | 42 (64.6) | 557.8 | 7.5 | 8.6 (5.5, 12.9) | 39.1 (26.7, 51.3) |
| **Pairwise Comparisons** | | | | | Hazard Ratio[b] (95% CI)[b] | p-Value |
| Lenvatinib + Pembrolizumab vs. TPC | | | | | 0.37 (0.22, 0.62) | <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.
[c] One-sided p-value based on log-rank test.
NR = Not reached.
TPC = Treatment Physician's Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

**Figure 32 - Kaplan-Meier estimates of overall survival in dMMR participants (ITT Population)**




**n at risk**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Lenvatinib + Pembrolizumab | 65 | 61 | 52 | 50 | 38 | 27 | 19 | 12 | 2 | 0 |
| TPC | 65 | 54 | 38 | 27 | 18 | 10 | 7 | 0 | 0 | 0 |

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

***Table 62 – Summary of best overall response based on BICR assessment per RECIST 1.1 in dMMR participants (ITT population)***

| Response Evaluation | Lenvatinib + Pembrolizumab | | | TPC | | |
|---|---|---|---|---|---|---|
| | N | % | 95% CIa | N | % | 95% CIa |
| **Participants in population** | **65** | | | **65** | | |
| Complete Response (CR) | 9 | 13.8 | (6.5, 24.7) | 2 | 3.1 | (0.4, 10.7) |
| Partial Response (PR) | 17 | 26.2 | (16.0, 38.5) | 6 | 9.2 | (3.5, 19.0) |
| **Objective Response (CR+PR)** | **26** | **40.0** | **(28.0, 52.9)** | **8** | **12.3** | **(5.5, 22.8)** |
| Stable Disease (SD) | 25 | 38.5 | (26.7, 51.4) | 28 | 43.1 | (30.8, 56.0) |
| **Disease Control [CR+PR+(SD ≥ 7 Weeks)]** | **48** | **73.8** | **(61.5, 84.0)** | **31** | **47.7** | **(35.1, 60.5)** |
| **Clinical Benefit [CR+PR+(SD ≥ 23 Weeks)]** | **36** | **55.4** | **(42.5, 67.7)** | **14** | **21.5** | **(12.3, 33.5)** |
| Progressive Disease (PD) | 7 | 10.8 | (4.4, 20.9) | 15 | 23.1 | (13.5, 35.2) |
| Not Evaluable (NE) | 3 | 4.6 | (1.0, 12.9) | 1 | 1.5 | (0.0, 8.3) |
| No Assessment (NA) | 4 | 6.2 | (1.7, 15.0) | 13 | 20.0 | (11.1, 31.8) |

[a]Based on binomial exact confidence interval method.
NE: Post-baseline assessment(s) available, but not evaluable.
No Assessment: No post-baseline assessment available for response evaluation.
For best overall response of CR and PR, only confirmed responses are included.
BICR = Blinded independent central review.
TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

**Table 63 – Summary of time to response and duration of response based on BICR assessment per RECIST 1.1 in participants with confirmed response in dMMR participants (ITT population)**

| | Lenvatinib + Pembrolizumab (N=65) | TPC (N=65) |
|---|---|---|
| Number of participants with responsea | 26 | 8 |
| **Time to Response (months)** | | |
| Mean (SD) | 3.7 (3.0) | 2.1 (0.7) |
| Median (Range) | 2.9 (1.7-16.3) | 1.9 (1.8-3.7) |
| **Response Durationb (months)** | | |
| Median (Range) | NR (2.1+ - 20.4+) | 4.1 (1.9+ - 15.6+) |
| **Number (%[b]) of Participants with Extended Response Duration:** | | |
| ≥6 months | 23 (96.0) | 3 (42.9) |
| ≥12 months | 15 (81.7) | 1 (42.9) |
| ≥18 months | 5 (74.9) | 0 (NR) |

[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.
NR = Not Reached.
TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

- ***Patients with prior systemic therapy in neo-adjuvant/adjuvant setting only***

Approximately 35% of subjects in both arms received study treatment as first line for advanced/metastatic setting, i.e. after relapse to platinum-based chemotherapy received as (neo)adjuvant therapy. In those subjects, the median platinum-free interval was generally similar between the 2 treatment groups (median PFI 6.2 vs 5.6 months).

**Table 64: Summary of Efficacy Results in Participants with Prior Systemic Therapy in Neo-adjuvant/Adjuvant Setting Only (ITT population)**

| Endpoint | All-comer Participants | | pMMR Participants | |
|---|---|---|---|---|
| | Lenvatinib Plus Pembrolizumab (N=144) | TPC (N=159) | Lenvatinib Plus Pembrolizumab (N=125) | TPC (N=133) |

| | | | | |
|---|---|---|---|---|
| **PFS**[a] | | | | |
| Median PFS, months (95% CI)[b] | 6.8 (5.6, 7.8) | 3.9 (3.6, 5.4) | 6.4 (5.5, 7.5) | 4.0 (3.5, 5.5) |
| HR (95% CI)[c] | 0.55 (0.42, 0.73) | | 0.58 (0.43, 0.78) | |
| **OS** | | | | |
| Median OS, months (95% CI)[b] | 17.2 (13.9, NR) | 12.5 (10.6, 14.5) | 17.2 (13.9, NR) | 12.5 (10.5 (14.3) |
| HR (95% CI)[c] | 0.67 (0.48, 0.92) | | 0.64 (0.45, 0.90) | |
| **Objective Response** | | | | |
| ORR % (95% CI)[a] | 32.6 (25.1, 40.9) | 17.0 (11.5, 23.7) | 32.8 (24.7, 41.8) | 16.5 (10.7, 24.0) |
| ORR Difference % (95% CI)[d] | 15.7 (6.0, 25.3) | | 16.3 (5.8, 26.6) | |

- **Subsequent anticancer treatment**

***All comers***

**Table 65 - Summary of subsequent Systemic anti-cancer treatment in all comer participants (ITT population)**

| | Lenvatinib + Pembrolizumab (N=411) | TPC (N=416) | Total (N=827) |
|---|---|---|---|
| **Started Study Treatment** | 406 (98.8) | 388 (93.3) | 794 (96.0) |
| **Discontinued Study Treatment** | 282 (68.6) | 285 (68.5) | 567 (68.6) |
| **Received Any Subsequent Systemic Anti-cancer Therapy** | 115 (28.0) | 200 (48.1) | 315 (38.1) |
| **Subsequent systemic therapy by type** | | | |
| Chemotherapy | 97 (23.6) | 129 (31.0) | 226 (27.3) |
| Hormonal therapy | 25 (6.1) | 55 (13.2) | 80 (9.7) |
| Other | 7 (1.7) | 16 (3.8) | 23 (2.8) |
| Any PD1/PD-L1 checkpoint | 4 (1.0) | 53 (12.7) | 57 (6.9) |
| Targeted therapy | 8 (1.9) | 12 (2.9) | 20 (2.4) |
| Any VEGF/VEGFR inhibitor | 10 (2.4) | 46 (11.1) | 56 (6.8) |
| **Subsequent lenvatinib and pembrolizumab** | 3 (0.7) | 32 (7.7) | 35 (4.2) |
| **Subsequent systemic therapy by lines** | | | |
| 1 subsequent line | 6 (1.5) | 13 (3.1) | 19 (2.3) |
| 2 subsequent lines | 85 (20.7) | 152 (36.5) | 237 (28.7) |
| >=3 subsequent lines | 58 (14.1) | 85 (20.4) | 143 (17.3) |

Every subject is counted a single time for each applicable specific anti-cancer treatment.
A subject with multiple anti-cancer treatments within a therapy category is counted a single time for that category.
TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

***pMMR***

**Table 66- Summary of subsequent Systemic anti-cancer treatment in pMMR participants (ITT population)**

| | Lenvatinib + Pembrolizumab (N=346) | TPC (N=351) | Total (N=697) |
|---|---|---|---|
| **Started Study Treatment** | 342 (98.8) | 325 (92.6) | 667 (95.7) |
| **Discontinued Study Treatment** | 247 (71.4) | 238 (67.8) | 485 (69.6) |
| **Received Any Subsequent Systemic Anti-cancer Therapy** | 109 (31.5) | 176 (50.1) | 285 (40.9) |
| **Subsequent systemic therapy by type** | | | |
| Chemotherapy | 92 (26.6) | 119 (33.9) | 211 (30.3) |
| Hormonal therapy | 24 (6.9) | 51 (14.5) | 75 (10.8) |
| Other | 7 (2.0) | 13 (3.7) | 20 (2.9) |
| Any PD1/PD-L1 checkpoint | 4 (1.2) | 42 (12.0) | 46 (6.6) |
| Targeted therapy | 8 (2.3) | 12 (3.4) | 20 (2.9) |
| Any VEGF/VEGFR inhibitor | 10 (2.9) | 43 (12.3) | 53 (7.6) |
| **Subsequent lenvatinib and pembrolizumab** | 3 (0.9) | 32 (9.1) | 35 (5.0) |
| **Subsequent systemic therapy by lines** | | | |
| 1 subsequent line | 6 (1.7) | 11 (3.1) | 17 (2.4) |
| 2 subsequent lines | 81 (23.4) | 134 (38.2) | 215 (30.8) |
| >=3 subsequent lines | 55 (15.9) | 78 (22.2) | 133 (19.1) |

Every subject is counted a single time for each applicable specific anti-cancer treatment.
A subject with multiple anti-cancer treatments within a therapy category is counted a single time for that category.
TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

- **PFS sensitivity analyses**

All PFS analyses are summarized in the table below:

**Table 67: PFS analyses of KEYNOTE-775**

| | **PFS by BICR - primary analysis** | **PFS by BICR – censoring rules 1** | **PFS by BICR – censoring rules 2** | **PFS by INV** |
|---|---|---|---|---|
| ***All comers*** | | | | |
| HR (95%CI) | 0.56 (0.47, 0.66) | 0.58 (0.49, 0.68) | 0.53 (0.45, 0.61) | 0.56 (0.47, 0.66) |
| ***pMMR*** | | | | |
| HR (95%CI) | 0.60 (0.50, 0.72) | 0.62 (0.53, 0.74) | 0.56 (0.48, 0.66) | 0.60 (0.50, 0.72) |

(table made by assessor)

## *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 68: Summary of Efficacy for Study 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: 126191, EudraCT: 2017-004387-35) | | |
| Design | Phase 3, two-arm, multicenter, open-label, randomized, controlled study | | |
| | Duration of main phase:<br><br>Duration of run-in phase:<br>Duration of extension phase: | Enrollment started on 11-JUN-2018;<br>Data cut off: 26-OCT-2020. Study ongoing.<br>not applicable<br>not applicable | |
| Hypothesis | Superiority | | |
| Treatments groups | Lenvatinib + Pembrolizumab<br>N=411 | Lenvatinib 20 mg orally QD + pembrolizumab 200 mg IV Q3W (max 35 cycles of pembro) | |
| | TPC<br>N=416 | Doxorubicin 60 mg/m$^2$ IV Q3W<br>or<br>Paclitaxel 80 mg/m$^2$ IV every week, 3 weeks on/1 week off<br>(per site standard) | |
| Endpoints and definitions | Dual Primary endpoint | PFS | Time from date of randomization to 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 | Time from date of randomization to date of death from any cause. |
| | Secondary endpoint | ORR | 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, i.e. final for PFS and interim for OS) | | |
| Analysis population and time point description | Intent-to-treat (ITT) population<br>(2 populations analysed: all comers and pMMR) | | |
| Descriptive statistics and estimate variability | **ITT Population – All Comers** | | |
| | 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 | | Comparison groups | Lenvatinib + Pembrolizumab Vs. TPC |
| | PFS (dual primary endpoint) | HR | 0.56 |
| | | 95% CI | 0.47, 0.66 |
| | | P-value | <0.0001 |
| | OS (dual primary endpoint) | HR | 0.62 |
| | | 95% CI | 0.51, 0.75 |
| | | P-value | <0.0001 |
| | **ITT Population – pMMR** | | |

| | | | |
|---|---|---|---|
| Descriptive statistics and estimate variability | 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 | | Comparison groups | Lenvatinib + Pembrolizumab TPC |
| | PFS (dual primary endpoint) | HR | 0.60 |
| | | 95% CI | 0.50, 0.72 |
| | | P-value | <0.0001 |
| | OS (dual primary endpoint) | HR | 0.68 |
| | | 95% CI | 0.56, 0.84 |
| | | 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 |
| Note: p-values are one-sided | | | |

## *Clinical studies in special populations*

**Elderly population**

No dedicated clinical studies have been performed. For KEYNOTE-775 study, subgroup analyses by age group are presented below:

- **PFS**

**Table 69 - All comers**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| < 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) |

**Table 70 - pMMR participants**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| < 65 | 171 | 118 | (69.0) | 165 | 117 | (70.9) | 0.53 (0.41, 0.69) |
| 65-74 | 147 | 109 | (74.1) | 147 | 96 | (65.3) | 0.70 (0.53, 0.93) |
| >= 75 | 28 | 20 | (71.4) | 39 | 25 | (64.1) | 0.50 (0.27, 0.93) |

- **OS**

**Table 71 - All comers**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| < 65 | 206 | 89 | (43.2) | 204 | 116 | (56.9) | 0.61 (0.46, 0.80) |
| 65-74 | 170 | 81 | (47.6) | 169 | 99 | (58.6) | 0.63 (0.47, 0.85) |
| >= 75 | 35 | 18 | (51.4) | 43 | 30 | (69.8) | 0.62 (0.35, 1.12) |

**Table 72 - pMMR participants**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| < 65 | 171 | 78 | (45.6) | 165 | 92 | (55.8) | 0.70 (0.51, 0.94) |
| 65-74 | 147 | 73 | (49.7) | 147 | 84 | (57.1) | 0.71 (0.52, 0.97) |
| >= 75 | 28 | 14 | (50.0) | 39 | 27 | (69.2) | 0.57 (0.30, 1.08) |

- **ORR**

**Table 73- All comers**

| | | | | | |
|---|---|---|---|---|---|
| < 65 | 206 | 70 (34.0) | 204 | 28 (13.7) | 20.3 (12.2, 28.2) |
| 65-74 | 170 | 53 (31.2) | 169 | 26 (15.4) | 15.8 (6.9, 24.6) |
| >= 75 | 35 | 8 (22.9) | 43 | 7 (16.3) | 6.6 (-11.2, 25.3) |

**Table 74- pMMR participants**

| | | | | | |
|---|---|---|---|---|---|
| < 65 | 171 | 55 (32.2) | 165 | 24 (14.5) | 17.6 (8.7, 26.4) |
| 65-74 | 147 | 43 (29.3) | 147 | 23 (15.6) | 13.6 (4.1, 23.0) |
| >= 75 | 28 | 7 (25.0) | 39 | 6 (15.4) | 9.6 (-9.6, 30.4) |

## *Supportive study(ies)*

**Phase 1b/2 Single arm Study 111/KEYNOTE-146**

Study 111/KEYNOTE-146 is a multicenter, open-label phase 1b/2 trial of Lenvatinib plus Pembrolizumab in subjects with selected solid tumors. In this study, among the 283 treated subjects in the phase 2 portion who receive the RP2D, 124 subjects had EC (All EC Set); and 108 of these subjects (the EC 2L+ Set) had EC that was previously treated with 1 systemic anticancer therapy and met the pre-specified criteria for follow-up for the efficacy analysis. The data cutoff of 10 Jan 2019 was established based on the date when at least 100 subjects with histologically confirmed EC that was previously treated with at least 1 systemic anticancer therapy would have sufficient follow-up to provide a median follow-up of at least 12 months, and for all responders, an opportunity for follow-up after initial objective response as assessed by the investigator of at least 6 months. At the time of data cutoff, the median follow-up for the EC 2L+ Set (n=108) was 18.7 months.

Baseline characteristics: in the EC 2L+ Set (**n=108**), the majority of subjects were white (86.1%) and from the US (86.1%). Median age was 66.0 years. In the EC 2L+ Set, the ECOG score was 0 in 49.1% of subjects and 1 in 50.9% of subjects. In the EC 2L+ Set, all enrolled subjects had metastatic disease, and median time since original diagnosis was 22.7 months. The most common histologic EC subtypes were endometrioid

adenocarcinoma (50.9%) and serous adenocarcinoma (32.4%). The majority of subjects (70.4%) had FIGO Grade 3 tumors at original diagnosis. In the EC 2L+ Set, **94** subjects had Non-MSI-H/pMMR tumors, **11** subjects had MSI-H/dMMR tumors, and for 3 subjects, MSI/MMR status was not available (MSI status was determined centrally, initially by PCR then by IHC). Tumors were PD-L1 positive for 53 (49.1%) subjects, and PD-L1 negative for 43 (39.8%) subjects, while PD-L1 status was not available for 12 (11.1%) subjects. All subjects in the EC 2L+ Set received at least one prior systemic anticancer treatment, and all received prior platinum-based chemotherapy; 52.8% of subjects received 1 prior regimen, 37.0% of subjects received 2 prior regimens, and 10.2% subjects received ≥3 prior regimens.

Results:

**Table 75 – 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.

EC 2L+ = subjects with histologically confirmed EC that was previously treated with at least 1 systemic anticancer therapy, and who had sufficient follow-up to provide a median follow-up of at least 12 months, and for all responders, an opportunity for follow-up after initial objective response as assessed by the investigator of at least 6 months. Subjects with a status of Non-MSI-H/pMMR (n=94) or MSI-H/dMMR (n=11), or whose MSI status was not available (n=3), are included in total EC 2L+ Set (N=108).

All EC = all subjects with histologically confirmed EC regardless of prior anticancer therapy or length of follow-up as of the data cutoff date.

2L+ = second line or greater, dMMR = mismatch repair deficient, EC = endometrial carcinoma, MSI-H = microsatellite instability high, ORR = objective response rate , pMMR = mismatch repair proficient, Q3W = every 3 weeks. QD = once daily, RECIST = Response Evaluation Criteria for Solid Tumors.

a: Percentages are calculated based on the total number of subjects in the relevant header columns.

b: Six subjects had no target lesions at Baseline per IIR assessment. Non-CR/Non-PD for subjects with no target lesions at Baseline was treated as, and combined with, SD for purposes of analysis for ORR and BOR.

c NE = not evaluable; refers to subjects (n=8 in the EC 2L+ Set) with either no postbaseline tumor assessment(s) or with postbaseline tumor assessment(s) that were not evaluable, ie, due to insufficient data for assessment of response per applied response criteria (RECIST 1.1) or an early SD with duration <5 weeks.

d: UNK = Unknown; refers to subjects with no baseline tumor assessment.

e: 95% CI constructed using the method of Clopper and Pearson.

f: m is number of subjects with both baseline and postbaseline sum of diameters of target lesions and is used as the denominator for the respective percentages.

Source: Table 14.2.1.2.1e.

**Contribution of component**

Results from Study 204, KEYNOTE-158, and KEYNOTE-028 were provide in order to provide evidence of the contribution of lenvatinib and pembrolizumab monotherapies to the efficacy of the combination. The pivotal study and supportive studies are described in the below table:

**Table 76 - Summary of clinical studies to evaluate the contribution of Lenvatinib and Pembrolizumab monotherapies to the efficacy of the combination**

| Study | Design | Number of Participants | Data Cutoff Date |
|---|---|---|---|
| Study 309/ KEYNOTE-775 | Phase 3 study to compare the efficacy and safety of **lenvatinib in combination with pembrolizumab** versus TPC in participants with advanced EC who had been treated with at least 1 prior platinum-based chemotherapy regimen | N=827<br>pMMR=697 (346 in combo arm)<br>dMMR=130 (65 in combo arm) | 26-OCT-2020 |
| Study 204 | Phase 2 study of **lenvatinib monotherapy** in participants with advanced endometrial carcinoma and PD following first-line platinum-based chemotherapy | N=133<br>MMR status not determined | 21-MAY-2012 |
| KEYNOTE-158 | Phase 2 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<br>pMMR: n=90<br>dMMR: n=11<br>Unknown: n=6<br><br>Cohort K: N=79 dMMR (n=68 included in the efficacy analysis) | pMMR/not-MSI-H Analysis: 06-DEC-2018<br><br>dMMR/MSI-H Analysis[a]: 05-OCT-2020 |
| KEYNOTE-028 | Phase 1b study of **pembrolizumab monotherapy** in participants with PD-L1 positive advanced solid tumors, including endometrial carcinoma | N=24<br>pMMR: N=18<br>dMMR: N=1<br>Unknown: N=5 | 23-JAN-2019 |

Abbreviations: dMMR = mismatch repair deficient; EC = endometrial carcinoma; 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.

[a] The dMMR/MSI-H analysis with a data cutoff of 05-OCT-2020 included pooling of participants from Cohorts D and K (n=90), and for efficacy analysis, only participants with ≥6 months of follow-up were included (n=79).

At the time of the data cut-off of each supportive study, 25 of the 133 participants (18.8%) with EC treated with lenvatinib monotherapy had treatment ongoing in Study 204, while all patients had completed or discontinued pembrolizumab monotherapy in KEYNOTE-158 Cohort D and in KEYNOTE-028. Of the total 90 MSI-H patients in KEYNOTE-158 (n=11 in cohort D and n=79 in cohort K), 20 patient (22.2%) had treatment with pembrolizumab ongoing at the cut-off date.

Number of patients analysed:

In KEYNOTE-158 study, a total of 90 patients with MSI-H (n=11 in cohort D and n=79 in cohort K) were enrolled up to 23-Sep-2020. The population for efficacy analysis is however provided for a total of 79 patients (i.e. n=11 in cohort D and n=68 in cohort K) including only participants with at least 6 months of follow up. It is understood that the 11 subjects in cohort K excluded from the efficacy analysis with less than 6 months of follow up were all treatment still on treatment at the data cut-off date.

Comparison of inclusion/exclusion criteria:

The 3 studies presented as supportive are single arm trials. All enrolled a population with advanced/metastatic endometrial carcinoma who have received prior treatment. KEYNOTE-158 and -028 allowed the enrolment of more pretreated patients compared to KEYNOTE-775 and Study 204 which mandate radiological disease progression to platinum-based treatment.

Endometrial sarcomas were excluded from all studies with the exceptions of KEYNOTE-028, however in this study only one patient had a carcinosarcoma (see baseline characteristics below). All studies included only patients with measurable disease.

Compared to the pivotal study KEYNOTE-775 and the pembrolizumab monotherapy supportive studies KEYNOTE-158 and 028, Study 204 allowed the enrolment of patients with ECOG 2. Of note, KEYNOTE-028 enrolled only patients with PD-L1 positive disease.

Comparison of dose regimens:

The dose of lenvatinib used in the supportive Study-204 (24 mg OD) was higher than the one used as part of the combination treatment with pembrolizumab (20 mg OD). No data are available for lenvatinib 20 mg OD as monotherapy. On the contrary, the dose of pembrolizumab monotherapy in KEYNOTE-158 was the same as in the pivotal trial KEYNOTE-775. The dose of 10 mg/kg Q2W was instead used in KEYNOTE-028.

Overall response rate:

Patients in all trials had measurable disease by RECIST 1.1, and the primary evaluation of ORR was conducted by BICR per RECIST 1.1 in KEYNOTE-775, KEYNOTE-158 and Study-204. On the contrary, in KEYNOTE-028 the primary response evaluation was conducted by investigator. However, BICR revision was performed for regulatory purposes also in this study and results has been presented by the MAH. This is welcomed for the cross-study comparison.

Radiology assessment was performed every 8 weeks in KEYNOTE-775 and Study-204, but every 9 weeks in KEYNOTE-158.

**Table 77- Key Baseline Characteristics Across Study 309/KN-775 and Monotherapy Studies**

| | 309/KN-775 pMMR (N=346) | 309/KN-775 dMMR (N=65) | 204[a] (N=133) | KN-158 pMMR/MSS[b] (N=90) | KN-158 dMMR/ MSI-H[c] (N=79) | KN-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 *53 (81.5%)* | 132 (99.2) | 26 (28.9) | 38 (48.1) | 7 (29.2) |
| 2 | 92 (26.6) | NA *11 (17%)* | 1 (0.8) | 21 (23.3) | 19 (24.1) | 6 (25.0) |
| ≥3 | 10 (2.9) | NA *1 (1.5%)** | 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.

[b] In Study 204, MMR status in participants was not assessed.

[c] Data cutoff date: 06-OCT-2018.

[d] Data cutoff date: 05-OCT-2020.

[e] This participant was enrolled in error.

**number of prior anticancer regimen in dMMR KN-775 as difference between ITT (table 14.1-19 CSR KN775) - pMMR population (in this table)*

A comparison of baseline characteristics of patients enrolled in KEYNOTE-775 and in the supportive studies has been presented. While in KEYNOTE-775 and KEYNOTE-158 study the MMR status of patients is available, this is unknown in KEYNOTE-028 and in Study-204.

The main differences noted in baseline characteristics noted are:

1) patients in KEYNOTE-775 have better performance status compared to patients enrolled in the supportive studies;

2) patients in the pembrolizumab monotherapy studies KEYNOTE-158 and -028 were more pretreated;

3) slightly lower median age in Study-204;

4) few more Asian patients in KEYNOTE-755.

It cannot be excluded that point 1) and 2) above could have possibly ameliorate the outcome of KEYNOTE-775 population with respect to subjects receiving monotherapy in the supportive studies, while the relevance of the other two aspects could possibly be marginal.

PD-L1 status was not collected in KEYNOTE-775 nor in Study-204. While this is comprehensible for the lenvatinib Study-204, this is not understood for KEYNOTE-775. Data on PD-L1 status are limited in KEYNOTE-158 (not available in 70% of patients with dMMR status) while in KEYNOTE-028 all subjects were PD-L1 positive per inclusion criteria. This is considered a limit for data interpretation for the time being.

No relevant differences are seen in histology (endometrioid vs non endometrioid) among studies based on additional data provided (not shown). In the dMMR population of KEYNOTE-775 study, most of the subject has endometrioid histology, which is in line with the characteristics of dMMR EC.

**Table 78 - Summary of Efficacy Results of Lenvatinib plus Pembrolizumab, Lenvatinib Monotherapy, and Pembrolizumab Monotherapy Based on BICR Assessment in pMMR or All-comer Participants**

| Parameters | Study 309/KN-775 Combination Therapy[a] | Study 309/KN-775 TPC Chemotherapy)[a] | Lenvatinib Monotherapy Study-204[b] | Pembrolizumab Monotherapy | |
|---|---|---|---|---|---|
| | | | | KN-028[c] | KN158 |
| Therapy | Pembrolizumab plus lenvatinib | Doxorubicin or paclitaxel | Lenvatinib (24 mg) | Pembrolizumab | Pembrolizumab |
| Population | ≥1 previous systemic therapy | ≥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 participants | pMMR (N=346) | pMMR (N=351) | (N=133) (MMR status unknown) | (N=24) (MMR status unknown) | pMMR[d] (N=90) |
| Median PFS (months) (95% CI) | 6.6 (5.6, 7.4) | 3.8 (3.6, 5.0) | 5.6 (3.7, 6.3) | 1.8 (1.6, 2.7) | 2.1 (2.1, 2.2) |
| Median OS (months) (95% CI) | 17.4 (14.2, 19.9) | 12.0 (10.8, 13.3) | 10.6 (8.9, 14.9) | 13.6 (2.2, 25.2) | 10.1 (7.7, 14.9) |
| ORR (%) (95% CI) | 30.3 (25.5, 35.5) | 15.1 (11.5, 19.3) | 14.3 (8.8, 21.4) | 9.5 (1.2, 30.4) | 7.8 (3.2, 15.4) |
| CR n (%) | 18 (5.2) | 9 (2.6) | 1 (0.8) | 1 (4.8) | 0 |
| Median DOR (months) (range) | 9.2 (1.6+ - 23.7+)[e] | 5.7 (0.0+ - 24.2+)[e] | 7.2 (4.5 - NE) | NR | NR |

Abbreviations: BICR = blinded independent central review; CI = confidence interval; CR = complete response; DOR = duration of response; EC = endometroid carcinoma; MMR = mismatch repair; 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); 26-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, participants were not assessed for MMR status.

[c] Data cutoff date: 23-JAN-2019.

[d] Data cutoff date: 06-DEC-2018.

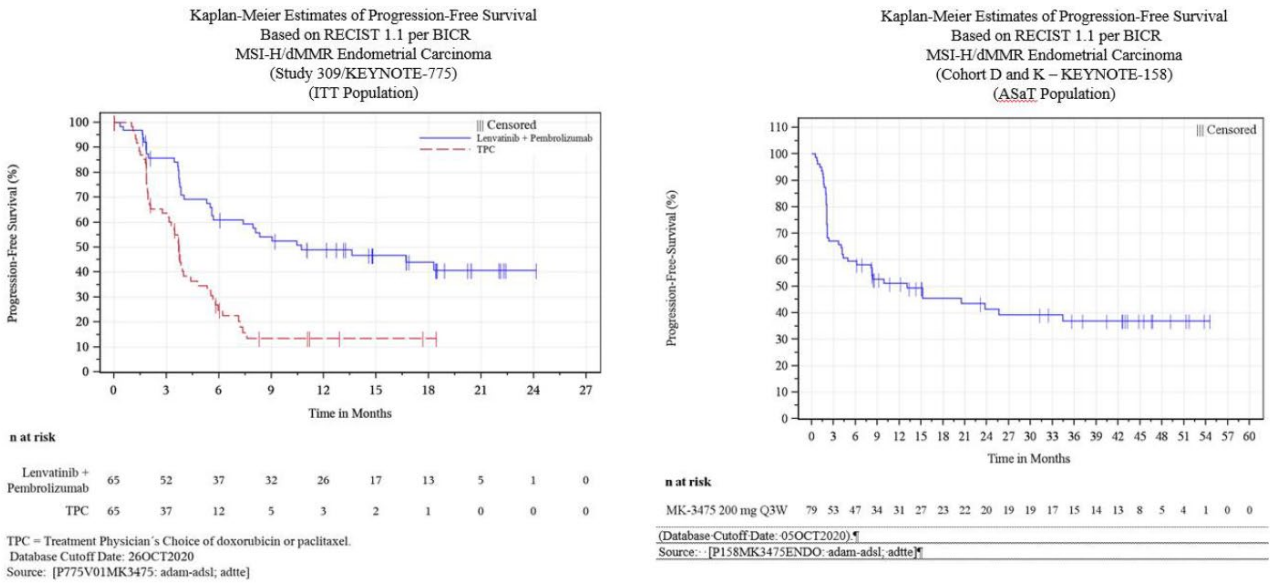
"+" indicates there is no progressive disease by the time of last disease assessment

**Table 79 - Summary of Efficacy Results of Lenvatinib Plus Pembrolizumab and Pembrolizumab Monotherapy in dMMR Participants with Advanced Endometrial Carcinoma**

| Parameters | Study 309/KN-775[a] Combination Therapy | Study 309/KN-775[a] TPC (Chemotherapy) | KN158 Pembrolizumab Monotherapy (data cutoff date: 06-DEC-2018) | KN158 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) | 6.5 (0.5, 56.1) |

**Figure 33 -**

Kaplan-Meier Estimates of Progression-Free Survival Based on BICR in dMMR Participants in KEYNOTE-158 and Study 309/KEYNOTE-775




**KEYNOTE-158 – dMMR population (pembrolizumab + lenvatinib)**

**Table 80 and 81**

Summary of Time to Response and Duration of Response
Based on BICR Assessment per RECIST 1.1 in Participants with Confirmed Response
in dMMR Participants
(ITT Population)

| | Lenvatinib + Pembrolizumab (N=65) | TPC (N=65) |
|---|---|---|
| Number of participants with responsea | 26 | 8 |
| **Time to Response (months)** | | |
| Mean (SD) | 3.7 (3.0) | 2.1 (0.7) |
| Median (Range) | 2.9 (1.7-16.3) | 1.9 (1.8-3.7) |
| **Response Durationb (months)** | | |
| Median (Range) | NR (2.1+ - 20.4+) | 4.1 (1.9+ - 15.6+) |
| **Number (%b) of Participants with Extended Response Duration:** | | |
| ≥6 months | 23 (96.0) | 3 (42.9) |
| ≥12 months | 15 (81.7) | 1 (42.9) |
| ≥18 months | 5 (74.9) | 0 (NR) |

[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.
NR = Not Reached.
TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

Summary of Best Overall Response
Based on BICR Assessment per RECIST 1.1
in dMMR Participants
(ITT Population)

| Response Evaluation | Lenvatinib + Pembrolizumab | | | TPC | | |
|---|---|---|---|---|---|---|
| | N | % | 95% CIa | N | % | 95% CIa |
| **Participants in population** | **65** | | | **65** | | |
| Complete Response (CR) | 9 | 13.8 | (6.5, 24.7) | 2 | 3.1 | (0.4, 10.7) |
| Partial Response (PR) | 17 | 26.2 | (16.0, 38.5) | 6 | 9.2 | (3.5, 19.0) |
| **Objective Response (CR+PR)** | **26** | **40.0** | **(28.0, 52.9)** | **8** | **12.3** | **(5.5, 22.8)** |
| Stable Disease (SD) | 25 | 38.5 | (26.7, 51.4) | 28 | 43.1 | (30.8, 56.0) |
| **Disease Control [CR+PR+(SD ≥ 7 Weeks)]** | **48** | **73.8** | **(61.5, 84.0)** | **31** | **47.7** | **(35.1, 60.5)** |
| **Clinical Benefit [CR+PR+(SD ≥ 23 Weeks)]** | **36** | **55.4** | **(42.5, 67.7)** | **14** | **21.5** | **(12.3, 33.5)** |
| Progressive Disease (PD) | 7 | 10.8 | (4.4, 20.9) | 15 | 23.1 | (13.5, 35.2) |
| Not Evaluable (NE) | 3 | 4.6 | (1.0, 12.9) | 1 | 1.5 | (0.0, 8.3) |
| No Assessment (NA) | 4 | 6.2 | (1.7, 15.0) | 13 | 20.0 | (11.1, 31.8) |

[a]Based on binomial exact confidence interval method.
NE: Post-baseline assessment(s) available, but not evaluable.
No Assessment: No post-baseline assessment available for response evaluation.
For best overall response of CR and PR, only confirmed responses are included.
BICR = Blinded independent central review.
TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

**KEYNOTE-158 – dMMR population (pembrolizumab monotherapy)**

**Table 82 and 83 -**

Summary of Time to Response and Duration of Response
Based on RECIST 1.1 per Central Radiology Assessment in Participants with Confirmed Response
(Baseline MSI-H)
(Cohort D and K – Endometrial Carcinoma)
(MK3475 200 mg Q3W)
(Responders)

| | MK-3475 200 mg Q3W (N=79) |
|---|---|
| Number of participants with response[a] | 38 |
| **Time to Response (months)** | |
| Mean (SD) | 3.5 (2.3) |
| Median (Range) | 2.3 (1.3-10.6) |
| **Response Duration[b] (months)** | |
| Median (Range) | NR (2.9 - 49.7+) |
| **Number (%[b]) of Participants with Extended Response Duration:** | |
| ≥6 months | 34 (91.8) |
| ≥12 months | 24 (88.1) |
| ≥18 months | 19 (72.9) |
| ≥24 months | 18 (72.9) |
| ≥30 months | 17 (72.9) |
| ≥36 months | 12 (68.1) |

[a] Includes participants with confirmed 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.
NR = Not Reached.
(Database Cutoff Date: 05OCT2020).

Summary of Best Objective Response Based on RECIST1.1 per Central Radiology Assessment
(Baseline MSI-H)
(Cohort D and K – Endometrial Carcinoma)
(MK3475 200 mg Q3W)
(ASaT Population for Efficacy Analysis)

| Response Evaluation | MK3475 200mg Q3W (N=79) | | |
|---|---|---|---|
| | n | % | 95% CI[a] |
| Complete Response (CR) | 11 | 13.9 | (7.2, 23.5) |
| Partial Response (PR) | 27 | 34.2 | (23.9, 45.7) |
| **Objective Response (CR+PR)** | **38** | **48.1** | **(36.7, 59.6)** |
| Stable Disease (SD) | 14 | 17.7 | (10.0, 27.9) |
| Progressive Disease (PD) | 23 | 29.1 | (19.4, 40.4) |
| Non-evaluable (NE) | 1 | 1.3 | (0.0, 6.9) |
| No Assessment | 3 | 3.8 | (0.8, 10.7) |

Central radiology assessed responses per RECIST 1.1 (confirmed) are included in this table.
[a] Based on binomial exact confidence interval method.
'No Assessment' (NA) counts participants who had a baseline assessment evaluated by the central radiology assessment but no post-baseline assessment on the data cutoff date including missing, discontinuing or death before the first post-baseline scan.
(Database Cutoff Date: 05OCT2020).

## 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. As a result, almost all patients in clinical trials received the 20 mg lenvatinib OD + pembrolizumab 200 mg Q3W dose. However, in KEYNOTE-775 approximately two/third of subjects had to reduce the dose of lenvatinib due to side effect.

From the efficacy perspective, in this supportive study Study 111/KEYNOTE-146, a total of 108 patients with endometrial cancer in 2L+ received the combination, of whom the majority had pMMR tumor and only 11 were dMMR. Overall, the ORR results are supportive of the activity of the combination observed in the pivotal study KEYNOTE-775. In particular, higher ORR is observed in dMMR compared to pMMR tumors, although the limited number of dMMR subjects preclude definitive conclusion.

Pivotal study

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 vs treatment of physician's choice (paclitaxel or doxorubicin) in participants with measurable advanced endometrial cancer (EC). Patients should have progressed to 1 prior platinum-based therapy (if given in the adjuvant/neoadjuvant setting, one rechallenge with platinum was permitted). Prior hormonal therapy was allowed with no restriction. Approximately 37% of patients in both arms received the treatment study as 1L for advanced/metastatic disease.

As all enrolled subjects (except one in the investigational arm, which was an important protocol deviation) received prior platinum-based therapy (77.5% one line and 22.2% two lines), and taking into account that platinum-based treatment is considered the standard first-line in EC[15] [16], the wording of the indication was amended to specify the use of a **prior platinum-containing therapy**.

Doxorubicin and paclitaxel are regarded valid second-line treatment options after platinum-based treatment of endometrial cancer. Approximately three-quarters of subjects in the control arm received doxorubicin, while less than 30% received paclitaxel. Of the latter, approximately 80% received also paclitaxel as previous treatment. For patients in the control arm receiving paclitaxel, outcome is similar regardless whether they have received paclitaxel previously. This is reassuring, although, as there are few patients who were not rechallenged with paclitaxel, no definitive conclusion can be made. The performance of patients treated with doxorubicin in the control arm appear unexpectedly inferior to patients who received paclitaxel. It is acknowledged however that patients who received paclitaxel are limited, and it is difficult to draw definitive conclusion. When analyzed by chemotherapy chosen prior to randomization for all randomized participant, an advantage of the pembrolizumab+lenvatinib combination is maintained vs each chemotherapy drug.

Inclusion/exclusion criteria reflect the usual criteria used for immunotherapy trials, which are already reflected in the pembrolizumab SmPC. In addition, there were several quite strict exclusion criteria related to hypertension, proteinuria, history of CV disease, previous bleeding, fistula, which is considered acceptable given the known toxicity of lenvatinib, and have been added to the SmPC section 5.1 in the description of study population.

In addition, as only patients with ECOG 0-1 were allowed, a significant number of real-world endometrial cancer patients being treated in second-line setting would have been excluded (as also underlined at the

[15] N. Colombo, C. Creutzberg, F. Amant, T. Bosse, et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer. Ann Oncol 2016; 27: 16-41.
[16] NCCN Guidelines Uterine Neoplasm, version 2.2021.

time of the Scientific Advice, where it was suggested to consider inclusion of ECOG PS 2 patients). Not qualifying ECOG, together with inadequate organ function or condition that may confound the results, were indeed the most common reasons for screen failure, suggesting that the target population of advanced endometrial cancer in the post platinum setting include a not negligible amount of frail subjects with comorbidities. Therefore, the population included in this study possibly reflect a fitter subgroup of subjects with advanced endometrial carcinoma and might not be fully representative of an endometrial cancer population in late line with generally dismal prognosis. The enrolment of only ECOG 0-1 patients is mentioned in the SmPC.

Apart from that, baseline disease characteristics were overall reflective of a population with advanced EC. Few more pretreated patients were however included in the control arm.

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. Not unexpectedly in an open-label trial, more patients in the control rather than in the investigational arm did not receive the treatment they were randomized to, as well as there were more patients who discontinued therapy due to subject or physician's decision.

The study has PFS and OS in the all-comer and in the pMMR population as dual primary endpoints. ORR in both populations was key secondary endpoint. This is acceptable. At the time of the SA, indeed, the CHMP questioned that "PFS does not seem acceptable as a primary endpoint. Approval based on PFS without fully powered OS superiority would be improbable in advanced endometrial carcinoma after at least one prior platinum-based treatment." Study 309/KEYNOTE-775 study is powered also for OS, which is in line with prior advice. Statistical methods appear standard. Assumptions for median PFS and OS in the control arm were in line with literature data[17] [18].

Patients were stratified according to MMR status, ECOG, geographic region and prior history of pelvic radiation, which is acceptable. MMR status was assessed centrally with IHC, using a clinical trial assay testing all four MMR proteins (MLH1, MSH2, MSH6 and PMS2), as usually recommended. The enrolment of dMMR patients was capped at 15%, which is in line with the expected prevalence of in line with prevalence of MSI-H EC reported in literature[19] [20].

Number of important protocol deviation was low and similar in both arms, which is reassuring on the study conduction.

## Efficacy data and additional analyses

Results of the Interim Analysis 1 (i.e. final for PFS, interim for OS) with data cut-off date 26 Oct 2020 were submitted. The median duration of follow up in the overall population of 11.4 months (range 0.3, 26.9).

Baseline patients and disease characteristics were overall well balanced between the two treatment arms in the ITT population (411 vs 416 patients) as well as in the pMMR population (346 vs 351, comprising 85% of the all comers). The characteristics of pMMR subpopulation were similar to all comers. PD-L1 expression, as well as POLE mutations, was not assessed by the MAH.

[19] Basil JB, Goodfellow PJ, Rader JS, Mutch DG, Herzog TJ. Clinical significance of microsatellite instability in endometrial carcinoma. Cancer. 2000 Oct 15;89(8):1758-64.
[20] Prendergast EN, Holman LL, Liu AY, Lai TS, Campos MP, Fahey JN, et al. Comprehensive genomic profiling of recurrent endometrial cancer: implications for selection of systemic therapy. Gynecol Oncol. 2019;154:461-6.

Not unexpectedly in an open-label trial, there are more patients in the control rather than in the investigational arm who did not receive the treatment they were randomized to, and who discontinued due to subject's or physician's decision. Most common reason for discontinuation in both arms was PD, with more clinical progression among patients treated with chemotherapy. A higher rate of discontinuations due to adverse event was observed in the combination arm.

All-comer population

The combination of lenvatinib plus pembrolizumab demonstrated a statistically significant and clinically meaningful superiority to TPC with respect to PFS and OS in all-comers.

Death event occurred in almost half of the subjects overall, but about 10% more events were reported in the control arm (46% vs 59%). HR for **OS** was 0.62 (95%CI 0.51, 0.75, p<0.0001 one-sided), with a gain of about 7 months in median survival (18.3 vs 11.4 months). OS curves overlap up to month 3 and remained consistently separated throughout the duration of the evaluation period, although difficult to be interpreted after month 9 due to high rate of censoring. As OS data is not fully mature yet, the MAH will submit final OS data for the overall population as well as for MMR subgroups as recommendation **(REC)** which is expected in 4Q2022.

Although similar **PFS** event rates occurred in both arms (ca 68%), a clinically relevant advantage is seen in PFS [HR of 0.56 (95%CI 0.47, 0.66, p>0.0001 one-sided)] with almost doubled median PFS (7.2 vs 3.8 months in the pembrolizumab+lenvatinib vs TPC arm, respectively) and maintained benefit long-term as seen in consistent separation of KM curves. PFS sensitivity analyses were consistent with the primary one. PFS2 data is considered further supportive (HR 0.56). PFS assessed by BICR and investigator was similar. The rate of agreement between INV and BICR was approximately 80-85%, with no relevant differences in agreement/disagreement rates noted between the two arms.

**ORR** was almost doubled in patients receiving pembrolizumab + lenvatinib compared to standard chemotherapy (31.9% vs 14.7%), with higher rate of CR (6.6% vs 2.6%). Although the ORR of the combination does not appear particularly outstanding, the improvement compared to standard chemotherapy is relevant. The higher rate of patients with missing assessment in the control arm compared to the experimental arm (roughly 13% vs 5%) was due to consent withdrawn after being assigned or having started treatment in the control arm, which is somewhat related to the open-label study design, despite the MAH's intervention to monitor and mitigate discontinuations.

As expected, the median **DOR** was longer in the experimental arm (14.4 vs 5.7 months), with higher number of durable responses (71.9% vs 42.6% of responding subjects for ≥6 months).

The percentage of patients who receive at least one subsequent line of treatment was higher in the control arm compared to the investigational arm (28% vs 48.1%), despite a similar rate of subjects who discontinued study treatment in both arms, as well as similar rate of subjects experiencing a PFS event of disease progression. This raises concern on the ability to receive additional line(s) of treatment, in particular in subjects who discontinued therapy due to AEs. Additional data showed that 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%). Such difference is not evident in subjects who had progressive disease, as about half in each treatment arm received subsequent anticancer therapy. The MAH discussed that 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 pembrolizumab+lenvatinib arm than in the control arm, although the low number of subjects assessed should be noted. However, the outcome in terms of OS and PFS of patients who discontinued treatment due to AE in the two arms appear similar. The post-hoc nature of the analyses provided as well as the low number of subjects analysed, especially in the TPC arm, is acknowledged. However, the data provided remarked that pembrolizumab+lenvatinib combination does not have a trivial toxicity, suggesting its use in a more fit population possibly more able to tolerate such treatment. Also in this context, the inclusion of more detailed information on the patient population selected in the study (i.e. with exclusion criteria related to the known toxicity of lenvatinib) is considered relevant.

Although crossover was not permitted, in the control arm 9.1% of ITT patients and 7.7% of pMMR patients received pembrolizumab+lenvatinib as subsequent line. It's unlikely that this had relevant impact on final OS results.

Most of the patients receiving subsequent therapy, were indeed able to receive at least two additional lines of treatment, and a relevant percentage also 3 or more. Taking into account the dismal prognosis of endometrial cancer, this observation could further underline the fact that subjects enrolled in this study were more fit than the general population with advanced pretreated endometrial cancer as discussed above.

No relevant differences are seen in older patients from an efficacy perspective. The PFS, OS and ORR benefit of pembrolizumab + lenvatinib compared to TPC was consistent across classes of age in KEYNOTE-775 study.

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.

pMMR population

The results in the pMMR subgroup, representing about 85% of the all-comers, were overall similar although slightly inferior compared to the whole population, but were still statistically significant and can be deemed clinically relevant. OS HR was 0.68 (0.56, 0.84, p=0.0001 one sided), with improvement in median OS from 12 months in the control arm to 17.4 months in the investigational arm, with similar appearance of the OS curves as the all comers. The PFS event rate was slightly higher in the investigational arm, but with a final PFS improvement (HR 0.60, 95%CI 0.50, 0.72, p<0.0001 one sided, median PFS 6.6 vs 3.8 months). PFS sensitivity analyses and PFS2 (HR 0.62) support the primary results. An improvement was seen also in terms of ORR (30.3% vs 15.1%), median DOR (9.2 vs 5.7 months) and durable responses (65.6% vs 42.1% responses lasted ≥6 months).

Subgroup analyses

Treatment benefit in terms of OS, PFS and ORR for lenvatinib plus pembrolizumab compared with TPC appears overall consistent across all major subgroups analysed, in pMMR and all-comer participants.

*dMMR subgroup*

The dMMR subgroup was not prespecified in the multiplicity strategy for Type I error control, therefore only nominal p-values have been provided for the efficacy endpoints. MMR status was however a stratification factor.

A total of 130 (65 in each arm) had a tumor status of dMMR, representing 15.7% of the all comers population. The rate of patients still receiving pembrolizumab + lenvatinib at the data cut-off date was higher in the dMMR compared to the pMMR subgroup (45.3% vs 27.9%). Baseline characteristics in the

dMMR subgroup were balanced between treatment arms and quite similar to the pMMR population, with the exception of histology, as most of the pMMR tumor were endometrioid: this is however in line with literature data[21]. The rate of patients still receiving pembrolizumab + lenvatinib at the data cut-off date was higher in the dMMR compared to the pMMR subgroup (45.3% vs 27.9%).

The combination of lenvatinib plus pembrolizumab was superior to TPC with respect to PFS and OS for the treatment of dMMR participants. Although dMMR was not statistically tested, PFS and OS benefit are deemed clinically relevant, and efficacy of the combination appears higher compared to what observed in the pMMR population (PFS HR 0.36, OS HR 0.37, ORR 40% vs 12.3%, CR 13.8% vs 3.1%, median DOR NR vs 4.1 months).

The efficacy results in the control arm of dMMR subgroup appear quite similar to the control arm of pMMR population, although the limited number of subjects preclude further conclusion. OS data for pMMR and dMMR populations are reflected in the section 5.1 of the SmPC

Contribution of components to the combination

Results from Study 204, KEYNOTE-158, and KEYNOTE-028 in order to provide evidence of the contribution of lenvatinib and pembrolizumab monotherapies to the efficacy of the combination were provided. **KEYNOTE-158** is a phase 2 study of pembrolizumab monotherapy in participants with multiple types of advanced solid tumors progressed 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 used in combination with pembrolizumab in Study 309/KEYNOTE-775 (20 mg OD). On the contrary, the same dose of pembrolizumab (200 mg Q3W) was used in Study 309/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 Study 309/KEYNOTE-775 at this stage is a limit for data interpretation.

For the pMMR subgroup, the ORR of Study 309/KEYNOTE-775 [30.3% (95%CI 25.5, 35.5)], including rate of CR (5.2%) is indeed greater than ORRs and CRs observed for lenvatinib monotherapy [ORR 14.3%, 95%CI 8.8, 21.4; CR 2.6%) and for pembrolizumab monotherapy [ORR 7.8% (95%CI 3.2, 15.4) with 0% of CR in KEYNOTE-158; ORR 9.5% (95%CI 1.2, 30.4), CR 4.8%]. The lower bound of the 95% CI of the ORR for lenvatinib + pembrolizumab was greater than that of the observed point estimate for either lenvatinib or pembrolizumab administered as monotherapy. Based on the overall data available, a limited activity of both pembrolizumab and lenvatinib as single agents is observed in previously treated advanced/metastatic endometrial cancer with pMMR based on single-arm data. The indirect comparison appears 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, hampering the possibility to draw definitive conclusion. No meaningful conclusion can be made with regard 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.

[21] Basil JB, Goodfellow PJ, Rader JS, Mutch DG, Herzog TJ. Clinical significance of microsatellite instability in endometrial carcinoma. Cancer. 2000 Oct 15;89(8):1758-64.

In patients with dMMR endometrial cancer, the activity of the combination pembrolizumab + lenvatinib in KEYNOTE-775 appears similar to what shown by pembrolizumab alone in KEYNOTE-158, in terms of ORR, rate of CR, and DOR. Also PFS and OS did not suggest relevant differences, acknowledging the overall limited number of dMMR patients as well as the limitation in the assessment of time-related endpoints in the single arm study. It is noted that in Study 309/KEYNOTE-775 study, the overall number of dMMR patients is limited, which is consistent with the expected prevalence of this treatment setting. As a result, confidence intervals are wide. These aspects limit the ability to make cross-study comparison. Furthermore, KEYNOTE-775 study was designed and powered to compare lenvatinib plus pembrolizumab with TPC in the pMMR and all-comer populations. However, although the wide confidence intervals in Study 309/KEYNOTE-775 are noted, both the point estimates and the confidence intervals of all efficacy endpoints do not suggest any relevant difference in activity of the combination as compared to pembrolizumab alone in dMMR pretreated EC.

The MAH argued that the KM curve for the combination of lenvatinib plus pembrolizumab in Study 309/KEYNOTE-775 demonstrates a lower PFS event rate within the first 3 months of treatment initiation compared with the KM curve for pembrolizumab monotherapy in KEYNOTE-158, suggesting more rapid disease control with the addition of lenvatinib to pembrolizumab compared with pembrolizumab monotherapy. However, this is not supported as the same time to response was observed with the combination and the monotherapy. It is recognised that a higher rate of stable disease was reported with the combination, but it is not clear whether this translate to a long-term benefit, as no relevant difference are envisaged in PFS and OS between combination and monotherapy based on indirect comparison.

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 Study 309/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

Overall, favourable efficacy of the pembrolizumab with lenvatinib combination is observed consistently for primary and secondary endpoints. 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

To support the safety and tolerability of the combination of lenvatinib+pembrolizumab (oral lenvatinib 20 mg QD in combination with IV pembrolizumab 200 mg Q3W) for the treatment of patients with advanced EC who have disease progression following prior platinum-based systemic therapy in any setting and are not candidates for curative surgery or radiation, interim analysis data from the pivotal, open-label, randomized Phase 3, Study 309/KEYNOTE-775 are submitted.

- **Study 309/KEYNOTE-775 combination lenvatinib + pembrolizumab** (N=406): Subjects 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. (*KN-775 lenvatinib plus pembrolizumab group*)
- **Study 309/KEYNOTE-775 chemotherapy doxorubicin or paclitaxel** (N=388): Subjects 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. (*TPC group*)

In addition, 3 supportive safety datasets are presented:

- **Combination lenvatinib +pembrolizumab – Non-endometrial** (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. (*Lenvatinib and pembrolizumab non-EC group*)
- **Lenvatinib Monotherapy Safety Set** (N=1119): Pooled safety data from participants treated with lenvatinib monotherapy in 11 studies. (*Lenvatinib monotherapy Safety Dataset*)
- **Pembrolizumab Monotherapy Reference Safety Dataset** (N=5884): Pooled safety data from participants treated with pembrolizumab monotherapy, including all participants who received at least one dose of pembrolizumab in in melanoma, lung, cHL, bladder, and HNSCC in EU-approved conditions (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 Reference Safety Dataset*)

To assess potential indication-specific safety concerns, the safety profile of lenvatinib+pembrolizumab observed in KN-775 (endometrial carcinoma) is compared with that found in the non-endometrial Carcinoma Safety Dataset from Study 111/KEYNOTE-146.

Data from the Lenvatinib Monotherapy Safety Dataset and the Pembrolizumab Monotherapy RSD are used to allow for comparison of the safety profile of KN-775 lenvatinib+pembrolizumab with the established safety profiles for lenvatinib and pembrolizumab monotherapy.

**Table 84 – 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]).<br>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

As of the 26-OCT-2020 data cutoff, 406 participants received at least 1 dose of the lenvatinib plus pembrolizumab combination, and 388 participants received at least 1 dose of the doxorubicin or paclitaxel chemotherapy in Study 309/KEYNOTE-775.

**Table 85 – 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)

Source: [ISS: adam-adsl; adexsum]

**Table 86 – 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[i] (N=1119) | | | Pembrolizumab Monotherapy Reference Safety Dataset[j] (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 |
| ≥ 24 | 5 | (1.2) | 128.2 | 1 | (0.3) | 25.8 | 28 | (12.2) | 944.5 | 186 | (16.6) | 7,313.1 | 103 | (1.8) | 2,610.2 |

Each participant is counted once on each applicable duration category row.

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)

Source: [ISS: adam-adsl; adexsum]

**Table 87 – Summary of administration for Lenvatinib (APaT population)**

| | KN775 Lenvatinib + Pembrolizumab (N=406) | KN146 Lenvatinib + Pembrolizumab (Non-Endometrial Cancer) (N=230) | Lenvatinib Monotherapy Safety Dataset[i] (N=1119) |
|---|---|---|---|
| Duration on Lenvatinib (month) | | | |
| n | 406 | 229 | 1119 |
| Mean | 8.27 | 11.56 | 11.61 |
| Median | 6.95 | 9.59 | 5.55 |
| SD | 6.286 | 10.578 | 14.066 |
| Range | 0.03 to 26.84 | 0.10 to 50.40 | 0.03 to 78.66 |
| Dose Intensity (mg/day) | | | |
| n | 406 | 229 | 1119 |
| Mean | 13.98 | 14.47 | 18.70 |
| Median | 13.77 | 14.03 | 20.07 |
| SD | 4.380 | 4.130 | 5.205 |
| Range | 3.27 to 20.00 | 3.25 to 20.00 | 5.08 to 25.48 |
| Received Dose as Percentage of Planned Starting Dose (%) | | | |
| n | 406 | 229 | 1119 |
| Mean | 69.91 | 72.34 | 77.93 |
| Median | 68.85 | 70.16 | 83.61 |
| SD | 21.899 | 20.651 | 21.688 |
| Range | 16.34 to 100.00 | 16.23 to 100.00 | 21.15 to 106.17 |

Duration on lenvatinib (month) is calculated as (last dose date of lenvatinib - first dose date of lenvatinib + 1) / 30.4367.
Dose intensity (mg/day) = total dose received / treatment duration
Received dose as percentage of planned starting dose (%) = dose intensity (mg/day) / planned daily dose (mg/day) x 100
[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.
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; adexsum]

**Table 87 – Summary of administration for Pembrolizumab (APaT population)**

| | KN775 Lenvatinib + Pembrolizumab (N = 406) Pembrolizumab n (%) | KN146 Lenvatinib + Pembrolizumab (Non-Endometrial Cancer) (N = 230) Pembrolizumab n (%) | Pembrolizumab Monotherapy Reference Safety Dataset[j] (N = 5884) Pembrolizumab n (%) |
|---|---|---|---|
| Number of Administrations | | | |
| ≥ 1 | 406 (100.0) | 230 (100.0) | 5884 (100.0) |
| ≥ 2 | 383 (94.3) | 219 (95.2) | 5481 (93.2) |
| ≥ 3 | 361 (88.9) | 205 (89.1) | 5023 (85.4) |
| ≥ 4 | 337 (83.0) | 192 (83.5) | 4438 (75.4) |
| ≥ 5 | 319 (78.6) | 177 (77.0) | 4013 (68.2) |
| ≥ 6 | 295 (72.7) | 163 (70.9) | 3608 (61.3) |
| ≥ 7 | 270 (66.5) | 155 (67.4) | 3269 (55.6) |
| Mean | 12.1 | 14.3 | 11.6 |
| Median | 10.0 | 12.0 | 8.0 |
| SD | 8.7 | 10.6 | 10.1 |
| Range | 1 to 35 | 1 to 35 | 1 to 59 |

Each subject is counted once on each applicable number of administrations category row.
[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; adexsum]

### Demographic and Other Characteristics of Study Population

**Table 88 – Participants 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) |

## Adverse events

AEs were coded using MedDRA (v23.1). AEs in Study 309/KEYNOTE-775 were reported according to NCI CTCAE v4.03.

The All Participants as Treated (APaT) population was used for the analysis of safety data of KN-775 study. The APaT population consists of all randomized participants who received at least 1 dose of study treatment. Participants are included in the treatment group corresponding to the study treatment they actually received.

**Table 89 – Adverse events summary (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 event | 1 | (0.2) | 2 | (0.5) | 0 | (0.0) | 11 | (1.0) | 194 | (3.3) |
| with drug-related[a] 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) | – | | -- | | – | | -- | |

[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 90 – Exposure adjusted Adverse events 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[i] | | Pembrolizumab Monotherapy Reference Safety Dataset[j] | |
| 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) |

| | 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[i] | | Pembrolizumab Monotherapy Reference Safety Dataset[j] | |
| 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) | -- | |

| | 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[i] | | Pembrolizumab Monotherapy Reference Safety Dataset[j] | |
| 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.

[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]

## Most Common Adverse Events

**Table 91 – 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)

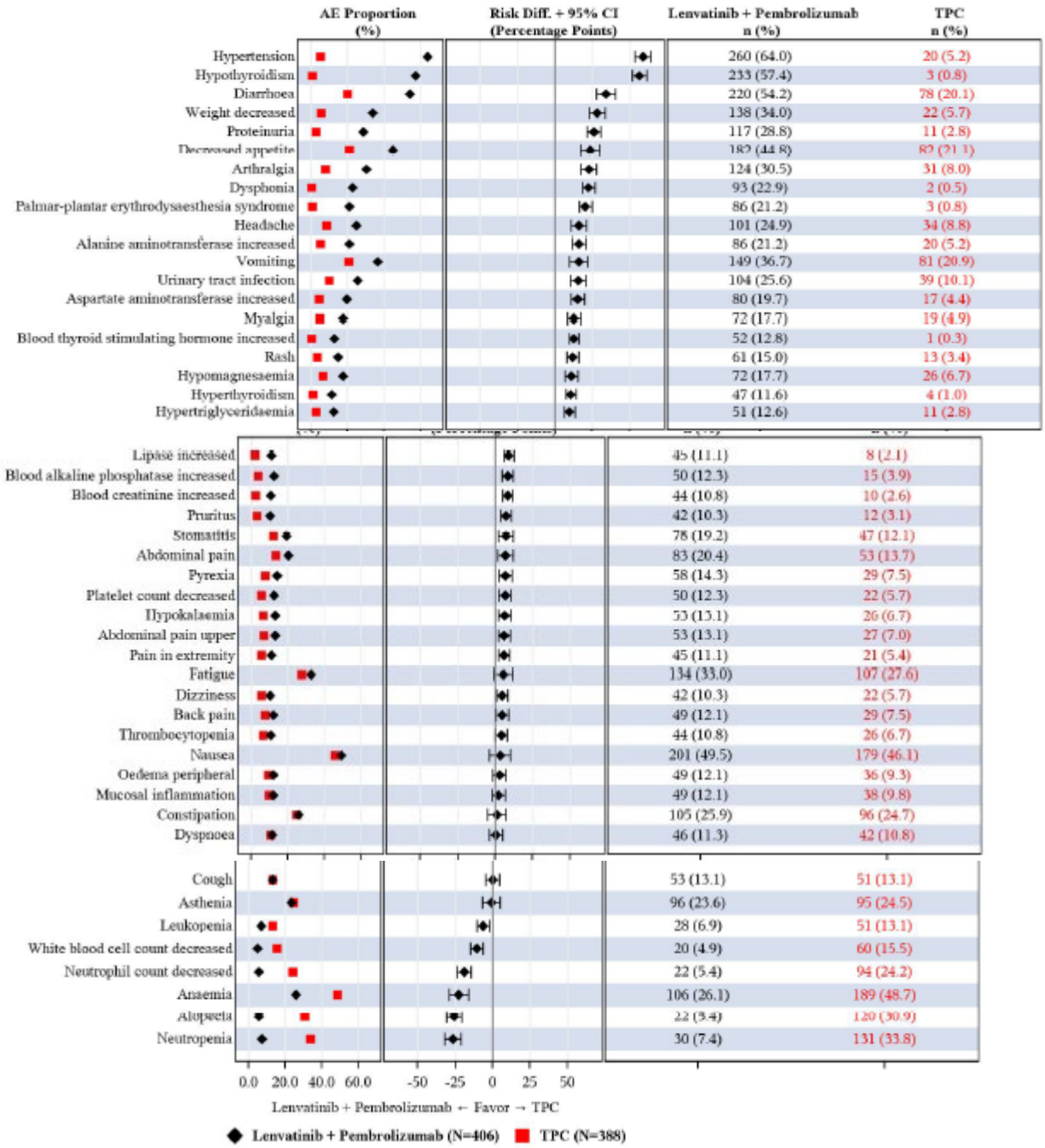
Database cutoff date for Adenocarcinoma (E7080-G000-209: 01SEP2016)

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

Source: [ISS: adam-adsl; adae]

Risk difference between KN-775 treatment groups for common AEs are shown in the Figure below.

**Figure 34 – Rainfall plot for adverse events (incidence ≥10% in one or more treatment groups) in all-comer participants (APaT population)**




While most common AEs found in the lenvatinib+pembrolizumab arm were generally consistent with the safety profile of lenvatinib and pembrolizumab monotherapies, the frequency of the following AEs incidence was higher in the combination group compared to, respectively, each monotherapy dataset: hypothyroidism (57.4% vs 13% and 11.1%), anemia (26.1% vs 8.2% and 14.2%), UTI (25.6% vs 10.6% and 6.5%), ALT increased (21.2% vs 8% and 6.7%), AST increased (19.7% vs 7.3% and 6.5%), hypomagnesemia (17.7% vs 4.6% and 2.7%), hypokalaemia (13.1% vs 8.6% and 4.6%), blood TSH increased (12.8% vs 7.1% and 1.6%), hypertriglyceridemia (12.6 % vs 3.1 and 1.5%), blood alkaline phosphate increased (12.3% vs 5.0 and 4.1%), platelet count decreased (12.3% vs 4.9% and 1.2%), mucosal inflammation (12.1% vs 2.2%

and 1.6%), hyperthyroidism (11.6% vs 2.6% and 4.2%), lipase increased (11.1% vs 3.7% and 0.5%), blood creatinine increased (10.8% vs 4.8% and 4.4%).

**Table 92 – 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]

SOCs with higher exposure-adjusted incidence (>2 x 100 person-months) in the lenvatinib+pembrolizumab arm than in the TPC arm were the following: Endocrine disorders (8.7 vs 0.5 x 100 p-m), Metabolism and nutrition disorders (22.6 vs 18.0 x 100 p-m), Musculoskeletal and connective tissue disorders (14.0 vs 9.5 p-m), Renal and urinary disorders (8.7 vs 3.9 x 100 p-m), Vascular disorders (12.8 vs 5.0 x 100 p-m).

**Drug-related Adverse Events**

SOCs of drug-related AEs with higher incidence (>10% difference) in the lenvatinib+pembrolizumab group versus the TPC group were the following:

- Endocrine disorders 58.9% vs 0.3%
- Gastrointestinal disorders 74.4% vs 60.6%
- Investigations 61.1% vs 39.2%
- Metabolism and nutrition disorders 53% vs 22.7%
- Musculoskeletal and connective tissue disorders 36.9% vs 12.9%
- Renal and urinary disorders 30% vs 3.4%
- Respiratory, thoracic and mediastinal disorders 32% vs 9%
- Vascular disorders 62.8% vs 6.4%

On the contrary, Blood and lymphatic disorders SOC was less frequent in the lenvatinib+pembrolizumab group when compared to the TPC group (23.9% vs 60.3%, respectively).

**Table 93 – 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[j] | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 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)

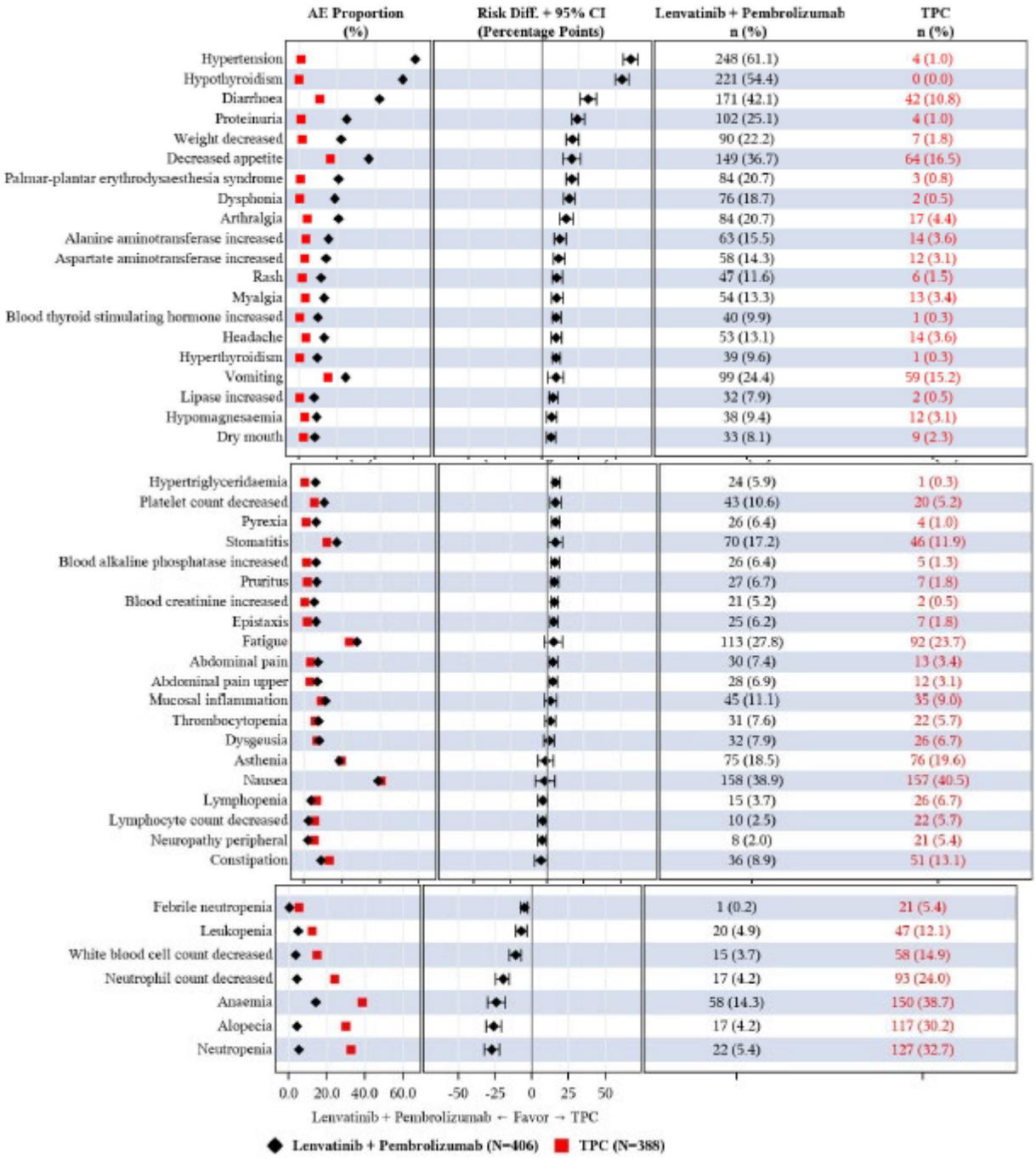
Database cutoff date for Renal Cell Carcinoma (E7080-G000-205: 15MAR2018)

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]

**Figure 35– Rainfall plot for drug related adverse events (incidence ≥ 5% in one or more treatment groups) in all-comer participants (APaT population)**




## All Grade 3 to 5 Adverse Events

**Table 94 - Participants With Grade 3-5 Adverse Events by Decreasing Incidence (Incidence >2% 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 | 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) |

The risk difference between KN-775 study arms for Grade 3-5 AEs is shown in the Figure below.

**Figure 36– Rainfall plot for grade 3-5 adverse events (incidence ≥ 5% in one or more treatment groups) in all-comer participants (APaT population)**

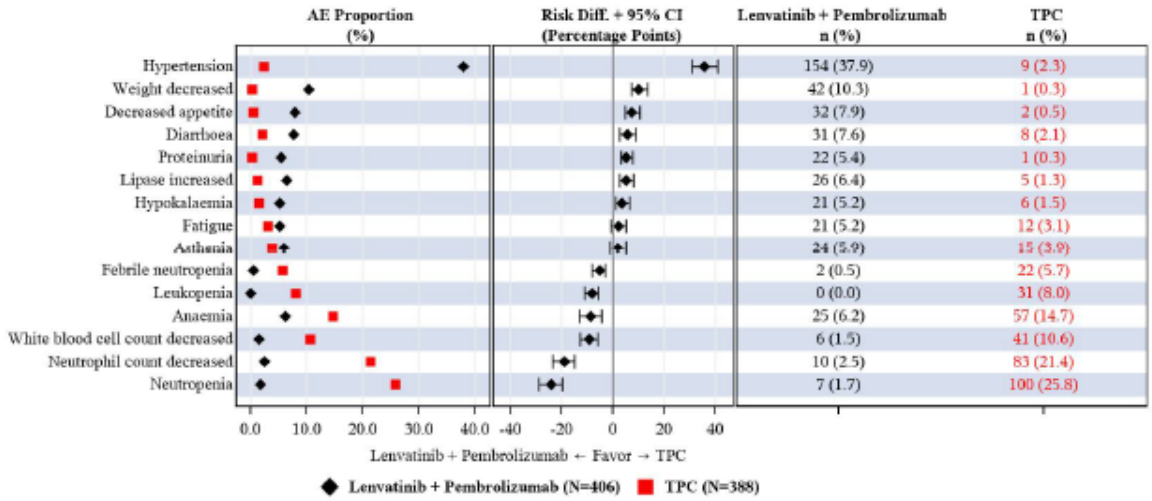



**Table 95 - Exposure-Adjusted Grade 3-5 Adverse Events (Including Multiple Occurrences of Events) (Incidence ≥ 5% in One or More Treatment Groups) in All-comer Participants (APaT Population)**

| | 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)** |

## Grade 3 to 5 Drug-related Adverse Events

**Table 96 - 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[i] | | Pembrolizumab Monotherapy Reference Safety Dataset[i] | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 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) |

| | 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 | (%) |
| 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]

Drug-related Grade 3-5 AEs were highest in the KN-775 combination treatment arm (77.8%, vs 59% in KN-775 TPC group, 64.7% in the non-EC combination treatment, 65.7% in lenvatinib monotherapy, 15.5% in pembrolizumab monotherapy).

Drug-related Grade 3 and 4 AEs were reported respectively in 70.4% and 25.8% of KN-775 subjects who received the combination treatment and in 5.9% and 31.2% of those who were treated with TPC.

## Safety Data Supporting Section 4.8 Of Summary Of Product Characteristics

Section 4.8 of the SmPC combines in a new single column the ADRs from pembrolizumab plus lenvatinib and pembrolizumab plus axitinib therapies. Pembrolizumab plus Lenvatinib is based on KEYNOTE-581 (Study 307), KEYNOTE-146 (Study 111) and KEYNOTE-775 (Study 309), and pembrolizumab plus axitinib is based on KEYNOTE-426.
The frequencies included are based on all reported adverse drug reactions, regardless of the investigator assessment of causality.

Adverse reactions included in Table 2 of the SmPC:

Table below encompasses the adverse reactions included in Table 2 of the SmPC section 4.8 with related frequency categories and figures from the KEYNOTE-581, KEYNOTE-146, KEYNOTE-775, and KEYNOTE-426 studies with the combination of pembrolizumab plus lenvatinib or pembrolizumab plus axitinib.

Database cutoff dates were:

- for Endometrial Cancer: KN146 18AUG2020; KN775 26OCT2020;
- for RCC: KN426 24AUG2018; KN581 28AUG2020

The criteria for populating Table 2 in the Keytruda SmPC are as follows (meeting at least one of the criteria):

- Keytruda 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 not already ADRs for Keytruda and occurring at an incidence higher than the respective monotherapy safety profiles were assessed for additive or potentiated effect and clinical relevance.

No new ADRs were assessed for the individual monotherapies or for the combination; therefore, no new ADRs were added.

**Table 97: Adverse Reactions in Participants Treated With Pembrolizumab in Combination With Lenvatinib or Axitinib - EC / RCC Participants in KN146, KN426, KN581 and KN775 (APaT Population)**

| | | Combination Therapy (N=1456) | |
|---|---|---|---|
| | | All AEs % (n) | Gr 3-5 AEs n |
| **Infections and infestations** | | | |
| Very common | urinary tract infection | 15.0% (218) | 31 |
| Common | pneumonia | 3.6% (52) | 23 |
| **Blood and lymphatic system disorders** | | | |
| Very common | anaemia | 14.6% (213) | 42 |
| Common | neutropenia | 3.4% (49) | 11 |
| Common | thrombocytopenia | 5.4% (79) | 9 |
| Common | lymphopenia | 2.5% (37) | 9 |
| Common | leukopenia | 2.7% (39) | 0 |

| | | | |
|---|---|---|---|
| Uncommon | eosinophilia | 0.4% (6) | 0 |
| **Immune system disorders** | | | |
| Common | infusion reactions[a] | 2.0% (29) | 6 |
| **Endocrine disorders** | | | |
| Very common | hypothyroidism | 46.1% (671) | 12 |
| Common | adrenal insufficiency[b] | 3.4% (49) | 15 |
| Common | hyperthyroidism | 9.8% (143) | 8 |
| Common | thyroiditis[c] | 1.8% (26) | 1 |
| Uncommon | hypophysitis[d] | 0.8% (11) | 8 |
| **Metabolism and nutrition disorders** | | | |
| Very common | decreased appetite | 40.2% (586) | 63 |
| Common | hyponatraemia | 8.2% (119) | 64 |
| Common | hypokalaemia | 8.4% (122) | 39 |
| Common | hypocalcaemia | 2.1% (31) | 8 |
| Uncommon | type 1 diabetes mellitus[e] | 0.5% (7) | 6 |
| **Psychiatric disorders** | | | |
| Common | insomnia | 9.6% (140) | 1 |
| **Nervous system disorders** | | | |
| Very common | headache | 22.9% (334) | 11 |
| Very common | dysgeusia | 10.3% (150) | 3 |
| Common | dizziness | 9.9% (144) | 2 |
| Common | neuropathy peripheral | 1.5% (22) | 0 |
| Common | lethargy | 1.2% (18) | 0 |

| | | Combination Therapy (N=1456) | |
|---|---|---|---|
| | | All AEs % (n) | Gr 3-5 AEs n |
| Uncommon | myasthenic syndrome[f] | 0.5% (7) | 5 |
| Uncommon | encephalitis[g] | 0.3% (4) | 4 |
| **Eye disorders** | | | |
| Common | dry eye | 2.0% (29) | 0 |
| Uncommon | uveitis[h] | 0.4% (6) | 1 |
| Rare | vogt-koyanagi-harada disease | 0.07% (1) | 1 |
| **Cardiac disorders** | | | |
| Common | cardiac arrhythmia (including atrial fibrillation)[i] | 7.9% (115) | 28 |
| Uncommon | myocarditis | 0.5% (7) | 6 |
| Uncommon | pericardial effusion | 0.3% (4) | 1 |
| **Vascular disorders** | | | |
| Very common | hypertension | 53.8% (783) | 422 |
| Uncommon | vasculitis[j] | 0.2% (3) | 1 |
| **Respiratory, thoracic and mediastinal disorders** | | | |
| Very common | dyspnoea | 16.0% (233) | 26 |
| Very common | cough | 21.5% (313) | 3 |
| Common | pneumonitis[k] | 2.9% (42) | 15 |
| **Gastrointestinal disorders** | | | |
| Very common | diarrhoea | 57.8% (841) | 129 |
| Very common | abdominal pain[l] | 28.0% (408) | 40 |
| Very common | nausea | 40.1% (584) | 36 |
| Very common | vomiting | 27.9% (406) | 29 |
| Very common | constipation | 25.1% (366) | 7 |
| Common | colitis[m] | 3.7% (54) | 27 |
| Common | pancreatitis[n] | 2.0% (29) | 16 |
| Common | gastritis | 3.3% (48) | 3 |
| Common | dry mouth | 9.8% (142) | 0 |
| Uncommon | gastrointestinal ulceration[o] | 0.5% (7) | 0 |

| | | | |
|---|---|---|---|
| Rare | small intestinal perforation | 0.07% (1) | 1 |
| **Hepatobiliary disorders** | | | |
| Common | hepatitis[p] | 2.0% (29) | 23 |

| | | Combination Therapy (N=1456) | |
|---|---|---|---|
| | | All AEs % (n) | Gr 3-5 AEs n |
| **Skin and subcutaneous tissue disorders** | | | |
| Very common | rash[q] | 25.8% (376) | 2 |
| Very common | pruritus[r] | 15.5% (226) | 0 |
| Common | severe skin reactions[s] | 3.7% (54) | 44 |
| Common | dermatitis | 1.9% (27) | 3 |
| Common | dry skin | 8.0% (117) | 2 |
| Common | erythema | 3.4% (49) | 2 |
| Common | dermatitis acneiform | 2.0% (29) | 2 |
| Common | alopecia | 4.4% (64) | 0 |
| Uncommon | eczema | 0.7% (10) | 1 |
| Uncommon | lichenoid keratosis[t] | 0.5% (8) | 1 |
| Uncommon | psoriasis | 0.3% (5) | 1 |
| Uncommon | vitiligo[u] | 0.5% (7) | 0 |
| Uncommon | papule | 0.3% (4) | 0 |
| Uncommon | hair colour changes | 0.2% (3) | 0 |
| Rare | stevens-johnson syndrome | 0.07% (1) | 1 |
| **Musculoskeletal and connective tissue disorders** | | | |
| Very common | arthralgia | 29.5% (430) | 25 |
| Very common | musculoskeletal pain[v] | 22.7% (330) | 17 |
| Very common | myositis[w] | 15.4% (224) | 17 |
| Very common | pain in extremity | 12.3% (179) | 16 |
| Common | arthritis[x] | 3.0% (43) | 4 |
| Uncommon | tenosynovitis[y] | 0.8% (11) | 1 |
| Rare | sjogren's syndrome | 0.07% (1) | 0 |
| **Renal and urinary disorders** | | | |
| Common | nephritis[z] | 1.3% (19) | 8 |
| Rare | cystitis noninfective | 0.07% (1) | 0 |
| **General disorders and administration site conditions** | | | |
| Very common | fatigue | 41.1% (599) | 70 |
| Very common | asthenia | 18.5% (269) | 63 |
| Very common | oedema[aa] | 14.6% (213) | 7 |
| Very common | pyrexia | 14.0% (204) | 6 |
| Common | influenza like illness | 2.5% (36) | 1 |
| Common | chills | 4.5% (66) | 0 |

| | | Combination Therapy (N=1456) | |
|---|---|---|---|
| | | All AEs % (n) | Gr 3-5 AEs n |
| **Investigations** | | | |
| Very common | lipase increased | 11.1% (162) | 107 |
| Very common | alanine aminotransferase increased | 19.0% (277) | 99 |
| Very common | aspartate aminotransferase increased | 18.0% (262) | 66 |
| Very common | blood creatinine increased | 12.3% (179) | 12 |
| Common | amylase increased | 8.2% (119) | 53 |
| Common | blood alkaline phosphatase increased | 8.5% (124) | 21 |
| Common | blood bilirubin increased | 5.5% (80) | 17 |

## Serious adverse event/deaths/other significant events

### All Serious Adverse Events

**Table 98 - 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[i] | | Pembrolizumab Monotherapy Reference Safety Dataset[i] | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 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) |

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; adae]

**Figure 37– Rainfall plot for serious adverse events (incidence ≥ 1% in one or more treatment groups) in all-comer participants (APaT population)**

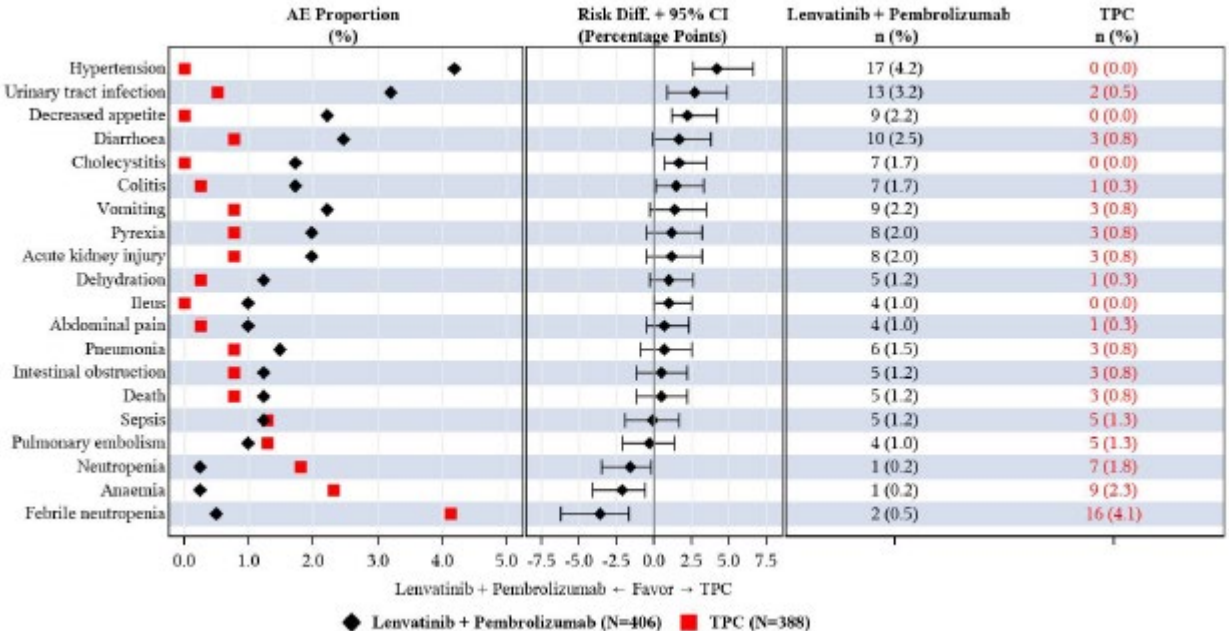


**Table 99 – Exposure-adjusted serious adverse events (including multiple occurences of events) (incidence ≥1% in one or more treatment group) in all-comer participants**

| | 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]

When comparing the exposure-adjusted incidence rates of SAEs in combination and TPC arms, only two SAEs resulted higher (>2 x 100 p-m) in the lenvatinib+pembrolizumab group UTI (0.4 vs 0.1 x 100 p-m) and hypertension (0.4 vs 0.00 x 100 p-m).

**Drug-related Serious Adverse Events**

**Table 100 – Participants with grud-related serious adverse events by decreasing incidence (incidence ≥1% in one or more treatment group) in all-comer participants (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]

**Deaths Due to Adverse Events**

PTs reported more than once in the KN-775 lenavitinib+pembrolizumab arm were: death (n=5; 1.2%) and pneumonia (n=2; 0.5%). The PT "death" was reported in situations where limited information on the cause of death was available, or where the investigator could not assign a specific AE term in a participant with comorbidities and confounding factors that led to death.

Out of the 23 subjects with fatal event receiving combination treatment, 6 participants (1.5%) were assessed by the investigator as having drug-related AEs resulting in death:

- 1 death due to multiorgan dysfunction syndrome was considered by the investigator as related to both lenvatinib and pembrolizumab;
- 1 death each due to cerebrovascular accident, right ventricular dysfunction, myelodysplastic syndrome, and death were considered by the investigator as related to lenvatinib;
- 1 death due to colitis was considered by the investigator as related to pembrolizumab.

Of 19 participants in the TPC group who experienced AEs resulting in death, 8 deaths (2.1%) were considered related to study intervention by the investigator. These events were all considered related to doxorubicin: 2 events of pneumonia, and 1 event each of aspiration, pulmonary embolism, cardiogenic shock, toxic cardiomyopathy, cardiac failure, and sepsis.

**Table 101- Participants With Adverse Events Resulting in Death by Decreasing Incidence (reported at least once in the indication group) (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 | 23 | (5.7) | 19 | (4.9) | 24 | (10.4) | 97 | (8.7) | 312 | (5.3) |
| with no adverse events | 383 | (94.3) | 369 | (95.1) | 206 | (89.6) | 1,022 | (91.3) | 5,572 | (94.7) |
| Death | 5 | (1.2) | 3 | (0.8) | 0 | (0.0) | 5 | (0.4) | 42 | (0.7) |
| Pneumonia | 2 | (0.5) | 2 | (0.5) | 2 | (0.9) | 6 | (0.5) | 36 | (0.6) |
| Acute kidney injury | 1 | (0.2) | 0 | (0.0) | 0 | (0.0) | 3 | (0.3) | 3 | (0.1) |
| Acute myocardial infarction | 1 | (0.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.0) |
| Assisted suicide | 1 | (0.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Cerebrovascular accident | 1 | (0.2) | 0 | (0.0) | 0 | (0.0) | 3 | (0.3) | 5 | (0.1) |
| Colitis | 1 | (0.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Decreased appetite | 1 | (0.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Intestinal perforation | 1 | (0.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.0) |
| Large intestine perforation | 1 | (0.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (0.0) |
| Lower gastrointestinal haemorrhage | 1 | (0.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Malignant gastrointestinal obstruction | 1 | (0.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Multiple organ dysfunction syndrome | 1 | (0.2) | 2 | (0.5) | 0 | (0.0) | 2 | (0.2) | 5 | (0.1) |
| Myelodysplastic syndrome | 1 | (0.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Pulmonary embolism | 1 | (0.2) | 1 | (0.3) | 1 | (0.4) | 5 | (0.4) | 10 | (0.2) |
| Right ventricular dysfunction | 1 | (0.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Urosepsis | 1 | (0.2) | 0 | (0.0) | 1 | (0.4) | 0 | (0.0) | 5 | (0.1) |
| Vaginal haemorrhage | 1 | (0.2) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |

## Clinically Significant Adverse Events for Lenvatinib (CSAEs)

### Table 102 – Adverse events summary for CSAE (APaT population)

| | KN775 Lenvatinib + Pembrolizumab | | KN775 Treatment Physician´s Choice | | KN146 Lenvatinib + Pembrolizumab (Non-Endometrial Cancer) | | Lenvatinib Monotherapy Safety Dataset[i] | |
|---|---|---|---|---|---|---|---|---|
| | 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.
[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.
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 102 – Participants with clinically significant adverse events by maximum toxicity grade (incidence >0% in one or more treatment groups)

| | KN775 Lenvatinib + Pembrolizumab | | KN775 Treatment Physician´s Choice | | KN146 Lenvatinib + Pembrolizumab (Non-Endometrial Cancer) | | Lenvatinib Monotherapy Safety Dataset[i] | |
|---|---|---|---|---|---|---|---|---|
| | 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) |
| Grade 1 | 36 | (8.9) | 63 | (16.2) | 26 | (11.3) | 103 | (9.2) |
| Grade 2 | 131 | (32.3) | 34 | (8.8) | 73 | (31.7) | 310 | (27.7) |
| Grade 3 | 196 | (48.3) | 40 | (10.3) | 90 | (39.1) | 500 | (44.7) |
| Grade 4 | 14 | (3.4) | 4 | (1.0) | 10 | (4.3) | 31 | (2.8) |
| Grade 5 | 8 | (2.0) | 5 | (1.3) | 7 | (3.0) | 28 | (2.5) |
| with no adverse events | 21 | (5.2) | 242 | (62.4) | 24 | (10.4) | 147 | (13.1) |

In KN-775, the following AEs were considered CSAEs, and were reported with decreasing frequency in the lenvatinib+pembrolizumab combination arm and are shown in respect to Lenvatinib monotherapy SD: Hypothyroidism (68.2% vs 19.8%), Hypertension (65% vs 62.8%), Hepatotoxicity (33.7% vs 17.5%), Proteinuria (29.6% vs 35.3%), Hemorrhage (24.4% vs 32.8%), Palmar-plantar Erythrodysesthesia

Syndrome (22.2% vs 22.3%), Renal Events (18.2% vs 10.0%), GI Perforation (3.9% vs 2.2%), Hypocalcemia (3.9% vs 8.8%), QT Prolongation (3.9% vs 4.8%), Arterial Thromboembolic Events (3.7% vs 5.7%), Fistula Formation (2.5% vs 2.1%), Cardiac Dysfunction (1.0% vs 5.5%), Posterior Reversible Encephalopathy Syndrome (0.2% vs 0.3%). Creatinine increased was found in 10.8% of subjects receiving combination treatment and in 2.6% of those receiving TPC.

CSAEs reported in the KN-775 combination arm at data cut-off resolved in 20.8%, were resolving in 14%, and not resolved in 61% of cases.

**Hepatotoxicity CSAEs**

Hepatotoxicity CSAEs were observed more frequently in the lenvatinib plus pembrolizumab group compared with the lenvatinib monotherapy and lenvatinib plus pembrolizumab non-EC groups (33.7%, 17.5%, and 19.6%, respectively). CSAE severity was mostly Grade 1 to 3 and median time to onset was 56 days. The increased frequency in the lenvatinib plus pembrolizumab group was primarily driven by the incidence of ALT increased (21.2%) and AST increased (19.7%). Most ALT or AST increases were Grade 1 to 3, most did not result in discontinuation, and most were considered resolved or resolving.

**Hypothyroidism CSAEs**

The CSAE "hypothyroidism" was observed more frequently in the lenvatinib plus pembrolizumab group than in the lenvatinib monotherapy and lenvatinib plus pembrolizumab non-EC groups (68.2%, 19.8%, and 43.5%, respectively). Most events of hypothyroidism in the lenvatinib plus pembrolizumab group were Grade 1 or 2, and median time to onset was 62 days. Most CSAEs did not result in treatment discontinuation, and most were treated with hormone replacement and were considered resolved at data cut-off (22%).

**Renal events CSAEs**

The incidence of the CSAE "renal events" was higher in the lenvatinib plus pembrolizumab group (18.2%) compared with the lenvatinib monotherapy group (10%), and was similar to that of the lenvatinib plus pembrolizumab non-EC group (18.7%). Most renal events were Grade 1 or 2, and median time to onset was 86 days. Few renal events resulted in treatment discontinuation, and most were considered resolved or resolving. The most frequently reported renal event was blood creatinine increased 10.8% in the KN-775 combination arm.

**Adverse Events of Special Interest for Pembrolizumab (AEOSIs)**

AEOSI are immune-related events and infusion-related reactions associated with pembrolizumab treatment.

**Table 103 – Adverse events 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 104 – Participants with adverse events by AEOSI and preferred term (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 | 273 | (67.2) | 17 | (4.4) |
| with no adverse events | 133 | (32.8) | 371 | (95.6) |
| **Adrenal Insufficiency** | **5** | **(1.2)** | **0** | **(0.0)** |
| Adrenal insufficiency | 5 | (1.2) | 0 | (0.0) |
| **Colitis** | **19** | **(4.7)** | **1** | **(0.3)** |
| Colitis | 16 | (3.9) | 1 | (0.3) |
| Enterocolitis | 3 | (0.7) | 0 | (0.0) |
| **Encephalitis** | **2** | **(0.5)** | **0** | **(0.0)** |
| Encephalitis | 1 | (0.2) | 0 | (0.0) |
| Encephalitis autoimmune | 1 | (0.2) | 0 | (0.0) |
| **Hepatitis** | **6** | **(1.5)** | **0** | **(0.0)** |
| Hepatitis | 1 | (0.2) | 0 | (0.0) |
| Immune-mediated hepatitis | 5 | (1.2) | 0 | (0.0) |
| **Hyperthyroidism** | **47** | **(11.6)** | **4** | **(1.0)** |
| Hyperthyroidism | 47 | (11.6) | 4 | (1.0) |
| **Hypophysitis** | **2** | **(0.5)** | **0** | **(0.0)** |
| Hypophysitis | 1 | (0.2) | 0 | (0.0) |
| Hypopituitarism | 1 | (0.2) | 0 | (0.0) |
| **Hypothyroidism** | **234** | **(57.6)** | **3** | **(0.8)** |
| Hypothyroidism | 233 | (57.4) | 3 | (0.8) |
| Primary hypothyroidism | 1 | (0.2) | 0 | (0.0) |
| **Infusion Reactions** | **12** | **(3.0)** | **6** | **(1.5)** |
| Anaphylactic reaction | 2 | (0.5) | 0 | (0.0) |
| Drug hypersensitivity | 4 | (1.0) | 2 | (0.5) |
| Hypersensitivity | 6 | (1.5) | 3 | (0.8) |
| Infusion related reaction | 0 | (0.0) | 1 | (0.3) |
| **Myasthenic Syndrome** | **1** | **(0.2)** | **0** | **(0.0)** |
| Myasthenia gravis | 1 | (0.2) | 0 | (0.0) |
| **Myocarditis** | **1** | **(0.2)** | **0** | **(0.0)** |
| Myocarditis | 1 | (0.2) | 0 | (0.0) |
| **Myositis** | **2** | **(0.5)** | **0** | **(0.0)** |
| Myositis | 2 | (0.5) | 0 | (0.0) |
| **Nephritis** | **2** | **(0.5)** | **0** | **(0.0)** |
| Autoimmune nephritis | 1 | (0.2) | 0 | (0.0) |
| Nephritis | 1 | (0.2) | 0 | (0.0) |
| **Pancreatitis** | **5** | **(1.2)** | **0** | **(0.0)** |
| Immune-mediated pancreatitis | 1 | (0.2) | 0 | (0.0) |
| Pancreatitis | 1 | (0.2) | 0 | (0.0) |
| Pancreatitis acute | 3 | (0.7) | 0 | (0.0) |
| **Pneumonitis** | **5** | **(1.2)** | **1** | **(0.3)** |
| Pneumonitis | 5 | (1.2) | 1 | (0.3) |
| **Severe Skin Reactions** | **13** | **(3.2)** | **1** | **(0.3)** |
| Dermatitis bullous | 2 | (0.5) | 1 | (0.3) |
| Erythema multiforme | 3 | (0.7) | 0 | (0.0) |
| Pemphigoid | 1 | (0.2) | 0 | (0.0) |
| Rash | 2 | (0.5) | 0 | (0.0) |
| Rash maculo-papular | 4 | (1.0) | 0 | (0.0) |
| Rash pustular | 1 | (0.2) | 0 | (0.0) |
| Stevens-Johnson syndrome | 1 | (0.2) | 0 | (0.0) |
| Toxic skin eruption | 1 | (0.2) | 0 | (0.0) |
| **Thyroiditis** | **8** | **(2.0)** | **0** | **(0.0)** |
| Thyroid disorder | 2 | (0.5) | 0 | (0.0) |
| Thyroiditis | 6 | (1.5) | 0 | (0.0) |
| **Type 1 Diabetes Mellitus** | **4** | **(1.0)** | **0** | **(0.0)** |
| Diabetic ketoacidosis | 1 | (0.2) | 0 | (0.0) |
| Type 1 diabetes mellitus | 3 | (0.7) | 0 | (0.0) |
| **Uveitis** | **3** | **(0.7)** | **0** | **(0.0)** |
| Iridocyclitis | 1 | (0.2) | 0 | (0.0) |

| | | | | |
|---|---|---|---|---|
| **Uveitis** | **3** | **(0.7)** | **0** | **(0.0)** |
| Uveitis | 2 | (0.5) | 0 | (0.0) |
| **Vasculitis** | **1** | **(0.2)** | **2** | **(0.5)** |
| Vasculitis | 1 | (0.2) | 2 | (0.5) |

Every participant is counted a single time for each applicable row and column.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 120 days of last dose are included.
TPC = Treatment Physician's Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

Source: [P775V01MK3475: adam-adsl; adae]

Most AEOSI in the lenvatinib plus pembrolizumab group (approximately 81%) were mild to moderate in severity (Grade 1 or 2). Most Grade 3 to 4 AEOSI were reported in ≤1% of participants in the lenvatinib plus pembrolizumab group, except for Grade 3 severe skin reactions (2.5%), Grade 3 colitis (1.5%), and Grade 3 hepatitis (1.5%). There was 1 death in the lenvatinib plus pembrolizumab 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.

**Hypothyroidism**

Hypothyroidism was observed more frequently in the lenvatinib plus pembrolizumab group compared with the lenvatinib plus pembrolizumab non-EC group or the pembrolizumab monotherapy RSD (57.6%, 37.8%, 11.1%, respectively).

Most events of hypothyroidism in the lenvatinib plus pembrolizumab group were Grade 1 (17.2%) or 2 (39.2%) in severity and only 1 (0.2%) resulted in treatment discontinuation. Few events of hypothyroidism were treated with corticosteroids (0.4%) and were instead treated with hormone replacement therapy, as per protocol. Most hypothyroidism in the lenvatinib plus pembrolizumab group were considered not resolved (n=145/234, 62.0%) as of the data cutoff.

The median time to onset for events of hypothyroidism in the lenvatinib plus pembrolizumab group (63.0 days) was shorter than that in the pembrolizumab monotherapy RSD (105.0 days). The median episode duration has not been reached for either the lenvatinib plus pembrolizumab group or pembrolizumab monotherapy RSD.

**Hyperthyroidism**

Hyperthyroidism was observed more frequently in the lenvatinib plus pembrolizumab group compared with the lenvatinib plus pembrolizumab non-EC group or the pembrolizumab monotherapy RSD (11.6%, 4.8%, and 4.2%, respectively).

Most events of hyperthyroidism in the lenvatinib plus pembrolizumab group were Grade 1 (7.4%) or 2 (3.4%) in severity and none resulted in treatment discontinuation. Few events of hyperthyroidism were treated with corticosteroids (4.3%), and most were considered resolved (n=41/47, 87.2%).

The median time to onset for hyperthyroidism in the lenvatinib plus pembrolizumab group (43.0 days) was consistent with that in the pembrolizumab monotherapy RSD (44.0 days); however, the median episode duration was shorter than that in the pembrolizumab monotherapy RSD (43.0 days vs 56.0 days).

**Colitis**

Colitis in the lenvatinib plus pembrolizumab group was observed at a similar frequency as in the lenvatinib plus pembrolizumab non-EC group, but more frequently if compared with the pembrolizumab monotherapy RSD (4.7%, 5.7%, and 1.9%, respectively).

Most events of colitis in the lenvatinib plus pembrolizumab group (11 of 19, approximately 58%) were Grade 1 (1.2%) or 2 (1.5%) in severity, 6 (1.5%) were Grade 3, 1 was Grade 4, and 1 was fatal. Four events of colitis resulted in treatment discontinuation (3 participants discontinued both lenvatinib and

pembrolizumab, 1 discontinued lenvatinib). Eight events of colitis were treated with corticosteroids (42.1%), and most were considered resolved (n=12/19, 63.2%).

The median time to onset for colitis was longer in the lenvatinib plus pembrolizumab group (161.0 days) compared with pembrolizumab monotherapy RSD (132.0 days). The median episode duration was similar compared with the pembrolizumab monotherapy RSD (31.0 vs 27.0 days).

## Laboratory findings

All-grade ALT increased and AST increased were found, respectively, in 53.4% and 58.3% of KN-775 combination treatment participants and in 20.7% and 22.4% of controls. Frequency was higher than in the lenvatinib monotherapy SD (41.1% and 41.7%), the non-EC lenvatinib+pembrolizumab group (35.1% and 43.6%) and the pembrolizumab monotherapy RSD (27.5% and 28.5%). Most events were Grade 1 or 2.

Cholesterol increased and Triglycerides increased of all-grades were observed, respectively, in 53.3% and 69.2% of subjects receiving combination treatment, which was somehow comparable with the proportion in the non-EC lenvatinib+pembrolizumab group (49.5% and 66.4%), but higher than in the pembrolizumab monotherapy RSD (21.9% and 35%). Most events were Grade 1 or 2.

Overall, 57.1% of subjects treated with lenvatinib+pembrolizumab had Glucose increased, while this AE was found in the lenvatinib monotherapy SD in 14.4%, in the non-EC lenvatinib+pembrolizumab group in 25.8%, and in the pembrolizumab monotherapy RSD in 11.6%.

Hypomagnesemia events were 53.6% in the lenvatinib plus pembrolizumab group and 38.3% in the non-EC lenvatinib+pembrolizumab group. Most events were of grade 1 or 2.

The most frequently (incidence ≥5%) reported Grade 3 to 4 laboratory abnormalities in the lenvatinib plus pembrolizumab group were:

Lymphocyte decreased (16.9%), sodium decreased (14.4%), potassium decreased (10.7%), AST increased (8.5%), hemoglobin 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%).

**Table 105 – Participants with liver function laboratory findings that met predetermined criteria in all-comer participants (APaT population)**

| Criteria | Lenvatinib + Pembrolizumab | | TPC | |
|---|---|---|---|---|
| | n/m | (%) | n/m | (%) |
| Participants in population | 406 | | 388 | |
| **Alanine Aminotransferase** | | | | |
| ≥3 x ULN | 60/402 | (14.9) | 14/379 | (3.7) |
| ≥5 x ULN | 31/402 | (7.7) | 5/379 | (1.3) |
| ≥10 x ULN | 9/402 | (2.2) | 2/379 | (0.5) |
| ≥20 x ULN | 1/402 | (0.2) | 0/379 | (0.0) |
| **Aspartate Aminotransferase** | | | | |
| ≥3 x ULN | 52/401 | (13.0) | 11/378 | (2.9) |
| ≥5 x ULN | 34/401 | (8.5) | 5/378 | (1.3) |
| ≥10 x ULN | 10/401 | (2.5) | 2/378 | (0.5) |
| ≥20 x ULN | 2/401 | (0.5) | 0/378 | (0.0) |
| **Aminotransferase (ALT or AST)** | | | | |
| ≥3 x ULN | 75/401 | (18.7) | 19/378 | (5.0) |
| ≥5 x ULN | 42/401 | (10.5) | 7/378 | (1.9) |
| ≥10 x ULN | 16/401 | (4.0) | 3/378 | (0.8) |
| ≥20 x ULN | 3/401 | (0.7) | 0/378 | (0.0) |
| **Bilirubin** | | | | |
| ≥2 x ULN | 20/402 | (5.0) | 7/379 | (1.8) |
| **Alkaline Phosphatase** | | | | |
| ≥1.5 x ULN | 119/402 | (29.6) | 52/378 | (13.8) |
| **Aminotransferase (ALT or AST) and Bilirubin** | | | | |
| AT ≥3 x ULN and BILI ≥1.5 x ULN | 16/402 | (4.0) | 6/380 | (1.6) |
| AT ≥3 x ULN and BILI ≥2 x ULN | 10/402 | (2.5) | 6/380 | (1.6) |
| **Aminotransferase (ALT or AST) and Bilirubin and Alkaline Phosphatase** | | | | |
| **Aminotransferase (ALT or AST) and Bilirubin and Alkaline Phosphatase** | | | | |
| AT ≥3 x ULN and BILI ≥2 x ULN and ALP <2 x ULN | 3/402 | (0.7) | 0/380 | (0.0) |

n = Number of participants with postbaseline test results (or combination of test results from the same day) that met predetermined criteria.
m = Number of participants with at least one postbaseline test result or combination of test results from the same day.
ALP = Alkaline phosphatase; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; AT = Aminotransferase (ALT or AST); BILI = Bilirubin; ULN = Upper limit of normal range.
TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 26OCT2020

Source: [P775V01MK3475: adam-adsl; addili]

## Safety in special populations

### Intrinsic Factors

The safety findings in the lenvatinib plus pembrolizumab group based on age, gender, ECOG performance status, and region are reported. Further, safety results in the lenvatinib plus pembrolizumab group are summarized by MMR status.

Age

**Table 106 – Adverse events 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[j] | | | | 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 | -- | | -- | | -- | | -- | |

**Table 107 – Adverse events summary by age category (<65, 65-47, ≥75 years) (APaT population)**

| | KN775 Lenvatinib + Pembrolizumab | | | | | | KN775 Treatment Physician´s Choice | | | | | | KN146 Lenvatinib + Pembrolizumab (Non-Endometrial Cancer) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | <65 | | 65-74 | | >=75 | | <65 | | 65-74 | | >=75 | | <65 | | 65-74 | | >=75 | |
| | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) |
| Participants in population | 205 | | 166 | | 35 | | 192 | | 157 | | 39 | | 127 | | 78 | | 25 | |
| with one or more adverse events | 204 | (99.5) | 166 | (100.0) | 35 | (100.0) | 191 | (99.5) | 156 | (99.4) | 39 | (100.0) | 127 | (100.0) | 78 | (100.0) | 25 | (100.0) |
| with no adverse event | 1 | (0.5) | 0 | (0.0) | 0 | (0.0) | 1 | (0.5) | 1 | (0.6) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| with drug-related[a]adverse events | 198 | (96.6) | 163 | (98.2) | 34 | (97.1) | 181 | (94.3) | 144 | (91.7) | 39 | (100.0) | 126 | (99.2) | 76 | (97.4) | 23 | (92.0) |
| with toxicity grade 3-5 adverse events | 178 | (86.8) | 152 | (91.6) | 31 | (88.6) | 137 | (71.4) | 116 | (73.9) | 29 | (74.4) | 110 | (86.6) | 70 | (89.7) | 23 | (92.0) |
| with toxicity grade 3-5 drug-related adverse events | 153 | (74.6) | 135 | (81.3) | 28 | (80.0) | 106 | (55.2) | 98 | (62.4) | 25 | (64.1) | 79 | (62.2) | 54 | (69.2) | 18 | (72.0) |
| with serious adverse events | 109 | (53.2) | 86 | (51.8) | 19 | (54.3) | 55 | (28.6) | 49 | (31.2) | 14 | (35.9) | 64 | (50.4) | 43 | (55.1) | 22 | (88.0) |
| with serious drug-related adverse events | 64 | (31.2) | 56 | (33.7) | 15 | (42.9) | 25 | (13.0) | 22 | (14.0) | 8 | (20.5) | 27 | (21.3) | 22 | (28.2) | 10 | (40.0) |
| with dose interruption of any drug due to an adverse event | 134 | (65.4) | 123 | (74.1) | 24 | (68.6) | 52 | (27.1) | 39 | (24.8) | 14 | (35.9) | 104 | (81.9) | 67 | (85.9) | 24 | (96.0) |
| interruption of Pembrolizumab | 103 | (50.2) | 82 | (49.4) | 18 | (51.4) | -- | | -- | | -- | | 63 | (49.6) | 41 | (52.6) | 18 | (72.0) |
| interruption of Lenvatinib | 111 | (54.1) | 107 | (64.5) | 20 | (57.1) | -- | | -- | | -- | | 99 | (78.0) | 64 | (82.1) | 24 | (96.0) |
| interruption of both Pembrolizumab and Lenvatinib | 65 | (31.7) | 49 | (29.5) | 11 | (31.4) | -- | | -- | | -- | | 44 | (34.6) | 29 | (37.2) | 16 | (64.0) |
| with dose reduction of Lenvatinib due to an adverse event | 130 | (63.4) | 124 | (74.7) | 16 | (45.7) | -- | | -- | | -- | | 80 | (63.0) | 58 | (74.4) | 14 | (56.0) |
| who died | 12 | (5.9) | 5 | (3.0) | 6 | (17.1) | 9 | (4.7) | 8 | (5.1) | 2 | (5.1) | 9 | (7.1) | 11 | (14.1) | 4 | (16.0) |
| who died due to a drug-related adverse event | 4 | (2.0) | 0 | (0.0) | 2 | (5.7) | 5 | (2.6) | 2 | (1.3) | 1 | (2.6) | 0 | (0.0) | 5 | (6.4) | 0 | (0.0) |
| discontinued any drug due to an adverse event | 61 | (29.8) | 59 | (35.5) | 14 | (40.0) | 11 | (5.7) | 15 | (9.6) | 5 | (12.8) | 25 | (19.7) | 30 | (38.5) | 10 | (40.0) |
| discontinued Pembrolizumab | 36 | (17.6) | 33 | (19.9) | 7 | (20.0) | -- | | -- | | -- | | 21 | (16.5) | 24 | (30.8) | 10 | (40.0) |
| discontinued Lenvatinib | 56 | (27.3) | 55 | (33.1) | 14 | (40.0) | -- | | -- | | -- | | 21 | (16.5) | 26 | (33.3) | 10 | (40.0) |
| discontinued both Pembrolizumab and Lenvatinib | 27 | (13.2) | 25 | (15.1) | 5 | (14.3) | -- | | -- | | -- | | 16 | (12.6) | 17 | (21.8) | 9 | (36.0) |
| discontinued any drug due to a drug-related adverse event | 47 | (22.9) | 50 | (30.1) | 11 | (31.4) | 10 | (5.2) | 8 | (5.1) | 4 | (10.3) | 13 | (10.2) | 22 | (28.2) | 5 | (20.0) |
| discontinued Pembrolizumab | 19 | (9.3) | 19 | (11.4) | -- | | -- | | -- | | -- | | -- | | -- | | -- | |
| discontinued Lenvatinib | 39 | (19.0) | 43 | (25.9) | -- | | -- | | -- | | -- | | -- | | -- | | -- | |
| discontinued both Pembrolizumab and Lenvatinib | 8 | (3.9) | 12 | (7.2) | -- | | -- | | -- | | -- | | -- | | -- | | -- | |
| discontinued any drug due to a serious adverse event | 40 | (19.5) | 39 | (23.5) | 9 | (25.7) | 5 | (2.6) | 7 | (4.5) | 2 | (5.1) | 15 | (11.8) | 18 | (23.1) | 8 | (32.0) |
| discontinued Pembrolizumab | 27 | (13.2) | 27 | (16.3) | 6 | (17.1) | -- | | -- | | -- | | 12 | (9.4) | 15 | (19.2) | 8 | (32.0) |
| discontinued Lenvatinib | 37 | (18.0) | 36 | (21.7) | 8 | (22.9) | -- | | -- | | -- | | 14 | (11.0) | 14 | (17.9) | 8 | (32.0) |
| discontinued both Pembrolizumab and Lenvatinib | 24 | (11.7) | 22 | (13.3) | 4 | (11.4) | -- | | -- | | -- | | 11 | (8.7) | 11 | (14.1) | 8 | (32.0) |
| discontinued any drug due to a serious drug-related adverse event | 26 | (12.7) | 28 | (16.9) | 7 | (20.0) | 4 | (2.1) | 3 | (1.9) | 1 | (2.6) | 6 | (4.7) | 12 | (15.4) | 3 | (12.0) |
| discontinued Pembrolizumab | 11 | (5.4) | 15 | (9.0) | -- | | -- | | -- | | -- | | -- | | -- | | -- | |
| discontinued Lenvatinib | 21 | (10.2) | 24 | (14.5) | -- | | -- | | -- | | -- | | -- | | -- | | -- | |
| discontinued both Pembrolizumab and Lenvatinib | 6 | (2.9) | 11 | (6.6) | -- | | -- | | -- | | -- | | -- | | -- | | -- | |

| | Lenvatinib Monotherapy Safety Dataset[i] | | | | | | Pembrolizumab Monotherapy Reference Safety Dataset[j] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | <65 | | 65-74 | | >=75 | | <65 | | 65-74 | | >=75 | |
| | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) |
| Participants in population | 700 | | 321 | | 98 | | 3,385 | | 1,737 | | 762 | |
| with one or more adverse events | 692 | (98.9) | 319 | (99.4) | 97 | (99.0) | 3,268 | (96.5) | 1,678 | (96.6) | 744 | (97.6) |
| with no adverse event | 8 | (1.1) | 2 | (0.6) | 1 | (1.0) | 117 | (3.5) | 59 | (3.4) | 18 | (2.4) |
| with drug-related[a]adverse events | 660 | (94.3) | 303 | (94.4) | 97 | (99.0) | 2,366 | (69.9) | 1,224 | (70.5) | 542 | (71.1) |
| with toxicity grade 3-5 adverse events | 542 | (77.4) | 273 | (85.0) | 84 | (85.7) | 1,505 | (44.5) | 891 | (51.3) | 433 | (56.8) |
| with toxicity grade 3-5 drug-related adverse events | 418 | (59.7) | 230 | (71.7) | 76 | (77.6) | 456 | (13.5) | 311 | (17.9) | 146 | (19.2) |
| with serious adverse events | 370 | (52.9) | 183 | (57.0) | 60 | (61.2) | 1,182 | (34.9) | 719 | (41.4) | 365 | (47.9) |
| with serious drug-related adverse events | 193 | (27.6) | 104 | (32.4) | 33 | (33.7) | 346 | (10.2) | 213 | (12.3) | 97 | (12.7) |
| with dose interruption of any drug due to an adverse event | 445 | (63.6) | 229 | (71.3) | 83 | (84.7) | 799 | (23.6) | 473 | (27.2) | 220 | (28.9) |
| interruption of Pembrolizumab | -- | | -- | | -- | | 799 | (23.6) | 473 | (27.2) | 220 | (28.9) |
| interruption of Lenvatinib | 445 | (63.6) | 229 | (71.3) | 83 | (84.7) | -- | | -- | | -- | |
| interruption of both Pembrolizumab and Lenvatinib | -- | | -- | | -- | | -- | | -- | | -- | |
| with dose reduction of Lenvatinib due to an adverse event | 303 | (43.3) | 175 | (54.5) | 53 | (54.1) | -- | | -- | | -- | |
| who died | 57 | (8.1) | 28 | (8.7) | 12 | (12.2) | 144 | (4.3) | 103 | (5.9) | 65 | (8.5) |
| who died due to a drug-related adverse event | 13 | (1.9) | 8 | (2.5) | 6 | (6.1) | 21 | (0.6) | 12 | (0.7) | 6 | (0.8) |
| discontinued any drug due to an adverse event | 172 | (24.6) | 93 | (29.0) | 34 | (34.7) | 399 | (11.8) | 246 | (14.2) | 145 | (19.0) |
| discontinued Pembrolizumab | -- | | -- | | -- | | 399 | (11.8) | 246 | (14.2) | 145 | (19.0) |
| discontinued Lenvatinib | 172 | (24.6) | 93 | (29.0) | 34 | (34.7) | -- | | -- | | -- | |
| discontinued both Pembrolizumab and Lenvatinib | -- | | -- | | -- | | -- | | -- | | -- | |
| discontinued any drug due to a drug-related adverse event | 115 | (16.4) | 68 | (21.2) | 25 | (25.5) | 207 | (6.1) | 135 | (7.8) | 68 | (8.9) |
| discontinued Pembrolizumab | -- | | -- | | -- | | 207 | (6.1) | 135 | (7.8) | 68 | (8.9) |
| discontinued Lenvatinib | 115 | (16.4) | 68 | (21.2) | 25 | (25.5) | -- | | -- | | -- | |
| discontinued both Pembrolizumab and Lenvatinib | -- | | -- | | -- | | -- | | -- | | -- | |
| discontinued any drug due to a serious adverse event | 100 | (14.3) | 57 | (17.8) | 22 | (22.4) | 287 | (8.5) | 174 | (10.0) | 111 | (14.6) |
| discontinued Pembrolizumab | -- | | -- | | -- | | 287 | (8.5) | 174 | (10.0) | 111 | (14.6) |
| discontinued Lenvatinib | 100 | (14.3) | 57 | (17.8) | 22 | (22.4) | -- | | -- | | -- | |
| discontinued both Pembrolizumab and Lenvatinib | -- | | -- | | -- | | -- | | -- | | -- | |
| discontinued any drug due to a serious drug-related adverse event | 53 | (7.6) | 38 | (11.8) | 14 | (14.3) | 123 | (3.6) | 81 | (4.7) | 41 | (5.4) |
| discontinued Pembrolizumab | -- | | -- | | -- | | 123 | (3.6) | 81 | (4.7) | 41 | (5.4) |
| discontinued Lenvatinib | 53 | (7.6) | 38 | (11.8) | 14 | (14.3) | -- | | -- | | -- | |
| discontinued both Pembrolizumab and Lenvatinib | -- | | -- | | -- | | -- | | -- | | -- | |

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

A similar age-gradient, even though to a lesser extent for pembrolizumab, was found in both the monotherapy datasets:

- Lenvatinib monotherapy SD: drug-related Grade 3-5 AEs were 77.6% vs 71.7 and 59.7%, drug-related SAEs 33.7 vs 32.4% and 21.6%, drug-related discontinuation due to AE 14.3% vs 11.8 and 7.6%, drug-related fatal events 6.1% vs 2.5% and 1.9%.
- Pembrolizumab monotherapy RSD: drug-related Grade 3-5 AEs were 19.2% vs 17.9 and 13.5%, drug-related SAEs 12.7 vs 12.3% and 10.2%, drug-related discontinuation due to AE 5.4% vs 4.7 and 3.6%, drug-related fatal events 0.8% vs 0.7% and 0.6%.

The incidences and severity of the most frequently reported AEs (incidence ⩾15%) in the lenvatinib plus pembrolizumab and TPC groups were provided. Rates were generally similar between the different age categories, with the following AEs having >10% difference between any age category (<65, 65-74, and ⩾75 age groups) for the lenvatinib plus pembrolizumab group:

- o Anaemia: 27.3%, 22.9%, 34.3%
- o UTI: 22.0%, 28.3%, 34.4%
- o Hypertension: Grade 3 and higher 33.2%, 42.2%, 45.7%

Tables with the AE Summary and AEOSIs AE categories by 75-year age cut-off (i.e. <75 and ≥75 years) were also provided. Safety assessment of pembrolizumab+lenvatinib is limited by the small number of subjects aged ≥75 years in the KN-775 Study and the pooled pembrolizumab+lenvatinib datasets. Compared to the younger age group, older aged subjects showed higher proportions of subjects with drug-related SAEs, who discontinued any drug due to AE, and who died due to a drug-related AE in both pembrolizumab+lenvatinib datasets (KN-775, pooled pembrolizumab+lenavtinib) as well as in the lenvatinitb monotherapy safety dataset. Proportions of AEOSIs AE categories were generally not dissimilar between KN-775 age groups (<75 y vs >75 y). Safety profile across age groups was not significantly different in subjects receiving TPC in KN-775 and in those of the pembrolizumab monotherapy dataset.

Sex

As in KN-775 study all participants were females, sub-group analysis based on sex is not considered informative for the present submission.

ECOG

**Table 108 – Adverse events summary by ECOG performance status category (0, 1) (APaT population)**

| | KN775 Lenvatinib + Pembrolizumab | | | | KN775 Treatment Physician's Choice | | | | KN146 Lenvatinib + Pembrolizumab (Non-Endometrial Cancer) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | [0] Normal Activity | | [1] Symptoms, but ambulatory | | [0] Normal Activity | | [1] Symptoms, but ambulatory | | [0] Normal Activity | | [1] Symptoms, but ambulatory | |
| | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) |
| Participants in population | 244 | | 162 | | 224 | | 164 | | 105 | | 125 | |
| with one or more adverse events | 244 | (100.0) | 161 | (99.4) | 224 | (100.0) | 162 | (98.8) | 105 | (100.0) | 125 | (100.0) |
| with no adverse event | 0 | (0.0) | 1 | (0.6) | 0 | (0.0) | 2 | (1.2) | 0 | (0.0) | 0 | (0.0) |
| with drug-related[h]adverse events | 238 | (97.5) | 157 | (96.9) | 215 | (96.0) | 149 | (90.9) | 105 | (100.0) | 120 | (96.0) |
| with toxicity grade 3-5 adverse events | 219 | (89.8) | 142 | (87.7) | 163 | (72.8) | 119 | (72.6) | 90 | (85.7) | 113 | (90.4) |
| with toxicity grade 3-5 drug-related adverse events | 194 | (79.5) | 122 | (75.3) | 137 | (61.2) | 92 | (56.1) | 70 | (66.7) | 81 | (64.8) |
| with serious adverse events | 121 | (49.6) | 93 | (57.4) | 61 | (27.2) | 57 | (34.8) | 48 | (45.7) | 81 | (64.8) |
| with serious drug-related adverse events | 79 | (32.4) | 56 | (34.6) | 30 | (13.4) | 25 | (15.2) | 22 | (21.0) | 37 | (29.6) |
| with dose interruption of any drug due to an adverse event | 177 | (72.5) | 104 | (64.2) | 65 | (29.0) | 40 | (24.4) | 92 | (87.6) | 103 | (82.4) |
| interruption of Pembrolizumab | 125 | (51.2) | 78 | (48.1) | -- | | -- | | 55 | (52.4) | 67 | (53.6) |
| interruption of Lenvatinib | 148 | (60.7) | 90 | (55.6) | -- | | -- | | 89 | (84.8) | 98 | (78.4) |
| interruption of both Pembrolizumab and Lenvatinib | 85 | (34.8) | 40 | (24.7) | -- | | -- | | 41 | (39.0) | 48 | (38.4) |
| with dose reduction of Lenvatinib due to an adverse event | 169 | (69.3) | 101 | (62.3) | -- | | -- | | 81 | (77.1) | 71 | (56.8) |
| who died | 6 | (2.5) | 17 | (10.5) | 8 | (3.6) | 11 | (6.7) | 4 | (3.8) | 20 | (16.0) |
| who died due to a drug-related adverse event | 1 | (0.4) | 5 | (3.1) | 5 | (2.2) | 3 | (1.8) | 1 | (1.0) | 4 | (3.2) |
| discontinued any drug due to an adverse event | 77 | (31.6) | 57 | (35.2) | 18 | (8.0) | 13 | (7.9) | 21 | (20.0) | 44 | (35.2) |
| discontinued Pembrolizumab | 40 | (16.4) | 36 | (22.2) | -- | | -- | | 17 | (16.2) | 38 | (30.4) |
| discontinued Lenvatinib | 70 | (28.7) | 55 | (34.0) | -- | | -- | | 16 | (15.2) | 41 | (32.8) |
| discontinued both Pembrolizumab and Lenvatinib | 27 | (11.1) | 30 | (18.5) | -- | | -- | | 11 | (10.5) | 31 | (24.8) |
| discontinued any drug due to a drug-related adverse event | 65 | (26.6) | 43 | (26.5) | 13 | (5.8) | 9 | (5.5) | 14 | (13.3) | 26 | (20.8) |
| discontinued Pembrolizumab | 26 | (10.7) | 14 | (8.6) | -- | | -- | | -- | | -- | |
| discontinued Lenvatinib | 54 | (22.1) | 38 | (23.5) | -- | | -- | | -- | | -- | |
| discontinued both Pembrolizumab and Lenvatinib | 13 | (5.3) | 7 | (4.3) | -- | | -- | | -- | | -- | |
| discontinued any drug due to a serious adverse event | 48 | (19.7) | 40 | (24.7) | 9 | (4.0) | 5 | (3.0) | 10 | (9.5) | 31 | (24.8) |
| discontinued Pembrolizumab | 29 | (11.9) | 31 | (19.1) | -- | | -- | | 9 | (8.6) | 26 | (20.8) |
| discontinued Lenvatinib | 43 | (17.6) | 38 | (23.5) | -- | | -- | | 7 | (6.7) | 29 | (23.2) |
| discontinued both Pembrolizumab and Lenvatinib | 22 | (9.0) | 28 | (17.3) | -- | | -- | | 6 | (5.7) | 24 | (19.2) |
| discontinued any drug due to a serious drug-related adverse event | 35 | (14.3) | 26 | (16.0) | 6 | (2.7) | 2 | (1.2) | 6 | (5.7) | 15 | (12.0) |
| discontinued Pembrolizumab | 17 | (7.0) | 11 | (6.8) | -- | | -- | | -- | | -- | |
| discontinued Lenvatinib | 28 | (11.5) | 22 | (13.6) | -- | | -- | | -- | | -- | |
| discontinued both Pembrolizumab and Lenvatinib | 10 | (4.1) | 7 | (4.3) | -- | | -- | | -- | | -- | |

| | Lenvatinib Monotherapy Safety Dataset[i] | | | | Pembrolizumab Monotherapy Reference Safety Dataset[j] | | | |
|---|---|---|---|---|---|---|---|---|
| | [0] Normal Activity | | [1] Symptoms, but ambulatory | | [0] Normal Activity | | [1] Symptoms, but ambulatory | |
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Participants in population | 492 | | 452 | | 2,761 | | 2,931 | |
| with one or more adverse events | 487 | (99.0) | 448 | (99.1) | 2,671 | (96.7) | 2,835 | (96.7) |
| with no adverse event | 5 | (1.0) | 4 | (0.9) | 90 | (3.3) | 96 | (3.3) |
| with drug-related[h]adverse events | 477 | (97.0) | 422 | (93.4) | 2,085 | (75.5) | 1,940 | (66.2) |
| with toxicity grade 3-5 adverse events | 391 | (79.5) | 381 | (84.3) | 1,112 | (40.3) | 1,605 | (54.8) |
| with toxicity grade 3-5 drug-related adverse events | 335 | (68.1) | 292 | (64.6) | 410 | (14.8) | 471 | (16.1) |
| with serious adverse events | 239 | (48.6) | 284 | (62.8) | 872 | (31.6) | 1,294 | (44.1) |
| with serious drug-related adverse events | 144 | (29.3) | 137 | (30.3) | 311 | (11.3) | 325 | (11.1) |
| with dose interruption of any drug due to an adverse event | 338 | (68.7) | 333 | (73.7) | 636 | (23.0) | 804 | (27.4) |
| interruption of Pembrolizumab | -- | | -- | | 636 | (23.0) | 804 | (27.4) |
| interruption of Lenvatinib | 338 | (68.7) | 333 | (73.7) | -- | | -- | |
| interruption of both Pembrolizumab and Lenvatinib | -- | | -- | | -- | | -- | |
| with dose reduction of Lenvatinib due to an adverse event | 284 | (57.7) | 205 | (45.4) | -- | | -- | |
| who died | 19 | (3.9) | 59 | (13.1) | 79 | (2.9) | 217 | (7.4) |
| who died due to a drug-related adverse event | 7 | (1.4) | 14 | (3.1) | 14 | (0.5) | 25 | (0.9) |
| discontinued any drug due to an adverse event | 106 | (21.5) | 125 | (27.7) | 304 | (11.0) | 452 | (15.4) |
| discontinued Pembrolizumab | -- | | -- | | 304 | (11.0) | 452 | (15.4) |
| discontinued Lenvatinib | 106 | (21.5) | 125 | (27.7) | -- | | -- | |
| discontinued both Pembrolizumab and Lenvatinib | -- | | -- | | -- | | -- | |
| discontinued any drug due to a drug-related adverse event | 85 | (17.3) | 73 | (16.2) | 193 | (7.0) | 200 | (6.8) |
| discontinued Pembrolizumab | -- | | -- | | 193 | (7.0) | 200 | (6.8) |
| discontinued Lenvatinib | 85 | (17.3) | 73 | (16.2) | -- | | -- | |
| discontinued both Pembrolizumab and Lenvatinib | -- | | -- | | -- | | -- | |
| discontinued any drug due to a serious adverse event | 55 | (11.2) | 82 | (18.1) | 198 | (7.2) | 350 | (11.9) |
| discontinued Pembrolizumab | -- | | -- | | 198 | (7.2) | 350 | (11.9) |
| discontinued Lenvatinib | 55 | (11.2) | 82 | (18.1) | -- | | -- | |
| discontinued both Pembrolizumab and Lenvatinib | -- | | -- | | -- | | -- | |
| discontinued any drug due to a serious drug-related adverse event | 39 | (7.9) | 38 | (8.4) | 106 | (3.8) | 130 | (4.4) |
| discontinued Pembrolizumab | -- | | -- | | 106 | (3.8) | 130 | (4.4) |
| discontinued Lenvatinib | 39 | (7.9) | 38 | (8.4) | -- | | -- | |

| | | | | |
|---|---|---|---|---|
| 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]

Ethnicity

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); therefore, the data should be interpreted with caution.
Within the lenvatinib plus pembrolizumab and TPC groups, the overall incidence and severity of AEs was generally similar between the different race categories.

The incidences and severity of the most frequently reported AEs (incidence ⩾15%) in the lenvatinib plus pembrolizumab group were generally similar between the different race categories with the following differences (>10% difference) within the lenvatinib plus pembrolizumab group noted:
• AEs higher in Whites than Asians: 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: Stomatitis (37.6% vs 13.1%), platelet count decreased (32.9% vs 7.0%, Grade ⩾3: 10.6% vs 0.8%), proteinuria (51.9% vs 22.3%; Grade ⩾3: 10.6% vs 3.5%), PPE (40.0% vs 13.3%; Grade ⩾3: 5.9% vs 2.0%), and pyrexia (31.8% vs 10.5%).

**Extrinsic Factors**

Geographic Region

**Table 109– Adverse events summary by geographical region (EU, Ex-EU) (APaT population)**

| | KN775 Lenvatinib + Pembrolizumab | | | | KN775 Treatment Physician's Choice | | | | KN146 Lenvatinib + Pembrolizumab (Non-Endometrial Cancer) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | EU | | Ex-EU | | EU | | Ex-EU | | EU | | Ex-EU | |
| | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) |
| Participants in population | 114 | | 292 | | 128 | | 260 | | 14 | | 216 | |
| with one or more adverse events | 114 | (100.0) | 291 | (99.7) | 127 | (99.2) | 259 | (99.6) | 14 | (100.0) | 216 | (100.0) |
| with no adverse event | 0 | (0.0) | 1 | (0.3) | 1 | (0.8) | 1 | (0.4) | 0 | (0.0) | 0 | (0.0) |
| with drug-related[h]adverse events | 112 | (98.2) | 283 | (96.9) | 122 | (95.3) | 242 | (93.1) | 13 | (92.9) | 212 | (98.1) |
| with toxicity grade 3-5 adverse events | 100 | (87.7) | 261 | (89.4) | 85 | (66.4) | 197 | (75.8) | 10 | (71.4) | 193 | (89.4) |
| with toxicity grade 3-5 drug-related adverse events | 85 | (74.6) | 231 | (79.1) | 72 | (56.3) | 157 | (60.4) | 9 | (64.3) | 142 | (65.7) |
| with serious adverse events | 60 | (52.6) | 154 | (52.7) | 40 | (31.3) | 78 | (30.0) | 8 | (57.1) | 121 | (56.0) |
| with serious drug-related adverse events | 34 | (29.8) | 101 | (34.6) | 21 | (16.4) | 34 | (13.1) | 5 | (35.7) | 54 | (25.0) |
| with dose interruption of any drug due to an adverse event | 79 | (69.3) | 202 | (69.2) | 33 | (25.8) | 72 | (27.7) | 10 | (71.4) | 185 | (85.6) |
| interruption of Pembrolizumab | 60 | (52.6) | 143 | (49.0) | -- | | -- | | 4 | (28.6) | 118 | (54.6) |
| interruption of Lenvatinib | 67 | (58.8) | 171 | (58.6) | -- | | -- | | 9 | (64.3) | 178 | (82.4) |
| interruption of both Pembrolizumab and Lenvatinib | 40 | (35.1) | 85 | (29.1) | -- | | -- | | 3 | (21.4) | 86 | (39.8) |
| with dose reduction of Lenvatinib due to an adverse event | 65 | (57.0) | 205 | (70.2) | -- | | -- | | 7 | (50.0) | 145 | (67.1) |
| who died | 4 | (3.5) | 19 | (6.5) | 1 | (0.8) | 18 | (6.9) | 1 | (7.1) | 23 | (10.6) |
| who died due to a drug-related adverse event | 0 | (0.0) | 6 | (2.1) | 1 | (0.8) | 7 | (2.7) | 1 | (7.1) | 4 | (1.9) |
| discontinued any drug due to an adverse event | 38 | (33.3) | 96 | (32.9) | 12 | (9.4) | 19 | (7.3) | 4 | (28.6) | 61 | (28.2) |
| discontinued Pembrolizumab | 20 | (17.5) | 56 | (19.2) | -- | | -- | | 3 | (21.4) | 52 | (24.1) |
| discontinued Lenvatinib | 36 | (31.6) | 89 | (30.5) | -- | | -- | | 4 | (28.6) | 53 | (24.5) |
| discontinued both Pembrolizumab and Lenvatinib | 16 | (14.0) | 41 | (14.0) | -- | | -- | | 2 | (14.3) | 40 | (18.5) |
| discontinued any drug due to a drug-related adverse event | 30 | (26.3) | 78 | (26.7) | 7 | (5.5) | 15 | (5.8) | 4 | (28.6) | 36 | (16.7) |
| discontinued Pembrolizumab | 11 | (9.6) | 29 | (9.9) | -- | | -- | | -- | | -- | |
| discontinued Lenvatinib | 24 | (21.1) | 68 | (23.3) | -- | | -- | | -- | | -- | |
| discontinued both Pembrolizumab and Lenvatinib | 5 | (4.4) | 15 | (5.1) | -- | | -- | | -- | | -- | |
| discontinued any drug due to a serious adverse event | 26 | (22.8) | 62 | (21.2) | 4 | (3.1) | 10 | (3.8) | 3 | (21.4) | 38 | (17.6) |
| discontinued Pembrolizumab | 17 | (14.9) | 43 | (14.7) | -- | | -- | | 2 | (14.3) | 33 | (15.3) |
| discontinued Lenvatinib | 24 | (21.1) | 57 | (19.5) | -- | | -- | | 2 | (14.3) | 34 | (15.7) |
| .. | .. | (..) | .. | (..) | .. | (..) | .. | (..) | .. | (..) | .. | (..) |
| discontinued both Pembrolizumab and Lenvatinib | 15 | (13.2) | 35 | (12.0) | -- | | -- | | 1 | (7.1) | 29 | (13.4) |
| discontinued any drug due to a serious drug-related adverse event | 17 | (14.9) | 44 | (15.1) | 2 | (1.6) | 6 | (2.3) | 3 | (21.4) | 18 | (8.3) |
| discontinued Pembrolizumab | 8 | (7.0) | 20 | (6.8) | -- | | -- | | -- | | -- | |
| discontinued Lenvatinib | 13 | (11.4) | 37 | (12.7) | -- | | -- | | -- | | -- | |
| .. | .. | (..) | .. | (..) | .. | (..) | .. | (..) | .. | (..) | .. | (..) |
| discontinued both Pembrolizumab and Lenvatinib | 4 | (3.5) | 13 | (4.5) | -- | | -- | | -- | | -- | |

| | Lenvatinib Monotherapy Safety Dataset[i] | | | | Pembrolizumab Monotherapy Reference Safety Dataset[j] | | | |
|---|---|---|---|---|---|---|---|---|
| | EU | | Ex-EU | | EU | | Ex-EU | |
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Participants in population | 385 | | 734 | | 2,092 | | 3,792 | |
| with one or more adverse events | 382 | (99.2) | 726 | (98.9) | 2,014 | (96.3) | 3,676 | (96.9) |
| with no adverse event | 3 | (0.8) | 8 | (1.1) | 78 | (3.7) | 116 | (3.1) |
| with drug-related[h]adverse events | 363 | (94.3) | 697 | (95.0) | 1,430 | (68.4) | 2,702 | (71.3) |
| with toxicity grade 3-5 adverse events | 322 | (83.6) | 577 | (78.6) | 960 | (45.9) | 1,869 | (49.3) |
| with toxicity grade 3-5 drug-related adverse events | 257 | (66.8) | 467 | (63.6) | 317 | (15.2) | 596 | (15.7) |
| with serious adverse events | 245 | (63.6) | 368 | (50.1) | 796 | (38.0) | 1,470 | (38.8) |
| with serious drug-related adverse events | 132 | (34.3) | 198 | (27.0) | 241 | (11.5) | 415 | (10.9) |
| with dose interruption of any drug due to an adverse event | 275 | (71.4) | 482 | (65.7) | 523 | (25.0) | 969 | (25.6) |
| interruption of Pembrolizumab | -- | | -- | | 523 | (25.0) | 969 | (25.6) |
| interruption of Lenvatinib | 275 | (71.4) | 482 | (65.7) | -- | | -- | |
| interruption of both Pembrolizumab and Lenvatinib | -- | | -- | | -- | | -- | |
| with dose reduction of Lenvatinib due to an adverse event | 177 | (46.0) | 354 | (48.2) | -- | | -- | |
| who died | 57 | (14.8) | 40 | (5.4) | 109 | (5.2) | 203 | (5.4) |
| who died due to a drug-related adverse event | 14 | (3.6) | 13 | (1.8) | 12 | (0.6) | 27 | (0.7) |
| discontinued any drug due to an adverse event | 113 | (29.4) | 186 | (25.3) | 267 | (12.8) | 523 | (13.8) |
| discontinued Pembrolizumab | -- | | -- | | 267 | (12.8) | 523 | (13.8) |
| discontinued Lenvatinib | 113 | (29.4) | 186 | (25.3) | -- | | -- | |
| discontinued both Pembrolizumab and Lenvatinib | -- | | -- | | -- | | -- | |
| discontinued any drug due to a drug-related adverse event | 74 | (19.2) | 134 | (18.3) | 151 | (7.2) | 259 | (6.8) |
| discontinued Pembrolizumab | -- | | -- | | 151 | (7.2) | 259 | (6.8) |
| discontinued Lenvatinib | 74 | (19.2) | 134 | (18.3) | -- | | -- | |
| discontinued both Pembrolizumab and Lenvatinib | -- | | -- | | -- | | -- | |
| discontinued any drug due to a serious adverse event | 76 | (19.7) | 103 | (14.0) | 193 | (9.2) | 379 | (10.0) |
| discontinued Pembrolizumab | -- | | -- | | 193 | (9.2) | 379 | (10.0) |
| discontinued Lenvatinib | 76 | (19.7) | 103 | (14.0) | -- | | -- | |
| discontinued both Pembrolizumab and Lenvatinib | -- | | -- | | -- | | -- | |
| discontinued any drug due to a serious drug-related adverse event | 41 | (10.6) | 64 | (8.7) | 89 | (4.3) | 156 | (4.1) |
| discontinued Pembrolizumab | -- | | -- | | 89 | (4.3) | 156 | (4.1) |
| discontinued Lenvatinib | 41 | (10.6) | 64 | (8.7) | -- | | -- | |

| | | | | |
|---|---|---|---|---|
| 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]

## MMR Status

**Table 110 – Adverse events 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-relateda 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 modificationb due to an adverse event | 316 | (92.4) | 64 | (100.0) | 137 | (42.2) | 24 | (38.1) |
| with dose interruptionc 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 reductiond 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) |
| discontinuede 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: adam-adsl; adae]

**Table 111 – Exposure adjusted adverse events 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.
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
Source: [Annex Table 55] [Annex Table 56]

**Table 112 – Exposure adjusted adverse events summary (including multiple occurrences of events) AEOSI (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 | 351 | (11.06) | 77 | (10.33) |
| with no adverse event | 116 | (3.65) | 17 | (2.28) |
| with drug-related[c] adverse events | 319 | (10.05) | 66 | (8.86) |
| with toxicity grade 3-5 adverse events | 52 | (1.64) | 9 | (1.21) |
| with toxicity grade 3-5 drug-related adverse events | 45 | (1.42) | 8 | (1.07) |
| with serious adverse events | 44 | (1.39) | 7 | (0.94) |
| with serious drug-related adverse events | 40 | (1.26) | 6 | (0.81) |
| with dose modification[d] due to an adverse event | 77 | (2.43) | 10 | (1.34) |
| with dose interruption[e] due to an adverse event | 52 | (1.64) | 7 | (0.94) |
| interruption of Pembrolizumab | 37 | (1.17) | 6 | (0.81) |
| interruption of Lenvatinib | 31 | (0.98) | 6 | (0.81) |
| interruption of both Pembrolizumab and Lenvatinib | 16 | (0.50) | 5 | (0.67) |
| with dose reduction[f] due to an adverse event | 14 | (0.44) | 1 | (0.13) |
| who died | 1 | (0.03) | 0 | (0.00) |
| who died due to a drug-related adverse event | 1 | (0.03) | 0 | (0.00) |
| discontinued[e] due to an adverse event | 23 | (0.72) | 2 | (0.27) |
| discontinued Pembrolizumab | 20 | (0.63) | 2 | (0.27) |
| discontinued Lenvatinib | 15 | (0.47) | 1 | (0.13) |
| discontinued both Pembrolizumab and Lenvatinib | 12 | (0.38) | 1 | (0.13) |
| discontinued due to a drug-related adverse event | 22 | (0.69) | 2 | (0.27) |
| discontinued Pembrolizumab | 19 | (0.60) | 2 | (0.27) |
| discontinued Lenvatinib | 9 | (0.28) | 0 | (0.00) |
| discontinued both Pembrolizumab and Lenvatinib | 6 | (0.19) | 0 | (0.00) |
| discontinued due to a serious adverse event | 18 | (0.57) | 2 | (0.27) |
| discontinued Pembrolizumab | 15 | (0.47) | 2 | (0.27) |
| discontinued Lenvatinib | 15 | (0.47) | 1 | (0.13) |
| discontinued both Pembrolizumab and Lenvatinib | 12 | (0.38) | 1 | (0.13) |
| discontinued due to a serious drug-related adverse event | 17 | (0.54) | 2 | (0.27) |
| discontinued Pembrolizumab | 14 | (0.44) | 2 | (0.27) |
| discontinued Lenvatinib | 9 | (0.28) | 0 | (0.00) |
| discontinued both Pembrolizumab and Lenvatinib | 6 | (0.19) | 0 | (0.00) |

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.
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
Source: [Annex Table 57] [Annex Table 58]

**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. 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

**Table 113 - Participants With Adverse Events Resulting in Discontinuation of Pembrolizumab and Lenvatinib or Treatment of Physician's Choice (APaT Population)**

| | KN775 Lenvatinib + Pembrolizumab | | KN775 Treatment Physician's Choice | | KN146 Lenvatinib + Pembrolizumab (Non-Endometrial Cancer) | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Participants in population | 406 | | 388 | | 230 | |
| with one or more adverse events | 57 | (14.0) | 31 | (8.0) | 42 | (18.3) |
| with no adverse events | 349 | (86.0) | 357 | (92.0) | 188 | (81.7) |

**Table 114 - Participants With Adverse Events Resulting in Discontinuation of Pembrolizumab or Lenvatinib or Treatment of Physician's Choice (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 | 134 | (33.0) | 31 | (8.0) | 65 | (28.3) | 299 | (26.7) | 790 | (13.4) |
| with no adverse events | 272 | (67.0) | 357 | (92.0) | 165 | (71.7) | 820 | (73.3) | 5,094 | (86.6) |

**Table 115 - Participants With Adverse Events Resulting in Discontinuation of Lenvatinib or Treatment of Physician's Choice (APaT Population)**

| | KN775 Lenvatinib + Pembrolizumab | | KN775 Treatment Physician´s Choice | | KN146 Lenvatinib + Pembrolizumab (Non-Endometrial Cancer) | | Lenvatinib Monotherapy Safety Dataset[i] | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Participants in population | 406 | | 388 | | 230 | | 1,119 | |
| with one or more adverse events | 125 | (30.8) | 31 | (8.0) | 57 | (24.8) | 299 | (26.7) |
| with no adverse events | 281 | (69.2) | 357 | (92.0) | 173 | (75.2) | 820 | (73.3) |

**Table 116 - Participants With Adverse Events Resulting in Discontinuation of Pembrolizumab or Treatment of Physician's Choice (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 | 76 | (18.7) | 31 | (8.0) | 55 | (23.9) | 790 | (13.4) |
| with no adverse events | 330 | (81.3) | 357 | (92.0) | 175 | (76.1) | 5,094 | (86.6) |

**Table 117 - Participants With Drug-Related Adverse Events Resulting in Discontinuation of Pembrolizumab or Lenvatinib or Treatment of Physician's Choice (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 | 108 | (26.6) | 22 | (5.7) | 40 | (17.4) | 208 | (18.6) | 410 | (7.0) |
| with no adverse events | 298 | (73.4) | 366 | (94.3) | 190 | (82.6) | 911 | (81.4) | 5,474 | (93.0) |

### Drug-related Adverse Events Leading to Treatment Discontinuation

The incidence of drug-related AEs resulting in lenvatinib discontinuation was generally consistent between the lenvatinib plus pembrolizumab group (22.7%) and the lenvatinib monotherapy group (18.6%). Drug-related AEs in the lenvatinib plus pembrolizumab group resulting in lenvatinib discontinuation (regardless of action taken for pembrolizumab) in ≥1% of participants included hypertension, asthenia, weight

decreased, decreased appetite, proteinuria, diarrhea, and vomiting. The incidence of drug-related AEs resulting in pembrolizumab discontinuation (regardless of action taken for lenvatinib) was higher for the lenvatinib plus pembrolizumab group (9.9%) as compared to the pembrolizumab monotherapy group (5.2%). ALT increased was the only AE in the Lenvatinib plus pembrolizumab group resulting in pembrolizumab discontinuation in ≥1% of participants.

**Adverse Events Leading to Treatment Interruption**

The incidence of AEs resulting in lenvatinib interruption (regardless of action taken for pembrolizumab) was similar in the lenvatinib plus pembrolizumab group (58.6%) and the lenvatinib monotherapy group (67.6%). AEs in the lenvatinib plus pembrolizumab group resulting in lenvatinib discontinuation in ≥5% of participants included hypertension, diarrhea, proteinuria, and vomiting. The incidence of AEs resulting in pembrolizumab interruption (regardless of action taken for lenvatinib) was higher in the lenvatinib plus pembrolizumab group (50.0%) than in the pembrolizumab monotherapy RSD group (25.4%). Diarrhea was the only AE in the lenvatinib plus pembrolizumab group resulting in pembrolizumab discontinuation 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%).

**Drug-related Adverse Events Leading to Treatment Interruption**

The incidence of drug-related AEs resulting in lenvatinib interruption (regardless of action taken for pembrolizumab) was lower in the lenvatinib plus pembrolizumab group (45.8%) than in the lenvatinib monotherapy group (61.3%). Drug related AEs in the lenvatinib plus pembrolizumab group resulting in lenvatinib discontinuation in ≥2% of participants included hypertension, diarrhea, proteinuria, decreased appetite, vomiting, fatigue, nausea, and weight decreased. The incidence of AEs resulting in pembrolizumab interruption (regardless of action taken for lenvatinib) was higher in the lenvatinib plus pembrolizumab group (25.6%) than in the pembrolizumab monotherapy RSD group (14.2%). Drug-related AEs in the lenvatinib plus pembrolizumab group resulting in pembrolizumab discontinuation in ≥2% of participants included diarrhea and ALT increased.

**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 group (66.5%) than in the lenvatinib monotherapy group (47.5%). The most frequently reported (incidence ≥10%) AEs leading to lenvatinib dose reduction were hypertension and diarrhea in the lenvatinib plus pembrolizumab group.

The overall incidence of AEs resulting in a dose reduction of lenvatinib in the lenvatinib plus pembrolizumab group (66.5%) was consistent with the lenvatinib plus pembrolizumab non-EC group (66.1%).

**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 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, diarrhea, PPES, proteinuria, fatigue, decreased appetite, and weight decreased in the lenvatinib plus pembrolizumab group.

## 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. The safety profile of pembrolizumab was summarized in the Periodic Safety Update Report covering the period 04-SEP-2019 through 03-SEP-2020.

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

**Exposure and study population characteristics**

As of KN-775 data cut-off, median duration of treatment exposure for the lenvatinib+pembrolizumab group was more than twice as long as for the TPC group (7.59 vs 3.43 months, respectively). Drug exposure >=6 and >=12 months was reached by respectively 59.9% and 27.1% of participants receiving combination treatment, and by 10.8% and 2.6% of the participants treated with TPC. While median duration of exposure was slightly longer for non-EC lenvatinib+pembrolizumab safety DS (9.79 months), it was shorter for both the monotherapy safety DS (5.55 for Lenvatinib and 4.86 for pembrolizumab). With regards to dose exposure, KN-775 lenvatinib+pembrolizumab participants received a mean dose lenvatinib dose of 69% (range, 16-100) on the total planned starting dose, and a mean number of pembrolizumab administrations of 12 (1-35). In the KN-775 lenvatinib+pembrolizumab group, median duration on lenvatinib was 211.5 (SD+191.3) days and 211.0 (SD+190.9) days for pembrolizumab.

Concerning population characteristics, study participants of KN-775, as expected, were all females, whereas the non-EC lenvatinib-pembrolizumab safety dataset comprised both genders. KN-775 treatment groups were well-balanced for patient characteristics (age category >65 years in ~50%, ~2/3 white, ECOG PS 0 in ~60%), and geographic region of enrolment was similar across study arms, with a slightly lower prevalence of EU-based participants in lenvatinib+pembrolizumab group as compared to the TPC group (28% vs 33%, respectively).

**Safety profile**

In KN-775 study, the summary of AEs, despite showing similar overall proportions of subjects with at least one AE in the two arms (99.8% and 99.5% in the lenvatinib+pembrolizumab and the TPC group, respectively) displayed a worse safety profile for the combination treatment group when compared to standard chemotherapy, 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 a drug related AE (26.6% vs 5.7%). Proportions of fatal events and drug-related fatal events were comparable across study arms.

When evaluating exposure-adjusted incidence rates including multiple occurrences of events, a partially reversed safety picture is found. In fact, lower incidence rates per 100 person-months are registered, respectively, in the lenvatinib+pembrolizumab group when compared to the control group for the following safety items: AEs 231 vs 256, 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. 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), deaths (0.59 and 1.08), and deaths due to drug-related AE (0.15 and 0.45) the incidence rate of events was quite comparable across study arms. On the contrary, the proportion of subjects with dose modification (37.9 vs 18.6 per 100 person-months), dose interruption (21 vs 11.5), dose reduction (15 vs 4.76), and discontinuation due to AE (5 vs 2.32) all remained higher in the study group of interest.

Overall exposure-adjusted AE incidence rate in the KN-775 pembrolizumab-lenvatinib group (231.94 per 100 person-months of exposure) was:

- lower than the rate for KN-775 TPC group (256.41 per 100 person-months of exposure);

- comparable to rates for the non-EC pembrolizumab-lenvatinib dataset (232.30 per 100 person-months of exposure) and the lenvatinib monotherapy dataset (226.70);

- higher than the rate reported for the pembrolizumab monotherapy RSD (128.64 per 100 person-months of exposure).

At safety comparisons between KN-775 group of interest and the other three safety datasets, the safety profile of lenvatinib+pembrolizumab was consistent with that of the non-EC lenvatinib+pembrolizumab dataset and mirrored that of the lenvatinib monotherapy, showing however slightly higher proportions of subjects with drug-related grade 3-5 AEs (77.8% vs 65.7%), drug-related SAEs (33.3% vs 25.7%), and who discontinued any drug due to drug-related AEs (26.6% vs 18.6%). In respect to pembrolizumab monotherapy, combination treatment showed a considerably worse safety profile with increased frequencies of drug-related AEs (97.3% vs 70.2%), grade 3-5 drug-related AEs (77.8% vs 15.5%), drug-related SAEs (33.3% vs 11.1%), subjects who discontinued due to AEs (33% vs 13.4%) in the KN-775 lenvatinib+pembrolizumab group.

The most common AEs (occurring in >30% of subjects) in the KN-775 lenvatinib+pembrolizumab group were the following with decreasing frequency: 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%). In the TPC arm the following AEs had >30% incidence (decreasing frequency): anaemia (48.7%), nausea (46.1%), neutropenia (33.8%), alopecia (30.9%). The risk difference (>30%) favouring TPC in respect to lenvatinib+pembrolizumab was greatest for hypertension, hypothyroidism, diarrhoea.

Most commonly reported AEs for KN-775 lenvatinib+pembrolizumab treatment were consistent with the safety pattern found in the non-EC lenvatinib+pembrolizumab SD, and mirrored the well-known safety profile of lenvatinib and pembrolizumab monotherapies, showing however higher proportions for most frequently reported most common AEs, as compared with single-drug therapies. The ADR table in section 4.8 of the SmPC combines in a new single column the ADRs from pembrolizumab+lenvatinib (KEYNOTE-581, KEYNOTE-146, KEYNOTE-775) and pembrolizumab+axitinib (KEYNOTE-426). Identification of ADRs for pembrolizumab when given in combination with lenvatinib or axitinib for treatment of EC and RCC is based on frequency of harmful events found in a pooled dataset of several active-controlled trials (KN-581, KN-775, KN-426) and a single-arm cohort (KN-146). Further, it takes advantage of the well-established safety profiles of pembrolizumab, lenvatinib and axitinib when given as monotherapies.

The proportion of subjects with drug-related AEs were similar in KN-775 combination treatment and control arms, as well as in the lenvatinib monotherapy dataset (97.3%, 93.8% and 94.7%, respectively), while in the pembrolizumab monotherapy dataset a lower proportion is observed (70.2%). Drug-related AEs with the highest incidence rates (>=30% incidence) in the KN-775 combination treatment group were the

following, as compared to the TPC arm: hypertension (61.1% vs 1%, respectively), hypothyroidism (54.4% vs 0), diarrhoea (42.1% vs 10.8%), nausea (38.9% vs 40.5%), decreased appetite (36.7% vs 16.5%). Type of most frequently reported drug-related AEs in the KN-775 lenvatinib+pembrolizumab group was consistent with drug-related AEs of the lenvatinib monotherapy dataset.

In respect to the non-EC lenvatinib+pembrolizumab SD, KN775 lenvatinib+pembrolizumab group had higher frequency (>10% difference) of the following drug-related AEs: hypertension (61.1% vs 39.1%, respectively), hypotyroidism (54.4% vs 33.5%), asthenia (18.5% vs 4.3%), mucosal inflammation (11.1% vs 0).

In KN-775, Grade 3-5 AEs were reported in 88.9% of subjects receiving lenvatinib+pembrolizumab and 72.7% of those receiving standard chemotherapy. While the risk difference between study arms was in favour of the combination treatment for neutropenia, neutrophil count decreased, white blood cells decreased, anaemia, leukopenia and febrile neutropenia, it resulted favouring the TPC arm for hypertension, weight decreased, decreased appetite, diarrhoea, proteinuria, and lipase increased. Also, drug-related Grade 3-5 AEs were found more often in the combination arm when compared to TPC arm (77.8% vs 59%, respectively); among these hypertension events (36% vs 0.3%, respectively) were the most prevalent AE being the only event with a frequency >10%.

When comparing the frequency of Grade 3-5 AEs and of drug-related Grade 3-5 AEs in the KN-775 combination arm (88.9% and 77.8%, respectively) with the supportive safety datasets, proportions were comparable or slightly lower in the non-EC lenvatinib+pembrolizumab SD (88.3% and 65.7%, respectively) and in the lenvatinib monotherapy SD (80.3% and 64.7%, respectively), while being much higher than in the pembrolizumab monotherapy RSD (48.1% and 15.5%, respectively).

In KN-775, non-fatal SAEs were reported in 52.7% of subjects treated with lenvatinib+pembrolizumab and in 30.4% of those treated with TPC. Similar findings were observed in the other lenvatinib-based safety datasets: 56.1% in the non-EC lenvatinib+pembrolizumab group and 54.8% in the lenvatinib monotherapy SD. In the pembrolizumab monotherapy RSD a lower proportion of subjects developed SAEs (38.5%). Most commonly recorded (>2% incidence) SAEs for the KN combination arm were the following: hypertension (4.2%), UTI (3.2%), diarrhoea (2.5%), decreased appetite (2.2%), and vomiting (2.2%). Risk difference between study arms showed that non-fatal SAEs favouring the combination arm were febrile neutropenia, anaemia, and neutropenia, while those in favour of controls were: hypertension, UTI, and decreased appetite. In KN-775, drug-related non-fatal SAEs occurred in 33.3% of subjects receiving at least one dose of lenvatinib+pembrolizumab and in 14.2% of those receiving at least one dose of chemotherapy.

Fatal AEs occurred in 5.7% of subjects participating to the KN-775 lenvatinib+permbrolizumab group and in 4.9% of those participating to the TPC group, suggesting that there was no increased risk of death in the group of interest. Overall, proportion of deaths in the KN-775 lenvatinib+pembrolizumab group was lower than in the non-EC lenvatinitib+pembrolizumab (10.4%) and the lenvatinib monotherapy (8.7%) datasets, and comparable to that of the pembrolizumab monotherapy RSD (5.3%). Number of fatal events assessed by the KN-775 investigator to be drug-related were 6/23 (1.5%) in the combination treatment group and 8/19 (2.1%) in the TPC group.

Clinically Significant Adverse Events for Lenvatinib (CSAEs)

When compared to the non-EC lenvatinib+pembrolizumab group and the lenvatinib monotherapy DS, incidence in the KN lenvatinib+pembrolizumab arm were quite comparable for all-grade CSAEs (94.8% vs 89.6% and 86.9%, respectively), serious CSAEs (19.7% vs 20.4% and 18.1%), and CSAEs leading to treatment discontinuation (14.8% vs 10% and 9.7%). The following AEs were considered CSAEs and were reported with decreasing frequency in the KN-775 lenvatinib+pembrolizumab combination arm: Hypothyroidism (68.2%), Hypertension (65%), Hepatotoxicity (33.7%), Proteinuria (29.6%), Hemorrhage

(24.4%), Palmar-plantar Erythrodysesthesia Syndrome (22.2%), Renal Events (18.2%), GI Perforation (3.9%), Hypocalcemia (3.9%), QT Prolongation (3.9%), Arterial Thromboembolic Events (3.7%), Fistula Formation (2.5%), Cardiac Dysfunction (1.0%), Posterior Reversible Encephalopathy Syndrome (0.2%).

Eight deaths (2.0%) due to CSAE were registered in the lenvatinib+pembrolizumab group, and 2 out of these (cerebrovascular accident and right ventricular dysfunction) were considered by the investigator to be related to lenvatinib. As of data cut-off, only a minority (20.8%) of CSAEs had resolved.

The frequency and severity of CSAEs in the KN-775 lenvatinib+pembrolizumab group was generally consistent with those in the non-EC lenvatinib plus pembrolizumab and the lenvatinib monotherapy groups, with the exception of the CSAEs of hepatotoxicity (33.7% vs 17.5% and 19.6%, respectively), hypothyroidism (68.2% vs 19.8% and 43.5%), and renal events (18.2% vs 10.0% and 18.7%). Most CSAEs resolved, and only few resulted in treatment discontinuation.

Adverse Events of Special Interest for pembrolizumab (AEOSIs)

AEOSIs were reported in 67.2% of KN-775 combination arm participants, and showed a pattern that was consistent with the well-established pembrolizumab safety profile. Notably, the overall frequency of AEOSIs in the KN-775 combination arm was slightly higher than that reported for the non-EC lenvatinib+pembrolizumab safety dataset (51.3%), but much increased in respect to that found in the pembrolizumab monotherapy RSD (25.1%).

Most often reported AEOSIs in the KN-775 combination arm were hypothyroidism (57.6%), hyperthyroidism (11.6%), and colitis (4.7%). The proportions of thyroid disorders were higher than in the non-EC lenvatinib+pembrolizumab group and the pembrolizumab monotherapy RSD where hypothyroidism was found in 37.8%, and 11.1%, respectively, and hyperthyroidism in 4.8%, and 4.2%. Frequency of colitis was similar in the non-EC Lenvatinib+pembrolizumab group, but higher than for pembrolizumab monotherapy (1.9%). In respect to severity, the majority of AEOSIs were Grade 1 and 2, and Grade 3 AEOSIs were severe skin reactions (2.5%), colitis (1.5%), and hepatitis (1.5%). One drug-related fatal event due to a colitis was recorded. In general, AEOSIs were manageable with only few events leading to drug discontinuation. Outcome of AEOSIs showed that most events resolved and two-thirds of hypothyroidisms persisted at data cut-off.

Discontinuation due to Adverse events

In the lenvatinib+pembrolizumab arm, frequencies of AEs leading to dose interruption or dose reduction of lenvatinib, or discontinuation of any drug were found, respectively, in 69.2%, 66.5%, and 33.0%, and were consistent with those observed in the non-EC lenvatinib+pembrolizumab group (84.8%, 66.1%, and 28.3%) and of the lenvatinib monotherapy SD (67.6%, 47.5%, and 26.7%).

In KN-775 study, 14.0% of participants discontinued both lenvatinib and pembrolizumab, with discontinuation of lenvatinib (30.8%) higher than for pembrolizumab (18.7%). In the KN-775 combination arm, the only AE (incidence of ≥1%) resulting in discontinuation of lenvatinib and pembrolizumab was intestinal obstruction, while AEs of hypertension, decreased appetite, asthenia, weight decreased, diarrhea, proteinuria, intestinal obstruction, and vomiting resulted in lenvatinib discontinuation in ≥1% of participants, and no AE resulted in pembrolizumab discontinuation in >1% of participants.

Treatment discontinuation was more frequent for Lenvatinib than for pembrolizumab (30.8 vs 18.7%). While hypertension was the only AE resulting in discontinuation of lenvatinib in >2% of participants, no specific AE resulted in >1% discontinuation of pembrolizumab.

Laboratory findings

No new laboratory safety AE was identified in the KN-775 lenvatinib+pembrolizumab group. Laboratory abnormalities were mirrored the lenvatinib monotherapy and the lenvatinib+pembrolizumab safety profile, however with higher proportions for ALT and AST increased, cholesterol increased, triglycerides increased, glucose increased, hypomagnesemia. Most AEs were of Grade 1 or 2 in severity. Grade 3 or 4 laboratory abnormalities with incidence >=10% were: lymphocyte decreased (16.9%), sodium decreased (14.4%), potassium decreased (10.7%).

Three participants in the lenvatinib plus pembrolizumab group met the prespecified drug induced liver injury criteria.

Safety profile by intrinsic and extrinsic factors

*Age categories*. In KN-775, the safety profile of lenvatinib+pembrolizumab worsened the higher the age category considered. Compared to younger age groups (<65 and 65-74 years), the category >75 years of age presented the highest proportions of drug-related AEs and frequencies were the following: drug-related Grade 3-5 AEs 81.3% and 80% vs 74.6%, drug-related SAEs 33.7% and 42.9% vs 31.2%, drug-related discontinuation due to AE 30.1% and 31.1% vs 22.9%. Fatal events and drug-related fatal events were highest in the age category >75 years: 17.1% and 5.7% (respectively 3.0 and 0 in 65-75 category, and 5.9 and 2.0 in age category <65 years). Though limited by the small sample size (n=35), a worse safety profile (in particular regarding drug-related AEs) is noted in the older age group (i.e. age >75 years) for lenvatinib+pembrolizumab, when compared to younger age categories. In the older age group (≥75 years), 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.

*Gender*. As in KN-775 study all participants were females, sub-group analysis based on sex is not considered informative for the present submission.

*Ethnicity.* Safety evaluation of pembrolizumab+lenvatinib according to ethnicity is limited due to the small number of KN-775 study participants who were Asian. As AEs with higher frequency in Asians than in Whites were almost all ADR for Lenvatinib; thus, it is agreed that the Keytruda SmPC should not be amended.

Safety analyses based on *ECOG PS* and *Geographic region* did not highlight differences across subgroups.

*MMR status*. As for the overall population, within each of MMR status comparison of KN-775 study arms showed a worse safety profile in the combination group in respect to TPC.

In the lenvatinib+pembrolizumab group higher proportions were found in the dMMR group compared to the pMMR group for the following: subjects with Grade 3-5 AEs (95.3% vs 87.7%, respectively), Grade 3-5 drug-related AEs (85.9% vs 76.3%), SAEs (68.8% vs 49.7%), drug-related SAEs (45.3% vs 31%), fatal event due to an AE (3.1% vs 1.2%), dose modifications due to AEs (100% vs 92.4%), dose interruptions due to AEs (71.9% vs 68.7%), and discontinuation due to AEs (43.8% vs 31%). As an approximately three-times longer duration of exposure to lenvatinib+pembrolizumab is found in the dMMR group in respect to the pMMR group, table with exposure-adjusted incidence rates by MMR status and KN-775 study arms was requested. Exposure-adjusted rates of AEs and AEOSIs were generally similar or lower in the dMMR group compared to the pMMR group, suggesting that the higher AE proportions are due to drug exposure.

Data received after initial assessment: Fifty-two AEs for 6 clinical study participants enrolled at a single study center started prior to the data cutoff for interim analysis 1 (IA1) (data cutoff 26-Oct-2020) of KN775, but were not entered into the database at the time of the database lock (20-Nov-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-Feb-2021

(database lock on 22-Mar-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 MAH submitted/was requested to submit an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 33.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 33.0 with the following content:

### *Safety concerns*

**Table 118 – Summary of safety concerns**

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | Immune-related adverse reactions (including immune related pneumonitis, colitis, hepatitis, nephritis, and endocrinopathies) |
| Important potential risks | For hematologic malignancies: increased risk of severe complications of allogeneic stem cell transplantation (SCT) in patients who have previously received pembrolizumab<br><br>Graft versus host disease (GVHD) after pembrolizumab administration in patients with a history of allogeneic stem cell transplant (SCT) |
| Missing information | None |

No new safety concerns were identified as part of this extension of indication in advanced endometrial cancer.

### *Pharmacovigilance plan*

No new additional pharmacovigilance activities were identified as a result of this extension of indication in advanced endometrial cancer. Routine pharmacovigilance activities remain sufficient to mitigate the risks for Keytruda in all approved indications.

### *Risk minimisation measures*

**Table 119 - Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern**

| **Safety Concern** | **Risk minimisation Measures** | **Pharmacovigilance Activities** |
|---|---|---|
| **Important Identified Risks: Immune-Related Adverse Reactions** | | |

**Table 119 - Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern**

| Safety Concern | Risk minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and endocrinopathies) | Routine risk minimisation measures:<br>• The risk of the immune-related adverse reactions (including immune-related pneumonitis colitis, hepatitis, nephritis, and endocrinopathies) associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk. | Routine pharmacovigilance activities<br><br>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>Targeted questionnaire for spontaneous postmarketing reports of all adverse events |
| | Additional risk minimisation measures:<br>Patient educational materials | Additional pharmacovigilance including:<br>• Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types |

**Table 119 - Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern**

| Safety Concern | Risk minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| **Important Potential Risks** | | |
| For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab | Routine risk minimisation measures:<br>• For Hematologic malignancies: the increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab is described in the SmPC, Section 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.<br>No additional risk minimisation measures warranted | Routine pharmacovigilance activities<br>Additional pharmacovigilance including:<br>• Safety monitoring in the ongoing HL trials (KN087, KN204). |
| GVHD after pembrolizumab administration in patients with a history of allogeneic SCT | Routine risk minimisation measures:<br>• GVHD after pembrolizumab administration in patients with a history of allogeneic SCT is described in the SmPC, Section 4.4 and appropriate advice is provided to the prescriber to minimize the risk.<br>No additional risk minimisation measures warranted | Routine pharmacovigilance activities<br>Additional pharmacovigilance including:<br>• Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types |

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, 4.8, 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

### 2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the 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 initially submitted claimed indications for Keytruda was:

- KEYTRUDA, in combination with lenvatinib, is indicated for the treatment of advanced endometrial carcinoma in adults who have disease progression following prior systemic therapy in any setting and who are not candidates for curative surgery or radiation (see section 5.1)

During the procedure, the indication was updated as follows:

- KEYTRUDA, 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[22] 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[23]. Microsatellite unstable tumours (MSI-H) is one of the four clinically significant molecular subtypes of endometrial cancer with different clinical prognoses[24].

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[25]. Approximately 20% of EC cases recur with poor prognosis[26]. In general, the median survival of patients with recurrent or advanced disease is 12 months[27].

## 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[28]. 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,

[22] 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.
[23] Tran AQ, Gehrig P. Recent advances in endometrial cancer. F1000Res. 2017 Jan 27;6(F1000 Faculty Rev):81.
[24] 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.
[25] 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.
[26] 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.
[27]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.
[28] N. Colombo, C. Creutzberg, F. Amant, T. Bosse, et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer. Ann Oncol 2016; 27: 16-41.

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[29].

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.

### 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 vs 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 Oct 2020 have been submitted. The median duration of follow up in the overall population is 11.4 months (range 0.3, 26.9).

## *3.2. Favourable effects*

- Study 309/KEYNOTE-755 showed a statistically significant and clinically relevant PFS benefit of pembrolizumab+lenvatinib vs 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 pembrolizumab+lenvatinib vs 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 vs 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 vs 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.
- ORR improvement was seen in all comers [31.9% (27.4, 36.6), vs 14.7% (11.4, 18.4)] as well as in pMMR population [30.3% (25.5, 35.5) vs 15.1% (11.5, 19.3)]. CR rates was 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% vs 42.6% of responding subjects for ≥6 months). Same trend was observed in pMMR subgroup (median DOR 9.2 vs 5.7 months, durable responses lasting ≥6 months 65.6% vs 42.1%).
- Consistent treatment effect across all main subgroups analysed.

[29] McMeekin S, Dizon D, Barter J, Scambia G, Lisyanskaya A, Oaknin 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.

- 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% vs 12.3%, CR 13.8% vs 3.1%, median DOR NR vs 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 vs 153, Grade 3-5 AEs 31.02 vs 48.78, drug-related Grade 3-5 AEs 18.52 versus 34.5. 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), deaths (0.59 and 1.08), 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 KN-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 KN-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 KN-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/KN775).

## *3.6. Effects Table*

**Effects Table for KEYTRUDA in combination with Lenvatinib in advanced, recurrrent or metastatic Endometrial cancer adult patients progressed after platinum-based therapy (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, which is however based on indirect comparison | CSR KN-775 |
| | | 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 | *All comers* | | | OS results statistically significant and clinically relevant in ITT and pMMR population | CSR KN-775 |
| | | months (95% CI) | 18.3 (15.2, 20.5) | 11.4 (10.5, 12.9) | | |

| 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 |
|---|---|---|---|---|---|---|
| | any cause | 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 KN-775 |
| | | % (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 summary** | | | **Lenvatinib+ pembro (n=406)** | **TPC (n=388)** | | CSR KN-775 |
| | **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

## 3.6.1. Importance of favourable and unfavourable effects

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 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. Based on indirect comparison, it is 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, while lenvatinib add toxicity. The lack of direct comparison and limitations of cross trial comparison, the limited number of patients and wider confidence intervals in the dMMR population, added to some baseline differences in populations enrolled in the studies provided for the indirect comparison, preclude however definitive conclusions. Overall, the combination appears 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.

### 3.6.2. Balance of benefits and risks

The combination of lenvatinib plus pembrolizumab represents an effective 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 is different compared to chemotherapy, as expected, and consistent with the known safety profile of both drugs and the safety profile of the combination in non-EC, with no new safety concern identified, although the combination overall appears not to be particularly well tolerated.

### 3.6.3. Additional considerations on the benefit-risk balance

None.

## *3.7. Conclusions*

The overall B/R of Keytruda in combination with lenvatinib in advanced or recurrent EC 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 the variation to the terms of the Marketing Authorisation, concerning the following change:

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

Extension of indication to include pembrolizumab in combination with lenvatinib for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who 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 33.0 of the RMP has also been agreed.

## *Amendments to the marketing authorisation*

In view of the data submitted with the variation, amendments to Annexes I, IIIB and to the Risk Management Plan are recommended.