14 October 2021
EMA/621567/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: pembrolizumab

Procedure No. EMEA/H/C/003820/II/0104

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

1L	first-line
ADR	adverse drug reaction
AE	adverse event
AEOSI	adverse events of special interest
BOR	best overall response
CR	complete response
CSE	clinically significant event
CSR	clinical study report
DCO	data cut-off
DLT	dose-limiting toxicity
DOR	duration of response
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
HNSCC	head and neck squamous cell carcinoma
HR	hazard ratio
HRQoL	health-related quality of life
IA	interim analysis
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IIR	independent imaging review
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
KN-581	KEYNOTE-581 or Study 307 or E7080-G000-307/
KN-146	KEYNOTE-146 or E7080 A001 111
KPS	Karnofsky Performance Score
mAb	monoclonal antibody
MSKCC	Memorial Sloan-Kettering Cancer Center
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
NDA	New Drug Application
NSCLC	non-small-cell lung cancer

ORR	objective response rate
OS	overall survival
PD	progressive disease; disease progression
PD-1	programmed cell death 1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PPES	palmar-plantar erythrodysesthesia syndrome
Q3W	once every 3 weeks
QD	once daily
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RET	RET proto-oncogene
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
VEGF	vascular endothelial growth factor
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 Keytruda in combination with lenvatinib first line treatment of adults with advanced renal cell carcinoma (RCC); 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 32.1 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 (EMEA-001474-PIP01-13-M01) covering the condition 'Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH received Scientific advice from the CHMP on 18 October 2018 (EMEA/H/SA/3261/1/FU/1/2018/II) and 1 April 2016 (EMEA/H/SA/3261/1/2016/II). The Scientific advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: <N/A> Co-Rapporteur: Jan Mueller-Berghaus

Timetable	Actual dates
Submission date	10 March 2021
Start of procedure:	27 March 2021
CHMP Rapporteur Assessment Report	21 May 2021
CHMP Co-Rapporteur Assessment Report	21 May 2021
PRAC Rapporteur Assessment Report	27 May 2021
PRAC Outcome	10 June 2021
CHMP members comments	14 June 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	17 June 2021
Request for supplementary information (RSI)	24 June 2021
CHMP Rapporteur Assessment Report	24 August 2021
CHMP members comments	06 September 2021
Updated CHMP Rapporteur Assessment Report	10 September 2021
Request for supplementary information (RSI)	16 September 2021
CHMP Rapporteur Assessment Report	29 September 2021
CHMP members comments	04 October 2021
Updated CHMP Rapporteur Assessment Report	n/a
Opinion	14 October 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

This application concerns an extension of indication for pembrolizumab (Keytruda) in combination with lenvatinib to include the first-line (1L) treatment of advanced renal cell carcinoma. Consequently, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the Summary of Product Characteristics (SmPC) are updated, the Package Leaflet is updated in accordance and Version 32.1 of the Risk Management Plan (RMP) has also been submitted.

Disease or condition, Epidemiology, Biological Feature

Renal cell carcinoma (RCC) represents the sixth most common cancer in men and the eighth most common cancer in women, accounting for 3%-4% of all adult malignancies in the US (Siegel et al. CA A

Cancer J Clin. 2019). In 2020, an estimated 138,611 new cases of kidney cancer were expected to be diagnosed in Europe with approximately 54,054 people expected to die from the disease (GLOBOCAN, 2020).

Clear cell renal cell carcinoma (ccRCC) is the most common type of kidney cancer, comprising 80-90% of all kidney tumours (2020 European Association of Urology [EAU] RCC guidelines).

Well-known risk factors for RCC are cigarette smoking, obesity and hypertension (Chow et al. 2010).

Renal cell carcinoma generally resists both traditional chemotherapy and radiation therapy. Surgical resection can be curative for patients presenting with localized disease. However, one third of patients present with regional or distant metastases and the 5-year survival rate for metastatic disease is approximately 12%. Of patients with localized RCC treated with nephrectomy with curative intent, approximately one quarter relapse at distant sites. The prognosis in these cases is poor (Choueiri and Motzer 2017). Advanced' RCC entails both locally advanced disease that is not amenable to local therapy, i.e. curative surgery or radiation therapy, as well as metastatic disease. Advanced RCC thus requires systemic treatment.

State the claimed the therapeutic indication

The proposed new indication for Keytruda in this procedure is:

"KEYTRUDA in combination with lenvatinib is indicated for the first-line treatment of advanced renal cell carcinoma in adults

The proposed posology for this new indication is 200 mg pembrolizumab intravenous (IV) every 3 weeks (Q3W) or 400 mg pembrolizumab intravenous (IV) every 6 weeks (Q6W) in combination with 20 mg lenvatinib administered orally once daily (QD).

Clinical presentation, diagnosis

Many renal masses remain asymptomatic until the late disease stages. Currently, >50% of RCCs are detected accidentally by non-invasive imaging investigating various non-specific symptoms and other abdominal diseases (2020 EAU RCC guidelines; Escudier et al. An Oncol. 2019). In addition, 25-40% of the patients that are radically treated (nephrectomy) will eventually relapse. '*Advanced*' RCC (hereafter simply referred to as advanced RCC) entails both locally advanced disease that is not amenable to local therapy, i.e. curative surgery or radiation therapy, as well as metastatic disease. Advanced RCC thus requires systemic treatment. All histological epithelial subtypes of RCC (clear cell, papillary, chromophobe) can present with sarcomatoid differentiation, which is the most aggressive form of RCC. A high proportion of RCC patients with sarcomatoid features presents with metastatic disease. These features are found in 5-8% of clear cell RCC.

RCC with sarcomatoid features is characterised by limited therapeutic options due to its relative resistance to established systemic targeted therapy. Most trials report on a poor median OS of 5 to 12 months. Studies have shown that sarcomatoid RCC express programmed death 1 (PD-1) and its ligand (PD-L1) at a much higher level than non-sarcomatoid RCC, suggesting that blockade of the PD-1/PD-L1 axis may be an attractive new therapeutic strategy (Pichler et al. Cancers (Basel). 2019).

Management

Current systemic treatment of advanced RCC

The choice of treatment is normally based on prognostic risk factors historically developed in the era of frontline vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs). The most commonly used prognostic models are the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic model or the Memorial Sloan–Kettering Cancer Center (MSKCC) prognostic model (Hatakeyama et al. 2019) including the following adverse factors:

IMDC	MSKCC
Karnofsky performance status (KPS) <80%	Karnofsky performance status (KPS) <80%
time from diagnosis to treatment <1 year	time from diagnosis to treatment <1 year
haemoglobin concentration less than the lower limit of normal	haemoglobin concentration less than the lower limit of normal
serum calcium greater than the upper limit of normal	serum calcium greater than the upper limit of normal
neutrophil count greater than the upper limit of normal and	LDH >1.5x the upper limit of normal
platelet count greater than the upper limit of normal.	-

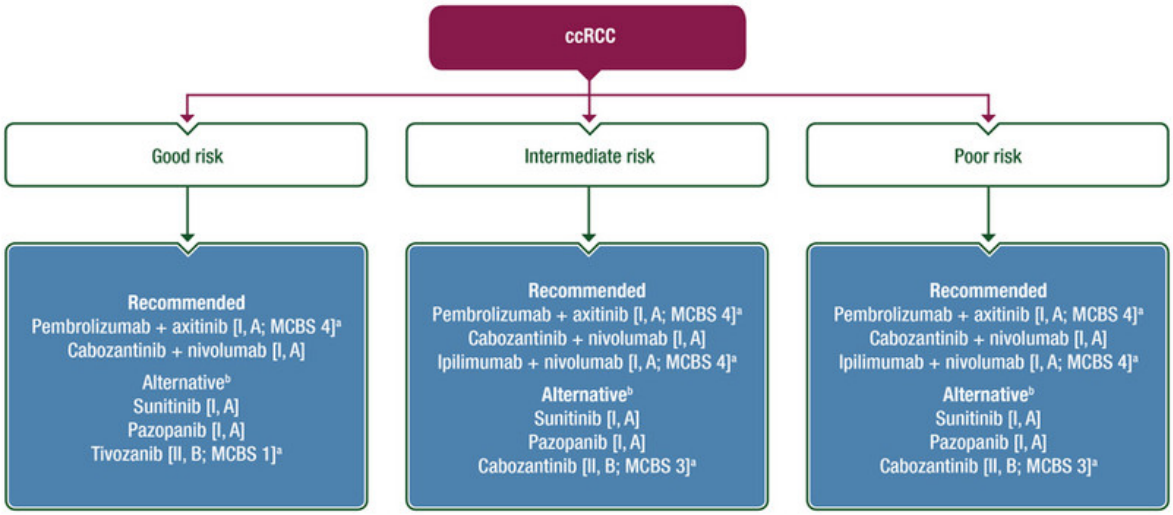
Patients with none (0) of these risk factors are considered good risk, those with one or two (1-2) are considered intermediate risk, and those with three or more (≥3) are considered poor risk.

The estimated median overall survival (OS) for the patients in the IDMC risk groups is 43.2 months, 22.5 months, and 7.8 months, respectively (Ljungberg et al. 2019).

First-line systemic treatment

The algorithm for first-line (1L) systemic treatment in ccRCC that is currently recommended by ESMO is presented in

Figure 1 Systemic first-line treatment of clear cell renal cell carcinoma



[a] Where recommended treatment not available or contra-indicated.

Abbreviation: ccRCC= clear cell renal cell carcinoma

In addition, the combination of avelumab + axitinib has been approved by EMA for the 1L treatment of adult patients with advanced RCC.

In spite of recent additions to the (systemic) treatment armamentarium, both (median) progression-free survival (PFS) and OS for patients with advanced RCC are still rather limited, especially for patients in the intermediate and poor risk groups. There thus remains an unmet medical need.

2.1.2. About the product

Pembrolizumab is a humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to inhibit the interaction between PD-1 and its ligands, PD-L1 and PD-L2. This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and, ultimately, immune rejection. In vitro and in vivo experiences have shown that PD-1 and PD-L1 blockade using a mAb can result in activation of antitumor T cells and subsequent tumor regression. In T-cell activation assays using human donor blood cells, the EC50 was in the range of 0.1 to 0.3 nM. Pembrolizumab also modulates the level of IL 2, TNFα, IFNγ, and other cytokines. The antibody potentiates existing immune responses in the presence of antigen only; it does not nonspecifically activate T cells. Blockade of PD 1 or PD-L1, using mAbs, has demonstrated substantial clinical activity in patients with metastatic RCC (Deleuze et al. 2020).

Currently, Keytruda is approved in the EU (SmPC Keytruda):

- as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.
- as monotherapy is indicated for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection.
- as monotherapy is indicated for the first line treatment of metastatic non-small cell lung carcinoma in adults whose tumours express PD L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.

- in combination with pemetrexed and platinum chemotherapy, is indicated for the first line treatment of metastatic non squamous non-small cell lung carcinoma in adults whose tumours have no EGFR or ALK positive mutations.
- in combination with carboplatin and either paclitaxel or nab paclitaxel, is indicated for the first line treatment of metastatic squamous non-small cell lung carcinoma in adults.
- as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung carcinoma in adults whose tumours express PD L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA.
- as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.
- as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum containing chemotherapy
- as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin containing chemotherapy and whose tumours express PD L1 with a combined positive score (CPS) ≥ 10.
- as monotherapy or in combination with platinum and 5 fluorouracil (5 FU) chemotherapy, is indicated for the first line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD L1 with a CPS ≥ 1.
- as monotherapy is indicated for the treatment of recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD L1 with a ≥ 50% TPS and progressing on or after platinum containing chemotherapy.
- in combination with axitinib, is indicated for the first line treatment of advanced renal cell carcinoma in adults.
- as monotherapy is indicated for the first line treatment of metastatic microsatellite instability high (MSI H) or mismatch repair deficient (dMMR) colorectal cancer in adults.
- in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 10.
- in combination with chemotherapy, is indicated for the treatment of locally recurrent unresectable or metastatic triple-negative breast cancer in adults whose tumours express PD-L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease

Lenvatinib inhibits the kinase activities of VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4).

Structural studies of VEGFR2-lenvatinib complexes revealed that lenvatinib exerts its inhibitory effects not only by interacting with the RTK adenosine triphosphate binding site, but also neighbouring regions of the kinase domain (allosteric site), distinguishing this agent as a distinctive Type V inhibitor. This unique binding mode results in high selectivity and leads to rapid association and slower dissociation kinetics at the receptor and results in longer receptor occupancy (Okamoto et al. 2015). A subsequent structural study of the FGFR1-lenvatinib complex indicated that the binding mode of lenvatinib to FGFR1 also meets

the 3 criteria that define a Type V kinase inhibitor: 1) binds to the ATP-binding site, 2) binds to the neighbouring allosteric region, and 3) fits to the kinase adopting the DFG-in conformation (Matsuki, et al., 2018).

Lenvatinib is approved in EU as Lenvima and Kisplyx

Lenvima is approved in the EU (SmPC Lenvima)

- as monotherapy for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI).
- as monotherapy for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy.

Kisplyx

- in combination with everolimus for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy

Scientific rationale for the combination

In nonclinical models, lenvatinib decreased the tumor-associated macrophage (TAM) population, which is known as an immune-regulator in the tumor microenvironment. The decrease in TAM was accompanied by increases in activated cytotoxic T-cell populations through stimulation of interferon-gamma signaling, resulting in increased immune activation. The immune-modulating effect of lenvatinib may result in a potent combination effect with PD-1/L1 signal inhibitors. The effect of combining lenvatinib with an anti-PD-1 mAb was investigated in 4 murine tumor isograft models, which showed significant tumor growth inhibition compared with control. In the RAG murine tumor isograft tumor model, survival in the group treated with the combination was significantly longer compared to that of the respective monotherapy groups (Study M18018 report). In the CT26 murine tumor isograft model, treatment with the combination significantly increased the population of activated cytotoxic T cells compared with that of the respective monotherapy groups (Kato et al. 2019). All treatments were well tolerated and severe body weight loss was not observed (data on file).

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

In the latest SA (EMEA/H/SA/3261/1/FU/1/2018/II), the CHMP agreed that data from the RCC cohort in Study 111/KEYNOTE 146 corroborated with data from Study 307/KEYNOTE 581 could be adequate to support the assessment of the benefit/risk for the combination of lenvatinib with pembrolizumab for the treatment of adult patients with advanced renal cell carcinoma . A specific concern was how the present study as well as available external data would serve to justify the relative contributions of lenvatinib as well as pembrolizumab to the clinical benefit of the proposed combination regimen. A randomised comparison, even of ORR rather than relevant time to event endpoints would be preferred. Whether the proposed basis to conclude on the contribution of both components to efficacy could be adequate would be, dependent on the actual ORR shown in the Study 307/KN 581 at the time of the review.

The applicant asked for the possibility to submit this variation based on data from the RCC cohort of Study 111/KEYNOTE 146 together with Interim Analysis Data from Study E7080-G000-307/KEYNOTE 581, which was not encouraged, because ORR is a pharmacodynamic endpoint which, in most settings, does not directly represent clinical benefit. Furthermore, the surrogacy of ORR for PFS and/or OS has in most cases not been established.

Control of the type I error for the testing of ORR in the lenvatinib + pembrolizumab arm in the interim analysis was not considered critical, whereas the protection of trial integrity was discussed

The applicant provided an overview of the operational plan for the interim analysis of the first 88 subjects in the lenvatinib + pembrolizumab arm for ORR, devised to protect the integrity of the study 307 data.

Regulatory concerns regarding the dissemination of results in case of positive IA findings in the US were discussed.

The applicant estimated that about 25% of patients in the control arm would still be on treatment at dissemination of IA findings, and that patients generally were not expected to change treatment unless facing tumour progression, potentially protecting the PFS endpoint. The applicant described that in case of a change in therapy prior to disease progression, patients would continue systematic scanning and a data analysis according to EU censoring rules would be possible.

Notwithstanding these measures, it would from a European point of view be preferable if this IA was discarded as there is potential for creating bias.

2.1.4. General comments on compliance with GLP, GCP

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

2.2. Non-clinical aspects

2.2.1. Introduction

To support the mechanism of action of the combination of pembrolizumab and lenvatinib, nonclinical studies conducted with lenvatinib were provided with this submission to investigate the antitumor activity of lenvatinib and the combination of lenvatinib with an anti-PD-1 mAb, clone RMP1-14 (used as a surrogate antibody for pembrolizumab), in murine tumor isograft models.

In addition, the immunomodulatory activity of lenvatinib in murine tumor isograft models using immunocompetent mice and athymic mice was investigated to determine the effects of lenvatinib on the host immune systems in the Tumor microenviroment (TME).

2.2.2. Pharmacology

Primary pharmacodynamic studies

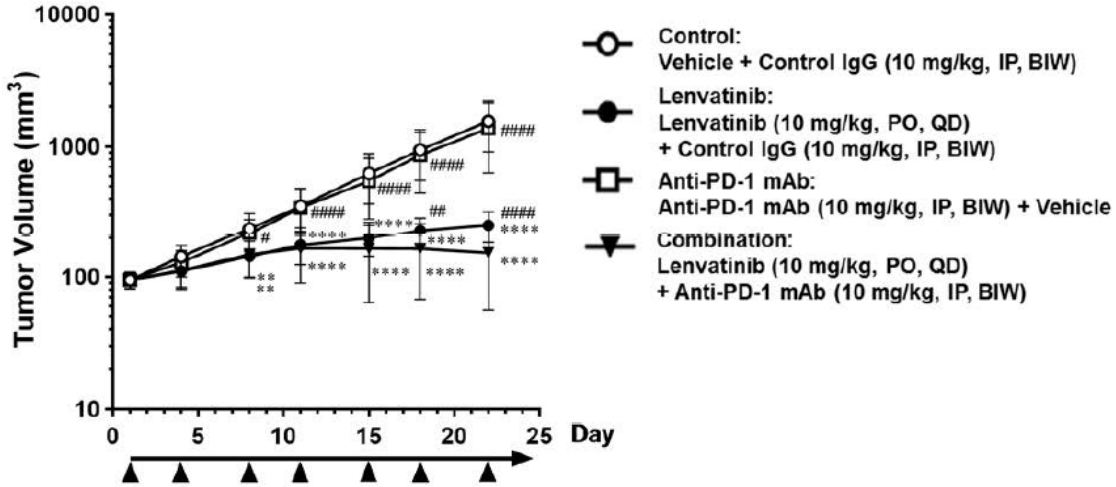
In vivo pharmacodynamics

1. Antitumor Activity of Lenvatinib in Combination With Anti-Murine PD-1 mAb in the **RAG Murine Renal Cell Carcinoma Isograft Model**

Rat anti-murine PD-1 mAb (anti-PD-1 mAb, clone RMP1-14) was used as a surrogate antibody for pembrolizumab, an anti-human PD-1 humanized mAb. RAG cells were inoculated subcutaneously into 6-week old female immunocompetent BALB/cAnNCrlCrlj mice.

At 7 days after inoculation, lenvatinib mesilate (10 mg/kg), anti-PD-1 mAb (10 mg/kg), and rat IgG2a isotype control (control immunoglobulin G [IgG], 10 mg/kg) were administered to mice (20/group).

Lenvatinib and vehicle were administered orally once daily for 28 days, and anti-PD-1 mAb and control IgG were administered intraperitoneally twice per week totaling 8 times (Days 1, 4, 8, 11, 15, 18, 22, and 25). A survival day was defined for each mouse as a duration from Day 1 to the day when the mouse was euthanized or found dead.

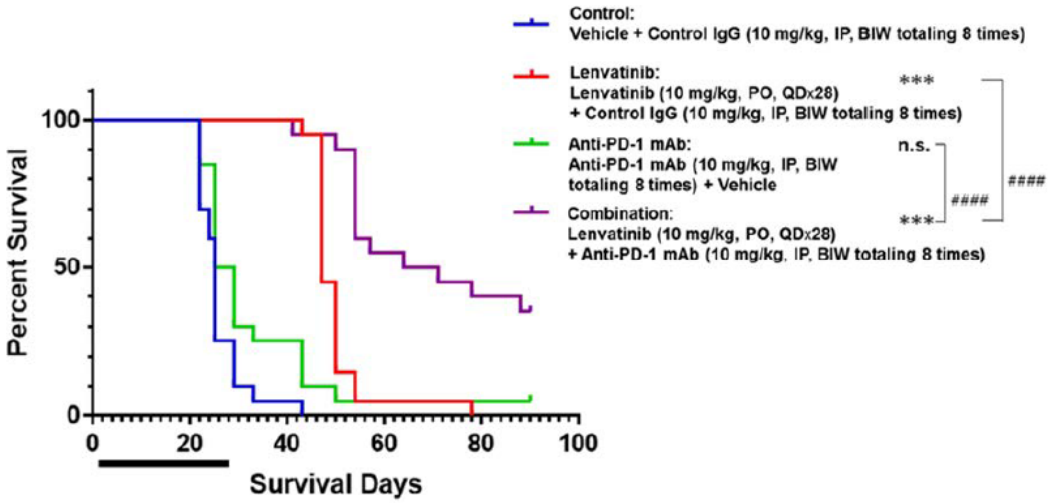


Each point represents the mean ±SD of 20 animals. Horizontal arrow signifies the dosing period for lenvatinib. The ▲ signifies the dosing day of anti-PD-1 mAb or control IgG. BIW = twice per week, IgG = immunoglobulin G, mAb = monoclonal antibody, QD = once daily, RCC = renal cell carcinoma. **P<0.01,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

Figure 2 Antitumor Activity of Lenvatinib in Combination With Anti-PD-1 mAb Against the RAG Murine RCC Isografts

The Tumor Volume (TV) and body weight were measured twice per week (Days 1 – 63 and Days 71 – 90) or once per week (Days 64 – 70). The TV was calculated according to the formula: TV (mm3) = length (mm) × width2 (mm2) × ½. The relative body weight (RBW) was calculated as a ratio of the mean body weight at a given time point to the mean body weight at the initiation of dosing.

Lenvatinib (10 mg/kg) monotherapy and lenvatinib in combination with anti-PD-1 mAb (10 mg/kg) showed significant TGI compared to the control group from Days 8 to 22 in the RAG isograft model, the antitumor activity of the combination of lenvatinib and anti-PD-1 mAb was only slightly greater than that of lenvatinib monotherapy on Days 18 and 22. Severe body weight loss (BWL) (>20% compared to Day 1) was not observed during the dosing period (Days 1 to 28) in any of the treatment groups. Figure 3 shows Kaplan–Meier curves of control and treated groups through Day 90 in the RAG isograft model.



Each line represents the percent survival of 20 animals per group through Day 90. The horizontal bar signifies the dosing period of lenvatinib and anti-PD-1 mAb. A total of 66 mice were euthanized on Days 22 – 90 because their TV was >2000 mm3. In the control group, 3/20 mice were found dead on Days 24 – 25. In the combination group, 2/20 mice were found dead on Days 41 and 54, and 1/20 mice was euthanized on Day 78 due to hemorrhage-related tumor rupture. BIW = twice per week, IgG = immunoglobulin G, mAb = monoclonal antibody, n.s. = not significant, QD×28 = once daily for 28 days, RCC = renal cell carcinoma, TV = tumor volume. ***P<0.001 versus control (log-rank test with Bonferroni's correction), n.s. versus control (log-rank test with Bonferroni's correction). ####P<0.0001 versus combination (logrank test). Source: Study No. M18018.

Figure 3 Survival of Mice Following Treatment With Lenvatinib in Combination With Anti-PD-1 mAb in the RAG Murine RCC Isograft Model

Comparable results were obtained when evaluating the antitumor activity of lenvatinib in combination with anti-Murine PD-1 mAb in the **LL/2 (LLC1) Murine Lewis Lung Carcinoma Isograft Model and in an the Hepa1-6 Murine HCC Isograft Model.**

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

Antitumor activity of lenvatinib in combination with anti-PD-1 mAb was also evaluated in the CT26 murine colon carcinoma isografts in syngeneic immunocompetent BALB/cAnNCrlCrlj mice and athymic CAnN.Cg-Foxn1nu/CrlCrlj mice (Kato et al. 2019). Here more extensive studies have been performed.

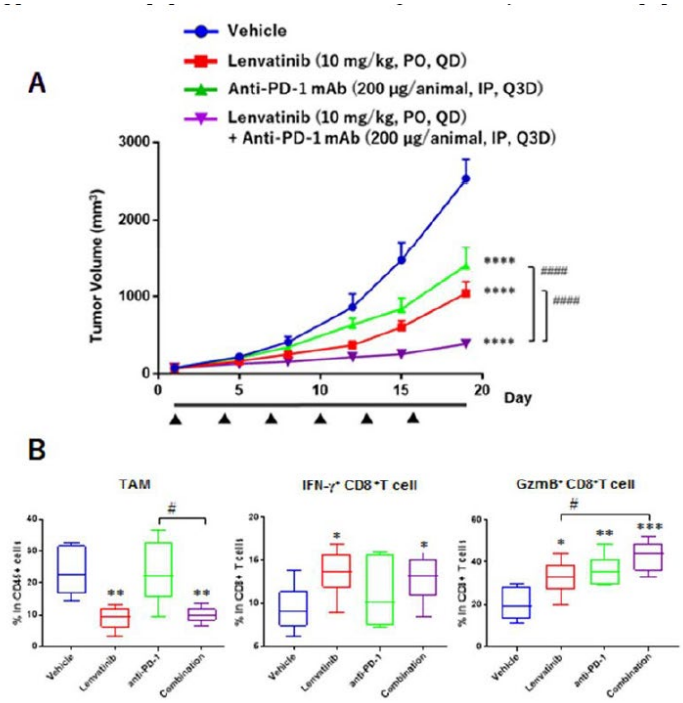
CT26 cells were inoculated in syngeneic immunocompetent BALB/cAnNCrlCrlj mice (7-week old females. When tumor sizes reached a mean volume of 33 mm3 (Day 1), vehicle (3 mmol/L HCl), lenvatinib mesilate (10 mg/kg), anti-PD-1 mAb; (200 µg/animal, clone RMP1-14), or the combination of lenvatinib and anti-PD-1 mAb was administered to the mice (8/group). Lenvatinib was administered orally once daily for 25 days for monotherapy, and once daily for 28 days for combination therapy. Anti-PD-1 mAb was administered intraperitoneally once every 3 days totalling 7 times for monotherapy, and once every 3 days totalling 10 times for combination therapy. The TV and body weight were measured twice per week.

As Figure 4 demonstrates lenvatinib (10 mg/kg) monotherapy and anti-PD-1 mAb (200 µg/animal) monotherapy showed Tumor Growth Inhibition (TGI) compared with the vehicle control. In addition, antitumor activity of their combination therapy was greater than that of either monotherapy on Day 19. Severe BWL (>20% compared to Day 1) was not noted in any treated groups.

As shown in Figure 4 (B), flow cytometric analysis showed that the percentage of the population of TAMs was decreased, and the populations of IFN-γ+CD8+ T cells and GzmB+CD8+ T cells (activated cytotoxic T cells) were increased in the tumors of mice treated with lenvatinib alone, and those treated with the combination of lenvatinib plus anti-PD-1 mAb compared with those of vehicle-control mice. The

GzmB+CD8+ T cell population expressing a cytotoxic enzyme, GzmB, was increased following treatment with the combination compared with that of lenvatinib monotherapy.

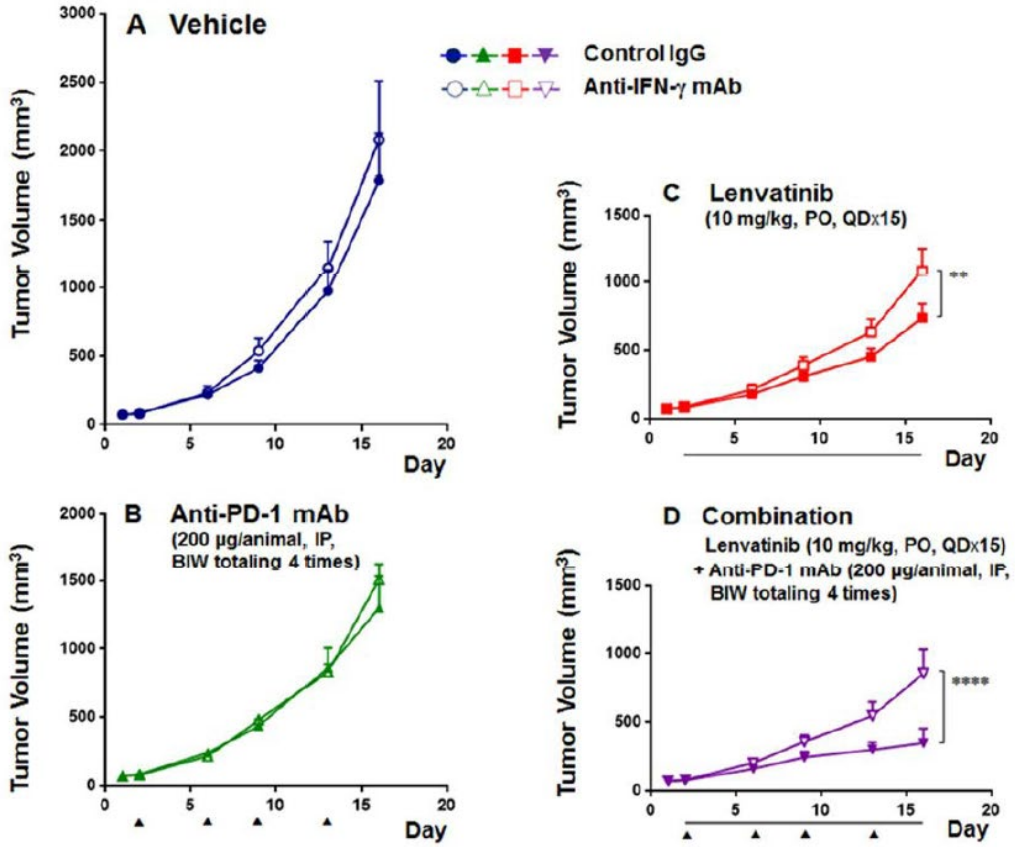
Therefore, lenvatinib could modulate the Tumor Microenviroment (TME) by decreasing the immunosuppressive TAM population and the increasing activated cytotoxic T cell population. Here no significant difference could be demonstrated between the TAM suppression and cytotoxic T-cell activation of lenvatinib monotherapy and the lenvatinib + pembrolizumab combination.



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

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

The antitumor activity of lenvatinib monotherapy and the combination therapy was also decreased in mice injected with anti-IFN-γ mAb, whereas the antitumor activity of anti-PD-1 mAb monotherapy was not affected by injection with anti-IFN-γ mAb. These results suggested that IFN-γ signaling contributed to the antitumor activity of lenvatinib and the combination of lenvatinib and anti-PD-1 mAb in this model.



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

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

Secondary pharmacodynamic studies

No secondary pharmacodynamics studies were conducted.

Safety pharmacology programme

No safety pharmacology studies were conducted.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were conducted.

2.2.1. Pharmacokinetics

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

2.2.1. Toxicology

The possibility of toxicologic interaction of lenvatinib and pembrolizumab is considered low based on the toxicity profiles of the 2 agents. The toxicities observed with the 2 agents are consistent with their respective mechanisms of action, and the combination of lenvatinib plus an anti-PD-1 mAb (surrogate for pembrolizumab) was well tolerated when studied in mouse isograft models. No significant mortality or body weight loss was observed in these studies.

The nonclinical safety of pembrolizumab was characterized in cynomolgus monkeys in toxicology studies up to 6-months duration. Pembrolizumab was well tolerated in cynomolgus monkeys up to a 200 mg/kg/dose with corresponding systemic exposure based on area under the concentration-time curve from zero time to Day 14 ($AUC_{0\text{-}14d}$) of approximately 67,500 µg·day/mL with biweekly dosing over the course of the 6-month study. No findings of toxicologic significance were observed and the NOAEL was ≥ 200 mg/kg. The exposure margins at the NOAEL based on $AUC_{0\text{-}tau}$ are ≥ 19-fold and ≥ 74-fold compared to exposures at the human dose of 10 mg/kg and 200 mg, respectively.

In the chronic toxicity studies in rats and cynomolgus monkeys with lenvatinib, target organ toxicity was primarily observed in the kidneys, gastro-intestinal tract, artery/arteriole in various organs, bone, and male and female reproductive organs (testis and ovary) in both species, and in the incisor and adrenals in rats. These findings were reversible and most were not evident at the end of a recovery period of 4 weeks. The no observed adverse effect levels (NOAELs) for the 26- and 39-week toxicity studies in rats and cynomolgus monkeys, respectively, were the lowest doses tested in those studies (0.4 and 0.1 mg/kg, respectively). The exposure margins at the NOAELs based on systemic exposure (area under the concentration-time curve from time zero to 24 hours; $AUC_{0\text{-}24}$) compared to exposures at the maximum recommended human dose (24 mg) were 0.7- to 0.8-fold in rats and 0.1-fold in monkeys.

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.

Discussion on non-clinical aspects

Lenvatinib is an oral multiple RTK inhibitor that selectively inhibits the kinase activities of VEGF receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other proangiogenic and oncogenic pathway-related RTKs including FGF receptors FGFR1, 2, 3, and 4; the PDGF receptor PDGFRα; KIT; and RET.

In vivo human tumor xenograft studies in athymic mice have shown that lenvatinib exerts antitumor activity against various tumor types including RCC, thyroid cancer, HCC, non-small cell lung cancer, melanoma, colorectal cancer, gastric cancer, and ovarian cancer, mainly through its potent inhibition of tumor angiogenesis driven by VEGFR and FGFR signaling.

The new provided nonclinical studies investigated the antitumor activity of lenvatinib and the combination of lenvatinib with an murine anti-PD-1 mAb in murine tumor isograft models. Several models (RCC, NSCLC, HCC and CRC) were investigated. Lenvatinib monotherapy and lenvatinib in combination with anti-PD-1 mAb showed inhibition of tumor growth, however, the antitumor activity of the combination of lenvatinib and anti-PD-1 mAb was only slightly greater than that of lenvatinib monotherapy in every

model investigated. Severe BWL (>20% compared to Day 1) was not observed during the dosing period (Days 1 to 28) in any of the treatment groups and tumor model.

In the CT26 murine tumor isograft models (Colon-CA), lenvatinib demonstrated greater antitumor activity in immunocompetent mice, including tumor regressions, than in athymic mice (data not shown).

Flow cytometric analysis showed that the TAM population in the TME was significantly decreased while the populations of IFN-γ+CD8+ T cells and GzmB+CD8+ T cells (activated cytotoxic T cells) in the TME were significantly increased following treatment with lenvatinib or combination of lenvatinib plus anti-PD-1 mAb in the CT26 isograft model. These new in vivo pharmacodynamics study results suggest that the immunomodulatory activity of lenvatinib in immunocompetent models involves the decrease of immunosuppressive TAMs and the increase of activated cytotoxic T cells in the TME. However, these experiments could not convincingly demonstrate an additive effect of ant-PD-1 treatment to the lenvatinib monotherapy.

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

2.2.2. Conclusion on the non-clinical aspects

The antitumor activity of the combination was greater than either monotherapy in all 4 murine isograft models tested, however the difference to lenvatinib monotherapy was not striking.

Nevertheless, the previously established antiangiogenic activity of lenvatinib resulting from the inhibition of VEGFR and FGFR signalling and its immunomodulatory activity with a different mode of action from a PD-1 immune checkpoint inhibitor (decrease of TAMs, increase of activated cytotoxic T cells and activation of IFN-γ signalling) could indeed lead to an additive effect of both components in RCC.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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 (Status)	Indication	Number of Study Centers (Locations)	Study Start[a]/ Data Cutoff	Study Design	Study Treatment: Dose, Route, & Regimen	Number of Subjects Treated/ Ongoing (No. on Treatment at Data Cutoff)	Relevant Data for This Application
E7080-G000-307/ **KEYNOTE-581**	Treatment-naïve advanced RCC	200 sites in North America, Europe, Asia, and Australia	13 Oct 2016/ 28 Aug 2020	Phase 3, open-label, multicenter, randomized; stratified by	Arm A: LENV 18 mg, PO, QD plus EVER 5 mg PO, QD	Final PFS analysis: 1047/321	Final PFS analysis: Approximately 582 PFS events (as determined by IIR)

Study ID (Status)	Indication	Number of Study Centers (Locations)	Study Start[a]/ Data Cutoff	Study Design	Study Treatment: Dose, Route, & Regimen	Number of Subjects Treated/ Ongoing (No. on Treatment at Data Cutoff)	Relevant Data for This Application
(Ongoing)				geographic region and MSKCC prognostic groups	**Arm B: LENV 20 mg, PO, QD plus PEMBRO 200 mg, IV, Q3W** **Arm C: SUNI 50 mg, PO, QD, 4 weeks on treatment followed by 2 weeks off (Schedule 4/2)**		among the 2 treatment groups (LENV plus PEMBRO and SUNI) and at least 388 events between each comparison
E7080-G000-205 (Completed)	Unresectable advanced or metastatic RCC following 1 prior VEGF-targeted treatment	37 sites in Czech Republic, Poland, Spain, United Kingdom, and United States	12 Aug 2010/ 13 Jun 2014[b]	Phase 1b/2, open-label, multicenter with Treatment and Extension Phases. Phase 1b: dose escalation in sequential cohorts to determine MTD and RP2D Phase 2: randomized (1:1:1); stratified by hemoglobin level and corrected serum calcium	Phase 1b: LENV 12 mg, 18 mg, or 24 mg + EVER 5 mg, QD Phase 2: LENV 18 mg + EVER 5 mg, PO, QD LENV 24 mg, PO QD; EVER 10 mg, PO, QD Continuous, 28-day cycles	Phase 1b: 20/0 Phase 2: 153/23	Phase 2 cohorts receiving monotherapy LENV 24 mg, PO QD (52 subjects). EVER 10 mg, PO, QD (50 subjects)
KEYNOTE-427 (Ongoing)	1st-line treatment of advanced/ metastatic RCC (Cohort A: clear-cell RCC; Cohort B: non-clear-cell RCC)	47 sites in Canada, Czech Republic, Denmark, Germany, Poland, Russia, Spain, South Korea, United Kingdom, and United States	04 Oct 2016/ 24 Feb 2020	Phase 2, open-label, multicenter, global study	PEMBRO 200 mg, IV, Q3W	Cohort A: 110/0	110 subjects with clear-cell RCC

DCO = data cut-off, EVER = everolimus, IIR = independent imaging review, IV = intravenous, LENV = lenvatinib, MSKCC = Memorial Sloan Kettering Cancer Center, MTD = maximum tolerated dose, PEMBRO = pembrolizumab, PFS = progression-free survival, PO = orally, QD = once daily, Q3W = every 3 weeks, RCC = renal cell carcinoma, RP2D = recommended Phase 2 dose, SUNI = sunitinib, VEGF = vascular endothelial growth factor.

a: Clinical start date is date of the first subject's signed informed consent.

b: Study 205 safety update report (DCO of 08 Feb 2018) is also available for the subjects who remained on treatment at the time of the DCO for the primary efficacy analysis.

2.3.2. Pharmacokinetics

The current submission concerns the extension of the indication for pembrolizumab in combination with lenvatinib for the treatment of subjects with advanced renal cell carcinoma (RCC). Pembrolizumab (200 mg Q3W) is approved in combination with axitinib for the treatment of advanced RCC. Pembrolizumab 400 mg Q6W was approved for combination therapies during this procedure. Lenvatinib (12 mg QD) is approved as monotherapy in patients with advanced HCC and lenvatinib (24 md QD) is approved as monotherapy for advanced thyroid carcinoma (DTC) and Lenvatinib (18 mg QD) is approved in combination with everolimus (RCC).

The basis of this submission is study KEYNOTE-581, an open-label, randomized, phase 3 trial to compare the efficacy and safety of Lenvatinib in Combination With Everolimus or Pembrolizumab Versus Sunitinib Alone in First-Line Treatment of Subjects With Advanced Renal Cell Carcinoma (CLEAR). Pembrolizumab and lenvatinib pharmacokinetics from study KEYNOTE-581 were analysed and compared with historical pharmacokinetic monotherapy data. PopPK analyses were performed for pembrolizumab and lenvatinib, adding data into the existing popPK models for each drug with the combination effect added as a

covariate, respectively. Pembrolizumab immunogenicity data are also presented from study KEYNOTE-581.

The clinical pharmacology of pembrolizumab and lenvatinib have been described in previously submitted clinical pharmacology packages and included single- and multiple-dose pharmacokinetic parameters, drug-drug interaction potential, pharmacodynamics, QT prolongation potential, popPK analyses for the various tumour indications and exposure-response analyses.

Bioanalytical methods

The pharmacokinetic samples from subjects in study KEYNOTE-581 were analysed by the same validated assays as used in previous applications. Validated bioanalytical methods are available for determining (1) serum concentrations of pembrolizumab; (2) anti-MK-3475 antibodies; and (3) neutralizing antibodies. Different generations of bioanalytical methods for the determination of pembrolizumab serum concentrations were used at different CROs. Population PK analysis has demonstrated that they are comparable where relevant.

Absorption, Distribution, Elimination

No new Absorption, Distribution and Elimination data have been submitted in this application

Special populations

Pharmacokinetic Analysis of Pembrolizumab in Subjects with Advanced Renal Cell Carcinoma in Combination with Lenvatinib

Observed concentration of pembrolizumab from Study 307 Arm B was compared graphically with historical pembrolizumab monotherapy reference existing data at the same dose level from completed studies. Using a dataset with sample size of 2993 participants administered with pembrolizumab monotherapy, a time-dependent PK model was created to describe the PK profile.

Table 1 Overview of Pembrolizumab Cohorts Included in Eisai 307 / KEYNOTE- 581 PK Analysis

Cohort	Treatment	Cancer Type	Number of subjects providing PK [a]	Last PK sample date
Arm B	lenvatinib 20 mg (orally, once daily) + 200 mg pembrolizumab Q3W	RCC	331	03-Jul-2020

[a] unique subjects providing PK samples, not all subjects have Cycle 1 day 1 samples.
RCC = renal cell carcinoma

Data Source – 05NHKJ: adpcpem

Summary statistics of the observed pembrolizumab trough (pre-dose) and post-dose concentrations in RCC subjects from KN-581 are presented in the table below

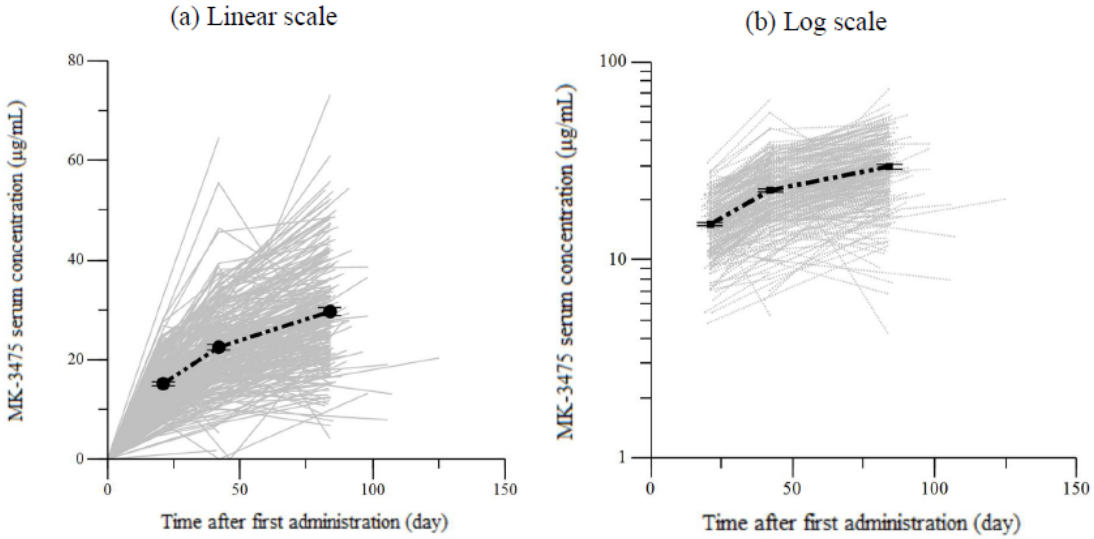
Table 2 Summary Statistics of Pembrolizumab Predose (Ctrough) and Postdose (Cmax) Serum Concentration Values Following Administration of Multiple I.V. Doses of 200 mg Q3W Pembrolizumab in Combination with Lenvatinib in Eisai Study 307 / KEYNOTE-581 Subjects.

Cycle	NOMTAFD (day)	N	GM (%CV)	GM (SD)	AM (SD)	Min	Median	Max
			(µg/mL)					
Predose (C_{trough})								
Cycle 2 (Week 3)	21.0	234	14.3 (34.8)	14.3 (4.9)	15.2 (4.9)	4.78	14.7	31.0
Cycle 3 (Week 6)	42.0	258			22.5 (8.5)	0.00	21.7	64.5
Cycle 5 (Week 12)	84	243	27.5 (42.7)	27.5 (11)	29.6 (11)	4.18	28.5	73.1
Postdose (C_{max})								
Cycle 1 (Week 0)	0.0210	236	65.6 (27.6)	65.6 (19.5)	68.1 (19.5)	30.0	65.5	192
Cycle 2 (Week 3)	21.021	203	85.0 (25.9)	85.0 (24.1)	87.9 (24.1)	47.6	82.5	214

NOMTAFD = Nominal time after first pembrolizumab administration;
GM = Geometric Mean; CV% = Geometric Coefficient of Variation;
SD = Standard Deviation; AM = Arithmetic Mean;
Results reported for time points with N > 3.

Data Source – 05NHKJ: adpcpem

The following figures show the individual and mean pre-dose concentration-time profiles:



Note: Grey lines represent individual concentration observations. Black dashed lines represent arithmetic mean concentrations and error bars are associated +/- SE. Actual times were used for this analysis.

Data Source – 05NHKJ: adpcpem

Figure 6 Individual and Arithmetic Mean Predose Serum Concentrations of Pembrolizumab Following Administration of Multiple I.V. Doses of 200 mg Q3W Pembrolizumab in Combination with Lenvatinib in Eisai Study 307 / KEYNOTE-581 Subjects (a) Linear scale, (b) Log scale

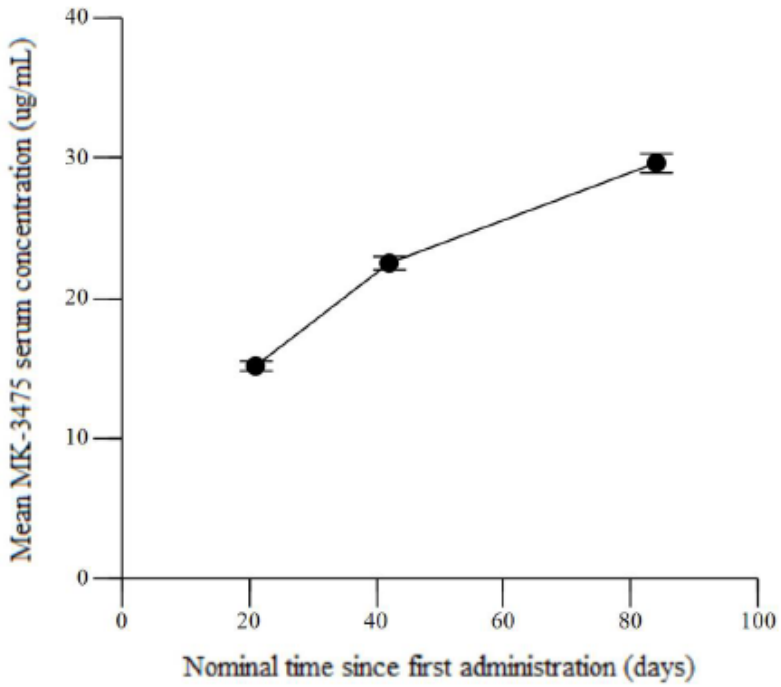


Figure 7 Arithmetic Mean (±SE) Predose Serum Concentrations of Pembrolizumab Following Multiple 200 mg Q3W I.V. Administrations in Combination with Lenvatinib to Subjects in Eisai Study 307 / KEYNOTE-581, Linear scale

Observed pembrolizumab concentration data in Study 307 Arm B are overlaid on the simulated profile using the reference model as shown in Figure 8.

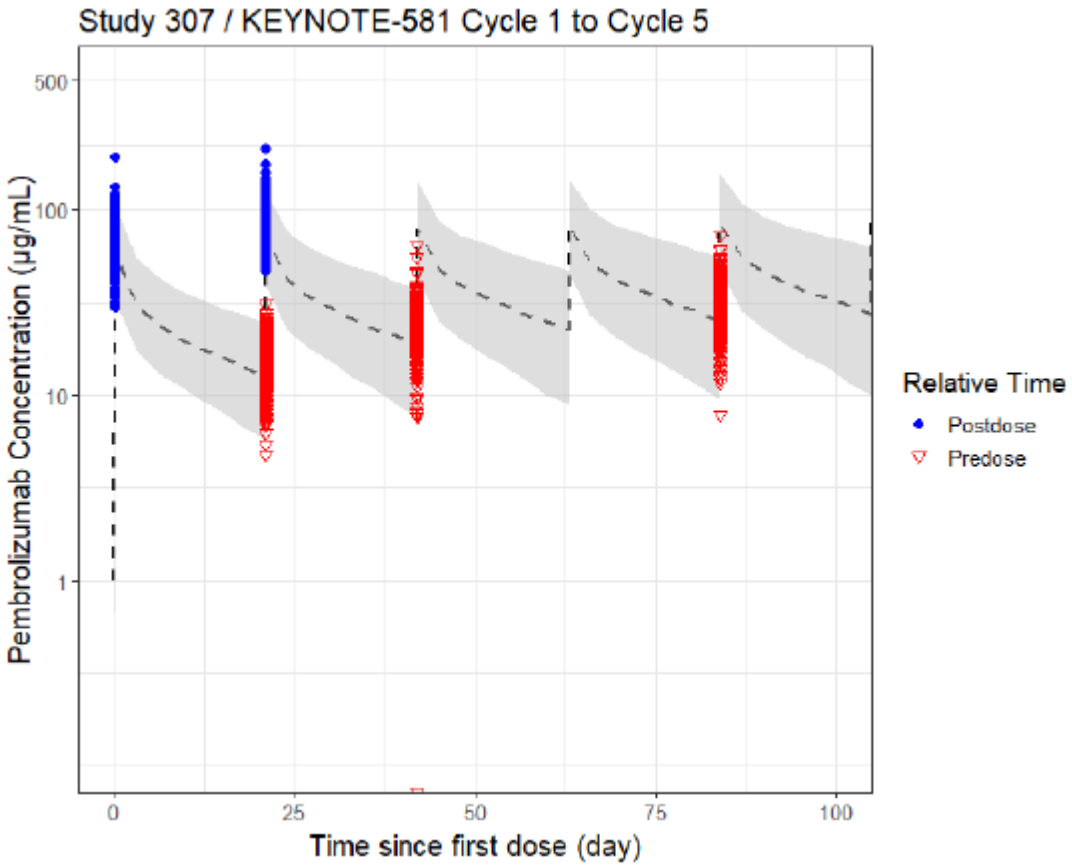


Figure 8 Observed Pembrolizumab Concentration Data in Study 307 with Subjects Receiving 200 mg Q3W Pembrolizumab in Combination with 20 mg QD Lenvatinib with Reference Model-Predicte Pharmacokinetic Profile for Pembrolizumab 200 mg Q3W Dos Regimen (Log-Linear Scale)

Symbols are individual observed data (nominal time) from Study 307 200 mg Q3W subjects; black line is median predicted concentrations from the model for a regimen of 200 mg Q3W and the grey shaded area represents the 90% prediction interval.

Population Pharmacokinetic of Lenvatinib and Pharmacokinetic /Pharmacodynamic Analysis of Safety in Subjects with Advanced Renal Cell Carcinoma in Combination with Pembrolizumab

Population PK analysis of lenvatinib was based on pooled PK data from the 21 studies, including Study 307 in RCC subjects. In the previous PK analysis (CPMS-E7080-013R), lenvatinib PK´was best described by a 3-compartment model with simultaneous first and zero order absorption and linear elimination from the central compartment parameterized for apparent total clearance following 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, DTC, 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.

The final 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 relative bioavailability (F1rel) for capsule formulation compared to tablet. The model included body weight as an allometric constant on clearances and volume parameters, albumin < 30 g/L and ALP > ULN on CL/F and CYP3A4 inhibitors on CL/F. In addition to the above, population effects on lenvatinib CL/F for RCC and HCC subjects and for healthy subjects were determined and included in the model. Finally, the effects of DTC and dosing (categorical) and exposure levels (AUC) of concomitant everolimus and concomitant pembrolizumab (categorical) were tested on lenvatinib CL/F. In these cases none was found to be significant. Population PK parameter estimates from the final model are presented in Table 3.

Table 3 Population Pharmacokinetic Parameter Estimates of Lenvatinib

Parameter	NONMEM Estimates		
	Point Estimate	%RSE	95% Confidence Interval
$CL/F\ [L/h] = \Theta_{CL} * (WGT/74.7)^{0.75} * \Theta_{INHIB}^{INHIB} * \Theta_{ALP}^{ALP} * \Theta_{ALB}^{ALB} * \Theta_{HV}^{HV} * \Theta_{HCC}^{HCC} * \Theta_{RCC}^{RCC}$			
Basal CL/F in L/h [Θ_{CL}]	6.28	1.47	6.10 – 6.46
Effect of inhibitors on CL/F [Θ_{INHIB}]	0.896 Fixed	–	–
Effect of ALP (>ULN) on CL/F [Θ_{ALP}]	0.930	0.776	0.916 – 0.944
Effect of ALB (<30 g/L) on CL/F [Θ_{ALB}]	0.860	1.99	0.826 – 0.894
Effect of healthy subjects on CL/F [Θ_{HV}]	1.19 Fixed	–	–
Effect of HCC population on CL/F [Θ_{HCC}]	0.873	2.36	0.833 – 0.913

Parameter	NONMEM Estimates		
	Point Estimate	%RSE	95% Confidence Interval
Effect of RCC population on CL/F [Θ_{RCC}]	0.854	1.77	0.824 – 0.884
V1/F [L] = Θ_{V1}*WGT/74.7			
Basal V1/F in L [Θ_{V1}]	47.7	1.57	46.2 – 49.2
V2/F [L] = Θ_{V2}*WGT/74.7			
Basal V2/F in L [Θ_{V2}]	22.9	4.10	21.1 – 24.7
V3/F [L] = Θ_{V3}*WGT/74.7			
Basal V3/F in L [Θ_{V3}]	30.9 Fixed	–	–
Q1/F [L/h] = Θ_{Q1}*(WGT/74.7)$^{0.75}$			
Basal Q1/F in L/h [Θ_{Q1}]	3.50	2.56	3.32 – 3.63
Q2/F [L/h] = Θ_{Q2}*(WGT/74.7)$^{0.75}$			
Basal Q2/F in L/h [Θ_{Q2}]	0.840	3.00	0.791 – 0.889
Ka [1/h] = Θ_{Ka}			
Basal Ka in 1/h [Θ_{Ka}]	0.803 Fixed	–	–
D1 [h] = Θ_{D1}			
Basal D1 in h [Θ_{D1}]	1.27 Fixed	–	–
F1 = Θ_{F1}			
Relative bioavailability of capsule vs tablet formulation [Θ_{F1}]	0.882 Fixed	–	–
Inter-individual variability (%CV)			
CL/F	34.2	3.20	–
V1/F	41.4	4.56	–
V2/F	67.3	9.25	–
V3/F	69.9	8.18	–
Ka	100	5.14	–
D1	35.4	8.16	–
Residual variability			
Proportional (%CV) (Clin pharm studies)	17.4	0.768	–
Proportional (%CV) (Patients studies)	40.9	1.07	–
Proportional (%CV) (TAD ≤ 2 h)	45.4	3.01	–
Additional (ng/mL) (TAD ≤ 2 h)	21.9	0.825	–

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 total clearance following oral administration, 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)

The RCC population was found to have a ***14.6% lower lenvatinib CL/F compared*** with patients with DTC and other cancer types excluding HCC.

The magnitude of each effect is within the intersubject variability for CL/F (%CV = 34.2 %).

Individual lenvatinib CL/F and AUC for RCC subjects receiving lenvatinib 20 mg in combination with pembrolizumab (Arm B) in Study 307 are summarized below. The median values and range of parameter values are comparable with CL/F and AUC dose-normalized to 20 mg in subjects with RCC who received lenvatinib monotherapy in Study 205 confirming the non-clinically relevant effect of pembrolizumab co-administration on lenvatinib exposure.

Table 4 Summary of Individual Model-Predicted Lenvatinib Pharmacokinetic Parameters in RCC Subjects of Lenvatinib + Pembrolizumab Arm (Arm B) in Study 307

Starting Dose	Parameter (unit)	N	Mean	SD	Median	Min	Max
20 mg	CL/F (L/h)	346	6.03	2.22	5.89	1.79	14.17
20 mg	AUC (ng•h/mL)	346	3374.3	1396.1	2995.8	1244.6	9867.1

AUC = area under the concentration × time curve, CL/F = apparent total clearance following oral administration, RCC – renal cell carcinoma
Source: Table 13 of CPMS-E7080-012R-LP

Table 5 Summary of Individual Model-Predicted Lenvatinib CL/F and AUC Dose Normalized to 20 mg in Subjects with RCC Received Lenvatinib Monotherapy

Tumor type	Parameter (unit)	N	Mean	SD	Median	Min	Max
RCC (Study 205)	CL/F (L/h)	48	6.31	1.9	6.15	2.78	11.6
	Dose-normalized (20 mg) AUC (ng•h/mL)	48	3080.0	1034.0	2867.3	1520.5	6354.2

AUC = area under the concentration × time curve, CL/F = apparent total clearance following oral administration, RCC – renal cell carcinoma

Pharmacokinetic interaction studies

Based on the existing robust characterization of pembrolizumab PK, a comparison was conducted between the observed PK of pembrolizumab for the current indication (RCC) in combination with lenvatinib and the predictions from the reference PK model developed with pembrolizumab monotherapy data (KEYNOTE-001, -002, -006, -010, and -024).

DDI between pembrolizumab and lenvatinib are unlikely, considering the divergent metabolic pathways for both compounds.

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.

Primary and secondary pharmacology

Immunogenicity

The existing immunogenicity assessment for pembrolizumab for the monotherapy setting is based on a sufficiently large dataset of patients across several indications, with very low observed rates of total treatment emergent ADA (1.4 - 3.8%) as well as of neutralizing antibodies (0.4 – 1.6%). This analysis has not demonstrated impact on efficacy or safety, as currently summarized in EU SmPC. This low rate of immunogenicity has been shown to be consistent across tumor type and no clinical consequences have been observed in the subjects with a positive immunogenicity reading.

Immunogenicity evaluation for study KEYNOTE-581

The incidence rate of anti-drug antibodies of pembrolizumab in combination with lenvatinib in Study 307 Arm B was summarized and compared with historical rates from monotherapy.

The observed incidence of treatment-emergent anti-drug antibodies in evaluable subjects based on a pooled analysis (pembrolizumab combination therapy) in subjects with advanced RCC is 0.3% (1 out of 314), based on 1 subject with treatment-emergent positive, no subjects with non-treatment emergent positive, and 313 with negative immunogenicity status. The treatment-emergent positive subject had no antibodies with neutralizing capacity.

Table 6 Summary of Subject Immunogenicity Results after Pembrolizumab Combination Therapy, 200 mg Pembrolizumab Q3W, in Combination with Lenvatinib in Study 307, Arm B

Immunogenicity status	Total
Assessable subjects[a]	332
Inconclusive subjects[b]	18
Evaluable subjects[c]	314
Negative[d]	313 (99.7%)
Non-Treatment emergent positive[d]	0
Neutralizing negative	0
Neutralizing positive	0
Treatment emergent positive[d]	1 (0.3%)
Neutralizing negative	1 (0.3%)
Neutralizing positive	0

Q3W = every 3 weeks
a. Included are subjects with at least one ADA sample available after treatment with pembrolizumab
b. Inconclusive subjects are the number of subjects with no positive ADA samples present and the drug concentration in the last sample above the drug tolerance level.
c. Evaluable subjects are the total number of negative and positive subjects (non-treatment emergent and treatment emergent.
d. Denominator was total number of evaluable subjects.
Source: Table 2 of HOPE307-PembroADA

2.3.4. PK/PD modelling

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

Population PK analysis of lenvatinib was based on PK data from the 21 studies, including study 307 in RCC subjects. Exposure-response analysis for AEs was based on data from Arm B of study 307.

Objectives

The objectives of the population pharmacokinetics (PK) analysis of lenvatinib were to characterize the PK of lenvatinib in subjects with RCC when administered alone and concomitantly with either everolimus or pembrolizumab and compare to that in healthy subjects and subjects with other types of cancer (mainly DTC and HCC) on pooled data from several studies including Study 307.

The objectives of the PK/PD analysis for safety of combination therapy of lenvatinib and pembrolizumab in subjects with RCC were to explore the relationship of lenvatinib exposure with the occurrence of adverse events (AEs) related to only lenvatinib in subjects with RCC, which were previously specified to include hypertension, proteinuria, weight decreased, vomiting and hypothyroidism (Arm B of study 307).

The PK/PD safety analysis included data from RCC subjects from the lenvatinib and pembrolizumab combination arm from study 307. Across the lenvatinib program, including this study, safety was assessed by evaluation of adverse events (AE), clinical laboratory tests (biochemistry and hematology), urinalysis, vital signs, physical examinations, electrocardiograms (ECG), echocardiograms and other examinations as clinically indicated.

Where possible AEs recorded throughout the treatment were graded on the five-point scale according to NCI Common Toxicity Criteria (CTC) version 4.0 or higher. AEs for hypertension, proteinuria, weight decrease, vomiting and hypothyroidism were analysed to examine their relationships with lenvatinib exposure.

Baseline and covariates

Table 7 Summary of Demographics and Covariates for RCC Subjects Included in the Population PK Analysis of Lenvatinib from Study 307/Arms A & B (N=699)

Demographic (unit)	Mean (SD)	Median	Range (Min-Max)
Age (years)	62.0 (10.6)	63.0	32 – 88
Weight (kg)	79.9 (18.5)	79.1	37 – 158
Albumin (g/L)	43.6 (4.3)	44.0	20 -55
ALP (IU/L)	94.8 (56.2)	82.0	29 – 696
ALT (IU/L)	19.8 (11.8)	17.0	3 – 128
AST (IU/L)	19.2 (7.9)	18.0	4 – 70
Bilirubin (umol/L)	7.8 (4.9)	7.0	2 – 76
Creatinine clearance (mL/min)	74.7 (27.3)	69.8	28 – 192
Gender	Male=512, Female=187		
ECOG performance status	0=572, 1=126, Missing=1		
Concomitant CYP3A4 inducers [a)]	Yes=2, No=697		
Concomitant CYP3A4 inhibitors [a)]	Yes=9, No=690		
Concomitant everolimus [a)]	Yes=352, No=347		
Concomitant pembrolizumab [a)]	Yes=347, No=352		
Formulation	Capsule=699		

a)Yes or No was decided based on during study visit

The PK/PD analysis for TEAEs included 347 subjects with RCC from study 307/Arm B.

Results

With the exception of hypothyroidism and to a smaller extent proteinuria, there was a generally weak, albeit positive relationship of TEAEs and lenvatinib AUC, with the 95% Cis for the exposure logit parameter including 0. For example, for hypothyroidism the probability of any Grade (1 to 3) increased from 56 to 75% across the exposure quantiles (table below). Proteinuria increased from 19% to 30% across the same lenvatinib concentration range.

Table 8 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 (2150 ng·h/mL)	0.442	0.191	0.269	0.373	0.563
Q2 (2700 ng·h/mL)	0.469	0.219	0.285	0.391	0.623
Q3 (3500 ng·h/mL)	0.496	0.250	0.302	0.410	0.681
Q4 (5000 ng·h/mL)	0.533	0.298	0.326	0.436	0.752

Age was associated with a decreased odd ratio of hypothyroidism 0.59 for subjects <65 years old. Proteinuria was weakly associated with a lower ECOG score, with an odds ratio of 0.45. At baseline, Japanese subjects were associated with a 2.5 higher odds ratio of proteinuria and hypothyroidism.

2.3.5. Discussion on clinical pharmacology

Clinical pharmacology results for the combination therapy of pembrolizumab together with lenvatinib specific to support approval for first line treatment of advanced or metastatic renal cell carcinoma (RCC), are available from the pivotal study KEYNOTE-581.

A substantial characterization of the key clinical pharmacology and immunogenicity findings of pembrolizumab as monotherapy have been provided in previous submissions.

Based on the existing robust characterization of pembrolizumab PK, a comparison was conducted between the observed PK of pembrolizumab for the current indication (RCC) in combination with lenvatinib and the predictions from the reference PK model developed with pembrolizumab monotherapy data (KEYNOTE-001, -002, -006, -010, and -024).

Pre-dose pembrolizumab serum concentrations (Ctrough) were obtained within 24 hours prior to dosing at cycles 1, 2, 3, 5 and during the off-treatment visit after pembrolizumab discontinuation. Post-dose serum concentrations (Cmax) were drawn within approximately 30 minutes after the end of the infusion in cycle 1 and cycle 2.

The observed concentrations in RCC patients treated with pembrolizumab in combination with lenvatinib generally fall within the range of predicted concentrations, both after first dose and at steady state, although some low concentrations do not fall in the 90% PI.

The MAH provided a direct comparison of the observed PK data (trough and peak concentrations at cycle1) with those obtained with the 200 mg Q3W flat dose for other tumor types in the monotherapy setting supporting the consistency among exposure obtained in monotherapy with those obtained in combination therapy.

Treatment comparison for lenvatinib PK parameters showed that median lenvatinib plasma concentration-time profiles were comparable when lenvatinib was administered alone and with pembrolizumab. Concomitant pembrolizumab dosing did not affect lenvatinib PK, and exposures of pembrolizumab were not impacted in the presence of lenvatinib when the 2 drugs were administered as a combination therapy.

The existing immunogenicity assessment for pembrolizumab for the monotherapy setting is based on a sufficiently large dataset of patients across several indications, with very low observed rates of total treatment emergent ADA (1.4 - 3.8%) as well as of neutralizing antibodies (0.4 – 1.6%).

For pembrolizumab combination therapy (200 mg pembrolizumab Q3W + 20 mg lenvatinib QD), ADA samples were available from 332 subjects (314 subjects were included in the final immunogenicity assessment).

The incidence of treatment-emergent ADA to pembrolizumab in subjects with RCC treated with pembrolizumab in combination with lenvatinib was ~0.3% (1 out of 314 total evaluable samples).

2.3.6. Conclusions on clinical pharmacology

The updated lenvatinib PK profile containing data from Study 307/KEYNOTE-581 is consistent with the current population PK profile of lenvatinib. The observed concentration from KEYNOTE-581 fall within the 90% CI of the model predicted median concentration.

The incidences of treatment emergent ADA is negligible when pembrolizumab is combined with lenvatinib which is consistent with the low immunogenicity incidence after pembrolizumab monotherapy of prior immunogenicity evaluations.

2.4. Clinical efficacy

2.4.1. Dose response studies

Study KEYNOTE 146 (E7080 A001 111) is an ongoing, open-label Phase 1b/2 study evaluating the safety and efficacy of lenvatinib plus pembrolizumab in subjects with selected metastatic solid tumor types, including endometrial carcinoma, non-small cell lung cancer, RCC, urothelial carcinoma, squamous cell carcinoma of the head and neck, and melanoma. The primary objective of the Phase 1b part of the study was to determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) for lenvatinib to be used in combination with pembrolizumab 200 mg Q3W (treatment dosage for all currently approved indications).

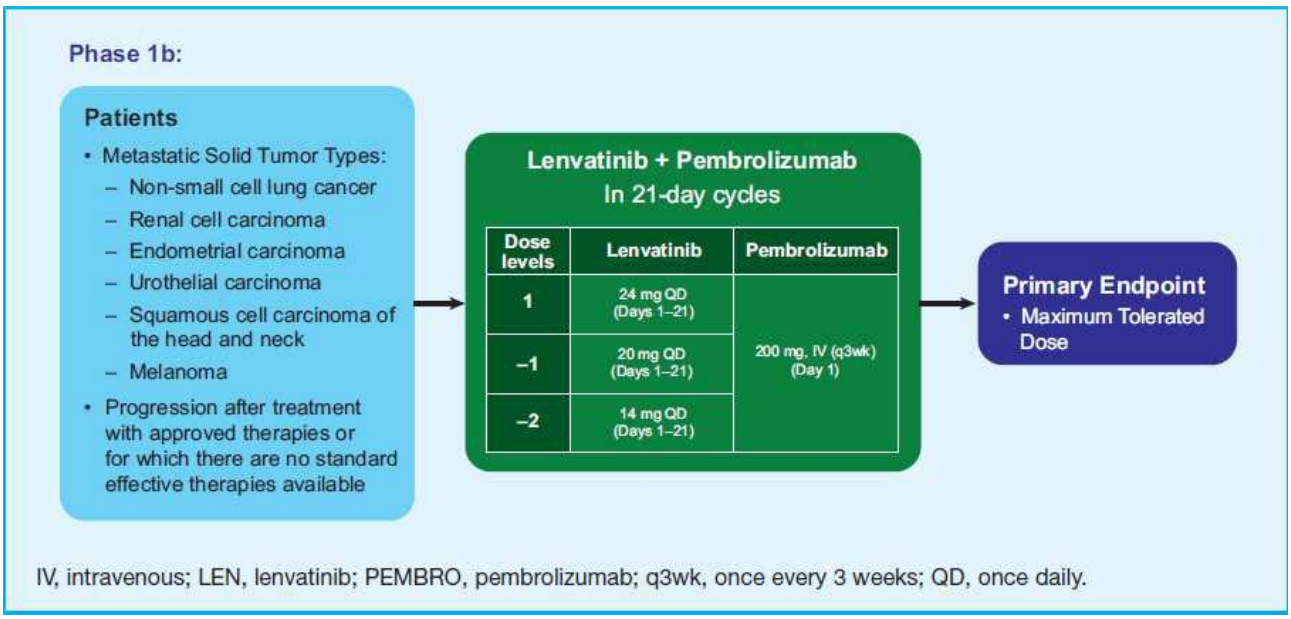


Figure 9 Study design Keynote 146

The MTD for lenvatinib was investigated in the Phase 1b dose-finding portion of the study using a dose de-escalation strategy with a 3 + 3 design. The pembrolizumab dosage was held constant at 200 mg intravenously (IV) Q3W. The initial dosage for lenvatinib was 24 mg/day (currently approved starting dosage as monotherapy in differentiated thyroid carcinoma), administered orally (PO). If none of the 3 subjects in a cohort experienced a dose-limiting toxicity (DLT), the cohort would be expanded with 7 additional subjects for confirmation of the MTD. If 1 of 3 subjects in a cohort experienced a DLT, 3 additional subjects would be added to the cohort. If 2 or 3 subjects experienced a DLT in a cohort, the subsequent cohort would evaluate 3 subjects at the next lowest dose level (ie, lenvatinib 20 mg/day). If the lenvatinib 20 mg/day dose level was not tolerated, a further dose de-escalation cohort of lenvatinib 14 mg/day would follow (Taylor et al. 2020).

Three subjects were enrolled in the lenvatinib 24 mg/day + pembrolizumab 200 mg dose level. There were 2 DLTs at this dose level (1 subject with Grade 3 arthralgia and another subject with Grade 3 fatigue) during Cycle 1. Ten patients were subsequently enrolled in the lenvatinib 20 mg/day + pembrolizumab 200 mg dose level. No DLTs were reported in this dose level. The MTD (and RP2D) for the combination was determined to be lenvatinib 20 mg/day + pembrolizumab 200 mg once every 3 weeks and this dose was used in Phase 2 of Keynote-146 and Keynote-581.

The RP2D was evaluated for efficacy and safety in the Phase 2 portion. Efficacy data for the first 30 subjects with RCC treated with zero to 5 prior therapies, revealed that the ORR was 70% (95% CI: 50.6, 85.3; per immune related RECIST 1.1 by investigator assessment; Taylor, et al., 2020). These efficacy data showed significant tumor reduction with durable responses in treatment naïve and previously treated subjects. Moreover, adverse events (AEs) were manageable with dose interruptions and dose reductions. Lenvatinib 20 mg QD (starting dosage) plus pembrolizumab 200 mg Q3W were the dosages used in Study 307, and have been implemented as the recommended starting dosages across the program.

The 200 mg Q3W dose is currently recommended for all the approved indications of pembrolizumab (as monotherapy or in combination with chemotherapy) and is being evaluated in multiple clinical studies.

2.4.2. Main study

Title of Study

KEYNOTE 581: *A Multicenter, Open-label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination with Everolimus or Pembrolizumab Versus Sunitinib Alone in First-Line Treatment of Subjects with Advanced Renal Cell Carcinoma (CLEAR).*

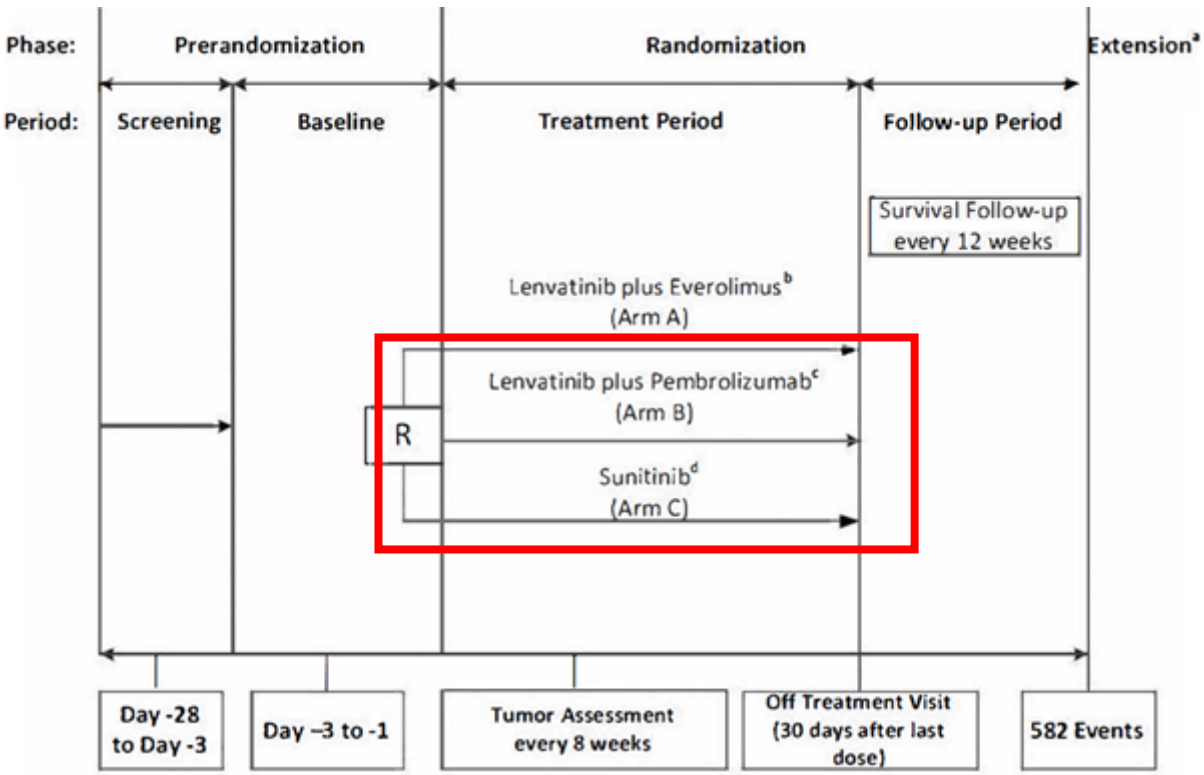


Figure 10 Study Design for Study 307 (KEYNOTE 581)

Methods

Study participants

Key inclusion criteria were:

- Histological or cytological confirmation of RCC with a clear-cell component (original tissue diagnosis of RCC is acceptable).
- Documented evidence of advanced RCC.
- At least 1 measurable target lesion according to RECIST 1.1 meeting the following criteria:
    - Lymph node (LN) lesion that measures at least 1 dimension as ≥1.5 cm in the short axis
    - Non-nodal lesion that measures ≥1.0 cm in the longest diameter
    - The lesion is suitable for repeat measurement using computed tomography/magnetic resonance imaging (CT/MRI). Lesions that have had external beam radiotherapy (EBRT) or locoregional therapy must show radiographic evidence of disease progression based on RECIST 1.1 to be deemed a target lesion.
- Karnofsky Performance Status (KPS) of ≥70.
- Adequate organ function.

Key exclusion criteria were:

- Prior systemic anticancer therapy for RCC (including VEGF/VEGFR or any systemic investigational agent).
    - Prior adjuvant treatment with an investigational anticancer agent is not allowed unless the investigator can provide evidence of subject's randomization to placebo arm.
- Subjects with central nervous system (CNS) metastases were not eligible, unless they have completed local therapy (eg, whole brain radiation therapy [WBRT], surgery or radiosurgery) and have discontinued the use of corticosteroids for this indication for at least 4 weeks before starting treatment in this study. Any signs (eg, radiologic) or symptoms of CNS metastases must be stable for at least 4 weeks before starting study treatment.
- Active malignancy (except for RCC, definitively treated basal or squamous cell carcinoma of the skin, and carcinoma in-situ of the cervix or bladder) within the past 24 months.
- Prior radiation therapy within 21 days prior to start of study treatment with the exception of palliative radiotherapy to bone lesions
- Prolongation of QTc interval to >480 ms.
- Bleeding or thrombotic disorders or subjects at risk for severe hemorrhage.
- Clinically significant hemoptysis or tumor bleeding within 2 weeks prior to the first dose of study drug.
- Significant cardiovascular impairment within 12 months of the first dose of study drug
- Active infection (any infection requiring systemic treatment).

- Known history of, or any evidence of, interstitial lung disease.
- Subjects with a diagnosis of immunodeficiency or who are receiving chronic systemic steroid therapy (doses exceeding 10 mg/day of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment. Physiologic doses of corticosteroids (up to 10 mg/day of prednisone or equivalent) may be used during the study.
- Active autoimmune disease (with the exception of psoriasis) that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs).
- Subject has had an allogenic tissue/solid organ transplant.

Treatments

Combination lenvatinib plus everolimus (Arm A): Lenvatinib 18 mg PO QD was given with everolimus 5 mg PO QD in each 21-day cycle

Combination lenvatinib plus pembrolizumab (Arm B): Lenvatinib 20 mg PO QD was given with pembrolizumab 200 mg IV Q3W during each 21-day cycle.

Sunitinib (Arm C): Sunitinib 50 mg PO QD was given for 4 weeks on treatment followed by 2 weeks off (Schedule 4/2).

Subjects could receive study treatment until independent imaging review (IIR) confirmed disease progression (PD), development of unacceptable toxicity, withdrawal of consent, or sponsor termination of the study. Disease progression was to be confirmed by IIR prior to the investigator discontinuing study treatment for a subject. In the case that RECIST 1.1 defined PD was confirmed by IIR, continuation of study treatment was permitted if the investigator considered that there was clinical benefit and the subject was tolerating study drug. Pembrolizumab was continued for a maximum of 24 months, treatment with lenvatinib could be continued beyond 24 months.

Objectives

Primary Objective

• To demonstrate that lenvatinib in combination with everolimus (Arm A) or pembrolizumab (Arm B) is superior compared with sunitinib alone (Arm C) in improving PFS by IIR using RECIST 1.1 as first-line treatment in subjects with advanced RCC.

Secondary Objectives

• To compare OS of subjects treated with lenvatinib in combination with everolimus or pembrolizumab versus sunitinib.

• To compare ORR by IIR using RECIST 1.1 of subjects treated with lenvatinib in combination with everolimus or pembrolizumab versus sunitinib.

• To compare safety and tolerability of treatment with lenvatinib in combination with everolimus or pembrolizumab versus sunitinib, including the assessment of the proportion of subjects who discontinued treatment due to toxicity and time to treatment failure due to toxicity.

• To compare the impact of treatment on Health-Related Quality of Life (HRQoL) as assessed by using the Functional Assessment of Cancer Therapy Kidney Symptom Index- Disease-Related Symptoms (FKSI-DRS), the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-30), and the European Quality of Life 5 Dimension 3 Level Version (EuroQOL EQ-5D-3L) instruments for subjects treated with lenvatinib in combination with everolimus or pembrolizumab versus sunitinib.

• To assess PFS on next-line of therapy (PFS2) as reported by investigator.

• To assess PFS based on investigator assessment per RECIST 1.1.

• To characterize the population PK of lenvatinib when coadministered with everolimus or pembrolizumab.

• To compare the PK of pembrolizumab from this study to historical data.

• To characterize the population PK of everolimus when coadministered with lenvatinib.

• To assess the PK/pharmacodynamic relationship between exposure and efficacy/biomarkers/safety, if possible, using a mechanistic approach.

Exploratory Objectives

• To compare ORR by investigator assessment using RECIST 1.1.

• To assess the duration of response (DOR) by IIR and investigator assessment using RECIST 1.1 for subjects in all treatment arms.

• To compare the disease control rate (DCR) (complete response [CR], PR, or stable disease) and clinical benefit rate (CBR) (CR, PR, or durable stable disease) by IIR and investigator assessment using RECIST 1.1 of subjects treated with lenvatinib in combination with everolimus or pembrolizumab versus sunitinib.

• To compare PFS by IIR and investigator assessment using RECIST 1.1 in subjects treated with lenvatinib in combination with everolimus (Arm A) versus lenvatinib in combination with pembrolizumab (Arm B).

• To investigate the relationship between candidate tumor and blood biomarkers and clinical outcome measures including antitumor activity of study treatment.

Outcomes/endpoints

Primary endpoint

The primary endpoint was PFS assessed by IIR, defined as the time from the date of randomization to the date of the first documentation of disease progression using RECIST 1.1 or death (whichever occurred first).

Key Secondary Endpoints

• OS, defined as the time from the date of randomization to the date of death from any cause. Subjects who were lost to follow-up, withdrew consent, and those who were alive at the data cut-off date were censored, either at the date the subject was last known alive or at the data cut-off date, whichever occurred first.

• ORR, defined as the proportion of subjects who had BOR of CR or PR as determined by IIR using RECIST 1.1. ORR was calculated for confirmed CR/PR, and for confirmed and unconfirmed CR/PR. Confirmed CR/PR was primary for ORR analysis.

Other Secondary Endpoints

• Safety was assessed summarizing the incidence of TEAEs and SAEs together with all other safety parameters.

• Proportion of subjects who discontinued treatment due to toxicity, defined as the proportion of subjects who discontinued study treatment due to TEAEs.

• Time to treatment failure due to toxicity, defined as time from the date of randomization to the date that a subject discontinued study treatment due to TEAEs.

• HRQoL, assessed using the FKSI-DRS, the EORTC QLQ-C30, and the EuroQOL EQ-5D-3L instruments.

• PFS2, defined as the time from randomization to disease progression as assessed by investigator on next-line treatment or death from any cause (whichever occurred first).

• PFS by investigator assessment, defined as the time from the date of randomization to the date of first documentation of disease progression based on the investigator assessment per RECIST 1.1 or death (whichever occurred first).

• Pembrolizumab PK comparison to historical data.

• Model-predicted clearance and area under the concentration-time curve (AUC) for lenvatinib in Arms A and B. This analysis is detailed in a separate analysis plan.

• Model-predicted clearance and AUC for everolimus in Arm A. This analysis is detailed in a separate analysis plan.

Exploratory Endpoints

• ORR, defined as the proportion of subjects who had BOR of CR or PR as determined by investigator assessment using RECIST 1.1.

• DOR, defined as the time from the date a response of CR or PR by IIR and investigator assessment was first documented until the date of the first documentation of disease progression or date of death from any case.

• DCR, defined as the proportion of subjects who had BOR of CR, PR, or stable disease by IIR and investigator assessment. Stable disease had to be achieved at ≥7 weeks after randomization to be considered BOR.

• CBR, defined as the proportion of subjects who had BOR of CR, PR, or durable stable disease (duration of stable disease ≥23 weeks after randomization) by IIR and investigator assessment.

• Blood and tumor biomarkers will be assessed for identifying potential correlation with clinical outcomes-related endpoints. The biomarker analyses will be detailed in a separate Biomarker Analysis Plan (BAP; TSBM-E7080-307-ANA-1P).

Sample size

The sample size was estimated based on the primary endpoint of PFS. Approximately 1050 subjects were planned to be randomized in a 1:1:1 ratio into 1 of 3 treatment arms: lenvatinib + everolimus, lenvatinib + pembrolizumab, or sunitinib alone.

An administrative α of 0.0001 was attributed to an early analysis of ORR, and for the two PFS comparisons (one for each test arm as compared to control), it was planned to split the remaining alpha

of 0.0499 (2-sided), as initial allocations in a graphical approach, into α = 0.045 for the comparison between Arm B and Arm C, and α = 0.0049 for the comparison between Arm A and Arm C.

Sample size calculation for PFS

The same treatment effect was assumed for the primary comparisons of lenvatinib + everolimus (Arm A) and lenvatinib + pembrolizumab (Arm B) each compared to sunitinib alone (Arm C). Assuming the median PFS of sunitinib to be 12.3 months and a targeted HR of 0.714 for the primary comparisons, this corresponds to a 40% improvement (4.9 months) in median PFS from 12.3 months to 17.2 months for Arm A versus Arm C and for Arm B versus Arm C. A yearly loss of PFS event rate of 22% was assumed in the sample size calculation.

The study was designed to achieve 90% power at α = 0.045 to detect a statistically significant difference in PFS in the comparison between Arm B and Arm C. Therefore, a total of 388 PFS events were required between Arms B and C in the final PFS analysis. Since the same number of PFS events was expected to be observed in Arms A and C, a total of 388 PFS events was expected in the final PFS analysis for the comparison between Arms A and C. The power to detect a statistically significant difference in PFS between Arm A and Arm C was approximately 70% at the initial assigned α = 0.0049, and was expected to be at least 90% if the hypothesis tests of PFS and OS in the comparison of Arm B and Arm C are statistically significant, and vice versa. In the power calculation for PFS analysis, it was assumed that one interim analysis of PFS was to be performed at the 80% information fraction and a Lan-DeMets spending function with O'Brien-Fleming boundary was planned to be used between the interim and final analysis of PFS.

Assuming an average enrolment rate of 31 subjects per month, the interim and final analysis of PFS were expected to occur approximately 38 and 45 months (34-month enrolment period) after the first subject is randomized. A total of 582 PFS events were expected in 3 arms by the time of planned final PFS analysis.

Sample size calculation for OS

For the key secondary endpoint of OS, a total of 304 deaths for each comparison (456 death events among the 3 arms) were expected in the final OS analysis. For OS testing, when the corresponding PFS testing is statistically significant at the initial assigned alpha, the study was expected to provide 80% power to detect a statistically significant difference at an α level of 0.045 for the comparison between Arms B and C, and 50% power at an α level of 0.0049 for the comparison between Arm A and C. By using the graphical approach, the power for the OS comparison between Arms A and C was expected to increase to at least 80% if the OS testing between Arms B and C is significant and both PFS testing are significant, and vice versa.

The assumptions that were used for the OS power calculations are: 1) the hazard ratio is 0.70 (median OS is 54.1 months in Arm A or Arm B and 37.9 months in Arm C), 2) interim analyses are performed at approximately 45%, 60%, and 80% information fraction of death events, 3) a Lan-DeMets spending function with Pocock boundary is used, and 4) the yearly rate for loss to follow-up is 3%. With the planned sample size and the assumptions for enrolment, the final analysis of OS was expected to occur approximately 69 months after the first subject is randomly assigned to treatment.

Sample size calculation for ORR

For the key secondary endpoint of ORR, assuming an ORR of 32% in Arm C and 48% in Arm A or Arm B, the study was expected to provide at least 95% power to detect a difference when testing of PFS and OS are positive for each comparison of Arm B vs Arm C and Arm A vs Arm C.

Initially planned sample size

Initially, the total sample size was planned to be n=745 subjects, and this was increased to n=1050 in protocol amendment 04 (30 Jun 2018), to address slow enrollment in the first 12 months and high loss of PFS event rate, and provide adequate power for intergroup comparisons of overall survival (OS).

Randomisation

Approximately 1,050 subjects were to be randomly assigned to 1 of 3 treatment arms in a 1:1:1 ratio, with approximately 350 subjects in each arm.

Subjects were planned to be stratified by geographic region (Region 1: Western Europe and North America or Region 2: rest of the world) and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic group (favorable, intermediate, and poor risk).

Blinding (masking)

The study was conducted in an open label fashion, with a blinded independent radiologist review of responses.

Statistical methods

Analysis population

The Full Analysis Set (Intent-to-Treat Analysis [ITT] Population) was planned as the group of all randomized subjects regardless of the treatment actually received. This was planned to be the primary analysis population used for all efficacy analyses which was planned to be based on the intent-to-treat principle.

Primary outcome variable: PFS

The primary endpoint was planned to be PFS assessed by independent review (IIR), defined as the time from the date of randomization to the date of the first documentation of disease progression using RECIST 1.1 or death (whichever occurs first).

Missing values and censoring of PFS

Progression date was planned to be assigned to the earliest date when any RECIST 1.1-defined disease progression is observed without missing more than one adequate radiologic assessment. The following rules were planned be used for censoring, with a prioritization described below.

Table 9 Censoring Rules for Derivation of Progression-Free Survival

No.	Situation	Date of Progression or Censoring	Outcome
1	No baseline or postbaseline tumor assessments	Date of randomization	Censored
2	Progression documented between scheduled visits	Date of first radiologic PD assessment	Progressed
3	No progression at the time of data cutoff	Date of last adequate radiologic assessment prior to or on date of data cutoff	Censored
4	New anticancer treatment started	Date of last adequate radiologic assessment prior to or on date of new anticancer treatment	Censored
5	Death before first PD assessment	Date of death	Progressed
6	Death between adequate assessment*	Date of death	Progressed
7	Death or progression after more than one missed visit/tumor assessment**	Date of last adequate radiologic assessment before missed tumor assessments	Censored

CR = complete response, PD = progressive disease, PR = partial response, SD = stable disease.

* Adequate tumor assessment is radiologic assessment of CR, PR, SD, non-CR/non-PD or PD as determined by investigators at regular interval as defined in the protocol. Any tumor assessments after new anticancer treatment starts will be removed in the definition of PFS.

** More than one missed visit/adequate tumor assessment is defined as having the duration between the last adequate tumor assessment and PD or death being longer than 16 weeks + 10 days (tumor assessment window) - 1 day, which is 121 days for subjects on the every 8 week tumor assessment schedule in this study.

The priority of the censoring rules was planned as follows:

1. If the subject had PD or death, the following sequence will be applied:

- If a subject did not have a baseline tumor assessment (No. 1), the subject will be censored on the date of randomization. However, if the subject died within 121 days after randomization and did not receive a new anticancer treatment, it will be counted as PFS event at the date of death. If a subject had new anticancer treatment before PD or death (No. 4), the subject will be censored on the date of the last adequate tumor assessment prior to or on the date of new anticancer treatment.
- If a subject missed two or more tumor assessments before PD or death (No. 7), the subject will be censored on the date of the last adequate tumor assessment before PD or death. Note that if a subject is censored by both this criterion and the anticancer treatment criterion, the earliest censoring date will be used.
- Otherwise, if a subject had an event (No. 2, No. 5, or No. 6), the earliest event date will be used.

2. If a subject did not have PD or death, the censoring date will be the earliest censoring date if the subject met multiple censoring criteria (No. 1, No. 3, No. 4, No. 7).

Key secondary outcome variable: OS

Overall survival (OS) was planned to be defined as the time from the date of randomization to the date of death from any cause. Subjects who are lost to follow-up and those who are alive at the date of data cut-

off were planned to be censored at the date the subject was last known alive, or date of data cut-off, whichever occurs first.

Analysis model and covariates

PFS was planned to be evaluated using Kaplan-Meier (K-M) estimates and the statistical significance of the difference in PFS for the 2 primary comparisons was planned to be tested by stratified logrank test. Geographic region and MSKCC prognostic groups were planned to be used as stratification factors for randomization. The hazard ratio (lenvatinib + everolimus relative to sunitinib and lenvatinib + pembrolizumab relative to sunitinib) and the corresponding 95% confidence intervals (CIs) were planned to be estimated using the Cox regression model with Efron's method for handling tied results, stratified by the same stratification factors.

The analysis of OS was planned accordingly:

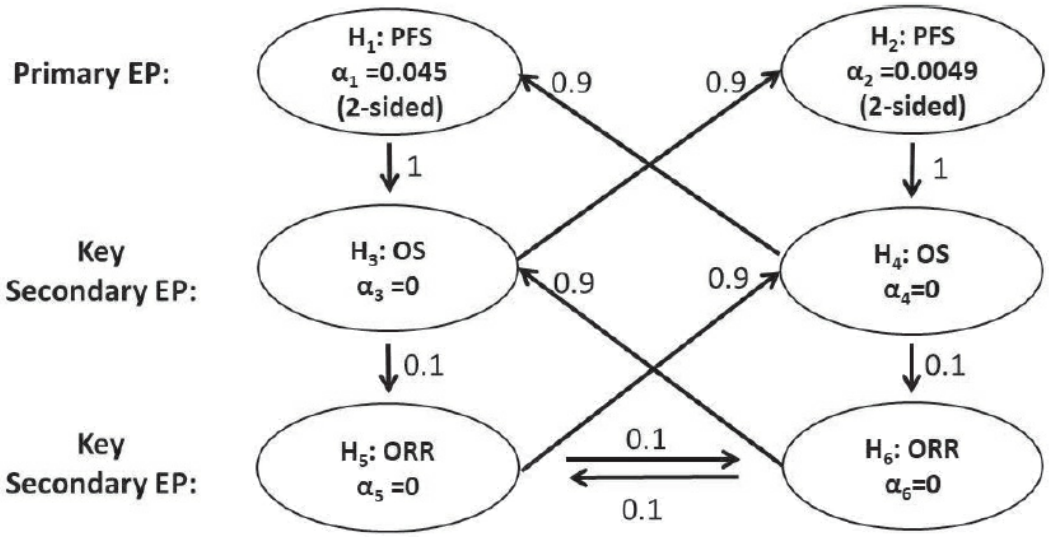
Overall Survival (OS) was planned to be compared between lenvatinib + everolimus (Arm A) vs. sunitinib alone (Arm C) and lenvatinib + pembrolizumab (Arm B) vs. sunitinib alone (Arm C) using the stratified logrank test with geographic region (Western Europe and North America vs. Other) and MSKCC prognostic groups (favorable, intermediate and poor risk) as strata. The hazard ratio and its 95% CI comparing lenvatinib + everolimus (Arm A) vs. sunitinib alone (Arm C) and lenvatinib + pembrolizumab (Arm B) vs. sunitinib alone (Arm C) was planned to be estimated by a stratified Cox proportional hazards model with Efron's method for handling tied results, stratified by geographic region and MSKCC prognostic groups. Median OS with 2-sided 95% CIs will be calculated using K-M product-limit estimates for each treatment arm and K-M estimates of OS were planned to be plotted over time.

Significance level and multiplicity

The significance level was set to α=0.05 two-sided.

To adjust for multiplicity and provide strong control of the overall family-wise error rate (FWER), the graphical approach of Maurer and Bretz (Maurer et al., 2013) was planned to be used in the primary endpoint of PFS and the key secondary efficacy endpoints (OS and ORR). No multiplicity adjustment was planned to be made for other secondary endpoints analyses and exploratory endpoints analyses.

An α of 0.0001 was planned be subtracted from the total α of 0.05 to account for the interim analysis of ORR from Arm B. Figure 11 shows the initial α-allocation (the remaining α = 0.0499) for each hypothesis and the graphical approach for multiple analyses of PFS, OS, and ORR.



EP = endpoint; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.
Hypothesis (H_1): The PFS of lenvatinib + pembrolizumab arm is superior to that of sunitinib arm.
Hypothesis (H_2): The PFS of lenvatinib + everolimus arm is superior to that of sunitinib arm.
Hypothesis (H_3): The OS of lenvatinib + pembrolizumab arm is superior to that of sunitinib arm.
Hypothesis (H_4): The OS of lenvatinib + everolimus is superior to that of sunitinib arm.
Hypothesis (H_5): The ORR of lenvatinib + pembrolizumab arm is superior to that of sunitinib arm.
Hypothesis (H_6): The ORR of lenvatinib + everolimus is superior to that of sunitinib arm.

Figure 11 Graphical Approach to Control Familywise Error Rate for Testing Primary and Key Secondary Endpoints

Initially, another approach to multiplicity was planned but was amended during the course of the study:

Initially, a truncated Hochberg method was planned for the two primary comparisons of PFS (arm A vs C, arm B vs C) with a truncation parameter of 0.7: At the final PFS analysis, if the larger p-value for both comparisons is less than 0.0425, then statistical significance for both comparisons was planned to be declared. Otherwise, if the other p-value is less than 0.025, then statistical significance for the corresponding comparison was planned to be declared.

In amendment 04, dated 30 Jun 2018, the analysis of ORR was introduced and a portion of α=0.0001 was allocated to this analysis, leaving α=0.0499 for PFS.

The graphical approach and bonferroni-type split of the significance level of α=0.045 for arm B vs C and α=0.0049 for arm A vs. C was introduced in protocol amendment 06, dated 10 Sep 2019, and replaced the previous strategy.

Interim analyses

Several interim analyses were planned.

One interim analysis of PFS after 310 events (80% information) and a final analysis of PFS after 388 events were planned to be performed. Four analyses of OS were planned, where the final analysis of OS was planned to be conducted based on 304 events, and interim analyses were planned at the time of interim and final PFS analysis (45% and 60% of information expected) and one year thereafter (80% information expected).

The nominal α level for each PFS comparison at the interim and final analyses was planned to be determined by a Lan-DeMets spending function with an O'Brien-Fleming (Table 11). The nominal α level for each OS comparison at the interim and final analyses was planned to be determined by a Lan-DeMets spending function with Pocock boundary (Table 12). The actual boundaries were planned to be calculated using the observed number of events at the interim and final analyses and α passed from previous tests.

Table 10 Summary of Interim and Final Efficacy Analyses

No.	Analysis	Endpoint(s)	Timing	Estimated Time after First Subject Randomized
1	Interim analysis of ORR and DOR (the first 88 subjects from Arm B)	ORR DOR	Median follow-up of 12 months and a minimum DOR follow-up of 6 months	~28 months
2	Interim analysis of PFS, Interim analysis of OS	PFS OS ORR*	Trigger: approximately 4 months after the last subject randomized and approximately 310 (80% IF) PFS events observed in Arms B and C (estimated to have ~140 (45% IF) deaths observed for each comparison)	~38 months
3	Final analysis of PFS,Interim analysis of OS	PFS OS	Trigger: ~ 388 PFS events observed for each comparison (estimated to have 182 (60% IF) deaths observed for each comaprison)	~45 months
4	Interim analysis of OS	OS	Trigger: ~243 (80% IF) deaths observed for each comparison	~57 months
5	Final analysis of OS	OS	Trigger: ~304 deaths observed for each comparison	~69 months

DOR = duration of response; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; IF=information fraction.

*: The p-value for hypothesis testing of ORR will be based on the ORR data at the analysis No 2.

Table 11 Efficacy Boundaries and Properties for PFS H1 and PFS H2 (LDOF spending function) Based on Initial Assigned Alpha

Analysis (2 arms)	Value	H_1 (α=0.045)	H_2 (α=0.0049) [d]
IA: 80%[a] N: 700 Events: 310 Month: 38	*P* (2-sided)[b]	0.0216	0.0014
	HR at boundary[c]	0.7705	0.6964
	Power	75%	42%
Final: 100% N: 700 Events: 388 Month: 45	*P* (2-sided)[b]	0.0386	0.0046
	HR at boundary[c]	0.8105	0.7491
	Power	90%	69%

HR = hazard ratio, IA = interim analysis, N = number of subjects.

a: Information fraction, percentage of expected number of events at final analysis.

b: P-value (2-sided) is the nominal α for testing.

c: HR at boundary is the approximate HR required to reach an efficacy boundary.

d: The power of H_2 test will be at least 90% if H_1 and H_3 testing are significant.

Table 12 Efficacy Boundaries and Properties for OS H3 and OS H4 (LD-Pocpck spending function) when PFS testes are Significant

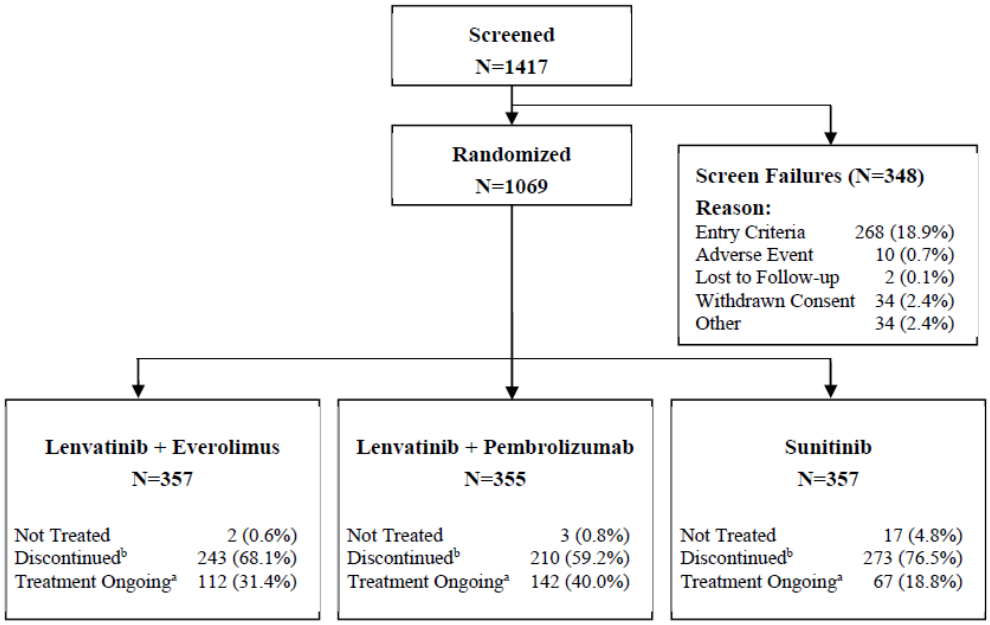
Analysis (2 arms)	Value	H_3 (α=0.045)	H_4 (α=0.0049)[d]
IA: 45%[a] N: 700 Events: 137 Month: 38	*P* (2-sided)[b]	0.0258	0.0028
	HR at boundary[c]	0.683	0.600
	Power	44%	20%
IA: 60%[a] N: 700 Events: 182 Month: 45	*P* (2-sided)[b]	0.0152	0.0014
	HR at boundary[c]	0.698	0.622
	Power	55%	27%
IA: 80%[a] N: 700 Events: 243 Month: 57	*P* (2-sided)[b]	0.0158	0.0014
	HR at boundary[c]	0.734	0.663
	Power	69%	41%
Final: N: 700 Events: 304 Month: 69	*P* (2-sided)[b]	0.0158	0.0014
	HR at boundary[c]	0.758	0.692
	Power	80%	51%

HR = hazard ratio, IA = interim analysis, N = number of subjects.
a: Information fraction, percentage of expected number of events at final analysis.
b: P-value (2-sided) is the nominal α for testing.
c: HR at boundary is the approximate HR required to reach an efficacy boundary.
d: The power of H_4 test will be at least 80% if H_1, H_3 and H_2 are significant.

In amendment 04 (30 Jun 2018), An interim analysis of ORR after 88 subjects in arm B, and an interim analysis of OS at the time of the primary PFS analysis were introduced. Further interim analyses for PFS and OS were introduced in amendment 06 (10 Sep 2019).

Results

Participant flow



Subject Disposition and Reason for Discontinuation From Study Treatment at IA3 – FAS
Data cutoff date: 28 Aug 2020.
Percentages except for screen failure reasons are based on total number of subjects in the Full Analysis Set within the relevant treatment group. Percentages for screen failure reasons are based on total number of screened subjects (N=1417).
a: Ongoing in study at data cutoff date refers to subjects who were still on study treatment or in survival follow-up as of the cutoff date.
b: Discontinued Treatment includes subjects who discontinued sunitinib or both study drugs in combination therapy.

a. Discontinued treatment refers to subjects who discontinued sunitinib or both study drugs in combination therapy
b. subject no longer wished to participate in the study or be contacted
c. subject chose to discontinue from the study and was willing to be contacted in Survival Follow-Up
d. Discontinued from study refers to subjects who were no longer followed up for survival as of the cutoff date.

Table 13 Subject Disposition and Reasons for Discontinuation from Treatment during Randomization Phase Full Analysis Set

Category	Lenvatinib + Everolimus (N = 357) n (%)	Lenvatinib + Pembrolizumab (N = 355) n (%)	Sunitinib (N = 357) n (%)	Total (N = 1069) n (%)
Randomized	357 (100)	355 (100)	357 (100)	1069 (100)
Not Treated	2 (0.6)	3 (0.8)	17 (4.8)	22 (2.1)
Treated	355 (99.4)	352 (99.2)	340 (95.2)	1047 (97.9)
Treatment Ongoing at Cutoff Date	112 (31.4)	142 (40.0)	67 (18.8)	321 (30.0)
On Both Study Drugs	100 (28.0)	60 (16.9)	NA	NA
On Lenvatinib Only	9 (2.5)	78 (22.0)	NA	NA
On Pembrolizumab Only	NA	4 (1.1)	NA	NA
On Everolimus Only	3 (0.8)	NA	NA	NA
Discontinued Treatment[a]	243 (68.1)	210 (59.2)	273 (76.5)	726 (67.9)
Primary Reason for Discontinuation from Treatment[b]				
Radiological Disease Progression	123 (34.5)	97 (27.3)	174 (48.7)	394 (36.9)
Clinical Disease Progression	20 (5.6)	19 (5.4)	22 (6.2)	61 (5.7)
Adverse Event	63 (17.6)	60 (16.9)	41 (11.5)	164 (15.3)
Subject Choice	29 (8.1)	17 (4.8)	23 (6.4)	69 (6.5)
Lost to Follow-Up	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)
Withdrawal of Consent	4 (1.1)	4 (1.1)	9 (2.5)	17 (1.6)
Other	4 (1.1)	13 (3.7)	3 (0.8)	20 (1.9)
Completed 35 Cycles of Pembrolizumab	NA	7 (2.0)	NA	NA
Discontinued Treatment but Remained in Survival Follow-Up at Data Cutoff Date	107 (30.0)	112 (31.5)	153 (42.9)	372 (34.8)

Recruitment

A total of 1417 participants were screened (first participant screened on 06-OCT-2016) and 1069 were randomly allocated across 200 global study sites in North America, Europe, and Asia. Enrolment occurred between 13 Oct 2016 (first subject gave informed consent) and 24 Jul 2019 (last subject randomized).

Data cut-off for IA3 occurred on 28-AUG-2020.

Conduct of the study

Protocol amendments

The key changes introduced by the protocol amendments are summarized below

Amendment 01 (26 Sep 2016) –Initial CTA

Summary of changes	Rationale
Recategorized PFS2 and HRQoL from exploratory objectives to secondary objectives. Recategorized PFS2 and HRQoL from exploratory endpoints to secondary end points. Proportion of subjects who discontinued treatment due to toxicity, and time to treatment failure due to toxicity were added as new secondary endpoints.	As requested by regulatory agency (EMA)
Characterization of the population PK of pembrolizumab was added as an exploratory objective.	As requested by regulatory agency (EMA)
Exploratory objective changed so DOR will be summarized by treatment group and no formal comparison will be performed	Clarification of the exploratory analysis
Exclusion Criterion 19 was changed from "known history of, or any evidence of, interstitial lung disease or active non-infectious Pneumonitis" to two separate criteria: -Exclusion Criterion 19 "known history of, or any evidence of, interstitial lung disease" -Exclusion Criterion 20 "Has a history of (non-infectious) pneumonitis that required steroids, or current pneumonitis"	To provide clarification for the criteria
Exclusion Criterion 26 was added to exclude men who do not agree to use the methods of contraception specified in the protocol.	Added for clarification

Amendment 02 (03 Feb 2017) – Response to Initial CTA

Summary of changes	Rationale
Assessment of PFS based on investigator assessment per RECIST 1.1 was added as a secondary objective/endpoint.	As requested by regulatory agency.
Exclusion Criterion 13 was updated to exclude carotid artery reference: "Bleeding or thrombotic disorders or subjects at risk for severe hemorrhage. The degree of tumor invasion/ infiltration of major blood vessels (eg, carotid artery) should be considered because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis following lenvatinib therapy.	Exclusion Criterion 13 was adapted for the study indication.

Exclusion Criterion 27 was added to capture "known intolerance to any of the study drugs (or any of the excipients).	As requested by regulatory agency.
Pembrolizumab dose modification guidelines for holding treatment for pneumonitis were amended from "Grade 3 to 4" to "Grade 3 to 4 or Recurrent Grade 2"	Pembrolizumab toxicity management guidelines were updated.
Pregnancy assessment was added to the Follow-up Period "A serum or urine pregnancy test will be performed in women of childbearing potential (i.e., premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months) at the Screening and Baseline Visits, on Day 1 of each cycle from Cycle 2 onwards, at the Off-Treatment Visit, and every 30 days up to 120 days post last dose of study medication or the start of a new anticancer therapy, whichever comes first."	As requested by regulatory agency.
The Follow-up Period for collecting SAE data was lengthened as follows: "SAEs regardless of causality assessment must be collected through the last visit and for 120 days after the subject's last dose, or 30 days following the last dose if the subject initiates new anticancer therapy, whichever is earlier."	As requested by regulatory agency.
PK and PK/PD related exploratory objectives were recategorized from exploratory to secondary, and the following secondary endpoints were added: Model-predicted clearance and AUC for lenvatinib in Arms A and B. Model-predicted clearance and AUC for everolimus in Arm A and for pembrolizumab in Arm B.	As requested by regulatory agency.

Amendment 03 (10 Jan 2018) – Substantial Amendment

Summary of changes	Rationale
Clarified no population PK analyses will be performed using pembrolizumab data in the study, only comparisons to historical data will be performed. PD data for pembrolizumab will not be measured.	Sponsor provided a PK/PD Analysis plan and rationale for not developing pembrolizumab population PK model and EMA agreed instead to have a graphical PK comparison for pembrolizumab.
Inclusion Criterion 7 was updated as adequate renal function defined as creatinine $\leq 1.5\times$ upper limit of normal (ULN); or for subjects with creatinine $>1.5\times$ ULN, the calculated creatinine clearance ≥ 30 mL/min (per the Cockcroft-Gault formula) is acceptable.	To provide clarification on adequate renal function.

Summary of changes	Rationale
Added note to Inclusion Criterion 8, adequate bone marrow function defined by: Absolute neutrophil count (ANC) ≥1500/mm^3 Platelets ≥100,000/mm^3 Hemoglobin ≥9 g/dL NOTE: Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within the previous 2 weeks.	To provide clarification that conditions must be met without erythropoietin dependency or blood transfusion.
Inclusion Criterion 9 was updated as adequate blood coagulation function defined by International Normalized ratio (INR) ≤1.5 unless participant is receiving anticoagulant therapy, as long as INR is within therapeutic range of intended use of anticoagulants.	To provide clarification for the criteria.
Exclusion Criterion 6 was updated if received a live vaccine within 30 days of planned start of study treatment (Cycle 1/ Day 1). Examples of live vaccines include, but are not limited to, measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette-Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.	To provide examples of live vaccines for clarification of the criteria.
Exclusion Criterion 15 was revised to change cardiovascular impairment window from 6 months to 12 months.	As requested by regulatory agency (EMA).
Dose modification guidelines for pembrolizumab were updated to specify irAE Management with corticosteroids and other therapies	To align with pembrolizumab toxicity management guideline update.

Guidelines for management of hypertension and proteinuria were revised. A) Management of Hypertension: 1.Requirement of repeat blood pressure (BP) measurements has changed. Repeat BP measurement now required only for subjects who have an elevated initial BP measurement as follows: systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg. 2. Definition of a BP assessment changed from 3 BP measurements to 2 BP measurements taken at least 5 minutes apart. 3. Time between BP assessments required for confirmation of hypertension changed from 2 BP assessments taken at least 1 hour apart to 2 BP assessments at least 30 minutes apart. 4. Clarified that subjects with uncontrolled hypertension (BP ≥160 mmHg or diastolic ≥100 mmHg) must have their BP monitored on Day 15 (or more frequently if clinically indicated) for 2 consecutive treatment cycles instead of 3 consecutive months. 5.Clarified that CTCAE grading for hypertension is to be based solely on BP measurements. B) Management for proteinuria:1.Clarified that CTCAE grading for proteinuria is to be based on a 24-hour urine result if available. 2. Added the option to use an immediate spot urine protein-to-creatinine ratio (UPCR) test as an alternative to a 24-hour urine protein test to quantify the 24-hour urine excretion if urine protein is ≥2+ (first occurrence or a subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib/sunitinib dose level, or at the new dose level when there has been a lenvatinib/sunitinib dose reduction). 3.Specified that a 24-hour urine protein test is required if the UPCR result is ≥2.4. 4. Clarified that subjects with proteinuria ≥2+ should be tested on Day 15 (or more frequently as clinically indicated) until the results have been 1+ or negative for 2 consecutive treatment cycles instead of 3 consecutive months.	To align with lenvatinib toxicity management guideline update.

Summary of changes	Rationale
C) Management for Hemorrhage: Clarified that dose modification guidelines for lenvatinib (Arm A, Arm B) and sunitinib (Arm C) related adverse events should be followed for the management of hemorrhage	

Amendment 04 (30 Jun 2018) - Substantial Amendment

Summary of changes	Rationale
Planned enrollment was increased from 735 (approx. 245 subjects per arm). to approx. 1050 subjects (approximately 350 subjects per arm).	To accommodate slow enrollment in the first 12 months and high loss of PFS event rate and provide adequate power for intergroup comparisons of OS.
Planned number of investigational sites was increased to 200 from 135 sites worldwide.	To accommodate the delay in study enrollment.
The estimated duration of the Study Randomization Period was increased to 43 months (29-month enrollment period; 14-month Follow-up Period) from previous of 37 months (25- month enrollment periods and 12 -month follow up period). The total study period was increased to approximately 53 months from approximately 37 months.	To accommodate the delay in study enrollment.
Reference to the Second Course (Pembrolizumab Retreatment) Phase and specific conditions under which subjects in Arm B could receive retreatment with pembrolizumab with or without lenvatinib, after discontinuation or completion of pembrolizumab were added.	To provide option of pembrolizumab rechallenge
Exclusion Criterion 2 was revised to clarify that CNS metastases (not just brain metastases) must be stable for at least 4 weeks before starting study treatment.	To provide clarification for the criteria.
Exclusion Criterion 28 was added to exclude subjects who had an allogenic tissue/solid organ transplant.	Consistency with pembrolizumab prescribing information.
Management of proteinuria section was updated to clarify that lenvatinib/sunitinib must be discontinued in the event of nephrotic syndrome.	Consistency with lenvatinib prescribing information.

Summary of changes	Rationale
Two interim analyses were added: 1. A planned interim analysis of ORR and DOR was added to include the first 88 treated subjects from the lenvatinib plus pembrolizumab arm who had completed a median follow-up of 12 months and had a minimum of 6 months follow-up for DOR. 2. A planned interim analysis of OS was added to be performed at the time of the primary analysis for PFS.	For potential submission to the FDA accelerated approval program.
Update in the statistical methods: 1 For the primary analysis of PFS, α was decreased to 0.0499 for all comparisons. 2. For the multiplicity adjustment, the P-value thresholds for the primary analysis of PFS were changed	Due to the addition of an interim analysis (IA1) to which an α of 0.0001 was allocated.

Amendment 05 (19 Dec 2018) - Substantial Amendment

Summary of changes	Rationale
Removed the second course retreatment phase option for pembrolizumab.	To address the assessors' request following the EU member states Voluntary Harmonisation Procedure regulatory authority review.
Rationale for IA1 was explained that the results of the planned interim analysis (IA1) of ORR and DOR may be considered for an early submission in regions outside of EMA jurisdiction.	Added for clarification.

Amendment 06 (10 Sep 2019) - Substantial Amendment

Summary of changes	Rationale
Added an interim analysis of PFS projected to occur ~38 months after the first subject was randomized in study. The final PFS analysis is projected to occur approximately ~45 months after the first subject was randomized in the study.	This interim analysis of PFS was added based on the results from publication of other IO+ VEGF studies.
Updated OS analysis:	Based on the results from publication of other IO+ VEGFi studies.

Summary of changes	Rationale
1. Number of interim analyses of OS increased from 1 to 3 and projected timing for IA. 2. Projected timing for final analysis of OS was updated from 53 months to 69 months after first subject randomized.	
Multiplicity adjustment strategy changed from truncated Hochberg procedure to Graphical approach with initial alpha of 0.045 assigned to test PFS lenvatinib/pembrolizumab vs sunitinib and initial alpha of 0.0049 assigned to test PFS lenvatinib+everolimus vs sunitinib.	Multiplicity test strategy was updated to optimize the probability of success of all hypothesis tests while to strongly control the familywise type I error rate under 0.05 (2-sided).

Amendment 07 (06 Aug 2020) - Substantial Amendment

Summary of changes	Rationale
Removal of the exploratory objective to assess PFS using immune-related RECIST in subjects treated with lenvatinib in combination with pembrolizumab.	Removed the irRECIST exploratory analysis due to low published pseudo progression rate in the renal cell cancer (RCC) population.

Protocol deviations

The categories for the major protocol deviations are summarized as follows:

• Exclusion criteria (2 subjects): One subject enrolled with active CNS metastasis and 1 subject had significant cardiovascular impairment.

• Inclusion criteria: One subject enrolled without histological confirmation of RCC with a clear cell component.

• Prohibited concomitant nondrug therapy: Ten subjects received a prohibited anticancer procedure (tumor resection or radiation therapy) during study leading to not evaluable tumor assessments and censoring of PFS event per IIR.

• Tumor assessment: Five subjects missed more than 1 consecutive tumor assessment scans leading to censoring of PFS event per IIR.

Table 14 Summary of Major Protocol Deviations – Full Analysis Set

Category	Lenvatinib + Everolimus (N=357) n (%)	Lenvatinib + Pembrolizumab (N=355) n (%)	Sunitinib (N=357) n (%)	Total (N=1069) n (%)
Subjects with at Least 1 Major Protocol Deviation	5 (1.4)	8 (2.3)	6 (1.7)	19 (1.8)
Exclusion criteria	1 (0.3)	1 (0.3)	0 (0.0)	2 (0.2)
Inclusion criteria	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Other prohibited conmeds/procedures	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Prohibited concomitant nondrug therapy	3 (0.8)	3 (0.8)	4 (1.1)	10 (0.9)
Tumor assessment	1 (0.3)	2 (0.6)	2 (0.6)	5 (0.5)

Data cutoff date: 28 Aug 2020.

Percentages are based on total number of subjects in the Full Analysis Set within the relevant treatment group. Some subjects may have multiple protocol deviations.

Baseline data

Table 15 Demographic and Baseline Characteristics – Full Analysis Set

Category	Lenvatinib + Everolimus (N=357)	Lenvatinib + Pembrolizumab (N=355)	Sunitinib (N=357)	Total (N=1069)
Age (years)				
Mean (SD)	61.9 (10.86)	62.3 (10.23)	60.8 (9.96)	61.7 (10.36)
Median	62.0	64.0	61.0	62.0
Min, Max	32, 86	34, 88	29, 82	29, 88
Age Group, n (%)				
<65 years	201 (56.3)	194 (54.6)	225 (63.0)	620 (58.0)

Category	Lenvatinib + Everolimus (N=357)	Lenvatinib + Pembrolizumab (N=355)	Sunitinib (N=357)	Total (N=1069)
≥65 years	156 (43.7)	161 (45.4)	132 (37.0)	449 (42.0)
Sex, n (%)				
Male	266 (74.5)	255 (71.8)	275 (77.0)	796 (74.5)
Female	91 (25.5)	100 (28.2)	82 (23.0)	273 (25.5)
Race, n (%)				
White	254 (71.1)	263 (74.1)	270 (75.6)	787 (73.6)
Black or African American	1 (0.3)	2 (0.6)	3 (0.8)	6 (0.6)
Asian	77 (21.6)	81 (22.8)	67 (18.8)	225 (21.0)
Japanese	44 (12.3)	42 (11.8)	31 (8.7)	117 (10.9)
Chinese	0 (0.0)	2 (0.6)	0 (0.0)	2 (0.2)
Other Asian	33 (9.2)	37 (10.4)	36 (10.1)	106 (9.9)
American Indian or Alaskan Native	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Native Hawaiian or Other Pacific Islander	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Other	7 (2.0)	4 (1.1)	7 (2.0)	18 (1.7)
Missing	16 (4.5)	5 (1.4)	10 (2.8)	31 (2.9)
Ethnicity, n (%)				
Hispanic or Latino	23 (6.4)	12 (3.4)	20 (5.6)	55 (5.1)
Not Hispanic or Latino	328 (91.9)	339 (95.5)	334 (93.6)	1001 (93.6)
Missing	6 (1.7)	4 (1.1)	3 (0.8)	13 (1.2)
BMI (kg/m^2)				
Mean (SD)	27.48 (5.613)	27.48 (5.179)	28.29 (5.809)	27.75 (5.547)
Median	26.75	26.90	27.45	27.00
Min, Max	14.4, 50.2	16.0, 46.8	16.9, 62.8	14.4, 62.8
Geographic Region per IxRS, n (%)				
Western Europe and North America	200 (56.0)	198 (55.8)	199 (55.7)	597 (55.8)
Rest of World	157 (44.0)	157 (44.2)	158 (44.3)	472 (44.2)
KPS Score Group, n (%)				
100 – 90	286 (80.1)	295 (83.1)	294 (82.4)	875 (81.9)
80 – 70	70 (19.6)	60 (16.9)	62 (17.4)	192 (18.0)
Missing	1 (0.3)	0 (0.0)	1 (0.3)	2 (0.2)

Data cutoff date: 28 Aug 2020.

Percentages are based on the total number of subjects in the Full Analysis Set within the relevant treatment group.

BMI = body mass index, IxRS = interactive voice and web response system, KPS = Karnofsky Performance Status, Max = maximum, Min = minimum, NA = not applicable, SD = standard deviation.

Table 16 Disease History and Characteristics at Study Entry – Full Analysis Set

Parameter	Lenvatinib + Everolimus (N=357)	Lenvatinib + Pembrolizumab (N=355)	Sunitinib (N=357)	Total (N=1069)
Time Since First RCC Diagnosis to Randomization (month)				
Mean (SD)	28.19 (44.997)	32.81 (51.521)	33.95 (51.733)	31.64 (49.528)
Median	7.10	9.89	8.71	8.28
Min, Max	0.39, 246.60	0.07, 263.13	0.33, 316.22	0.07, 316.22
Age at First Diagnosis (years)[a]				
Mean (SD)	59.6 (10.86)	59.6 (10.04)	58.1 (9.88)	59.1 (10.28)
Median	60.0	61.0	58.0	60.0
Min, Max	31, 85	33, 86	27, 82	27, 86
RCC Diagnosis Classification, n (%)				
Clear Cell	357 (100)	354 (99.7)	357 (100)	1068 (99.9)
Clear Cell with Additional Features[b]				
Papillary	22 (6.2)	23 (6.5)	21 (5.9)	66 (6.2)
Chromophobe	3 (0.8)	2 (0.6)	1 (0.3)	6 (0.6)
Sarcomatoid	24 (6.7)	28 (7.9)	21 (5.9)	73 (6.8)
Other	25 (7.0)	17 (4.8)	28 (7.8)	70 (6.5)
Other (Not Clear Cell)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Time Since Advanced/Metastatic RCC Diagnosis to Randomization (months)				
Mean (SD)	6.68 (12.912)	7.86 (20.795)	9.00 (20.864)	7.85 (18.570)
Median	2.04	2.10	2.30	2.10
Min, Max	0.03, 118.18	0.07, 263.13	0.07, 198.54	0.03, 263.13
Lesion Organs/Sites Location[b,c], n (%)				
Lung	245 (68.6)	252 (71.0)	228 (63.9)	725 (67.8)
Lymph Node	168 (47.1)	162 (45.6)	156 (43.7)	486 (45.5)
Bone	96 (26.9)	80 (22.5)	89 (24.9)	265 (24.8)
Kidney	86 (24.1)	91 (25.6)	88 (24.6)	265 (24.8)
Liver	71 (19.9)	63 (17.7)	70 (19.6)	204 (19.1)
Adrenal	62 (17.4)	53 (14.9)	66 (18.5)	181 (16.9)
Brain	3 (0.8)	6 (1.7)	10 (2.8)	19 (1.8)
Other	112 (31.4)	109 (30.7)	123 (34.5)	344 (32.2)

Parameter	Lenvatinib + Everolimus (N=357)	Lenvatinib + Pembrolizumab (N=355)	Sunitinib (N=357)	Total (N=1069)
Number of Metastatic Organs/Sites Involved[c,d], n (%)				
0	2 (0.6)	5 (1.4)	6 (1.7)	13 (1.2)
1	99 (27.7)	119 (33.5)	114 (31.9)	332 (31.1)
2	146 (40.9)	129 (36.3)	127 (35.6)	402 (37.6)
≥3	109 (30.5)	102 (28.7)	109 (30.5)	320 (29.9)
Missing	1 (0.3)	0 (0.0)	1 (0.3)	2 (0.2)
Stage Group at Diagnosis, n (%)				
I	30 (8.4)	50 (14.1)	35 (9.8)	115 (10.8)
II	24 (6.7)	16 (4.5)	21 (5.9)	61 (5.7)
III	68 (19.0)	60 (16.9)	67 (18.8)	195 (18.2)
IV	195 (54.6)	178 (50.1)	195 (54.6)	568 (53.1)
Not Assigned	40 (11.2)	51 (14.4)	39 (10.9)	130 (12.2)
MSKCC Prognostic Group at Baseline, n (%)				
Favorable Risk	98 (27.5)	96 (27.0)	97 (27.2)	291 (27.2)
Intermediate Risk	227 (63.6)	227 (63.9)	228 (63.9)	682 (63.8)
Poor Risk	32 (9.0)	32 (9.0)	32 (9.0)	96 (9.0)
IMDC Risk Group at Baseline[e], n (%)				
Favorable Risk	114 (31.9)	110 (31.0)	124 (34.7)	348 (32.6)
Intermediate Risk	195 (54.6)	210 (59.2)	192 (53.8)	597 (55.8)
Poor Risk	42 (11.8)	33 (9.3)	37 (10.4)	112 (10.5)
Missing	6 (1.7)	2 (0.6)	4 (1.1)	12 (1.1)
PD-L1 status[f], n (%)				
Positive (CPS≥1)	116 (32.5)	107 (30.1)	119 (33.3)	342 (32.0)
Negative (CPS<1)	118 (33.1)	112 (31.5)	103 (28.9)	333 (31.2)
Not Available	123 (34.5)	136 (38.3)	135 (37.8)	394 (36.9)

Data cutoff date: 28 Aug 2020.

Percentages are based on the total number of subjects in the Full Analysis Set within the relevant treatment group.

CPS = Combined Positive Score, IMDC = International Metastatic Renal Cell Carcinoma Database Consortium, KPS = Karnofsky Performance Status, MSKCC = Memorial Sloan-Kettering Cancer Center, PD-L1 = programmed cell death ligand-1, RCC = renal cell carcinoma, SD = standard deviation.

a: Age at First Diagnosis (years) = Age – [(Date of informed consent signed – Date of Diagnosis)/365.25].

b: Subjects may be represented in more than 1 category.

c: Lesion organ/sites involved were derived from independent imaging review.

d: Kidney is not included in the number of metastatic organs/sites.

e: IMDC prognostic group at baseline was derived based on total risk score from 6 prognostic factors at baseline: KPS, hemoglobin, corrected serum calcium, neutrophils, platelets, and time from first RCC diagnosis to randomization.

f: PD-L1 status was determined using an investigational version of the PD-L1 immunohistochemistry 22C3 pharmDx assay (Agilent, Santa Clara, California, USA) and a provisional CPS, which is defined as the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100. The CPS cutoff value is 1.

Numbers analysed

Efficacy analyses were based on the ITT population (Full Analysis Set), which included participants in the treatment group to which they were randomly assigned, regardless of whether or not they received study treatment.

Analysis Set	Lenvatinib + Everolimus (N=357) n (%)	Lenvatinib + Pembrolizumab (N=355) n (%)	Sunitinib (N=357) n (%)
Full Analysis Set[a]	357 (100)	355 (100)	357 (100)
Safety Analysis Set[b]	355 (99.4)	352 (99.2)	340 (95.2)
Per Protocol Analysis Set[c]	343 (96.1)	339 (95.5)	317 (88.8)
Subjects Excluded from Per Protocol Analysis Set[c]	14 (3.9)	16 (4.5)	40 (11.2)
No Treatment	2 (0.6)	3 (0.8)	17 (4.8)
Major Deviations	5 (1.4)	8 (2.3)	6 (1.7)
Missing Baseline or Postbaseline Tumor Assessment	10 (2.8)	7 (2.0)	34 (9.5)

Analysis Set	Lenvatinib + Everolimus (N=357) n (%)	Lenvatinib + Pembrolizumab (N=355) n (%)	Sunitinib (N=357) n (%)
Population PK Analysis Set[d]	352 (98.6)	348 (98.0)	NA
Pembrolizumab PK Analysis Set[e]	NA	331 (93.2)	NA
Pharmacodynamic Analysis Set[f]	256 (71.7)	256 (72.1)	NA

Data cutoff date: 28 Aug 2020.

Percentages are based on the total number of subjects in the Full Analysis Set within the relevant treatment group.

PK = pharmacokinetic.

a: Full Analysis Set: All randomized subjects regardless of the treatment actually received.

b: Safety Analysis Set: All subjects who received at least 1 dose of any study drug.

c: Per Protocol Analysis Set: All subjects who received at least 1 dose of any study drug, had no major protocol deviations, and had both baseline and at least 1 postbaseline tumor assessment. Subjects who died prior to the first postbaseline tumor assessment were also included. Subjects may be represented in more than 1 category.

d: Population PK Analysis Set: All subjects who received at least 1 dose of study treatment, with documented dosing history in the lenvatinib plus everolimus arm (Arm A) or the lenvatinib plus pembrolizumab arm (Arm B), and had measurable plasma levels of lenvatinib or whole blood levels of everolimus.

e: Pembrolizumab PK Analysis Set: All subjects who received at least 1 dose of study treatment, with documented dosing history in the lenvatinib plus pembrolizumab arm (Arm B) and had measurable serum concentrations of pembrolizumab.

f: Pharmacodynamic Analysis Set: All subjects who received at least 1 dose of study drug and had sufficient pharmacodynamic data to derive at least 1 pharmacodynamic measurement and had documented dosing history.

The efficacy data presented below correspond to the comparison of lenvatinib plus pembrolizumab versus sunitinib arm, which is the subject of this application.

Treatment duration

Table 17 Study Treatment Exposure Across Study 307 and the Monotherapy Studies

Extent of Exposure	Combination Therapy		Monotherapy	
	Study 307 (RCC-1L)		Study 205 (RCC-2L+)	KEYNOTE-427 (RCC-1L)
	Lenvatinib 20 mg + Pembrolizumab 200 mg (N=352)	Sunitinib 50 mg (N=340)	Lenvatinib 24 mg Monotherapy (N=52)	Pembrolizumab 200 mg Monotherapy (N=110)
Overall: Duration of Treatment (months)[a]				
n	352	340	NA	NA
Mean (StdDv)	17.29 (9.575)	11.33 (9.463)		
Median	17.00	7.84		
Q1, Q3	9.43, 25.35	3.68, 17.81		
Minimum, Maximum	0.07, 39.13	0.10, 36.96		
Lenvatinib: Duration of Treatment (months)[a]				
n	352	NA	52	NA
Mean (StdDv)	16.45 (9.839)		7.97 (5.56)	
Median	16.13		7.38	
Q1, Q3	8.25, 25.12		3.19 - 11.5	
Minimum, Maximum	0.07, 39.13		0.13 - 23.0	
Pembrolizumab/Sunitinib: Duration of Treatment (months)[a]	Pembrolizumab	Sunitinib	NA	Pembrolizumab
n	352	340	NA	110
Mean (StdDv)	14.45 (8.562)	11.33 (9.463)		11.34 (8.903)
Median	15.08	7.84		8.54
Q1, Q3	6.90, 23.46	3.68, 17.81		Not available
Minimum, Maximum	0.03, 29.60	0.10, 36.96		0.03, 26.68

Data cutoff date: 28 Aug 2020 for Study 307, 24 Feb 2020 for KEYNOTE-427 and 13 Jun 2014 for Study 205.

Percentages are based on the Safety Analysis Set for Study 307 and the Full Analysis Set for Study 205 and KN-427.

1L = first line, 2L+ = second line or greater, CI = confidence interval, CSR = Clinical Study Report, n = number of subjects, NA = not applicable, Q = quartile, RCC = renal cell carcinoma, StdDv = standard deviation.

a: Duration of treatment in Study 307 = (date of last dose of study drug–date of first dose of study drug+1)/30.4375. Duration of treatment in Study 205 = (date of last dose of study drug - date of first dose of study drug + 1)/30.4375. Duration of treatment in KEYNOTE-427 = number of days between first dose date and last dose date)/30.4375.

Source: Study 307 CSR, Table 14.3.1.1.1.1; Study 205 CSR, Table 14.3.1.1.1.2; KEYNOTE-427, Extent of Exposure.

Outcomes and estimation

Upon availability of IA3 results (DCO 28 Aug 2020), the MAH retrospectively reviewed the results from IA2 (DCO 15 Nov 2019); results from IA2 were consistent with those at IA3 with a statistically significant and clinically meaningful improvement in PFS, OS, and ORR. The results presented in this section are for the lenvatinib plus pembrolizumab, and sunitinib arms from IA3. Median follow-up time for PFS was 22.3 months (95% CI: 21.1, 25.6) in the lenvatinib plus pembrolizumab arm and 16.6 months (95% CI: 13.1, 18.5) in the sunitinib arm.

Primary endpoint: Progression-free Survival

Median PFS based on IIR using RECIST 1.1 was 23.9 months for lenvatinib plus pembrolizumab and 9.2 months for sunitinib (HR=0.39, [95% CI: 0.32, 0.49], P<0.0001];Table 18). The P value was less than the pre specified P value boundary of 0.0411 and the null hypothesis was rejected. This demonstrates a 2.6-fold increase in median PFS, and a 61% reduction in the risk of disease progression or death with lenvatinib plus pembrolizumab compared with sunitinib.

Results for PFS by investigator assessment were consistent with those of PFS by IIR. Median PFS was 22.1 months for lenvatinib plus pembrolizumab compared with 9.5 months for sunitinib (HR=0.47, [95% CI: 0.38, 0.58], nominal P<0.0001).

Table 18 Summary of Progression-Free Survival per Independent Imaging Review Using RECIST 1.1

	Lenvatinib 20 mg + Pembrolizumab 200 mg (N=355)	**Sunitinib 50 mg (N=357)**
Subjects with PFS events, n (%)	160 (45.1)	205 (57.4)
Median PFS (months)	23.9	9.2
95% CI for Median PFS	(20.8, 27.7)	(6.0, 11.0)
Median (95% CI) follow-up time for PFS (months)	22.3 (21.1, 25.6)	16.6 (13.1, 18.5)
Lenvatinib + Pembrolizumab vs Sunitinib		
Stratified HR (95% CI)[b,c]	0.39 (0.32, 0.49)	
Stratified Log-rank Test *P* value[c]	<0.0001	
Progression-Free Survival Rate (%) (95% CI)[d] at		
6 months	84.9 (80.6, 88.3)	57.0 (51.1, 62.5)
12 months	70.6 (65.3, 75.2)	38.4 (32.4, 44.3)
18 months	57.4 (51.5, 62.8)	31.2 (25.4, 37.2)
24 months	48.9 (42.7, 54.9)	20.7 (15.0, 26.9)

Data cutoff date: 28 Aug 2020 for Study 307

1L = first line, 2L+ = second line or greater, CSR = Clinical Study Report, HR = hazard ratio, IxRS = interactive voice and web response system, MSKCC = Memorial Sloan-Kettering Cancer Center, NA = not applicable, PFS = progression-free survival, RCC = renal cell carcinoma, RECIST 1.1 = Response Evaluation Criteria in Solid Tumors.a:Point estimates are based on Kaplan-Meier method and 95% CIs are based on the Greenwood formula using log-log transformation.b:Hazard ratio is based on a Cox Proportional Hazard Model including treatment group as a factor, Efron method is used for ties.c:Stratified by geographic region (Region 1: Western Europe and North America, Region 2: rest of the world) and MSKCC prognostic groups (favorable, intermediate and poor risk) in IxRS.d:PFS rate and 95% CIs are calculated using Kaplan-Meier product-limit method and Greenwood Formula

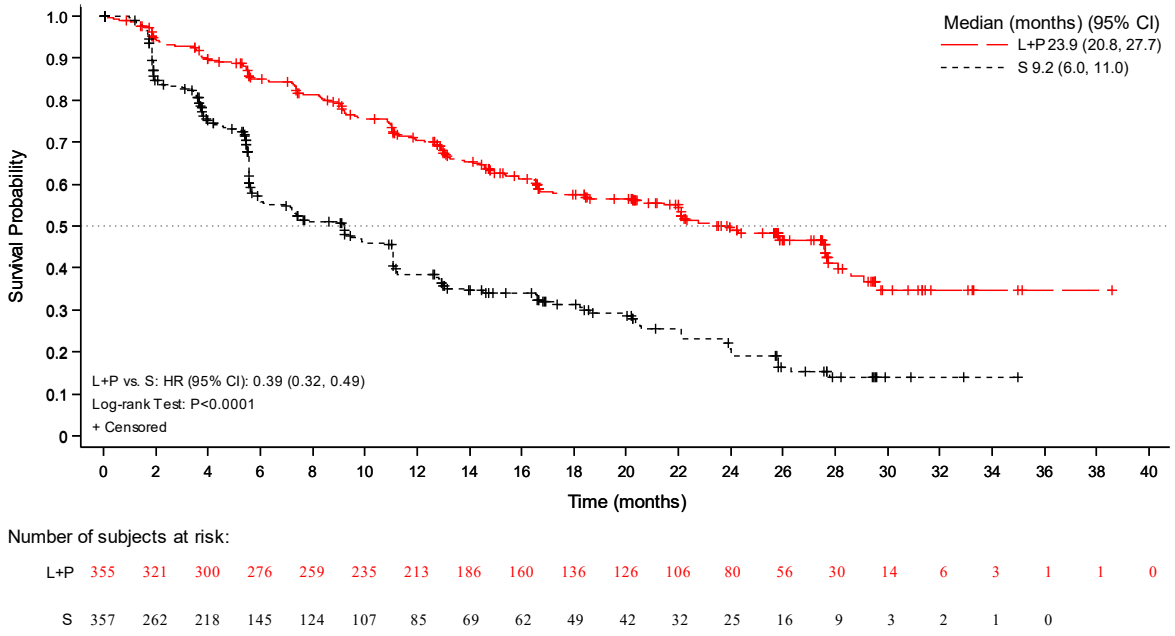


Figure 12 Study 307: Kaplan-Meier Plot of Progression-Free Survival by Independent Imaging Review Using RECIST 1.1 – Full Analysis Set

Data cutoff date: 28 Aug 2020.

CSR = Clinical Study Report, HR = hazard ratio, IxRS = interactive voice and web response system, L = lenvatinib, P = pembrolizumab, RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, S = sunitinib.Median was estimated by Kaplan-Meier method, and the 95% CIs were estimated with a generalized Brookmeyer and Crowley method.Hazard ratio was estimated from Cox Proportional Hazard Model including treatment group as a factor and stratified by IxRS stratification factors. Efron method was used for ties.P value was calculated using log-rank test stratified by IxRS stratification factors. + Censored observations

Secondary endpoints:

Overall Survival

The OS HR of 0.66 (95% CI: 0.49, 0.88, P=0.0049) represents a 34% reduction in the risk of death for lenvatinib plus pembrolizumab compared with sunitinib (Figure 13). The P value was less than the pre specified P value boundary of 0.0161 and the null hypothesis was rejected. Many subjects remained alive at the time of the DCO and median OS was not reached; fewer subjects had died in the lenvatinib plus pembrolizumab arm (80; 22.5%) than in the sunitinib arm (101; 28.3%). The median duration of survival follow-up was similar for both arms: 26.7 months (95% CI: 25.9, 27.4) for lenvatinib plus pembrolizumab and 26.3 months (95% CI: 25.4, 27.2) for sunitinib.

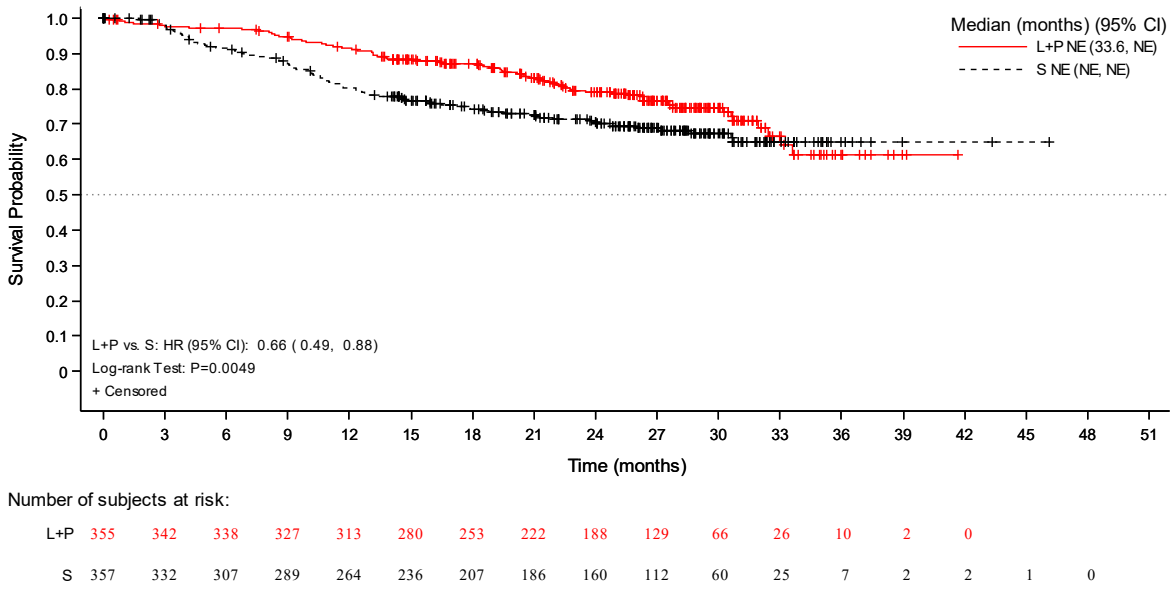
Table 19 OS summary

	Lenvatinib 20 mg + Pembrolizumab 200 mg (N=355)	**Sunitinib 50 mg (N=357)**
Deaths, n (%)	80 (22.5)	101 (28.3)
Median OS (months)	NR	NR

95% CI for Median OS	(33.6, NE)[a]	(NE, NE)[a]
Lenvatinib + Pembrolizumab vs Sunitinib		
Stratified HR (95% CI)[b,c]	0.66 (0.49, 0.88)	
Stratified Log-rank Test *P* value[c]	0.0049	
OS Rate (95% CI)[d] at		
3 months	NA	NA
6 months	NA	NA
9 months	NA	NA
12 months	91.4 (87.9, 93.9)	80.2 (75.5, 84.1)
18 months	87.1 (83.1, 90.3)	74.4 (69.3, 78.8)
24 months	79.2 (74.1, 83.3)	70.4 (65.0, 75.2)
Median Follow-Up Time for OS (months; 95% CI)	26.7 (25.9, 27.4)[a,e]	26.3 (25.4, 27.2)[a,e]

Data cutoff date: 28 Aug 2020. Percentages are based on the total number of subjects in the Full Analysis Set within the relevant treatment group.

CI = confidence interval, IxRS = interactive voice and web response system, MSKCC = Memorial Sloan-Kettering Cancer Center, NE = not estimable, Q = quartile. a: Quartiles are estimated by Kaplan–Meier method, and the 95% CIs are estimated with a generalized Brookmeyer and Crowley method. b: Hazard ratio is based on a Cox Proportional Hazard Model including treatment group as a factor, Efron method is used for ties. c: Stratified by geographic region (Region 1: Western Europe and North America or Region 2: rest of the world) and MSKCC prognostic groups (favorable, intermediate, and poor risk) in IxRS. d: Overall survival rate and 95% CIs are calculated using Kaplan–Meier product-limit method and Greenwood Formula e: Estimates for survival follow-up time are calculated in the same way as the Kaplan–Meier estimate of overall survival but with the meaning of 'censor' and 'event' status indicator reversed.



Data cutoff date: 28 Aug 2020.

Figure 13 Study 307: Kaplan-Meier Plot of Overall Survival – Full Analysis Set

Data cutoff date: 28 Aug 2020.

CSR = Clinical Study Report; HR = Hazard Ratio; IxRS = interactive voice and web response system, L = lenvatinib, NE = not evaluable, P = pembrolizumab, RECIST = Response Evaluation Criteria in Solid Tumors, S = sunitinib. Median was estimated by Kaplan-Meier method, and the 95% CIs were estimated with a generalized Brookmeyer and Crowley method. Hazard ratio was estimated from Cox Proportional Hazard Model including treatment group as a factor and stratified by IxRS stratification factors. Efron method was used for ties. *P* value was calculated using log-rank test stratified by IxRS stratification factors. + Censored observations. Source: Study 307 CSR, Figure 14.2.2.2.1.1

Overall Survival Results over Time

The HR in the Full Analysis Set at IA3 and IA2 was 0.66 (95% CI: 0.49, 0.88;) and 0.47 (95% CI: 0.32, 0.68), respectively. In addition, the proportion of subjects that received subsequent anticancer therapy increased between the 2 analyses time points; at IA3, 117 (33.0%) subjects in the lenvatinib plus pembrolizumab arm and 206 (57.7%) subjects in the sunitinib arm had received subsequent anticancer therapy compared with 75 (21.1%) and 160 (44.8%) subjects, respectively at IA2

PFS2

Table 20 Progression-Free Survival on Next-Line of Therapy (PFS2) Full Analysis Set

	Lenvatinib + Pembrolizumab (N = 355)	Sunitinib (N = 357)
Subjects with PFS2 Events, n (%)	99 (27.9)	156 (43.7)
Progressive Disease on Next Line of Therapy	41 (11.5)	87 (24.4)
Death	58 (16.3)	69 (19.3)
PFS2 Censored, n (%)	256 (72.1)	201 (56.3)
No Progressive Disease on Next Line of Therapy and No Death at the Time of Data Cutoff	59 (16.6)	83 (23.2)
Not Received Any Next Line of Therapy by the Time of Data Cutoff	197 (55.5)	118 (33.1)
PFS2 (months)[a]		
Median (95% CI)	NE (NE, NE)	28.7 (23.0, NE)
Q1 (95% CI)	21.7 (19.2, 27.3)	11.6 (9.4, 12.7)
Q3 (95% CI)	NE (NE, NE)	NE (NE, NE)
Lenvatinib + Everolimus vs Sunitinib		
Stratified Hazard Ratio (95% CI)[b,c]		
Stratified Log-rank Test P value[c]		
Lenvatinib + Pembrolizumab vs Sunitinib		
Stratified Hazard Ratio (95% CI)[b,c]	0.50 (0.39, 0.65)	
Stratified Log-rank Test P value[c]	<0.0001	
Time to Initiation of Next-Line Therapy (months)		
n	124	209
Mean (SD)	13.80 (8.116)	8.83 (6.574)
Median	12.21	6.44
Q1, Q3	7.49, 17.72	4.01, 11.83
Min, Max	1.45, 37.36	0.39, 28.52

Objective Response Rate and Duration of Response

Confirmed ORR per RECIST 1.1, as assessed by IIR in the lenvatinib plus pembrolizumab arm was approximately double the ORR in the sunitinib arm (71.0% and 36.1%, respectively). The difference in ORR between the treatment arms was 34.9% (95% CI: 28.0, 41.7). The odds ratio (OR) was 4.35 (95% CI: 3.16, 5.97; nominal P<0.0001) in favor of lenvatinib plus pembrolizumab (Table 21).

Table 21 Summary of Tumor Response per Independent Imaging Review Using RECIST 1.1 Across Study 307

	Lenvatinib 20 mg + Pembrolizumab 200 mg (N=355)	**Sunitinib 50 mg (N=357)**
Best Overall Response, n (%)		
Complete Response	57 (16.1)	15 (4.2)
Partial Response	195 (54.9)	114 (31.9)
Stable Disease	68 (19.2)	136 (38.1)
Progressive Disease	19 (5.4)	50 (14.0)
Unknown/Not Evaluable	16 (4.5)	42 (11.8)
No Baseline Tumor Assessment	0 (0.0)	1 (0.3)
No Post-baseline Tumor Assessment	12 (3.4)	38 (10.6)
≥1 Lesions not evaluable	1 (0.3)	2 (0.6)
Early SD (SD <7 Weeks)	3 (0.8)	1 (0.3)
No Assessment[a]	-	-
Objective Response Rate (CR + PR), n (%)	252 (71.0)	129 (36.1)
95% CI	(66.3, 75.7)[b]	(31.2, 41.1)[b]
Difference (%) (95% CI)[b]	34.9 (28.0, 41.7)	
Odds ratio (95% CI)[c]	4.35 (3.16, 5.97)	
P value[e]	<0.0001	
Duration of Objective Response (months)		
Median (95% CI)	25.8 (22.1, 27.9)[d]	14.6 (9.4, 16.7)[d]
Range (Min, Max)	(1.64+, 36.76+)	(1.64+, 33.15+)

Data cutoff date: 28 Aug 2020

n = number of subjects, max = maximum, min = minimum, PR = partial response, RECIST 1.1 = Response Evaluation Criteria in Solid Tumours, SD = stable disease.

a:'No Assessment' includes subjects discontinuing or death before the first post-baseline scan

b:95% CI is constructed using the method of Normal Approximation.

c:Odds Ratio and nominal *P* value are calculated using the Cochran-Mantel-Haenszel method, stratified by IxRS stratification factors.

d:95% CI was from a generalized Brookmeyer and Crowley method.

- Responses occurred early, with a median time to first objective response in the lenvatinib plus pembrolizumab arm of 1.94 months, which was approximately at the time of the first scheduled tumor assessment scan per protocol.

- Among subjects who responded, the DOR was longer in the lenvatinib plus pembrolizumab arm compared with the sunitinib arm. The median DOR in responders was 25.8 months (95% CI: 22.1, 27.9) in the lenvatinib plus pembrolizumab arm and 14.6 months (95% CI: 9.4, 16.7) in the sunitinib arm.

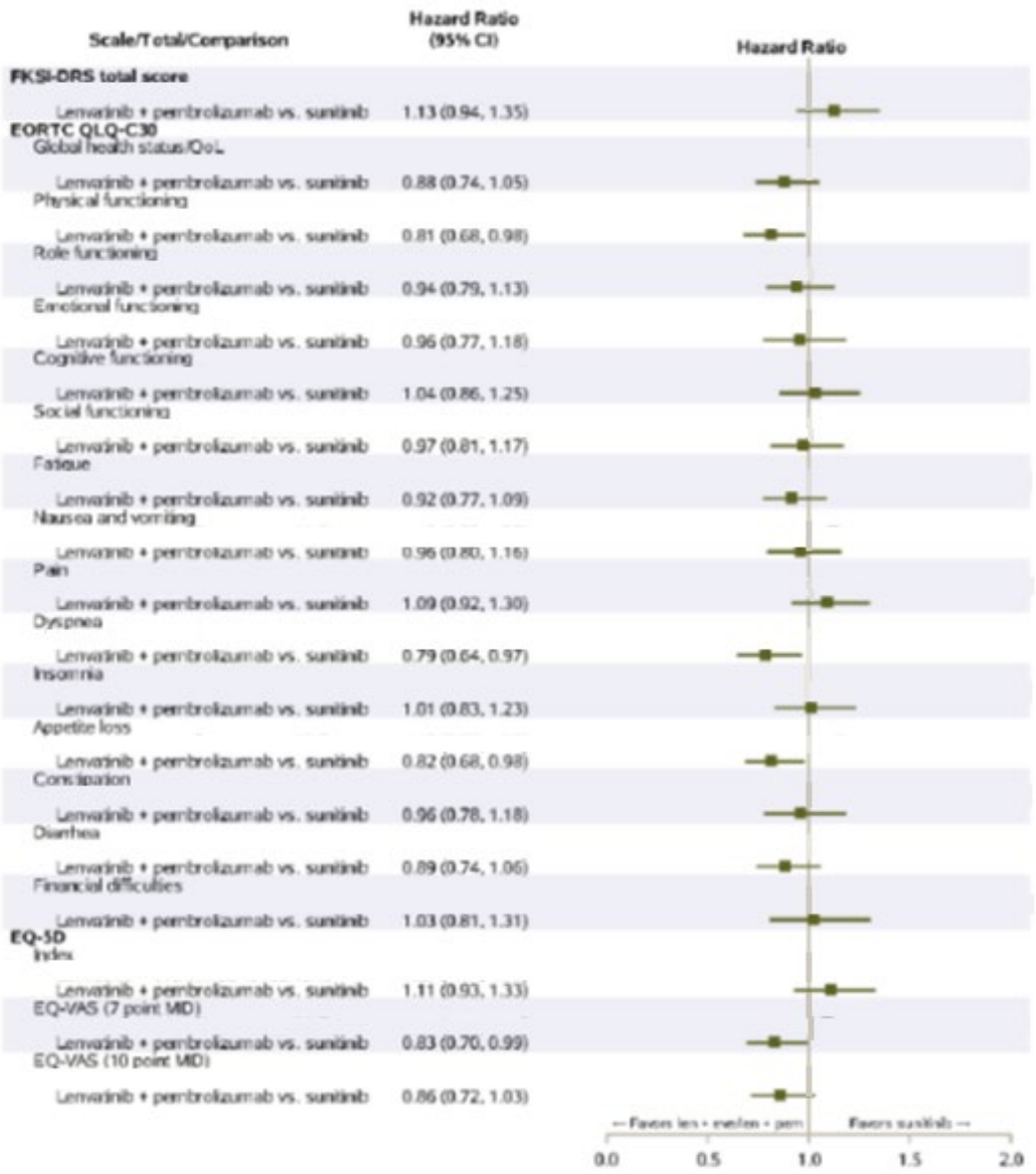
Confirmed ORR per investigator assessment was consistent with the confirmed ORR by IIR. The treatment difference between the arms was 34.6% (95% CI: 27.7, 41.4). The OR was 4.30 (95% CI: 3.13, 5.90; nominal P<0.0001) in favor of the combination treatment. The proportion of subjects who achieved a confirmed CR per investigator assessment from lenvatinib plus pembrolizumab and sunitinib was lower to that achieved by IIR (10.1% and 2.0%, respectively).

Health Related Quality of Life

The impact of treatment on health related quality of life (HRQoL) was assessed using the Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease-Related Symptoms (FKSI-DRS), the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Patients With Cancer–Core 30 (EORTC QLQ-C30), and the EQ-5D-3L with the associated EuroQoL Visual Analogue Scale (EQ-VAS). All statistical comparisons are nominal in nature and should be interpreted as exploratory.

Subjects who received lenvatinib plus pembrolizumab had better maintenance of HRQoL and less severe symptoms compared to those who received sunitinib. With a mean follow-up time of 46 weeks from baseline, the longitudinal analysis of changes from baseline favored lenvatinib plus pembrolizumab for many scales, and the difference was significant for the EORTC QLQ-C30 physical functioning scale as well as for symptoms of fatigue, dyspnea, and constipation. From the EORTC QLQ-C30, time to first deterioration HRs favored lenvatinib plus pembrolizumab for several measures, and the HRs indicated a significant difference for physical functioning, dyspnea and appetite loss. Time to definitive deterioration results all favored lenvatinib plus pembrolizumab, and the HRs indicated a significant difference for every scale except for cognitive functioning and financial difficulties. When compared to sunitinib, lenvatinib plus pembrolizumab had prolonged time to definitive deterioration of the following functions and symptoms: physical functioning (56 weeks longer), role functioning (27 weeks longer), social functioning (27 weeks longer), fatigue (51 weeks longer), insomnia (30 weeks longer), dyspnea (27 weeks longer), nausea and vomiting (16 weeks longer), pain (14 weeks longer), appetite loss (10 weeks longer), and diarrhea (6 weeks longer).

Figure 14 Hazard Ratios for Time to First Deterioration



CI = confidence interval; FKSI-DRS = Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease-Related Symptoms, MID = minimally important difference; QoL = quality of Life; VAS = visual analog scale

Ancillary analyses

Subgroup analysis

PFS

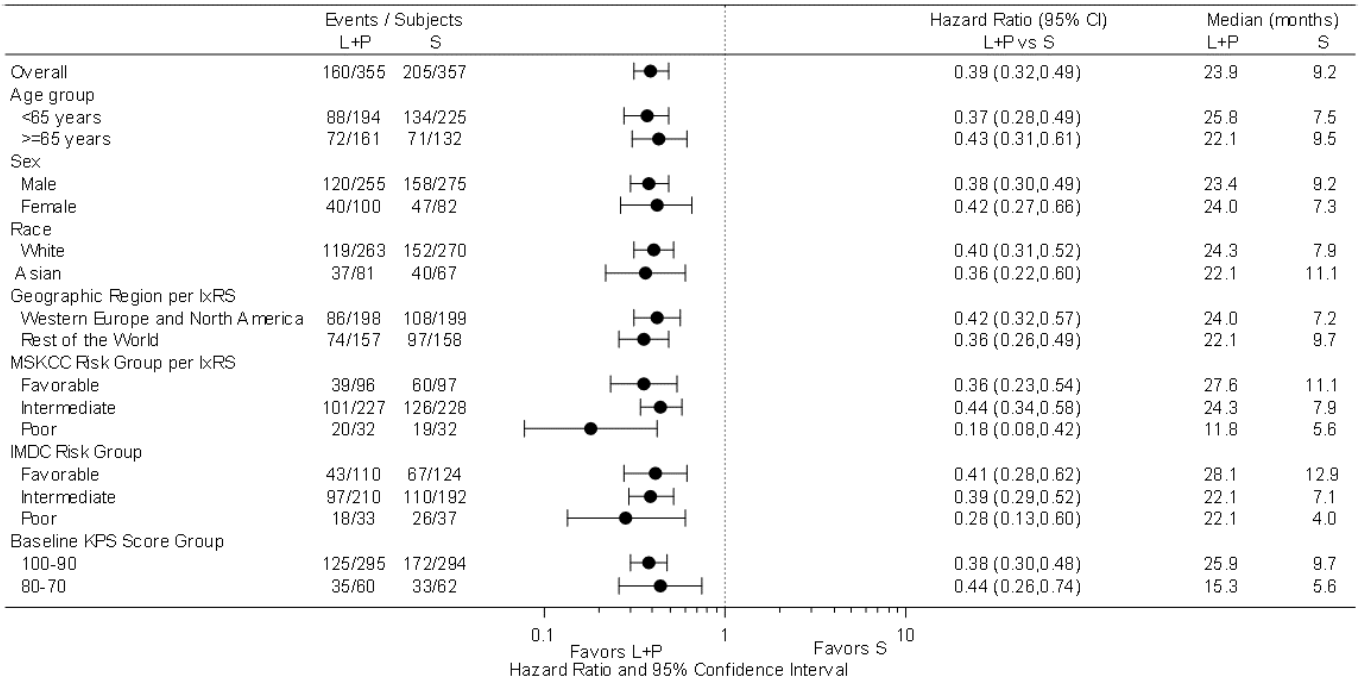


Figure 15 *Forest Plot of PFS Hazard Ratio by Subgroup Factors*

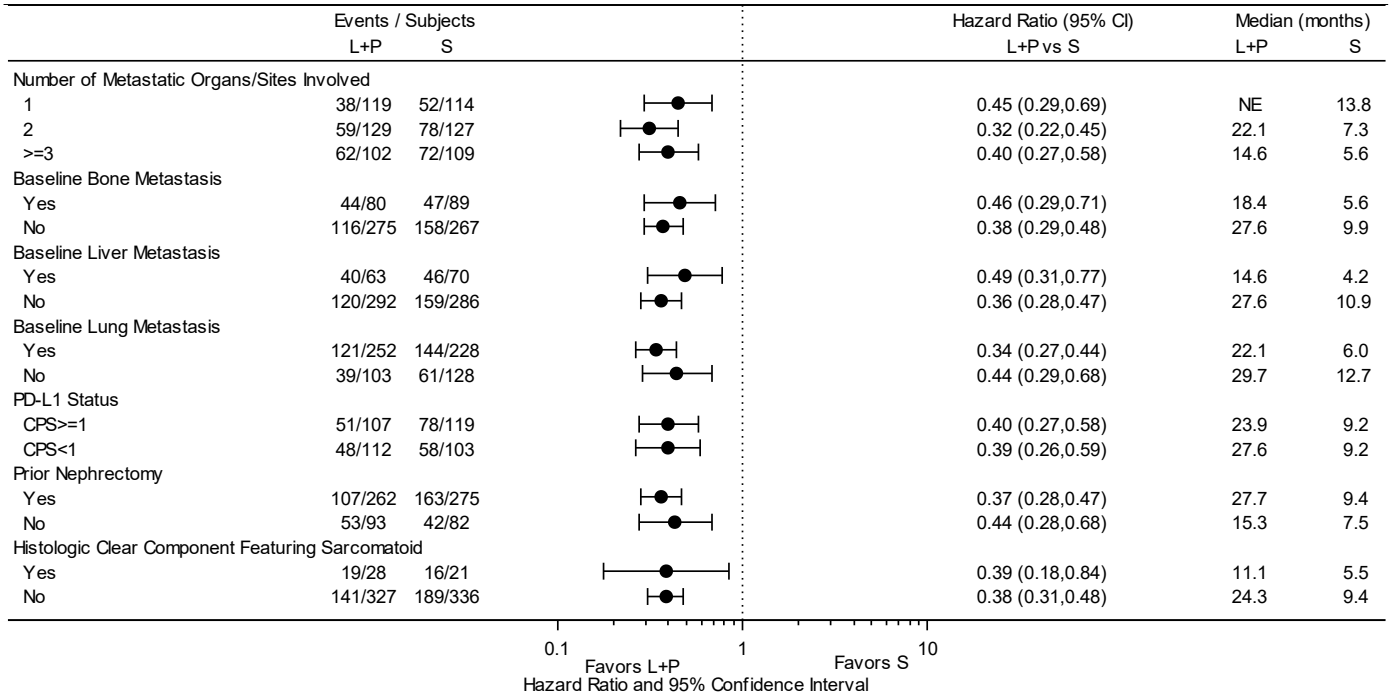


Figure 16 *Forest Plot of PFS Hazard Ratio by Subgroup Factors*

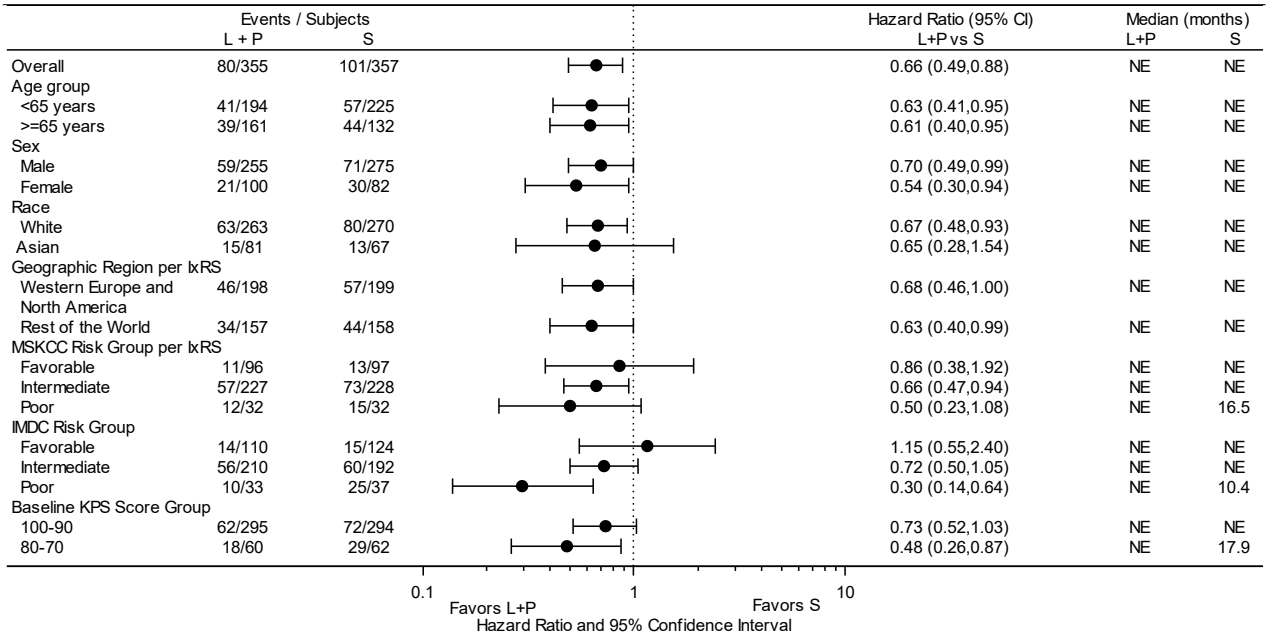
Data cutoff date: 28 Aug 2020.CPS = combined positive score, CSR = clinical study report, IMDC = International Metastatic Renal Cell Carcinoma Database Consortium, IxRS = interactive voice and web response system, KPS = Karnofsky Performance Status, MSKCC = Memorial Sloan-Kettering Cancer Center, L = lenvatinib, P = pembrolizumab, PD-L1 = programmed cell death ligand-1, RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, S = sunitinib.

If a stratification factor was the same as the respective subgroup, this factor was excluded from stratified analysis.

Median was estimated by Kaplan-Meier method and the 95% CIs were estimated with a generalized Brookmeyer and Crowley method.

Hazard ratio was estimated from Cox Proportional Hazard Model including treatment group as a factor and stratified by IxRS stratification factors. Efron method was used for ties.

OS subgroup analysis



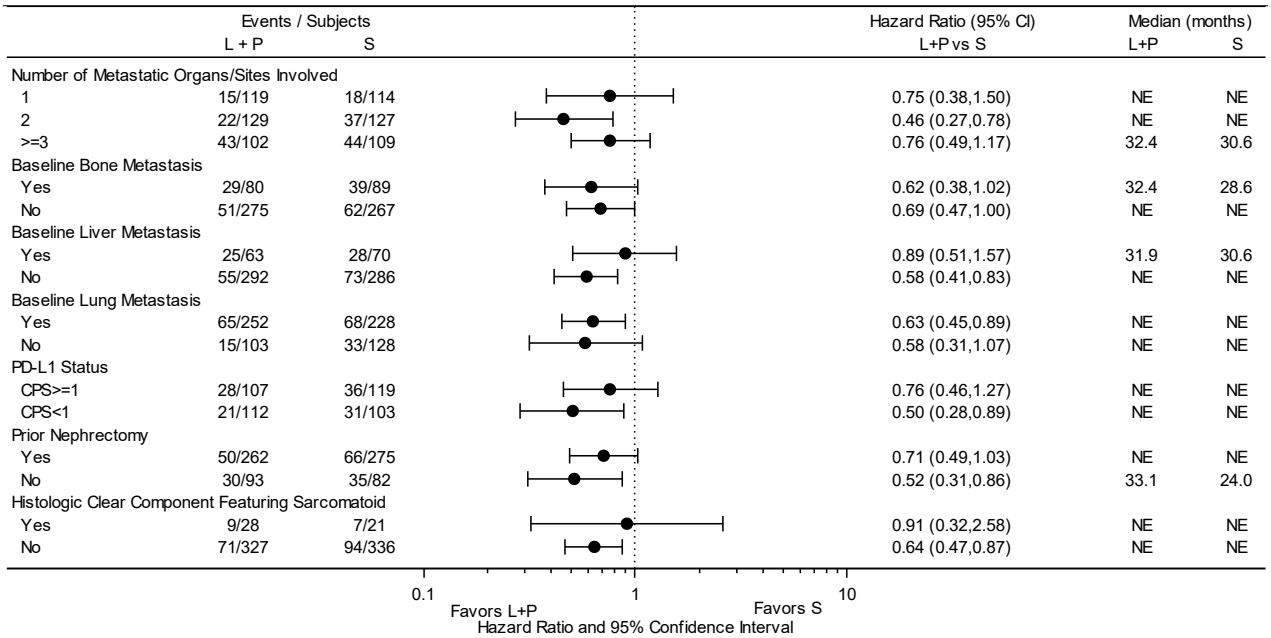


Figure 17 Study 307: Forest Plot of Hazard Ratio for Lenvatinib plus Pembrolizumab vs Sunitinib in Overall Survival – Full Analysis Set

Data cutoff date: 28 Aug 2020. CPS = combined positive score, CSR = clinical study report, IMDC = International Metastatic Renal Cell Carcinoma Database Consortium, IxRS = interactive voice and web response system, KPS = Karnofsky Performance Status, MSKCC = Memorial Sloan-Kettering Cancer Center, L = lenvatinib, P = pembrolizumab, PD-L1 = programmed cell death ligand-1, RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, S = sunitinib. If a stratification factor was the same as the respective subgroup, this factor was excluded from stratified analysis. Median was estimated by Kaplan-Meier method and the 95% CIs were estimated with a generalized Brookmeyer and Crowley method. Hazard ratio was estimated from Cox Proportional Hazard Model including treatment group as a factor and stratified by IxRS stratification factors. Efron method was used for ties. Source: Study 307 CSR, Figure 14.2.2.2.2.1.2.

Summary of main study

The following table summarise the efficacy results from the main study 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 22 Summary of Efficacy for trial KEYNOTE-581

Title: A Multicenter, Open-label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination with Everolimus or Pembrolizumab Versus Sunitinib Alone in First-Line Treatment of Subjects with Advanced Renal Cell Carcinoma (CLEAR).		
Study identifier	E7080-G000-307 / KEYNOTE 581	
Design	Study 307/KEYNOTE-581 (Study 307) is an ongoing multicenter, randomized, open-label, Phase 3 study evaluating lenvatinib plus everolimus (Arm A) or lenvatinib plus pembrolizumab (Arm B) versus sunitinib alone (Arm C) as first-line treatment in advanced renal cell carcinoma. This submission is for the combination of lenvatinib plus pembrolizumab, as such, the focus for efficacy data is the comparison of Arm B and Arm C. Primary objective: to determine the superiority of either combination relative to sunitinib alone in improving progression-free survival (PFS). Key secondary efficacy objectives were to assess overall survival (OS) and objective response rate (ORR).	
	Duration of main phase:	13 Oct 2016 (first subject signed informed consent) to 28 Aug 2020 (data cutoff date for this submission).
	Duration of Run-in phase:	Not applicable.
	Duration of Extension phase:	Will continue as long as the subject is alive, unless the subject withdraws consent, is lost to follow-up, or the sponsor terminates the study.
Hypothesis	Superiority Hypothesis: PFS of lenvatinib plus pembrolizumab is superior to sunitinib alone. Hypothesis: OS of lenvatinib plus pembrolizumab is superior to sunitinib alone. Hypothesis: ORR of lenvatinib plus pembrolizumab is superior to sunitinib alone.	
Treatments groups	Len + Pem (Arm B)	Lenvatinib 20 mg PO QD plus pembrolizumab 200 mg by intravenous infusion once every 3 weeks during each 21-day cycle. N=355 (Full Analysis Set)
	Sunitinib (Arm C)	Sunitinib 50 mg PO QD given for 4 weeks on followed by 2 weeks off (Schedule 4/2). N=357 (Full Analysis Set)

Endpoints and definitions	Primary endpoint	PFS	PFS as assessed by independent imaging review using RECIST 1.1, defined as the time from the date of randomization to the date of the first documentation of disease progression or death (whichever occurred first).
	Secondary endpoint	OS	OS, defined as the time from the date of randomization to the date of death from any cause. Subjects who were lost to follow-up and those who were alive at the data cutoff date were censored, either at the last date the subject was last known alive or at the data cutoff date, whichever occurred first.
	Secondary endpoint	ORR	ORR, defined as the proportion of subjects who had best confirmed overall response of complete response or partial response as determined by independent imaging review using RECIST 1.1.
Database lock	28 August 2020 (data cutoff date for this submission)		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set (Intent-to-Treat Analysis Population): All randomized subjects regardless of the treatment actually received. This was the primary analysis population used for all efficacy analyses, which was based on the intent-to-treat principle.		
Descriptive statistics and estimate variability	**Treatment group**	**Len + Pem (N=355)**	**Sunitinib (N=357)**
	Median PFS, mos. (95% CI)[a]	23.9 (20.8, 27.7)	9.2 (6.0, 11.0)
	Stratified HR vs Sunitinib (95% CI)[b,c]	0.39 (0.32, 0.49)	-
	Stratified Log-rank Test *P* value vs Sunitinib[c]	<0.0001	-
	Median OS, mos. (95% CI)[a]	NE (33.6, NE)	NE (NE, NE)
	Stratified HR vs Sunitinib (95% CI)[b,c]	0.66 (0.49, 0.88)	-
	Stratified Log-rank Test *P* value vs Sunitinib[c]	0.0049	-
	ORR, % (95% CI)[d]	71.0 (66.3, 75.7)	36.1 (31.2, 41.1)
	Difference (%) vs Sunitinib		
	(95% CI)[d]	34.9	
		(28.0, 41.7)	

	CI = confidence interval; HR = hazard ratio; Len = lenvatinib; mos = months; NE = not estimable; ORR = objective response rate; OS = overall survival; P = probability; Pem = pembrolizumab; PFS = progression-free survival a. Quartiles are estimated by Kaplan–Meier method, and the 95% CIs are estimated with a generalized Brookmeyer and Crowley method. b. Hazard ratio is based on a Cox Proportional Hazard Model including treatment group as a factor, Efron method is used for ties. c. Stratified by geographic region (Region 1: Western Europe and North America, Region 2: rest of the world) and MSKCC prognostic groups (favorable, intermediate, and poor risk) in IxRS. d. 95% CI is constructed using the method of Normal Approximation.
Notes	Analyses of efficacy data were also conducted using the Per Protocol Analysis Set, defined as all subjects who received at least 1 dose of any study drug, had no major protocol deviations, and had both baseline and at least 1 postbaseline tumor assessment. Prespecified subgroup analyses indicated that consistent results were observed across subgroups, MSKCC prognostic groups and PD-L1 tumor expression status.

Analysis performed across trials (pooled analyses and meta-analysis

Not applicable, see supportive studies

Clinical studies in special populations

The Applicant did not conduct clinical studies in special populations.

Supportive studies

Supportive studies to establish contribution of individual components

To establish the contribution of the individual components pembrolizumab and lenvatinib to the pembro+lenvatinib regimen in 1L advanced RCC, Keynote-581 results were assessed relative to lenvatinib monotherapy data from the 2L Study 205 and pembrolizumab monotherapy data from study KEYNOTE-427 in 1L advanced RCC, respectively. Key details of the study design, primary and secondary objectives of KEYNOTE-581, Study 205 and KEYNOTE-427 are summarized in Table 23.

Table 23 Comparison of Key Features of Study 307 versus Study 205 and KEYNOTE 427

	Study 307 (RCC-1L)		Study 205 (RCC-2L+)	KEYNOTE-427 (RCC-1L)
	Lenvatinib 20 mg + Pembrolizumab 200 mg (N=355)	**Sunitinib 50 mg (N=357)**	**Lenvatinib 24 mg Monotherapy (N=52)**	**Pembrolizumab 200 mg Monotherapy (N=110)**
Histology	Clear-cell or predominantly clear-cell RCC			Clear-cell RCC
Dose				
Lenvatinib	20 mg QD	NA	24 mg QD	NA
Pembrolizumab	200 mg Q3W	NA	NA	200 mg Q3W
Sunitinib	NA	50 mg QD[a]	NA	NA
Number of prior lines of therapy allowed	0		1 prior VEGF-targeted treatment	0
Site locations	Global, multicenter study		United States and Europe	Global, multicenter study
PD-L1 status	Enrolled regardless of status		Not collected	Enrolled regardless of status
Primary evaluation procedure	RECIST 1.1 (5 TL, up to 2 per organ)			Modified RECIST 1.1 (10 TL, up to 5 per organ)
Frequency of tumor assessment	Q8W			At Week 12, Q6W until Week 54, then Q12W until EOS

1L = first line, 2L+ = second line or greater, EOS = end of study, NA = not applicable, Q3W = every 3 weeks, Q6W = every 6 weeks, Q8W = every 8 weeks, Q12W = every 12 weeks, QD = once daily, RCC = renal cell carcinoma, RECIST = Response Evaluation Criteria in Solid Tumors, TL = target lesion, VEGF = vascular endothelial growth factor. a:Sunitinib was administered on a schedule of 4 weeks on then 2 weeks off.

Table 24 Key Demographic Characteristics Across Study 307 and the Monotherapy Studies

	Combination Therapy		**Monotherapy**	
	Study 307 (RCC-1L)		**Study 205 (RCC-2L+)**	**KEYNOTE-427 (RCC-1L)**
	Lenvatinib 20 mg + Pembrolizumab 200 mg (N=355)	**Sunitinib 50 mg (N=357)**	**Lenvatinib 24 mg Monotherapy (N=52)**	**Pembrolizumab 200 mg Monotherapy (N=110)**
Age (years)				
N	355	357	52	110
Mean (StdDv)	62.3 (10.23)	60.8 (9.96)	63.3 (8.6)	62.9 (11.0)
Median	64.0	61.0	64.0	64.0
Min, Max	34, 88	29, 82	41, 79	29, 87
Age Group, n (%)				
<65 years	194 (54.6)	225 (63.0)	29 (55.8)[a]	58 (52.7)
≥65 years	161 (45.4)	132 (37.0)	23 (44.2)[a]	52 (47.3)
Sex, n (%)				
Male	255 (71.8)	275 (77.0)	39 (75.0)	86 (78.2)
Female	100 (28.2)	82 (23.0)	13 (25.0)	24 (21.8)
Race, n (%)				
White	263 (74.1)	270 (75.6)	52 (100.0)	98 (89.1)
Black or African American	2 (0.6)	3 (0.8)	0	0
Asian	81 (22.8)	67 (18.8)	0	11 (10.0)
Other	4 (1.1)	7 (2.0)	0	1 (0.9)
Missing	5 (1.4)	10 (2.8)	-	-
Ethnicity, n (%)				
Hispanic or Latino	12 (3.4)	20 (5.6)	2 (3.8)	3 (2.7)
Not Hispanic or Latino	339 (95.5)	334 (93.6)	50 (96.2)	103 (93.6)
Not Reported	-	-	-	2 (1.8)
Unknown	4 (1.1)	3 (0.8)	0	2 (1.8)
KPS at Baseline, n (%)				

	Combination Therapy		Monotherapy	
	Study 307 (RCC-1L)		Study 205 (RCC-2L+)	KEYNOTE-427 (RCC-1L)
	Lenvatinib 20 mg + Pembrolizumab 200 mg (N=355)	Sunitinib 50 mg (N=357)	Lenvatinib 24 mg Monotherapy (N=52)	Pembrolizumab 200 mg Monotherapy (N=110)
100-90	295 (83.1)	294 (82.4)	Not collected	88 (80.0)
80-70	60 (16.9)	62 (17.4)		22 (20.0)
Missing	0 (0.0)	1 (0.3)		0
ECOG PS at Baseline, n (%)				
0	-	-	29 (55.8)	Not collected
1	-	-	23 (44.2)	

Data cutoff date: 28 Aug 2020 for Study 307, 07 Sep 2018 for KEYNOTE-427 and 13 Jun 2014 for Study 205. Percentages are based on total number of subjects in the Full Analysis Set (Study 307 and 205) or All Subjects as Treated (KEYNOTE-427) set within the relevant treatment group. 1L = first line, 2L+ = second line or greater, CSR = Clinical Study Report, ECOG = Eastern Cooperative Oncology Group, KPS = Karnofsky Performance Status, Max = maximum, min = minimum, PS = performance status, RCC = renal cell carcinoma, StdDV = standard deviation. a:Less than or equal to 65 and greater than 65.

Table 25 Key Baseline Disease History and Characteristics Across Study 307 and the Monotherapy Studies

	Combination Therapy		Monotherapy	
	Study 307 (RCC-1L)		Study 205 (RCC-2L+)	KEYNOTE-427 (RCC-1L)
	Lenvatinib 20 mg + Pembrolizumab 200 mg (N=355)	Sunitinib 50 mg (N=357)	Lenvatinib 24 mg Monotherapy (N=52)	Pembrolizumab 200 mg Monotherapy (N=110)
MSKCC Prognostic Group at Baseline, n (%)				
Favorable Risk	96 (27.0)	97 (27.2)	11 (21.2)	Not collected
Intermediate Risk	227 (63.9)	228 (63.9)	18 (34.6)	
Poor Risk	32 (9.0)	32 (9.0)	23 (44.2)	
IMDC Prognostic Group at Baseline[a], n (%)				
Favorable Risk	110 (31.0)	124 (34.7)	7 (13.5)	42 (38.2)
Intermediate Risk	210 (59.2)	192 (53.8)	33 (63.5)	52 (47.3)

	Combination Therapy		Monotherapy	
	Study 307 (RCC-1L)		Study 205 (RCC-2L+)	KEYNOTE-427 (RCC-1L)
	Lenvatinib 20 mg + Pembrolizumab 200 mg (N=355)	Sunitinib 50 mg (N=357)	Lenvatinib 24 mg Monotherapy (N=52)	Pembrolizumab 200 mg Monotherapy (N=110)
Poor Risk	33 (9.3)	37 (10.4)	12 (23.0)	16 (14.5)
Not evaluable	2 (0.6)	4 (1.1)	0	0
RCC Diagnosis Classification, n (%)				
Clear Cell	354 (99.7)	357 (100)	51 (98.1)	100 (90.9)
Clear Cell with Additional Features[b], n (%)				
Papillary	23 (6.5)	21 (5.9)	Not collected	Not collected
Chromophobe	2 (0.6)	1 (0.3)		
Sarcomatoid	28 (7.9)	21 (5.9)		
Other	17 (4.8)	28 (7.8)		
Other	1 (0.3)	0 (0.0)	0	10[c]
Lesion Organ/Site Locations[b], [d], n (%)				
Lung	252 (71.0)	228 (63.9)	Not collected	73 (66.4)
Lymph Node	162 (45.6)	156 (43.7)		46 (41.8)
Bone	80 (22.5)	89 (24.9)		23 (20.9)
Kidney	91 (25.6)	88 (24.6)		0
Liver	63 (17.7)	70 (19.6)		14 (12.7)
Adrenal	53 (14.9)	66 (18.5)		17 (15.5)
Brain	6 (1.7)	10 (2.8)		0
Other	109 (30.7)	123 (34.5)		0
Number of Metastatic Organs/Sites Involved[d, e], n (%)				
0	5 (1.4)	6 (1.7)	Not collected	0
1	119 (33.5)	114 (31.9)		29 (26.4)
2	129 (36.3)	127 (35.6)		NA
≥2	NA	NA		75 (68.2)
≥3	102 (28.7)	109 (30.5)		NA

	Combination Therapy		Monotherapy	
	Study 307 (RCC-1L)		Study 205 (RCC-2L+)	KEYNOTE-427 (RCC-1L)
	Lenvatinib 20 mg + Pembrolizumab 200 mg (N=355)	Sunitinib 50 mg (N=357)	Lenvatinib 24 mg Monotherapy (N=52)	Pembrolizumab 200 mg Monotherapy (N=110)
Missing	0	1 (0.3)		6 (5.5)
RCC Sarcomatoid Component by Histology, n (%)				
Yes	28 (7.9)	21 (5.9)	Not collected	11 (10.0)
No	327 (92.1)	336 (94.1)		60 (54.5)
Unknown	0	0		30 (27.3)
Missing	0	0		9 (8.2)
PD-L1 Status[f], n (%)				
Positive (CPS ≥1)	107 (30.1)	119 (33.3)	Not collected	52 (47.3)
Negative (CPS <1)	112 (31.5)	103 (28.9)		58 (52.7)
Not Available	136 (38.3)	135 (37.8)		0
Prior Nephrectomy, n (%)				
Yes	262 (73.8)	275 (77.0)	48 (96.0)[h]	92 (83.6)
No	93 (26.2)	82 (23.0)	2 (4.0)[h]	18 (16.4)
Prior Radiotherapy, n (%)				
Yes	48 (13.6)[g]	46 (13.5)[g]	11 (21.2)	16 (14.5)
No	304 (86.4)[g]	294 (86.5)[g]	41 (78.8)	94 (85.5)
Number of prior lines of systemic anticancer therapy, n (%)				
0	355 (100)	357 (100)	0	110 (100)
1	0	0	46 (88.5)	0
2	0	0	4 (7.7)	0
3	0	0	2 (3.8)	0

Data cutoff date: 28 Aug 2020 for Study 307, 07 Sep 2018 for KEYNOTE-427 and 13 Jun 2014 for Study 205.

Percentages are based on total number of subjects in the Full Analysis Set (Study 307 and 205) or All Subjects as Treated (KEYNOTE-427) set within the relevant treatment group.
1L = first line, 2L+ = second line or greater, CPS = combined positive score, CSR = Clinical Study Report, ECOG= Eastern Cooperative Oncology Group, IMDC = International Metastatic Renal Cell Carcinoma Database Consortium, KPS = Kanofsky Performance Status, Max = maximum, Min = minimum, MSKCC = Memorial Sloan Kettering Cancer Center; NA = not available, PD-L1 = programmed death ligand 1, RCC = renal cell carcinoma, StdDV = standard deviation.

a: IMDC prognostic group at baseline is based on total risk score from 6 prognostic factors at baseline: KPS, Hemoglobin, Corrected serum calcium, neutrophils, platelets, and time from first RCC diagnosis to randomization.

b: Subjects may be represented in more than 1 category.

c: In KN-427 there were 4 subjects with clear cell component and 6 unknown RCC diagnosis classification.

d: For Study 307, lesion organ/site locations were derived from independent imaging review. For KN-427 number of metastatic organ and sites of metastasis are based on investigator assessment.

e: Kidney is not included in the number of metastatic organs/sites.

f: PD-L1 status was determined using an investigational version of the PD-L1 immunohistochemistry 22C3 pharmDx (Agilent, Santa Clara, CA, USA) and a provisional CPS, which was defined as the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100. The CPS cutoff value is 1

g: Percentages are based on the total number of subjects in the Safety Analysis Set within the relevant treatment group (N = 352 for lenvatinib plus pembrolizumab, and N = 340 for sunitinib).

h: Source: Appendix Table 14.1.7.2.1 in Module 2.7.3 from the original RCC Study 205 submission for updated prior nephrectomy.

Table 26 Study Treatment Exposure Across Study 307 and the Monotherapy Studies

	Combination Therapy		**Monotherapy**	
	Study 307 (RCC-1L)		**Study 205 (RCC-2L+)**	**KEYNOTE-427 (RCC-1L)**
Extent of Exposure	**Lenvatinib 20 mg + Pembrolizumab 200 mg (N=352)**	**Sunitinib 50 mg (N=340)**	**Lenvatinib 24 mg Monotherapy (N=52)**	**Pembrolizumab 200 mg Monotherapy (N=110)**
Overall: Duration of Treatment (months)[a]				
n	352	340	NA	NA
Mean (StdDv)	17.29 (9.575)	11.33 (9.463)		
Median	17.00	7.84		
Q1, Q3	9.43, 25.35	3.68, 17.81		
Minimum, Maximum	0.07, 39.13	0.10, 36.96		
Lenvatinib: Duration of Treatment (months)[a]				
n	352	NA	52	NA
Mean (StdDv)	16.45 (9.839)		7.97 (5.56)	
Median	16.13		7.38	
Q1, Q3	8.25, 25.12		3.19 - 11.5	
Minimum, Maximum	0.07, 39.13		0.13 - 23.0	
Pembrolizumab/Sunitinib: Duration of Treatment (months)[a]	Pembrolizumab	Sunitinib	NA	Pembrolizumab

n	352	340	NA	110
Mean (StdDv)	14.45 (8.562)	11.33 (9.463)		11.34 (8.903)
Median	15.08	7.84		8.54
Q1, Q3	6.90, 23.46	3.68, 17.81		Not available
Minimum, Maximum	0.03, 29.60	0.10, 36.96		0.03, 26.68

Data cutoff date: 28 Aug 2020 for Study 307, 24 Feb 2020 for KEYNOTE-427 and 13 Jun 2014 for Study 205. Percentages are based on the Safety Analysis Set for Study 307 and the Full Analysis Set for Study 205 and All Subjects as Treated Set for KN-427. 1L = first line, 2L+ = second line or greater, CI = confidence interval, CSR = Clinical Study Report, n = number of subjects, NA = not applicable, Q = quartile, RCC = renal cell carcinoma, StdDv = standard deviation.a:Duration of treatment in Study 307 = (date of last dose of study drug–date of first dose of study drug+1)/30.4375. Duration of treatment in Study 205 = date of last dose of study drug - date of first dose of study drug + 1. Duration of treatment in KEYNOTE-427 = number of days between first dose date and last dose date.

Contribution of lenvatinib

Table 27 Summary of Efficacy data Across Study 307 and the Monotherapy Study KEYNOTE-427

	Combination Therapy		**Monotherapy**
	Study 307(RCC-1L)		**KEYNOTE-427 (RCC-1L)**
	Lenvatinib 20 mg + Pembrolizumab 200 mg (N=355)	**Sunitinib 50 mg (N=357)**	**Pembrolizumab 200 mg Monotherapy (N=110)**
Best Overall Response, n (%)			
Complete Response	57 (16.1)	15 (4.2)	4 (3.6)
Partial Response	195 (54.9)	114 (31.9)	36 (32.7)
Stable Disease	68 (19.2)	136 (38.1)	35 (31.8)
Progressive Disease	19 (5.4)	50 (14.0)	33 (30.0)
No Assessment[a]	-	-	2 (1.8)
Objective Response Rate (CR + PR), n (%)	252 (71.0)	129 (36.1)	40 (36.4)
95% CI	(66.3, 75.7)[b]	(31.2, 41.1)[b]	(27.4, 46.1)[s]
Subjects with PFS events, n (%)	160 (45.1)	205 (57.4)	80 (72.7)
Median PFS (months)	23.9	9.2	7.1
95% CI for Median PFS	(20.8, 27.7)	(6.0, 11.0)	(5.6, 11.0)

	Combination Therapy		**Monotherapy**
	Study 307(RCC-1L)		**KEYNOTE-427 (RCC-1L)**
	Lenvatinib 20 mg + Pembrolizumab 200 mg (N=355)	**Sunitinib 50 mg (N=357)**	**Pembrolizumab 200 mg Monotherapy (N=110)**
Median (95% CI) follow-up time for PFS (months)	22.3 (21.1, 25.6)	16.6 (13.1, 18.5)	NA
Lenvatinib + Pembrolizumab vs Sunitinib			
Stratified HR (95% CI)[b,c]	0.39 (0.32, 0.49)		NA
Stratified Log-rank Test *P* value[c]	<0.0001		NA
Deaths, n (%)	80 (22.5)	101 (28.3)	48 (43.6)
Median OS (months)	NR	NR	NR
95% CI for Median OS	(33.6, NE)[a]	(NE, NE)[a]	(31.2, NE)
Lenvatinib + Pembrolizumab vs Sunitinib			
Stratified HR (95% CI)[b,c]	0.66 (0.49, 0.88)		NA
Stratified Log-rank Test *P* value[c]	0.0049		NA
OS Rate (95% CI)[d] at			
12 months	91.4 (87.9, 93.9)	80.2 (75.5, 84.1)	88.2 (80.5, 93.0)
18 months	87.1 (83.1, 90.3)	74.4 (69.3, 78.8)	80.0 (71.2,86.3)
24 months	79.2 (74.1, 83.3)	70.4 (65.0, 75.2)	70.8 (61.3,78.4)
Median Follow-Up Time for OS (months; 95% CI)	26.7 (25.9, 27.4)[a]	26.3 (25.4, 27.2)[a]	34.2 (NA)[e]

The contribution of lenvatinib to the pembrolizumab+lenvatinib combination in KN-581 is supported by comparison with pembrolizumab monotherapy data from the uncontrolled KN-427 study.

A summary of key demographic and baseline characteristics for patients in the two studies is provided in Table 25.

Contribution of pembrolizumab

Study 205 demonstrated the efficacy of lenvatinib monotherapy in 2L. However, the efficacy of lenvatinib monotherapy in 1L advanced RCC can be estimated from: 1) data for VEGF TKIs approved as 1L therapy, and 2) data for VEGF TKIs with published activity in 1L and 2L advanced RCC.

Table 28 Summary of Tumor Response per Independent Imaging Review Using RECIST 1.1 Across Study 307 and the Monotherapy Studies

	Combination Therapy		**Monotherapy**
	Study 307 (RCC-1L)		**Study 205 (RCC-2L+)**
	Lenvatinib 20 mg + Pembrolizumab 200 mg (N=355)	**Sunitinib 50 mg (N=357)**	**Lenvatinib 24 mg Monotherapy (N=52)**
Best Overall Response, n (%)			
Complete Response	57 (16.1)	15 (4.2)	1 (1.9)
Partial Response	195 (54.9)	114 (31.9)	17 (32.7)
Stable Disease	68 (19.2)	136 (38.1)	NA
Progressive Disease	19 (5.4)	50 (14.0)	NA
Objective Response Rate (CR + PR), n (%)	252 (71.0)	129 (36.1)	18 (34.6)
95% CI	(66.3, 75.7)[b]	(31.2, 41.1)[b]	(22.0, 49.1)[c]
Subjects with PFS events, n (%)	160 (45.1)	205 (57.4)	33 (63.5)
Median PFS (months)	23.9	9.2	9.0[a]
95% CI for Median PFS	(20.8, 27.7)	(6.0, 11.0)	(5.6, 10.2)[a]
Median (95% CI) follow-up time for PFS (months)	22.3 (21.1, 25.6)	16.6 (13.1, 18.5)	12.7 (10.7, 18.4)[a]

Table 29 Efficacy of Monotherapy VEGF TKIs in 1L and 2L Advanced RCC

Drug	ORR (95% CI) in 1L setting	ORR (95% CI) in 2L setting
Pazopanib	30% (25.1, 35.6)[a]	27% [b, c]
Sunitinib	27.5% (23.0, 32.3)[d]	23% (13.2, 35.5)[e]
Cabozantinib	20% (12.0, 30.8)[f]	17% (13, 22)[f]
Sorafenib	NA	2% [c, g]
Axitinib	32%[c, h]	19.4% (15.4, 23.9)[i]

1L = first line, 2L = second line, NA = not applicable, ORR = objective response rate, RCC = renal cell carcinoma, TKI = tyrosine kinase inhibitor, VEGF = vascular endothelial growth factor.Approved 1L: pazopanib, sunitinib, and cabozantinib.Approved 2L: cabozantinib, sorafenib, axitinib.a:VOTRIENT USPI, 2020; VOTRIENT SmPC, 2020.b:Hainsworth, et al., 2013.c:95% CI not reported.d:SUTENT USPI, 2020; SUTENT SmPC, 2020.e:Rini, et al., 2008.f:CABOMETYX USPI, 2021; CABOMETYX SmPC, 2020; Choueiri et al., 2016.g:NEXAVAR USPI, 2020; NEXAVAR SmPC, 2019..h:Hutson, et al., 2013.i:INLYTA USPI, 2020; INLYTA SmPC, 2020; Rini et al., 2012.

Table 29 presents ORR, as a direct measure of anti-tumor activity, for VEGF TKIs as monotherapy in 1L and 2L advanced RCC. For approved 1L therapy (pazopanib, sunitinib and cabozantinib) the point estimate of ORR ranges from 20% to 30%; the highest upper bound CI is 35.6%. The difference in ORR between 1 and 2L is maximum 13%.

2.4.3. Discussion on clinical efficacy

The new claimed indication for Keytruda in combination with lenvatinib is for the treatment of previously untreated adult patients with advanced renal cell carcinoma (RCC). This application is based on the results of the pivotal study KEYNOTE-581.

KN-581 is a phase III, randomized, open-label study of pembrolizumab+lenvatinib vs. sunitinib in subjects with previously untreated, advanced renal cell carcinoma with a clear-cell component. No prior adjuvant or neoadjuvant therapy was allowed. The study was open-label but given that the primary endpoint PFS was BICR-assessed and that OS was a key secondary endpoint, this is acceptable.

The patient population was adequate and inclusion/exclusion criteria are acceptable in general. Only patients with KPS≥70% and measurable disease at baseline (RECIST 1.1) were enrolled. Tumour tissue, archival or recent acquisition was required at study entry. Subjects were enrolled regardless of PD-L1 expression level.

Although the Applicant is seeking approval in RCC (independent of the histology), no patients with non-clear cell RCC were included. However, in view of the mechanism of action of the combination it is not expected that efficacy is restricted to the clear-cell histological subtype.

Patients in the trial were classified according to MSKCC scores which includes 5 risk factors (KPS< 80, anemia, hypocalcemia, neutropenia and time from diagnosis to treatment initiation < 1 year). The MSKCC risk category was favorable for 27.2% of patients, intermediate for 63.8%, and poor for 9.0%.

A total of 1417 participants were screened and 1069 were randomly allocated from across 200 global study sites in North America, Europe, and Asia. Baseline demographics and disease characteristics were balanced for the pembro+lenvatinib arm and the sunitinib arm, in general.

. The use of sunitinib as comparator appears acceptable taking into account that this was the preferred option for patients with all risk groups at the time of study initiation in 2016. The shift to new standard of

care in first line RCC across IMDC risk categories to combination regimens (pembrolizumab + axitinib or nivolumab + ipilimumab) occurred in European guidelines (ESMO, EAU) during 2018, 2019 and 2020.

PFS as primary endpoint of the pivotal study is acceptable as prolonged PFS as such is considered to be of benefit to the patient and since OS is reported as key secondary endpoint (EMA/CHMP/205/95 Rev.6). OS and ORR as secondary endpoints are acceptable.

The primary endpoint PFS was planned to be tested by means of a stratified logrank test, stratified for the randomization stratification variables (Geographic region and MSKCC prognostic groups). Similarly, the key-secondary endpoint OS was planned to be tested next in hierarchy (in a graphical approach) by means of a stratified logrank test with the same stratification variables. This is considered adequate, although uncertainty exist with regard to the censoring rules for PFS. Subjects were censored if they progressed or died after initiation of subsequent anticancer therapy, and this type of censoring may likely be informative.

Multiplicity was accounted for by application of a graphical approach, An initial α of 0.045 was allocated to the comparison of lenvatinib + pembrolizumab (arm B) vs sunitinib (arm C), the remaining alpha was allocated as 0.0001 to an early analysis of ORR, and 0.0049 to the comparison of arm A vs C. It was planned to forward α from PFS to OS, and then to ORR, whereby portions of α were planned to be forwarded to the comparison of arm A vs C (and vice versa from A vs C to B vs C) higher in hierarchy (e.g. from OS to PFS). This is in principle considered acceptable. Interim analyses were introduced during the course of the study. These were planned to be adjusted for by means of alpha-spending functions, which is acceptable.

Regarding the randomized (ITT) patient population (Arm B and Arm C; n=712), there were no meaningful imbalances in patients' demographic and baseline characteristics among treatment arms. The median age of 62.0, and the male (74.4%) and white (74.9 %) preponderance of patients is considered representative of the EU target population. The percentage of enrolled patients across IDMC prognostic score categories (i.e. 32.9% favourable; 56.5 intermediate; and 9.8% poor risk) is acceptable, however patients with poor risk factors seemed to be underrepresented in this trial.

Acceptable mature PFS results (event rate pembrolizumab + lenvatinib 45.1%; sunitinib: 57.4%) show a statistically significant improvement in PFS per IIR for pembrolizumab+ lenvatinib compared with sunitinib. There was a clear, early separation (from 2 months on) of the PFS KM curves that widened over time. Results for PFS by investigator assessment were consistent with those of PFS by IIR Median PFS was 23.9 months for lenvatinib plus pembrolizumab compared with 9.2 months for sunitinib (HR=0.39, [95% CI: 0.32, 0.49], nominal P<0.0001 This PFS benefit can be regarded as clinically relevant.

Rather immature OS results (death rate pembrolizumab+lenvatinib: 22.5%; sunitinib: 28.3%; median OS not reached in either arm) already show a statistically significant improvement in OS for pembrolizumab+lenvatinib compared with sunitinib. There was a clear, separation after 3 month of the OS KM curves. This OS benefit (HR 0.66 (95% CI: 0.49, 0.88, P=0.0049) provides support for the primary endpoint PFS and the combination of PFS and OS benefit could be regarded as being (clinically) relevant to patients.

The Key secondary endpoint ORR as assessed by IIR was also statistically significantly higher with pembrolizumab+lenvatinib compared to sunitinib: 71.0% vs 36.1%. In addition, more patients in the pembrolizumab+lenvatinib arm had a CR compared to the sunitinib arm: 16.1% vs 4.2%. The investigator-assessed ORR results were confirmatory. Among subjects who responded, the DOR was longer in the lenvatinib plus pembrolizumab arm compared with the sunitinib arm. The median DOR in responders was 25.8 months (95% CI: 22.1, 27.9) in the lenvatinib plus pembrolizumab arm and 14.6 months (95% CI: 9.4, 16.7) in the sunitinib arm.

Secondary endpoint HRQoL results are considered of a descriptive, hypothesis-generating nature only. It is, nevertheless, noted that subjects who received lenvatinib plus pembrolizumab had better maintenance of HRQoL and less severe symptoms compared to those who received sunitinib.

PFS2 results were immature (event rate pembrolizumab +lenvatinib 27.9%; sunitinib: 43.7%; median PFS2 not reached in the pembrolizumab+lenvatinib arm and at IA3 a relatively low percentage of patients had received subsequent systemic anti-cancer therapy), however PFS2 data could be regarded as supportive.

Subgroup analysis

PFS and HRs for almost all subgroups favoured pembrolizumab+ lenvatinib vs sunitinib (HR <1).

Only in the subgroup of patients with favourable IMDC prognostic score (n=110), the point estimate of the OS HR (numerically) favoured sunitinib (1.15 (95% CI: 0.55, 2.40). However, an event rate of 12% is considered too immature to draw conclusions and updated OS data are requested post-approval. The 95% CI for OS HR was wide for some subgroups, indicating that there is still uncertainty on the effect on OS.

The combination of lenvatinib and pembrolizumab demonstrated superiority vs sunitinib in terms of PFS; in addition, OS and ORR results favour lenvatinib and pembrolizumab treatment vs sunitinib. However, the immaturity of OS data remains at present the main source of uncertainty for benefit/risk assessment, including in the relevant subgroups. The MAH is recommended to submit the final OS analysis from the E7080-G000-307/KEYNOTE 581 study which is comparing the efficacy and safety of pembrolizumab in combination with lenvatinib and lenvatinib plus everolimus vs. sunitinib monotherapy as a first-Line treatment of patients with advanced RCC.

Contribution of each component in the combination regimen.

The absence of a clinical trial testing the combination and monotherapies (pembrolizumab and lenvatinib) leads to uncertainties when it comes to reaching a benefit risk conclusion. Nevertheless the antitumor activity of the combination was greater than either monotherapy in murine isograft models tested, however the difference between the combination treatment and lenvatinib monotherapy was not striking. To support the contribution of lenvatinib, the applicant provided data from the phase 2 trial KN-427, where 110 patients with ccRCC were included in a pembrolizumab monotherapy cohort A. Considering that the measured baseline characteristics could be regarded as comparable and the ORR rate is almost doubled with the combination, this comparison indicates a contribution of lenvatinib. In addition, various data of other trials with sunitinib as comparator and PD-L1-inhibitor and TKI as active treatment indicate that PD-1 monotherapy treatment alone is not superior to sunitinib (Powles et al. 2020; Agata et al. 1996; Motzer et al. 2019).

For substantiating the individual contribution of pembrolizumab, the MAH had provided a cross-study comparison between KEYNOTE-581 and Study205. The ORR was also almost doubled in KEYNOTE-581 compared to the monotherapy treatment in Study205. However, Study205 included 2LRCC patients. The efficacy of lenvatinib monotherapy in 1L advanced RCC was estimated from: 1) data for VEGF TKIs approved as 1L therapy, and 2) data for VEGF TKIs with published activity in 1L and 2L advanced RCC. It can be agreed that this indirect comparison provides sufficient evidence for the contribution of pembrolizumab to the pembrolizumab+lenvatinib combination in 1L RCC patients.

The lack of monotherapy experimental arms in KEYNOTE-581 prevents a precise quantitative assessment of the contribution of each component of the pembrolizumab+lenvatinib combination. Nevertheless, the additive efficacy of both individual components has sufficiently been shown in a qualitative sense based

primarily on a substantial increase in ORR over the individual agents, even though based on cross-study comparisons only.

2.4.4. Conclusions on the clinical efficacy

In the single pivotal study KEYNOTE-581, the pembrolizumab+lenvatinib combination demonstrated a clinically relevant and statistically significant improvement in PFS per IIR compared with sunitinib treatment. Pembrolizumab+lenvatinib also demonstrated a statistically significant improvement in the key secondary endpoints OS and ORR (per IIR) compared to sunitinib. However, OS data are still immature and mOS was not reached in key subgroups even with the updated OS analysis provided during the procedure. Study 307 lacked monotherapy controls, hampering the assessment of contribution of components to the lenvatinib and pembrolizumab combination. Cross-trial comparisons have been provided but evaluation of contribution of lenvatinib, either additive or synergic to pembrolizumab, has limitations due to the fact that 1L therapy in study 307 is being compared with 2L therapy in study 205. Nevertheless, the numerically higher PFS, OS and ORR for lenvatinib and pembrolizumab in study 307 compared with lenvatinib monotherapy (2L) or pembrolizumab (1L) study comparison can be viewed as supportive.

In order to further evaluate the efficacy of Kisplyx in combination with pembrolizumab in the MSKCC favourable prognosis subgroups in first line treatment of adults patients with advanced renal cell carcinoma (RCC), the MAH is recommended to submit the final OS analysis from the E7080-G000-307/KEYNOTE 581 study which is comparing the efficacy and safety of pembrolizumab in combination with lenvatinib and lenvatinib plus everolimus vs. sunitinib monotherapy as a first-Line treatment of patients with advanced RCC.

2.5. Clinical safety

Introduction

The primary data to support the safety and tolerability of the combination of lenvatinib plus pembrolizumab for the first-line treatment of patients with advanced RCC indication are from the ongoing, open-label, phase 3 Study 307 (KEYNOTE-581). Safety data from 352 subjects enrolled in Arm B of Study 307 who received at least 1 dose of either study drug (lenvatinib or pembrolizumab) and 340 subjects enrolled in Arm C who received at least 1 dose of sunitinib were used for the safety assessment in this submission:

- **Indication Safety Set** (N=352): All subjects from Study 307 with 1L RCC who received at least 1 dose of lenvatinib 20 mg or pembrolizumab 200 mg as of the data cutoff date of 28 Aug 2020.
- **Sunitinib Safety Set** (N=340): All subjects from Study 307 with 1L RCC who received at least 1 dose of sunitinib 50 mg.

Further safety data are presented from the

- **All RCC Safety Set** (N=497): Subjects from Study 307 and Study 111 with RCC who received at least 1 dose of lenvatinib 20 mg QD + pembrolizumab 200 mg as starting dose, regardless of prior anticancer therapy.

- **Non-RCC Safety Set** (N=215): Subjects in non-RCC cohorts (NSCLC, endometrial carcinoma, urothelial carcinoma, head and neck squamous cell carcinoma, and melanoma) from Study 111 and Study 115 who were treated with lenvatinib 20 mg QD + pembrolizumab 200 mg as starting dose.
- **Lenvatinib Monotherapy Safety Set** (N=1119): All subjects with starting dose level of lenvatinib 24 mg QD monotherapy from 11 studies.
- **Pembrolizumab Monotherapy RSD-A Safety Set** (N=2799): Subjects treated with pembrolizumab in studies KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, and KN010, including 1567 subjects with advanced melanoma and 1232 subjects with NSCLC.
- **Pembrolizumab Monotherapy RSD-B Safety Set** (N=5884): Subjects treated with pembrolizumab, including 5884 subjects from studies of melanoma, NSCLC, cHL, urothelial cancer, and HNSCC in EU-approved indications.

Safety data from the Indication Safety Set are assessed relative to the data from the Lenvatinib and Pembrolizumab Monotherapy Safety Sets.

Patient exposure

At the time of data cut-off (28-Aug 2020), the median **duration of treatment** was 17.00 months in lenvatinib plus pembrolizumab arm and was 7.84 months in the sunitinib arm.

The median duration of treatment with each individual study drug was longer in the Indication Safety Set than in the respective monotherapy safety sets: 16.13 months and 5.55 months, respectively, for lenvatinib; 15.08 months and 4.86 months (RSD-B), respectively, for pembrolizumab (Table 30).

In the Indication Safety Set, similar percentages of subjects received lenvatinib and pembrolizumab beyond 1 year: 64.2%, 44.0%, and 29.0% of subjects received lenvatinib for ≥12 months, ≥18 months, and ≥24 months, respectively, and 60.5%, 39.8%, and 15.6% of subjects received pembrolizumab for ≥12 months, ≥18 months, and ≥24 months, respectively.

Table 30 Duration of treatment by safety set

Duration of Treatment (Months)	Indication N=352 n (%)	Sunitinib N=340 n (%)	All RCC N=497 n (%)	Non-RCC N=215 n (%)	Lenv Monotx N=1119 n (%)	Pembro Monotx RSD-A N=2799 n (%)	Pembro Monotx RSD-B N=5884 n (%)
Overall Lenv + Pembro Treatment[a]							
n	352	NA	497	215	NA	NA	NA
Mean (SD)	17.29 (9.575)	NA	16.17 (9.886)	10.86 (12.079)	NA	NA	NA
Median	17.00	NA	15.41	6.01	NA	NA	NA
Lenv[b]							
n	352	NA	497	214	1119	NA	NA
Mean (SD)	16.45 (9.839)	NA	15.50 (10.049)	10.43 (11.994)	11.61 (14.066)	NA	NA
Median	16.13	NA	14.82	5.82	5.55	NA	NA
Pembro or Sunitinib[b]							
n	352	340	497	215	NA	2799	5884
Mean (SD)	14.45 (8.562)	11.33 (9.463)	13.55 (8.325)	8.67 (8.244)	NA	6.51 (5.932)	7.25 (6.790)
Median	15.08	7.84	13.80	5.09	NA	4.17	4.86

Data cutoff date: 28 Aug 2020 for Study 307; for all other studies, the clinical cutoff dates specified in ISS SAP version 2.0 were used.
Indication Safety Set: Subjects from Study 307 with 1L RCC who received Lenv 20 mg QD + Pembro 200 mg Q3W.
Sunitinib Safety Set: Subjects from Study 307 with 1L RCC who received Sunitinib 50 mg QD.
All RCC Safety Set: Subjects from Study 307 and Study 111 with RCC who received at least 1 dose of Lenv 20 mg QD + Pembro 200 mg as starting dose, regardless of prior anticancer therapy.
Non-RCC Safety Set: Subjects from non-RCC cohorts (non-small-cell lung cancer, endometrial carcinoma, urothelial carcinoma, squamous cell carcinoma of the head and neck, and melanoma) from Studies 111 and 115 who were treated with Lenv 20 mg QD + Pembro 200 mg Q3W as starting dose.
Lenv Monotx Safety Set: Subjects with a starting dose level of Lenv 24 mg QD monotherapy from 11 studies.
Pembro Monotx RSD-A Safety Set: Subjects treated with Pembro from clinical studies (KN-001, KN-002, KN-006, and KN-010).
Pembro Monotx RSD-B Safety Set: Subjects treated with Pembro from clinical studies (RSD-A plus KN-012, KN-013, KN-024, KN-040, KN-042, KN-045, KN-048, KN-052, KN-054, KN-055, KN-087) in EU-approved indications as of 11 Sep 2020.
1L = first line, Lenv = lenvatinib, Monotx = monotherapy, NA = not applicable, Pembro = pembrolizumab, Q3W = once every 3 weeks, QD = once daily, RCC = renal cell carcinoma, RSD = Reference Safety Dataset.
a: Duration of Treatment (Months) = (date of last dose - date of first dose + 1)/30.4375.
b: Overall Duration of Treatment (Months) = (date of last dose of study drugs - date of first dose of study drugs + 1)/30.4375.

In the Indication Safety Set, the median percentage of the planned dose of lenvatinib received was 69.65% and the **median dose intensity** was 13.93 mg per day. In the Lenvatinib Monotherapy Safety Set, where subjects received a higher starting dose of lenvatinib (24 mg), the median percentage of planned dose and the median dose intensity were higher (83.61% and 20.07 mg per day, respectively) (Table 31).

The median dose intensity of sunitinib was 83.18% of intended dose (41.59 mg/day dose intensity per subject).

Table 31 Lenvatinib Administration by Safety Set

Parameter Statistic	Indication N=352	All RCC N=497	Non-RCC N=215	Lenv Monotx N=1119
Dose Intensity[a] (mg/day)				
n	352	497	214	1119
Mean (SD)	14.11 (4.603)	14.24 (4.393)	14.10 (4.589)	18.70 (5.205)
Median	13.93	13.99	13.99	20.07
Min, Max	2.5, 31.4	2.5, 31.4	3.2, 20	5.1, 25.5
Received Dose as Percentage of Planned Starting Dose[b] (%)				
n	352	497	214	1119
Mean (SD)	70.53 (23.016)	71.20 (21.965)	70.50 (22.944)	77.93 (21.688)
Median	69.65	69.94	69.95	83.61
Min, Max	12.6, 157.1	12.6, 157.1	16.2, 100	21.2, 106.2

a; dose intensity (mg/day)= Total dose received/(date of last dose-date of the first dose+1)

b: Received dose as percentage of planned starting dose = 100 × dose intensity (mg/day)/planned starting dose (20 mg/day for Lenv + Pembro combination therapy or 24 mg/day for Lenv Monot).

In the Indication Safety Set, the median number of doses of pembrolizumab per subject was 22.0 doses, higher than that in the Pembrolizumab Monotherapy (RSD-A and RSD-B) Safety Sets, where the median number of doses was 7.0 and 8.0 doses, respectively.

Table 32 Pembrolizumab Administration by Safety Set

Parameter Statistic	Indication N=352	All RCC N=497	Non-RCC N=215	Pembro Monotx RSD-A N=2799	Pembro Monotx RSD-B N=5884
Number of Administrations					
n	352	497	215	2799	5884
Mean (SD)	20.7 (11.86)	19.4 (11.54)	12.7 (11.35)	11.1 (9.64)	11.6 (10.17)
Median	22.0	19.0	8.0	7.0	8.0
Min, Max	1, 39	1, 39	1, 36	1, 59	1, 59

For discontinuation of drug or dose reductions and interruptions due to AEs, please see separate section below.

Characteristics of Study Population

Of the 352 subjects in the Indication Safety Set, the majority were overweight, white and male, and the overall median age was 63.5 years. Demographic characteristics of the Indication Safety Set were generally consistent with those of the Lenvatinib and Pembrolizumab Monotherapy Safety Sets, with the following exceptions:

- A higher proportion of male subjects were included in the Indication Safety Set (71.6%) than in the Lenvatinib Monotherapy and Pembrolizumab (RSD-A and RSD B) Monotherapy Safety Sets (49.5%, 59.3%, and 66.1%, respectively). Also, a greater proportion of subjects had baseline hypertension and impaired renal function (ie, a CrCl of <60 mL/min) in the Indication Safety Set (57.4% and 30.1%, respectively) than in the Lenvatinib Monotherapy Safety Set (47.3% and 14.0%, respectively; no data available for Pembrolizumab Monotherapy Safety Sets). These differences are expected considering the disease under study.
- The proportion of subjects from the Rest of World geographic region was higher in the Indication Safety Set (44.0%) than in the Lenvatinib Monotherapy and Pembrolizumab Monotherapy (RSD-A and RSD-B) Safety Sets (24.8%, 17.0%, and 27.2%).

Adverse events

Adverse event summary

An overview of adverse event profile is provided in Table 33.

Table 33 Overview of Treatment-Emergent Adverse Events by Safety Set

Subjects With at Least 1 of the Following:	Indication N=352 n (%)	Sunitinib N=340 n (%)	All RCC N=497 n (%)	Non-RCC N=215 n (%)	Lenv Monotx N=1119 n (%)	Pembro Monotx RSD-A N=2799 n (%)	Pembro Monotx RSD-B N=5884 n (%)
Any TEAEs	351 (99.7)	335 (98.5)	496 (99.8)	215 (100)	1108 (99.0)	2727 (97.4)	5690 (96.7)
TEAE With Worst CTCAE Grade[a] of							

≥3	290 (82.4)	244 (71.8)	415 (83.5)	193 (89.8)	899 (80.3)	1273 (45.5)	2829 (48.1)
3	223 (63.4)	201 (59.1)	321 (64.6)	134 (62.3)	701 (62.6)	1020 (36.4)	2165 (36.8)
4	52 (14.8)	32 (9.4)	69 (13.9)	36 (16.7)	103 (9.2)	143 (5.1)	353 (6.0)
5	15 (4.3)	11 (3.2)	25 (5.0)	23 (10.7)	95 (8.5)	110 (3.9)	311 (5.3)
Any Related TEAEs[b]	341 (96.9)	313 (92.1)	485 (97.6)	206 (95.8)	1060 (94.7)	2064 (73.7)	4136 (70.3)
Related TEAE With Worst CTCAE Grade[a] of							
≥3	252 (71.6)	200 (58.8)	347 (69.8)	149 (69.3)	724 (64.7)	387 (13.8)	915 (15.6)
3	207 (58.8)	175 (51.5)	289 (58.1)	124 (57.7)	644 (57.6)	336 (12.0)	778 (13.2)
4	41 (11.6)	24 (7.1)	51 (10.3)	21 (9.8)	53 (4.7)	40 (1.4)	97 (1.6)
5	4 (1.1)	1 (0.3)	7 (1.4)	4 (1.9)	27 (2.4)	11 (0.4)	40 (0.7)
Any Serious AEs[c]	178 (50.6)	113 (33.2)	251 (50.5)	132 (61.4)	613 (54.8)	1042 (37.2)	2266 (38.5)
Fatal Serious AEs	15 (4.3)	11 (3.2)	25 (5.0)	23 (10.7)	97 (8.7)	110 (3.9)	312 (5.3)
Any Nonfatal Serious AEs	176 (50.0)	111 (32.6)	246 (49.5)	129 (60.0)	580 (51.8)	984 (35.2)	2101 (35.7)
TEAEs Leading to Discontinuation of[d]	131 (37.2)	49 (14.4)	166 (33.4)	75 (34.9)	299 (26.7)	334 (11.9)	790 (13.4)
Lenv[e]	90 (25.6)	NA	118 (23.7)	69 (32.1)	299 (26.7)	NA	NA
Pembro[f]	101 (28.7)	NA	129 (26.0)	63 (29.3)	NA	334 (11.9)	790 (13.4)
Both Lenv and Pembro[g]	47 (13.4)	NA	64 (12.9)	51 (23.7)	NA	NA	NA
TEAEs Leading to Dose Reduction of Lenv or Sunitinib	242 (68.8)	171 (50.3)	340 (68.4)	142 (66.0)	531 (47.5)	NA	NA
TEAEs Leading to Drug Interruption[d] of	276 (78.4)	183 (53.8)	398 (80.1)	178 (82.8)	757 (67.6)	622 (22.2)	1492 (25.4)

Lenv[e]	257 (73.0)	NA	374 (75.3)	173 (80.5)	757 (67.6)	NA	NA
Pembro[f]	194 (55.1)	NA	269 (54.1)	116 (54.0)	NA	622 (22.2)	1492 (25.4)
Both Lenv and Pembro[g]	138 (39.2)	NA	192 (38.6)	93 (43.3)	NA	NA	NA
TEAEs Leading to Dose Modification[h] of Lenv or Sunitinib	298 (84.7)	239 (70.3)	429 (86.3)	192 (89.3)	835 (74.6)	NA	NA

MedDRA preferred terms "Neoplasm Progression," "Malignant Neoplasm Progression," and "Disease Progression," which are unrelated to the study drug are excluded.
For each row category, subjects with 2 or more AEs in that category were counted only once. Subjects may be counted in multiple categories.
For nonserious AEs, TEAEs used the window of 30 days within the last dose of study drug.
Data cutoff date: 28 Aug 2020 for Study 307; for all other studies, the clinical cutoff dates specified in ISS SAP version 2.0 were used.
1L = first line, AE = adverse event, CTCAE = Common Terminology Criteria for Adverse Events, Lenv = lenvatinib, Monotx = monotherapy, MedDRA = Medical Dictionary for Regulatory Activities, NA = not applicable, Pembro = pembrolizumab, Q3W = once every 3 weeks, QD = once daily, RCC = renal cell carcinoma, RSD = Reference Safety Dataset, TEAE = treatment emergent adverse event.
a: Adverse events were graded using CTCAE version 4.03.
b: Treatment-related TEAEs include TEAEs that were considered by the Investigator to be related, or possibly related to the study drug or TEAEs with a missing causality on the case report form. A total of 19 events (12 subjects) in the Pembro Monotx RSD-A and 31 events (21 subjects) in the Pembro Monotx RSD-B with missing causality were considered 'related' to study drug.
c: For the combination of Lenv 20 mg + Pembro, the serious AE follow-up window was 90 days after the last dose for Studies 111 and 115 and 120 days after the last dose date for Study 307. For Lenv Monotx and Pembro Monotx, the window was 30 days and 90 days after the last dose, respectively.
d: Lenv or Pembro (or sunitinib).
e: Drug discontinuation (or interruption) for Lenv, regardless of the action taken for Pembro.
f: Drug discontinuation (or interruption) for Pembro, regardless of the action taken for Lenv.
g: Drug discontinuation (or interruption) for both Lenv and Pembro occurred at the same time due to the same AE.
h: Dose modification includes dose reduction or drug interruption.

Exposure adjusted analyses are presented in Table 34.

Table 34 Overview of Treatment Emergent Adverse Events Adjusted by Drug Exposure

	Indication N=352 n (AE Rate)	**Sunitinib N=340 n (AE Rate)**	**All RCC N=497 n (AE Rate)**	**Non-RCC N=215 n (AE Rate)**	**Lenv Monotx N=1119 n (AE Rate)**	**Pembro Monotx RSD-A N=2799 n (AE Rate)**	**Pembro Monotx RSD-B N=5884 n (AE Rate)**
Total Exposure (subject-years)	524.87	344.23	694.70	211.18	1171.03	1708.79	3990.21
All TEAE Episodes Adjusted by Subject-years	8211 (15.64)	6266 (18.20)	11842 (17.05)	5234 (24.78)	25483 (21.76)	31554 (18.47)	61600 (15.44)
Treatment-Related TEAE Episodes Adjusted by Subject-years	4812 (9.17)	4090 (11.88)	7061 (10.16)	2811 (13.31)	15918 (13.59)	10336 (6.05)	19314 (4.84)
Grade 3, 4 or 5 TEAE Episodes Adjusted by Subject-years	1023 (1.95)	709 (2.06)	1363 (1.96)	728 (3.45)	2811 (2.40)	2631 (1.54)	6162 (1.54)
Serious TEAE Episodes Adjusted by Subject-years	378 (0.72)	188 (0.55)	520 (0.75)	306 (1.45)	1302 (1.11)	1901 (1.11)	4094 (1.03)
TEAE Episodes With Fatal Outcome Adjusted by Subject-years	19 (0.04)	12 (0.03)	31 (0.04)	25 (0.12)	101 (0.09)	111 (0.06)	319 (0.08)

	Indication N=352 n (AE Rate)	Sunitinib N=340 n (AE Rate)	All RCC N=497 n (AE Rate)	Non-RCC N=215 n (AE Rate)	Lenv Monotx N=1119 n (AE Rate)	Pembro Monotx RSD-A N=2799 n (AE Rate)	Pembro Monotx RSD-B N=5884 n (AE Rate)
Nonfatal Serious TEAE Episodes Adjusted by Subject-years	359 (0.68)	176 (0.51)	489 (0.70)	281 (1.33)	1201 (1.03)	1790 (1.05)	3775 (0.95)

MedDRA preferred terms "Neoplasm Progression," "Malignant Neoplasm Progression," and "Disease Progression," which are unrelated to the study drug are excluded.
Data cutoff date: 28 Aug 2020 for Study 307; for all other studies, the clinical cutoff dates specified in ISS SAP version 2.0 were used.
Treatment-related TEAEs include TEAEs that were considered by the Investigator to be related, or possibly/probably related to the study drug or TEAEs with a missing causality on the case report form. A total of 19 events (12 subjects) in the Pembro Monotx RSD-A and 31 events (21 subjects) in the Pembro Monotx RSD-B with missing causality were considered 'related' to study drug.
For combination of Lenv 20 mg + Pembro, the serious TEAE follow-up window is 90 days after the last dose for Studies 111/KN146 and 115/KN523 and 120 days after the last dose date for Study 307/KN581. For Lenv Monotx and Pembro Monotx (RSD-A and RSD-B), the window is 30 days and 90 days after the last dose, respectively.
Adverse events were graded using CTCAE version 4.03.
Total exposure = sum of overall drug exposure for all subjects in each safety set (including dose interruption). Drug exposure = (the earlier of (last dose date +30) or the database cutoff date - the first dose date + 1)/365.25 in years.
The letter n indicates the number of TEAE episodes.
AE Rate (episodes/subject-years) = total number of TEAE episodes (n) divided by total exposure in each safety set.

Lenvatinib plus pembrolizumab vs sunitinib

Nearly all subjects in both the lenvatinib plus pembrolizumab and sunitinib arms had at least 1 TEAE (99.7% vs 98.5%) and related TEAE (96.9% vs 92.1%). For other AE categories higher incidences were reported in the lenvatinib plus pembrolizumab arm compared to the sunitinib arm, including Grade ≥3 and related Grade ≥3 TEAEs (82.4% vs 71.8% and 71.6% vs. 58.8%), non-fatal SAEs (50.0% vs 32.6%), and TEAEs leading to discontinuation of either lenvatinib or pembrolizumab (37.2% vs 14.4%). The incidence of TEAEs leading to discontinuation of all study drugs was similar in the lenvatinib plus pembrolizumab and sunitinib arms (13.4% vs 14.4% of subjects). TEAEs leading to dose reduction of lenvatinib in the lenvatinib plus pembrolizumab arm occurred in 68.8% of subjects, which was higher than in the sunitinib arm (50.3% of subjects). TEAEs leading to dose interruption of either study drug in the lenvatinib plus pembrolizumab arm occurred in 78.4% of subjects, which was higher than in the sunitinib arm (53.8% of subjects). Fatal TEAEs (Grade 5) were reported in 15 subjects (4.3%) in the lenvatinib plus pembrolizumab arm, which was similar to 11 subjects (3.2%) in the sunitinib arm.

Adjusted by drug exposure, the rates of Grade ≥3 TEAEs was comparable at 1.95 and 2.06 per SY but remained numerically higher for SAEs (0.72 vs 0.55 per SY) in the lenvatinib plus pembrolizumab and sunitinib arms, respectively.

Lenvatinib plus pembrolizumab vs lenvatinib or pembrolizumab monotherapy

The incidences of most TEAEs categories were similar between the Indication Safety Set and the Lenvatinib Monotherapy Safety Set, including any TEAEs (99.7% and 99.0%, respectively), treatment-related TEAEs (96.9% and 94.7%), Grade ≥3 TEAEs (82.4% and 80.3%), nonfatal SAEs (50.0% and 51.8%), and fatal AEs (4.3% and 8.7%). The rate of related Grade ≥3 TEAEs was numerically higher in the Indication Safety Set compared to the Lenvatinib Monotherapy Safety Set (71.6% and 64.7%), mainly driven by Grade 4 events (11.6% and 4.7%). Adjusted by drug exposure, incidences for all TEAEs categories were numerically lower in the Indication Safety Set compared to the Lenvatinib Monotherapy Safety Set.

The comparison of the Indication Safety Set with pembrolizumab monotherapy demonstrated considerably lower incidences for pembrolizumab monotherapy across all TEAEs categories.

Most common Adverse Events

Table 35 Treatment Emergent Adverse Events Occurring in 5% or More of Subjects in the Indication Safety Set by MedDRA Preferred Term

Preferred Term	Indication N=352 n (%)	Sunitinib N=340 n (%)	All RCC N=497 n (%)	Non-RCC N=215 n (%)	Lenv Monotx N=1119 n (%)	Pembro Monotx RSD-A N=2799 n (%)	Pembro Monotx RSD-B N=5884 n (%)
Subjects with Any TEAEs	351 (99.7)	335 (98.5)	496 (99.8)	215 (100)	1108 (99.0)	2727 (97.4)	5690 (96.7)
Diarrhoea	216 (61.4)	168 (49.4)	307 (61.8)	127 (59.1)	580 (51.8)	625 (22.3)	1200 (20.4)
Hypertension	195 (55.4)	141 (41.5)	256 (51.5)	118 (54.9)	672 (60.1)	106 (3.8)	295 (5.0)
Hypothyroidism	166 (47.2)	90 (26.5)	224 (45.1)	96 (44.7)	146 (13.0)	236 (8.4)	651 (11.1)
Decreased appetite	142 (40.3)	105 (30.9)	209 (42.1)	118 (54.9)	509 (45.5)	630 (22.5)	1136 (19.3)
Fatigue	141 (40.1)	125 (36.8)	234 (47.1)	125 (58.1)	537 (48.0)	1044 (37.3)	1884 (32.0)
Nausea	126 (35.8)	113 (33.2)	197 (39.6)	116 (54.0)	475 (42.4)	685 (24.5)	1213 (20.6)
Stomatitis	122 (34.7)	131 (38.5)	182 (36.6)	62 (28.8)	310 (27.7)	59 (2.1)	144 (2.4)
Dysphonia	105 (29.8)	14 (4.1)	163 (32.8)	62 (28.8)	351 (31.4)	68 (2.4)	127 (2.2)
Weight decreased	105 (29.8)	31 (9.1)	147 (29.6)	70 (32.6)	390 (34.9)	220 (7.9)	561 (9.5)
Proteinuria	104 (29.5)	43 (12.6)	164 (33.0)	73 (34.0)	389 (34.8)	14 (0.5)	54 (0.9)
Palmar-plantar erythrodysaesthesia syndrome	101 (28.7)	127 (37.4)	144 (29.0)	47 (21.9)	233 (20.8)	9 (0.3)	19 (0.3)
Arthralgia	99 (28.1)	52 (15.3)	161 (32.4)	73 (34.0)	281 (25.1)	504 (18.0)	851 (14.5)
Rash	96 (27.3)	47 (13.8)	119 (23.9)	24 (11.2)	162 (14.5)	508 (18.1)	904 (15.4)
Vomiting	92 (26.1)	68 (20.0)	135 (27.2)	93 (43.3)	373 (33.3)	387 (13.8)	732 (12.4)
Constipation	89 (25.3)	64 (18.8)	132 (26.6)	69 (32.1)	300 (26.8)	498 (17.8)	995 (16.9)

Preferred Term	Indication N=352 n (%)	Sunitinib N=340 n (%)	All RCC N=497 n (%)	Non-RCC N=215 n (%)	Lenv Monotx N=1119 n (%)	Pembro Monotx RSD-A N=2799 n (%)	Pembro Monotx RSD-B N=5884 n (%)
Headache	80 (22.7)	55 (16.2)	122 (24.5)	61 (28.4)	357 (31.9)	400 (14.3)	711 (12.1)
Asthenia	78 (22.2)	61 (17.9)	84 (16.9)	34 (15.8)	193 (17.2)	362 (12.9)	666 (11.3)
Abdominal pain	74 (21.0)	28 (8.2)	106 (21.3)	57 (26.5)	230 (20.6)	274 (9.8)	480 (8.2)
Cough	70 (19.9)	53 (15.6)	136 (27.4)	55 (25.6)	245 (21.9)	615 (22.0)	1148 (19.5)
Lipase increased	64 (18.2)	44 (12.9)	92 (18.5)	28 (13.0)	41 (3.7)	5 (0.2)	27 (0.5)
Amylase increased	63 (17.9)	28 (8.2)	81 (16.3)	11 (5.1)	22 (2.0)	6 (0.2)	19 (0.3)
Back pain	59 (16.8)	52 (15.3)	88 (17.7)	40 (18.6)	201 (18.0)	349 (12.5)	662 (11.3)
Pruritus	58 (16.5)	26 (7.6)	78 (15.7)	30 (14.0)	69 (6.2)	580 (20.7)	1060 (18.0)
Myalgia	56 (15.9)	12 (3.5)	76 (15.3)	35 (16.3)	168 (15.0)	253 (9.0)	430 (7.3)
Dyspnoea	54 (15.3)	34 (10.0)	93 (18.7)	50 (23.3)	202 (18.1)	534 (19.1)	989 (16.8)
Pyrexia	54 (15.3)	44 (12.9)	75 (15.1)	22 (10.2)	134 (12.0)	357 (12.8)	746 (12.7)
Blood creatinine increased	48 (13.6)	34 (10.0)	74 (14.9)	16 (7.4)	54 (4.8)	108 (3.9)	256 (4.4)
Musculoskeletal pain	48 (13.6)	21 (6.2)	67 (13.5)	27 (12.6)	144 (12.9)	226 (8.1)	395 (6.7)
Anaemia	43 (12.2)	66 (19.4)	61 (12.3)	28 (13.0)	92 (8.2)	347 (12.4)	836 (14.2)
Dysgeusia	43 (12.2)	95 (27.9)	63 (12.7)	17 (7.9)	78 (7.0)	45 (1.6)	110 (1.9)
Alanine aminotransferase increased	42 (11.9)	35 (10.3)	59 (11.9)	29 (13.5)	90 (8.0)	172 (6.1)	393 (6.7)
Hypertriglyceridaemia	42 (11.9)	41 (12.1)	67 (13.5)	12 (5.6)	35 (3.1)	80 (2.9)	88 (1.5)
Oedema peripheral	42 (11.9)	35 (10.3)	67 (13.5)	49 (22.8)	193 (17.2)	285 (10.2)	512 (8.7)
Pain in extremity	41 (11.6)	33 (9.7)	69 (13.9)	26 (12.1)	155 (13.9)	237 (8.5)	391 (6.6)

Preferred Term	Indication N=352 n (%)	Sunitinib N=340 n (%)	All RCC N=497 n (%)	Non-RCC N=215 n (%)	Lenv Monotx N=1119 n (%)	Pembro Monotx RSD-A N=2799 n (%)	Pembro Monotx RSD-B N=5884 n (%)
Nasopharyngitis	40 (11.4)	25 (7.4)	42 (8.5)	11 (5.1)	77 (6.9)	182 (6.5)	360 (6.1)
Aspartate aminotransferase increased	39 (11.1)	37 (10.9)	55 (11.1)	29 (13.5)	82 (7.3)	168 (6.0)	384 (6.5)
Blood thyroid stimulating hormone increased	39 (11.1)	21 (6.2)	52 (10.5)	6 (2.8)	80 (7.1)	37 (1.3)	97 (1.6)
Dyspepsia	39 (11.1)	55 (16.2)	58 (11.7)	17 (7.9)	113 (10.1)	66 (2.4)	149 (2.5)
Insomnia	38 (10.8)	21 (6.2)	57 (11.5)	29 (13.5)	133 (11.9)	219 (7.8)	429 (7.3)
Dry mouth	36 (10.2)	11 (3.2)	55 (11.1)	32 (14.9)	147 (13.1)	142 (5.1)	284 (4.8)
Abdominal pain upper	35 (9.9)	26 (7.6)	46 (9.3)	16 (7.4)	168 (15.0)	115 (4.1)	213 (3.6)
Dizziness	35 (9.9)	29 (8.5)	61 (12.3)	34 (15.8)	153 (13.7)	244 (8.7)	430 (7.3)
Hypercholesterolaemia	31 (8.8)	7 (2.1)	31 (6.2)	4 (1.9)	30 (2.7)	25 (0.9)	31 (0.5)
Upper respiratory tract infection	31 (8.8)	21 (6.2)	39 (7.8)	29 (13.5)	82 (7.3)	182 (6.5)	387 (6.6)
Rash maculo-papular	29 (8.2)	7 (2.1)	53 (10.7)	29 (13.5)	15 (1.3)	100 (3.6)	202 (3.4)
Hyperkalaemia	28 (8.0)	18 (5.3)	38 (7.6)	4 (1.9)	34 (3.0)	61 (2.2)	149 (2.5)
Hyperthyroidism	28 (8.0)	12 (3.5)	34 (6.8)	14 (6.5)	29 (2.6)	96 (3.4)	247 (4.2)
Hypomagnesaemia	27 (7.7)	13 (3.8)	46 (9.3)	44 (20.5)	51 (4.6)	80 (2.9)	160 (2.7)
Hyponatraemia	27 (7.7)	21 (6.2)	47 (9.5)	31 (14.4)	66 (5.9)	146 (5.2)	345 (5.9)
Urinary tract infection	27 (7.7)	25 (7.4)	36 (7.2)	58 (27.0)	119 (10.6)	162 (5.8)	384 (6.5)
Epistaxis	25 (7.1)	37 (10.9)	46 (9.3)	22 (10.2)	140 (12.5)	49 (1.8)	83 (1.4)
Hyperglycaemia	25 (7.1)	18 (5.3)	36 (7.2)	11 (5.1)	58 (5.2)	130 (4.6)	289 (4.9)
Blood cholesterol increased	24 (6.8)	14 (4.1)	33 (6.6)	8 (3.7)	27 (2.4)	53 (1.9)	56 (1.0)
Hypotension	24 (6.8)	8 (2.4)	37 (7.4)	17 (7.9)	87 (7.8)	66 (2.4)	166 (2.8)
Muscle spasms	24 (6.8)	12 (3.5)	38 (7.6)	21 (9.8)	82 (7.3)	83 (3.0)	147 (2.5)
Oropharyngeal pain	23 (6.5)	12 (3.5)	47 (9.5)	28 (13.0)	119 (10.6)	90 (3.2)	196 (3.3)

Preferred Term	Indication N=352 n (%)	Sunitinib N=340 n (%)	All RCC N=497 n (%)	Non-RCC N=215 n (%)	Lenv Monotx N=1119 n (%)	Pembro Monotx RSD-A N=2799 n (%)	Pembro Monotx RSD-B N=5884 n (%)
Blood triglycerides increased	22 (6.3)	15 (4.4)	25 (5.0)	0	7 (0.6)	28 (1.0)	29 (0.5)
Dry skin	22 (6.3)	27 (7.9)	45 (9.1)	20 (9.3)	117 (10.5)	166 (5.9)	304 (5.2)
Electrocardiogram QT prolonged	22 (6.3)	13 (3.8)	27 (5.4)	11 (5.1)	53 (4.7)	9 (0.3)	10 (0.2)
Hypokalaemia	22 (6.3)	11 (3.2)	31 (6.2)	31 (14.4)	96 (8.6)	124 (4.4)	270 (4.6)
Hypophosphataemia	22 (6.3)	15 (4.4)	31 (6.2)	10 (4.7)	16 (1.4)	56 (2.0)	132 (2.2)
Platelet count decreased	22 (6.3)	61 (17.9)	29 (5.8)	13 (6.0)	55 (4.9)	29 (1.0)	73 (1.2)
Haemorrhoids	20 (5.7)	11 (3.2)	23 (4.6)	14 (6.5)	39 (3.5)	17 (0.6)	45 (0.8)
Sinusitis	19 (5.4)	6 (1.8)	21 (4.2)	9 (4.2)	41 (3.7)	75 (2.7)	146 (2.5)
Toothache	19 (5.4)	9 (2.6)	32 (6.4)	5 (2.3)	45 (4.0)	22 (0.8)	58 (1.0)
Pneumonitis	18 (5.1)	0	20 (4.0)	5 (2.3)	4 (0.4)	87 (3.1)	242 (4.1)

Percentages are based on the number of subjects in the relevant safety set.
MedDRA PTs "Neoplasm Progression," "Malignant Neoplasm Progression," and "Disease Progression," which are unrelated to the study drug are excluded.
PTs are included if the relevant frequency was ≥5% for the Indication Safety Set.
Subjects with 2 or more TEAEs for the same PT were counted only once for that PT.
Adverse event terms were coded using MedDRA version 23.0.
Data cutoff date: 28 Aug 2020 for Study 307; for all other studies, the clinical cutoff dates specified in ISS SAP version 2.0 were used.

In the Indication Safety Set, the most commonly reported (occurring in >30% of subjects) TEAEs, by decreasing incidence, were diarrhea (61.4%), hypertension (55.4%), hypothyroidism (47.2%), decreased appetite (40.3%), fatigue (40.1%), nausea (35.8%), and stomatitis (34.7%) (Table 35).

For sunitinib the most commonly reported TEAEs (>30%) were diarrhea (49.4%), hypertension (41.5%), stomatitis (38.5%), PPE (palmar-plantar erythrodysaesthesia) syndrome (37.4%), fatigue (36.8%), nausea (33.2%), and decreased appetite (30.9%).

TEAEs that occurred at a higher incidence in subjects in the lenvatinib plus pembrolizumab arm compared with the sunitinib arm (≥10% difference) were diarrhea (61.4% vs 49.4%), hypertension (55.4% vs 41.5%), hypothyroidism (47.2% vs 26.5%), abdominal pain (21% vs 8.2%), weight decreased (29.8% vs 9.1%), arthralgia (28.1% vs 15.3%), myalgia (15.9% vs 3.5%), proteinuria (29.5% vs 12.6%), dysphonia (29.8% vs 4.1%), and rash (27.3% vs 13.8%); additional notable TEAEs that occurred in subjects at a higher incidence but <10% difference included lipase increased (18.2% vs 12.9%), amylase increased (17.9% vs 8.2%), adrenal insufficiency (4.8% vs 0%), and pneumonitis (5.1% vs 0%).

When adjusted by episodes per treatment duration, the rates of aforementioned TEAEs became comparable between the two arms for the most frequently reported TEAEs: diarrhea, hypertension, hypothyroidism, decreased appetite, fatigue, nausea and stomatitis. The rates remain higher in the lenvatinib plus pembrolizumab arm compared to the sunitinib arm for dysphonia (0.26 vs 0.05 per SY), weight decreased (0.24 vs 0.09 per SY), proteinuria (0.37 vs 0.22 per SY), myalgia (0.12 vs 0.05 per SY), amylase increased (0.20 vs 0.12 per SY), adrenal insufficiency (0.04 vs 0 per SY), and pneumonitis (0.04 vs 0 per SY).

Common TEAEs with a higher incidence in the Indication Safety Set than in the monotherapy safety sets included diarrhea, hypothyroidism, increased lipase, increase amylase, increased blood creatinine, increased ALT and AST, hyperthyroidism, hypertriglyceridemia, hypercholesterolemia, rash and maculopapular rash, hyperkalemia, and hypophosphatemia.

Treatment-related all grade AEs

Table 36 Overview of related TEAEs by Safety Set

Subjects With at Least 1 of the Following:	**Indication N=352 n (%)**	**Sunitinib N=340 n (%)**	**All RCC N=497 n (%)**	**Non-RCC N=215 n (%)**	**Lenv Monotx N=1119 n (%)**	**Pembro Monotx RSD-A N=2799 n (%)**	**Pembro Monotx RSD-B N=5884 n (%)**
Any Related TEAEs	341 (96.9)	313 (92.1)	485 (97.6)	206 (95.8)	1060 (94.7)	2064 (73.7)	4136 (70.3)

Table 37 Overview of TEAEs Adjusted by Drug Exposure

	Indication N=352 n (AE Rate)	Sunitinib N=340 n (AE Rate)	All RCC N=497 n (AE Rate)	Non-RCC N=215 n (AE Rate)	Lenv Monotx N=1119 n (AE Rate)	Pembro Monotx RSD-A N=2799 n (AE Rate)	Pembro Monotx RSD-B N=5884 n (AE Rate)
Total Exposure (subject-years)	524.87	344.23	694.70	211.18	1171.03	1708.79	3990.21
Treatment-Related TEAE Episodes Adjusted by Subject-years	4812 (9.17)	4090 (11.88)	7061 (10.16)	2811 (13.31)	15918 (13.59)	10336 (6.05)	19314 (4.84)

The most common treatment-related TEAEs (≥30% of subjects in either arm) in the lenvatinib plus pembrolizumab arm and sunitinib arm, in decreasing incidence, were diarrhea (54.5% vs 44.4%), hypertension (52.3% vs 39.1%), hypothyroidism (42.6% vs 23.2%), stomatitis (32.1% vs 37.4%), fatigue (32.1% vs 32.1%), decreased appetite (34.9% vs 24.7%), and PPE (28.1% vs 35.9%).

The incidence of treatment related TEAEs in the Indication Safety Set were generally consistent with that in the Lenvatinib Monotherapy or Pembrolizumab Monotherapy Safety (RSD-A and RSD-B) Sets, with the exceptions of the following:

- Diarrhea (54.5%, 45.4%, 12.3%, and 10.7%, respectively)
- Hypothyroidism (42.6%, 11.1%, 7.6%, and 9.6%, respectively)
- Increased amylase (15.1%, 0.9%, 0.2%, and 0.2%, respectively)
- Increased lipase (14.2%, 2.8%, 0.1%, and 0.3%, respectively)

COVID-19 Treatment-Emergent Adverse Events

TEAEs due to COVID-19 were reported in 1 subject (0.3%) each in the lenvatinib plus pembrolizumab arm and the sunitinib arm; both cases reported a Grade 2 TEAE of COVID-19 pneumonia that were considered by the investigator not to be related to study drug. Study treatment was interrupted for both subjects but was resumed upon recovery at the same dose; both subjects continued on treatment as of the data cutoff date.

Grade ≥3 Adverse Events

Table 38 Overview of severe AEs

Subjects With at Least 1 of the Following:	**Indication N=352 n (%)**	**Sunitinib N=340 n (%)**	**All RCC N=497 n (%)**	**Non-RCC N=215 n (%)**	**Lenv Monotx N=1119 n (%)**	**Pembro Monotx RSD-A N=2799 n (%)**	**Pembro Monotx RSD-B N=5884 n (%)**
TEAE With Worst CTCAE Grade[a] of							
≥3	290 (82.4)	244 (71.8)	415 (83.5)	193 (89.8)	899 (80.3)	1273 (45.5)	2829 (48.1)
3	223 (63.4)	201 (59.1)	321 (64.6)	134 (62.3)	701 (62.6)	1020 (36.4)	2165 (36.8)
4	52 (14.8)	32 (9.4)	69 (13.9)	36 (16.7)	103 (9.2)	143 (5.1)	353 (6.0)
5	15 (4.3)	11 (3.2)	25 (5.0)	23 (10.7)	95 (8.5)	110 (3.9)	311 (5.3)
Related TEAE With Worst CTCAE Grade[a] of							
≥3	252 (71.6)	200 (58.8)	347 (69.8)	149 (69.3)	724 (64.7)	387 (13.8)	915 (15.6)
3	207 (58.8)	175 (51.5)	289 (58.1)	124 (57.7)	644 (57.6)	336 (12.0)	778 (13.2)
4	41 (11.6)	24 (7.1)	51 (10.3)	21 (9.8)	53 (4.7)	40 (1.4)	97 (1.6)
5	4 (1.1)	1 (0.3)	7 (1.4)	4 (1.9)	27 (2.4)	11 (0.4)	40 (0.7)

Grade ≥3 TEAEs were reported in 82.4% of subjects in the lenvatinib plus pembrolizumab arm and 71.8% of subjects in the sunitinib arm; the rate of severe TEAE episodes adjusted for treatment duration was similar between the 2 arms (1.95 and 2.06 per SY, respectively).

Compared to the Indication Safety Set, the incidence of Grade ≥3 TEAEs was similar in the Lenvatinib Monotherapy Safety Set (80.3%), but lower for Pembrolizumab Monotherapy RSD-A (45.5%) and RSD-B (48.1%).

Related Grade ≥3 TEAEs were numerically highest in the Indication Safety Set (71.6% vs. 58.5% for sunitib, 64.7% in the Lenvatinib Monotherapy Safety Set and only 15.6% for Pembrolizumab Monotherapy).

Grade 3 TEAEs were reported in 63.4% and 59.1% of subjects in the lenvatinib plus pembrolizumab and sunitinib arms, respectively. The most common Grade 3 TEAEs (≥5% of subjects in either arm) in lenvatinib plus pembrolizumab and sunitinib arms, respectively, were: hypertension (27.6% vs 18.8%), diarrhea (9.7% vs 5.0%), weight decreased (8.0% vs 0.3%), proteinuria (7.7% vs 2.9%), amylase increased (7.4% vs 2.1%), lipase increased (7.1% vs 6.2%), and asthenia (5.4% vs 4.4%).

Grade 4 TEAEs occurred in 14.8% of subjects in the combination arm and 9.4% of subjects in the sunitinib arm. The only Grade 4 TEAEs that occurred in 1% or more of subjects in the combination or sunitinib arms, respectively, were lipase increased (5.7% vs 2.6%) and amylase increased (1.7% vs 0.9%).

The incidence and type of Grade 3 and Grade 4 TEAEs observed in the Indication Safety Set were generally consistent with one or more monotherapy safety sets except for the following TEAEs: increased lipase and increased amylase, QT prolongation, pancreatitis, increased ALT and increased AST, adrenal insufficiency, acute myocardial infarction and myocardial infarction, rash, and renal failure (see Table 39).

Table 39 Worst Postbaseline Grade 3 or 4 TEAEs in ≥ 2% of Subjects in the Indication Safety Set, by Preferred Term

MedDRA Preferred Term	**Indication N=352 n (%)**		**Sunitinib N=340 n (%)**		**All RCC N=497 n (%)**		**Non-RCC N=215 n (%)**		**Lenv Monotx N=1119 n (%)**		**Pembro Monotx RSD-A N=2799 n (%)**	
	Gr 3	**Gr 4**	**Gr 3**	**Gr 4**	**Gr 3**	**Gr 4**	**Gr 3**	**Gr 4**	**Gr 3**	**Gr 4**	**Gr 3**	**Gr 4**
Subjects with at least 1 TEAE	223 (63.4)	52 (14.8)	201 (59.1)	32 (9.4)	321 (64.6)	69 (13.9)	134 (62.3)	36 (16.7)	701 (62.6)	103 (9.2)	1020 (36.4)	143 (5.1)
Hypertension	97 (27.6)	0	64 (18.8)	0	130 (26.2)	0	61 (28.4)	3 (1.4)	336 (30.0)	6 (0.5)	32 (1.1)	0
Lipase increased	25 (7.1)	20 (5.7)	21 (6.2)	9 (2.6)	37 (7.4)	27 (5.4)	12 (5.6)	6 (2.8)	16 (1.4)	6 (0.5)	2 (0.1)	0
Diarrhoea	34 (9.7)	0	17 (5.0)	1 (0.3)	47 (9.5)	0	21 (9.8)	0	82 (7.3)	0	36 (1.3)	0
Amylase increased	26 (7.4)	6 (1.7)	7 (2.1)	3 (0.9)	32 (6.4)	6 (1.2)	3 (1.4)	2 (0.9)	12 (1.1)	1 (0.1)	2 (0.1)	1 (<0.1)
Weight decreased	28 (8.0)	0	1 (0.3)	0	36 (7.2)	0	10 (4.7)	0	80 (7.1)	0	8 (0.3)	0

MedDRA Preferred Term	Indication N=352 n (%)		Sunitinib N=340 n (%)		All RCC N=497 n (%)		Non-RCC N=215 n (%)		Lenv Monotx N=1119 n (%)		Pembro Monotx RSD-A N=2799 n (%)	
Proteinuria	27 (7.7)	0	10 (2.9)	0	40 (8.0)	0	14 (6.5)	0	99 (8.8)	0	0	0
Asthenia	19 (5.4)	0	15 (4.4)	0	20 (4.0)	0	11 (5.1)	0	57 (5.1)	1 (0.1)	34 (1.2)	0
Hypertriglyceridaemia	17 (4.8)	0	17 (5.0)	5 (1.5)	24 (4.8)	2 (0.4)	2 (0.9)	2 (0.9)	7 (0.6)	0	14 (0.5)	2 (0.1)
Hyponatraemia	15 (4.3)	2 (0.6)	16 (4.7)	1 (0.3)	22 (4.4)	4 (0.8)	16 (7.4)	1 (0.5)	27 (2.4)	7 (0.6)	55 (2.0)	7 (0.3)
Alanine aminotransferase increased	13 (3.7)	2 (0.6)	8 (2.4)	0	14 (2.8)	2 (0.4)	11 (5.1)	0	15 (1.3)	0	24 (0.9)	1 (<0.1)
Fatigue	15 (4.3)	0	15 (4.4)	0	26 (5.2)	0	24 (11.2)	1 (0.5)	100 (8.9)	2 (0.2)	68 (2.4)	1 (<0.1)
Decreased appetite	14 (4.0)	0	5 (1.5)	0	17 (3.4)	0	9 (4.2)	0	41 (3.7)	0	26 (0.9)	0
Palmar-plantar erythrodysaesthesia syndrome	14 (4.0)	0	13 (3.8)	0	14 (2.8)	0	3 (1.4)	0	22 (2.0)	0	0	0
Rash	13 (3.7)	0	2 (0.6)	0	14 (2.8)	0	0	0	2 (0.2)	0	11 (0.4)	0
Hyperkalaemia	11 (3.1)	1 (0.3)	7 (2.1)	0	15 (3.0)	1 (0.2)	3 (1.4)	0	8 (0.7)	1 (0.1)	2 (0.1)	2 (0.1)
Vomiting	12 (3.4)	0	5 (1.5)	0	16 (3.2)	0	3 (1.4)	0	28 (2.5)	1 (0.1)	31 (1.1)	1 (<0.1)
Electrocardiogram QT prolonged	10 (2.8)	0	4 (1.2)	0	13 (2.6)	0	3 (1.4)	0	10 (0.9)	0	0	0
Aspartate aminotransferase increased	9 (2.6)	2 (0.6)	3 (0.9)	0	10 (2.0)	2 (0.4)	11 (5.1)	1 (0.5)	8 (0.7)	1 (0.1)	20 (0.7)	4 (0.1)
Nausea	9 (2.6)	0	2 (0.6)	0	12 (2.4)	0	8 (3.7)	0	31 (2.8)	0	33 (1.2)	0
Acute kidney injury	7 (2.0)	1 (0.3)	2 (0.6)	0	8 (1.6)	1 (0.2)	7 (3.3)	0	14 (1.3)	0	14 (0.5)	1 (<0.1)

MedDRA Preferred Term	Indication N=352 n (%)		Sunitinib N=340 n (%)		All RCC N=497 n (%)		Non-RCC N=215 n (%)		Lenv Monotx N=1119 n (%)		Pembro Monotx RSD-A N=2799 n (%)	
Hypophosphataemia	8 (2.3)	0	8 (2.4)	0	10 (2.0)	0	8 (3.7)	0	3 (0.3)	0	13 (0.5)	1 (<0.1)
Dyspnoea	7 (2.0)	1 (0.3)	8 (2.4)	0	11 (2.2)	2 (0.4)	6 (2.8)	1 (0.5)	28 (2.5)	1 (0.1)	71 (2.5)	5 (0.2)
Abdominal pain	7 (2.0)	0	3 (0.9)	0	11 (2.2)	0	7 (3.3)	0	29 (2.6)	3 (0.3)	26 (0.9)	1 (<0.1)
Anaemia	7 (2.0)	0	18 (5.3)	0	11 (2.2)	0	6 (2.8)	0	25 (2.2)	0	84 (3.0)	5 (0.2)
Pneumonia	7 (2.0)	0	6 (1.8)	0	10 (2.0)	0	1 (0.5)	1 (0.5)	33 (2.9)	4 (0.4)	71 (2.5)	2 (0.1)
Grade ≥3 AEs in < 2% of Subjects in the Indication Safety Set but with higher incidence compared to the monotherapy safety sets:												
Acute myocardial infarction	4 (1.1)	2 (0.6)	0	0	4 (0.8)	2 (0.4)	0	0	4 (0.4)	2 (0.2)	6 (0.2)	1 (<0.1)
Myocardial infarction	5 (1.4)	1 (0.3)	0	1 (0.3)	6 (1.2)	3 (0.6)	2 (0.9)	0	1 (0.1)	2 (0.2)	2 (0.1)	1 (<0.1)
Renal failure	3 (0.9)	2 (0.6)	1 (0.3)	0	5 (1.0)	2 (0.4)	0	0	3 (0.3)	1 (0.1)	8 (0.3)	3 (0.1)
Pancreatitis	5 (1.4)	0	0	0	6 (1.2)	0	4 (1.9)	0	8 (0.7)	0	4 (0.1)	0
Adrenal insufficiency	4 (1.1)	0	0	0	6 (1.2)	0	3 (1.4)	1 (0.5)	0	0	7 (0.3)	1 (<0.1)
Blood cholesterol increased	4 (1.1)	0	0	0	5 (1.0)	0	0	0	3 (0.3)	0	2 (0.1)	0
Blood triglycerides increased	4 (1.1)	0	4 (1.2)	0	5 (1.0)	0	0	0	0	0	2 (0.1)	0
Rash maculo-papular	4 (1.1)	0	0	0	6 (1.2)	0	5 (2.3)	0	0	0	7 (0.3)	0

Treatment-related Grade ≥3 AEs

In the Indication Safety Set, most common Grade 3 treatment-related TEAEs (occurring in ≥5% of subjects) were hypertension (25.3%), diarrhea (8.2%), proteinuria (7.4%), increased amylase and decreased weight (6.0% each), and increased lipase (5.4%). The only treatment related Grade 4 TEAEs that occurred in 3 or more subjects in the Indication Safety Set were increased lipase (4.3%), increased amylase (1.4%), and decreased neutrophil count and hyperlipasemia (0.9% each).

The incidence and type of severe treatment-related TEAEs observed in the Indication Safety Set was generally consistent with that in the Lenvatinib Monotherapy or Pembrolizumab Monotherapy (RSD-A and RSD-B) Safety Sets, with the following exceptions: increased lipase (9.7%, 1.1%, <0.1%, and 0.2%, respectively) and increased amylase (7.4%, 0.4%, <0.1%, and 0.1%, respectively). These findings are consistent with those for overall severe TEAEs.

ADRs pooled across RCC participants to support update of SmPC

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 A below encompasses the adverse reactions included in Table 2 of the SmPC 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 40 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

		Combination Therapy (N=1456)	
		All AEs % (n)	Gr 3-5 AEs n
Common	hypercalcaemia	3.9% (57)	7

Every subject is counted a single time for each applicable row.

a. infusion reactions (anaphylactic reaction, drug hypersensitivity, hypersensitivity, infusion related hypersensitivity reaction, infusion related reaction)

b. adrenal insufficiency (adrenal insufficiency, secondary adrenocortical insufficiency)

c. thyroiditis (autoimmune thyroiditis, thyroid disorder, thyroiditis)

d. hypophysitis (hypophysitis, hypopituitarism)

e. type 1 diabetes mellitus (diabetic ketoacidosis, type 1 diabetes mellitus)

f. myasthenic syndrome (myasthenia gravis, myasthenic syndrome)

g. encephalitis (encephalitis, encephalitis autoimmune, noninfective encephalitis)

h. uveitis (iridocyclitis, uveitis, vogt-koyanagi-harada disease)

i. cardiac arrhythmia (including atrial fibrillation) (arrhythmia, arrhythmia supraventricular, atrial fibrillation, atrial flutter, atrial tachycardia, atrioventricular block, atrioventricular block first degree, atrioventricular block second degree, bradyarrhythmia, bundle branch block left, bundle branch block right, electrocardiogram qt prolonged, electrocardiogram repolarisation abnormality, extrasystoles, sinus bradycardia, sinus node dysfunction, sinus tachycardia, supraventricular extrasystoles, supraventricular tachycardia, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation)

j. vasculitis (aortitis, giant cell arteritis, vasculitis)

k. pneumonitis (immune-mediated pneumonitis, interstitial lung disease, pneumonitis)

l. abdominal pain (abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper)

m. colitis (colitis, colitis microscopic, enterocolitis, enterocolitis haemorrhagic, immune-mediated enterocolitis)

n. pancreatitis (immune-mediated pancreatitis, pancreatitis, pancreatitis acute)

o. gastrointestinal ulceration (duodenal ulcer, gastric ulcer)

p. hepatitis (autoimmune hepatitis, drug-induced liver injury, hepatitis, immune-mediated hepatitis)

q. rash (genital rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular)

r. pruritus (pruritus, pruritus genital, urticaria)

s. severe skin reactions (dermatitis bullous, erythema multiforme, exfoliative rash, pemphigoid, pruritus, rash, rash maculo-papular, rash pruritic, rash pustular, stevens-johnson syndrome, toxic epidermal necrolysis, toxic skin eruption)

t. lichenoid keratosis (lichen planus, lichenoid keratosis)

u. vitiligo (skin depigmentation, skin hypopigmentation, vitiligo)

v. musculoskeletal pain (back pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, torticollis)

w. myositis (myalgia, myositis, polymyalgia rheumatica, rhabdomyolysis)

x. arthritis (arthritis, joint effusion, joint swelling)

y. tenosynovitis (synovitis, tendonitis, tenosynovitis)

z. nephritis (autoimmune nephritis, nephritis, nephrotic syndrome, tubulointerstitial nephritis)

aa. oedema (eyelid oedema, face oedema, fluid overload, fluid retention, generalised oedema, lip oedema, localised oedema, oedema, oedema peripheral, periorbital oedema)

Database cutoff date for Endometrial Cancer (KN146: 18AUG2020, KN775: 26OCT2020)

Database cutoff date for RCC (KN426: 24AUG2018, KN581: 28AUG2020)

Serious adverse event/deaths/other significant events

Serious Adverse Events (SAEs)

Nonfatal SAEs were reported in 50.0% and 32.6% of subjects in the lenvatinib plus pembrolizumab and sunitinib arms, respectively; the rate of nonfatal SAE episodes adjusted for treatment duration was 0.68 and 0.51 per SY, respectively.

In the Indication Safety Set, the most frequently reported nonfatal SAEs (occurring in >2% of subjects) were diarrhea (3.4%), vomiting (2.8%), pneumonitis (2.6%), and acute kidney injury and hypertension (2.3% each).

SAEs that occurred at a higher incidence in subjects in the lenvatinib plus pembrolizumab arm compared with the sunitinib arm, respectively, were: diarrhea (3.4% vs 1.2%), pneumonitis (2.6% vs 0%), vomiting (2.8% vs 0.9%), acute kidney injury (2.3% vs 1.2%), hypertension (2.3% vs 0.6%), adrenal insufficiency (2.0% vs 0%), myocardial infarction (1.7% vs 0.3%), acute myocardial infarction (1.4% vs 0%), immune-mediated hepatitis and lipase increased (1.1% vs 0% for both), renal failure (1.1% vs 0.6%), and pancreatitis (1.7% vs 0%).

Table 41 Nonfatal Serious Adverse Events Occurring in 1% or More of Subjects by Preferred Term and Safety Set

Preferred Term	**Indication N=352 n (%)**	**Sunitinib N=340 n (%)**	**All RCC N=497 n (%)**	**Non-RCC N=215 n (%)**	**Lenv Monotx N=1119 n (%)**	**Pembro Monotx RSD-A N=2799 n (%)**	**Pembro Monotx RSD-B N=5884 n (%)**
Subjects With Any Nonfatal Treatment-Emergent SAE[a]	176 (50.0)	111 (32.6)	246 (49.5)	129 (60.0)	580 (51.8)	984 (35.2)	2101 (35.7)
Diarrhoea	12 (3.4)	4 (1.2)	14 (2.8)	4 (1.9)	13 (1.2)	26 (0.9)	59 (1.0)
Vomiting	10 (2.8)	3 (0.9)	12 (2.4)	4 (1.9)	23 (2.1)	18 (0.6)	28 (0.5)
Pneumonitis	9 (2.6)	0	11 (2.2)	3 (1.4)	2 (0.2)	44 (1.6)	110 (1.9)
Acute kidney injury	8 (2.3)	4 (1.2)	13 (2.6)	4 (1.9)	17 (1.5)	20 (0.7)	47 (0.8)
Hypertension	8 (2.3)	2 (0.6)	12 (2.4)	10 (4.7)	28 (2.5)	0	1 (<0.1)
Adrenal insufficiency	7 (2.0)	0	9 (1.8)	4 (1.9)	0	8 (0.3)	18 (0.3)
Dyspnoea	7 (2.0)	2 (0.6)	12 (2.4)	6 (2.8)	19 (1.7)	43 (1.5)	76 (1.3)
Pneumonia	7 (2.0)	6 (1.8)	10 (2.0)	5 (2.3)	44 (3.9)	83 (3.0)	213 (3.6)
Myocardial infarction	6 (1.7)	1 (0.3)	9 (1.8)	2 (0.9)	4 (0.4)	3 (0.1)	13 (0.2)
Pancreatitis	6 (1.7)	0	7 (1.4)	4 (1.9)	8 (0.7)	6 (0.2)	8 (0.1)
Pathological fracture	6 (1.7)	2 (0.6)	8 (1.6)	0	3 (0.3)	7 (0.3)	9 (0.2)
Pyrexia	6 (1.7)	7 (2.1)	8 (1.6)	5 (2.3)	8 (0.7)	35 (1.3)	67 (1.1)

Abdominal pain	5 (1.4)	1 (0.3)	8 (1.6)	7 (3.3)	27 (2.4)	22 (0.8)	27 (0.5)
Acute myocardial infarction	5 (1.4)	0	5 (1.0)	0	6 (0.5)	6 (0.2)	11 (0.2)
Mental status changes	5 (1.4)	0	5 (1.0)	1 (0.5)	6 (0.5)	2 (0.1)	3 (0.1)
Nausea	5 (1.4)	1 (0.3)	8 (1.6)	7 (3.3)	17 (1.5)	18 (0.6)	28 (0.5)
Pulmonary embolism	5 (1.4)	3 (0.9)	6 (1.2)	2 (0.9)	26 (2.3)	39 (1.4)	62 (1.1)
Immune-mediated hepatitis	4 (1.1)	0	5 (1.0)	0	0	0	1 (<0.1)
Lipase increased	4 (1.1)	0	4 (0.8)	1 (0.5)	4 (0.4)	0	1 (<0.1)
Pleural effusion	4 (1.1)	4 (1.2)	5 (1.0)	4 (1.9)	8 (0.7)	48 (1.7)	82 (1.4)
Renal failure	4 (1.1)	2 (0.6)	5 (1.0)	0	3 (0.3)	15 (0.5)	22 (0.4)
Urinary tract infection	4 (1.1)	4 (1.2)	5 (1.0)	5 (2.3)	8 (0.7)	15 (0.5)	59 (1.0)

Percentages are based on the total number of subjects in the relevant safety set.
MedDRA PTs "Neoplasm Progression", "Malignant Neoplasm Progression", and "Disease Progression" which are unrelated to the study drug are excluded.
Preferred terms are included in this table if the relevant frequency was ≥1% in the Indication Safety Set.

Subjects with 2 or more TEAEs in the same PT were counted only once for that PT.
Adverse event terms were coded using MedDRA version 23.0.
Data cutoff date: 28 Aug 2020 for Study 307; for all other studies, the clinical cutoff dates specified in ISS SAP version 2.0 were used.

Drug-related Serious Adverse Events (SAEs)

Treatment-related SAEs were reported in 33.8% of subjects in the lenvatinib plus pembrolizumab arm and 15.0% of subjects in the sunitinib arm. In the lenvatinib plus pembrolizumab arm, the most frequently reported treatment-related SAEs (occurring in >1% of subjects) were diarrhoea (2.8%), vomiting (2%), hypertension (2%), and nausea, acute kidney injury, and myocardial infarction (1.1% each). In the sunitinib arm, pyrexia (1.5%) was the only related SAEs that occurred >1%.

Deaths

Progressive disease (PD) was monitored as part of the efficacy assessments and was not recorded as an AE, unless malignant neoplasm progression was the only term the study investigator could use to describe a fatal event. If PD led to an untoward medical occurrence (eg, pleural effusion, spinal cord compression), the medical occurrence was recorded as an AE. All death events, other than the reported terms of "malignant neoplasm progression", are included in the frequency count of fatal TEAEs.

AEs with Fatal Outcome in the Indication Safety Set (N=27)

- Malignant Neoplasm Progression (N=12)
- Other Fatal AEs (N=15)
    - Due to PD (N=5)
    - Treatment Related (N=4)
    - Not Related to Treatment or PD (N=6)

Treatment emergent deaths were reported for 27 subjects (7.7%) in the Indication Safety Set. Out of these 27 subjects, 12 (3.4%) deaths were reported to be due to 'malignant neoplasm progression' (no further discussion provided).

Among the 15 subjects with other fatal AEs (4.3%) in the Indication Safety Set, 5 subjects (1.4%) had other TEAEs that were associated with PD (dyspnoea, cardio-respiratory arrest, cardiac arrest, multiple organ dysfunction, and arrhythmia/cardio-respiratory arrest). Four subjects (1.1%) had fatal AEs attributed to study drug by the investigator (increased blood creatinine, hypertensive crisis, and myasthenic syndrome reported in 1 subject each and 1 subject who had a fatal AE of autoimmune hepatitis along with fatal AEs of myocarditis, pneumonitis, and nephritis).

Six subjects in the Indication Safety Set had fatal AEs that were neither attributed by the investigator to study treatment nor to PD (subarachnoid hemorrhage, ruptured aneurysm, Klebsiella sepsis, and death (unknown cause), reported in 1 subject each; and sepsis reported in 2 subjects). Sponsor assessment of attribution for these events was consistent with the investigator assessment except for the event of subarachnoid haemorrhage. Hemorrhagic events is a CSE for lenvatinib and this subject experienced subarachnoid hemorrhage during Cycle 14 in the setting of elevated BP while on study drugs; therefore, the sponsor considered subarachnoid hemorrhage as related to study treatment.

The incidence of fatal AEs, excluding 'malignant neoplasm progression', was 4.3% in the Indication Safety Set, 3.2% in the sunitinib arm, 8.7% in the Lenvatinib Monotherapy Safety Set, and 3.9% and 5.3%, respectively, in the Pembrolizumab Monotherapy (RSD-A and RSD-B) Safety Sets, indicating that there is no increased risk of fatal AEs with combination therapy. The same was observed when adjusted for exposure, the rate of fatal AEs was 0.04 episodes per subject-year in the Indication Safety Set, 0.03 in the sunitinib arm and 0.09, 0.06, and 0.08 episodes per subject-year in the Lenvatinib Monotherapy and Pembrolizumab Monotherapy (RSD-A and RSD-B) Safety Sets, respectively.

Table 42 Fatal Adverse Events Occurring in Subjects in the Indication Safety Set by Preferred Term and Safety Set

Preferred Term	**Indication N=352 n (%)**	**Sunitinib N=340 n (%)**	**All RCC N=497 n (%)**	**Non-RCC N=215 n (%)**	**Lenv Monotx N=1119 n (%)**	**Pembro Monotx RSD-A N=2799 n (%)**	**Pembro Monotx RSD-B N=5884 n (%)**
Subjects With at Least 1 Fatal TEAE	15 (4.3)	11 (3.2)	25 (5.0)	23 (10.7)	97 (8.7)	110 (3.9)	312 (5.3)
Cardio-respiratory arrest	2 (0.6)	0	2 (0.4)	0	3 (0.3)	1 (<0.1)	4 (0.1)
Sepsis	2 (0.6)	0	3 (0.6)	3 (1.4)	6 (0.5)	1 (<0.1)	9 (0.2)
Aneurysm ruptured	1 (0.3)	0	1 (0.2)	0	0	0	0
Arrhythmia	1 (0.3)	0	1 (0.2)	0	0	0	0
Autoimmune hepatitis	1 (0.3)	0	1 (0.2)	0	0	0	0
Blood creatinine increased	1 (0.3)	0	1 (0.2)	0	0	0	0
Cardiac arrest	1 (0.3)	0	3 (0.6)	0	1 (0.1)	2 (0.1)	9 (0.2)

Death	1 (0.3)	2 (0.6)	1 (0.2)	0	5 (0.4)	17 (0.6)	42 (0.7)
Dyspnoea	1 (0.3)	0	1 (0.2)	0	7 (0.6)	2 (0.1)	5 (0.1)
Hypertensive crisis	1 (0.3)	0	1 (0.2)	0	0	0	0
Klebsiella sepsis	1 (0.3)	0	1 (0.2)	0	0	0	0
Multiple organ dysfunction syndrome	1 (0.3)	0	1 (0.2)	0	2 (0.2)	1 (<0.1)	5 (0.1)
Myasthenic syndrome	1 (0.3)	0	1 (0.2)	0	0	0	0
Myocarditis	1 (0.3)	0	1 (0.2)	0	0	0	0
Nephritis	1 (0.3)	0	1 (0.2)	0	0	0	0
Pneumonitis	1 (0.3)	0	1 (0.2)	0	0	3 (0.1)	8 (0.1)
Subarachnoid haemorrhage	1 (0.3)	0	1 (0.2)	0	0	0	0

Percentages are based on the total number of subjects in the relevant safety set.
MedDRA PTs "Neoplasm Progression", "Malignant Neoplasm Progression", and "Disease Progression" which are unrelated to the study drug are excluded.
Subjects with 2 or more TEAEs in the same PT were counted only once for that PT.
Display is in decreasing order of frequency of fatal TEAEs in the Indication Safety Set.
Adverse event terms were coded using MedDRA version 23.0.
Data cutoff date: 28 Aug 2020 for Study 307; for all other studies, the clinical cutoff dates specified in ISS SAP version 2.0 were used.

Other clinically significant events

CSE for lenvatinib

The following events are established as Clinically Significant Adverse Events (CSEs) from the overall clinical development program for lenvatinib: arterial thromboembolic events, cardiac dysfunction, hypothyroidism, gastrointestinal perforation, fistula formation, hemorrhage, hepatotoxicity, hypertension, hypocalcemia, palmar-plantar erythrodysesthesia syndrome (PPES), posterior reversible encephalopathy syndrome (PRES), proteinuria, QT prolongation, and renal events.

The overall incidence of CSEs of all grades, serious CSEs, and CSEs leading to study drug discontinuation were generally similar in the Indication and Lenvatinib Monotherapy Safety Sets. In the Indication Safety Set, most of the Grade ≥3 CSEs were Grade 3. CSE leading to dose reductions were higher in the Indication Safety Set than in the Lenvatinib Monotherapy Safety Sets.

Fourteen (4.0%) subjects had **Grade 4 CSEs**: arterial thromboembolic events (3 subjects), hepatotoxicity events (5 subjects), hypertension events (1 subject), hypocalcemia events (1 subject), PRES events (1 subject), and renal events (3 subjects).

Five (1.4%) subjects had **fatal** events in the following CSE categories: hemorrhage events (2 subjects: PT ruptured aneurysm and subarachnoid hemorrhage), hepatotoxicity events (1 subject: PT autoimmune hepatitis), hypertension events (1 subject: PT hypertensive crisis), and renal events (2 subjects: PT increased blood creatinine and nephritis).

Table 43 Overview of Clinically Significant Adverse Events for Lenvatinib by Safety Set

Subjects With at Least 1 of the Following:	**Indication N=352 n (%)**	**Sunitinib N=340 n[a] (%)**	**All RCC N=497 n (%)**	**Non-RCC N=215 n (%)**	**Lenv Monotx N=1119 n (%)**

Any CSE	331 (94.0)	289 (85.0)	467 (94.0)	194 (90.2)	972 (86.9)
CSE With Worst CTCAE Grade[b]					
1	26 (7.4)	55 (16.2)	47 (9.5)	12 (5.6)	103 (9.2)
2	117 (33.2)	116 (34.1)	169 (34.0)	66 (30.7)	311 (27.8)
≥3	188 (53.4)	118 (34.7)	251 (50.5)	116 (54.0)	558 (49.9)
3	169 (48.0)	110 (32.4)	224 (45.1)	97 (45.1)	500 (44.7)
4	14 (4.0)	4 (1.2)	18 (3.6)	12 (5.6)	31 (2.8)
5	5 (1.4)	4 (1.2)	9 (1.8)	7 (3.3)	27 (2.4)
Serious CSEs	70 (19.9)	32 (9.4)	98 (19.7)	53 (24.7)	201 (18.0)
CSEs Leading to Discontinuation of Lenv or Sunitinib	40 (11.4)	13 (3.8)	50 (10.1)	27 (12.6)	108 (9.7)
CSEs Leading to Study Drug Modification[c]	179 (50.9)	129 (37.9)	252 (50.7)	109 (50.7)	478 (42.7)
Dose Reduction of Lenv or Sunitinib	116 (33.0)	75 (22.1)	160 (32.2)	69 (32.1)	265 (23.7)
Dose Interruption of Lenv or Sunitinib	124 (35.2)	83 (24.4)	179 (36.0)	85 (39.5)	376 (33.6)

Percentages are based on the total number of subjects in the relevant safety set. For each row category, a subject with 2 or more TEAEs in that category is counted only once **a**: Indicates the number of subjects who had events on sunitinib, which are considered CSEs for Lenv. **b**: If a subject had more than 1 CSE, the subject is only counted once at the worst CTCAE grade. **c**: Study drug modification includes dose reduction or drug interruption. A subject may be counted in both categories if the subject had TEAEs leading to both dose reduction and/or drug interruption.

Table 44 Clinically Significant AEs for Lenvatinib, Overall and Severe Incidence by Safety Set

	Indication N=352 n (%)		**Sunitinib N=340 n[a] (%)**		**All RCC N=497 n (%)**		**Non-RCC N=215 n (%)**		**Lenv Monotx N=1119 n (%)**	
CSE Group	**All Grades n (%)**	**Grade ≥ 3 n (%)**	**All Grades n (%)**	**Grade ≥ 3 n (%)**	**All Grades n (%)**	**Grade ≥ 3 n (%)**	**All Grades n (%)**	**Grade ≥ 3 n (%)**	**All Grades n (%)**	**Grade ≥ 3 n (%)**
Subjects With Any CSE[b]	331 (94.0)	188 (53.4)	289 (85.0)	118 (34.7)	467 (94.0)	251 (50.5)	194 (90.2)	116 (54.0)	972 (86.9)	558 (49.9)
Arterial thromboembolic events	19 (5.4)	13 (3.7)	7 (2.1)	2 (0.6)	27 (5.4)	19 (3.8)	13 (6.0)	6 (2.8)	64 (5.7)	35 (3.1)
Cardiac dysfunction	9 (2.6)	6 (1.7)	7 (2.1)	4 (1.2)	15 (3.0)	8 (1.6)	15 (7.0)	6 (2.8)	62 (5.5)	23 (2.1)
Fistula formation	2 (0.6)	0	2 (0.6)	1 (0.3)	3 (0.6)	1 (0.2)	7 (3.3)	3 (1.4)	23 (2.1)	12 (1.1)
Gastrointestinal perforation	5 (1.4)	4 (1.1)	3 (0.9)	1 (0.3)	8 (1.6)	7 (1.4)	8 (3.7)	5 (2.3)	25 (2.2)	20 (1.8)

Hemorrhage	96 (27.3)	18 (5.1)	90 (26.5)	13 (3.8)	146 (29.4)	23 (4.6)	73 (34.0)	13 (6.0)	367 (32.8)	24 (2.1)
Hepatotoxicity	96 (27.3)	35 (9.9)	82 (24.1)	18 (5.3)	129 (26.0)	40 (8.0)	49 (22.8)	27 (12.6)	196 (17.5)	61 (5.5)
Hypertension	198 (56.3)	101 (28.7)	145 (42.6)	66 (19.4)	260 (52.3)	135 (27.2)	120 (55.8)	65 (30.2)	703 (62.8)	360 (32.2)
Hypocalcemia	5 (1.4)	1 (0.3)	9 (2.6)	1 (0.3)	8 (1.6)	3 (0.6)	7 (3.3)	2 (0.9)	98 (8.8)	26 (2.3)
Hypothyroidism	200 (56.8)	5 (1.4)	109 (32.1)	0	268 (53.9)	5 (1.0)	101 (47.0)	1 (0.5)	222 (19.8)	9 (0.8)
Palmar-Plantar Erythrodysesthesia Syndrome	104 (29.5)	14 (4.0)	129 (37.9)	13 (3.8)	149 (30.0)	14 (2.8)	48 (22.3)	4 (1.9)	250 (22.3)	23 (2.1)
Proteinuria	104 (29.5)	27 (7.7)	43 (12.6)	10 (2.9)	164 (33.0)	40 (8.0)	73 (34.0)	14 (6.5)	395 (35.3)	100 (8.9)
Posterior Reversible Encephalopathy Syndrome	2 (0.6)	2 (0.6)	1 (0.3)	0	2 (0.4)	2 (0.4)	2 (0.9)	2 (0.9)	3 (0.3)	2 (0.2)
QT Prolongation	23 (6.5)	10 (2.8)	13 (3.8)	4 (1.2)	28 (5.6)	13 (2.6)	11 (5.1)	3 (1.4)	54 (4.8)	12 (1.1)
Renal events	78 (22.2)	20 (5.7)	60 (17.6)	8 (2.4)	112 (22.5)	24 (4.8)	26 (12.1)	8 (3.7)	112 (10.0)	31 (2.8)

a: Indicates the number of subjects who had events on sunitinib which are considered CSEs for lenvatinib.

b: CSE categories are based on either a standardized MedDRA query or customized MedDRA query

Higher incidences in the Indication Safety Set than in the Lenvatinib Monotherapy Safety Set were reported for the CSEs of hypothyroidism, renal events, and hepatotoxicity (see discussion below). CSEs of hypothyroidism and hepatotoxicity occurred at a similar incidence in the Indication Safety Set and the Non-RCC Safety Set; both lenvatinib and pembrolizumab are associated with hypothyroidism and liver toxicity.

Similar incidences in the Indication Safety Set and the Lenvatinib Monotherapy Safety Set are noted for all other CSEs. QT prolongation, arterial thromboembolic events, and cardiac dysfunction are discussed further.

Hypothyroidism

Thyroid dysfunction is a known class effect of tyrosine kinase inhibitors due to the antiangiogenic effect on the thyroid blood vessels. Hypothyroidism is also an AEOSI for pembrolizumab.

The incidence of the CSE of hypothyroidism in the Indication Safety Set (56.8%) was higher than that in the Lenvatinib Monotherapy Safety Set and similar to that in the Non-RCC Safety Set (19.8% and 47.0%, respectively). Of note, approximately half of subjects in the Lenvatinib Monotherapy Safety Set had thyroid cancers, likely had thyroid resection and/or radio iodine ablation, and were, therefore, already receiving thyroid replacement therapy. The majority of CSE of hypothyroidism in the Indication Safety Set were Grade 1 (14.5%) or Grade 2 (40.9%); the incidence of Grade 3 events was 1.4% in the Indication Safety Set, 0.8% in the Lenvatinib Monotherapy Safety Set, and 0.5% in the Non-RCC Safety Set.

Renal events

The incidence of the CSE of Renal events in the Indication Safety Set (22.2%) was higher than that in the Lenvatinib Monotherapy Safety Set (10.0%) and the Non-RCC Safety Set (12.1%;) but similar compared to the All RCC Safety Set (22.5%).

The majority of renal events in the Indication Safety Set were Grade 1 (9.4%) or Grade 2 (7.1%). Grade 3 and 4 events were reported with 4.3% and 0.9% (compared to 2.2% and 0.2% in the Lenvatinib Monotherapy Safety Set). Reported incidences in the Indication Safety Set compared to the Lenvatinib Monotherapy Safety Set were: 4.3% vs. 2.4% for SAEs, 1.7% vs. 0.4% for discontinuations of lenvatinib, and 5.1% vs. 1.9% for dose interruptions of lenvatinib.

Higher incidences in the Indication Safety Set compared to the Lenvatinib Monotherapy Safety Set were reported for the preferred terms increased blood creatinine (13.6% vs 4.8%), and renal failure (2.8% vs 0.9%). In the All RCC Safety Set, rate of increased blood creatinine was 14.9% and rate of renal failure was 2.6%. Acute kidney injury was reported in 3.7% in the Indication Safety Set vs 2.9% in the Lenvatinib Monotherapy Safety Set. Serious TEAEs of acute kidney injury were reported for 2.3% of subjects in the Indication Safety Set (and 1.8% of subjects in the Lenvatinib Monotherapy Safety Set).

Hepatotoxicity

The incidence of the CSE of hepatotoxicity in the Indication Safety Set (27.3%) was higher than that in the Lenvatinib Monotherapy Safety Set (17.5%) but similar compared to the Non RCC Safety Set (22.8%). The majority of events were Grade 1 (9.1%) or Grade 2 (8.2%) in the Indication Safety Set. Grade 3 events were 8.2% and 4.7%, Grade 4 events 1.4% and 0.4% in the Indication Safety Set and the Lenvatinib Monotherapy Safety Set, respectively. One subject (0.3%) in the Indication Safety Set had a Grade 5 event (autoimmune hepatitis); in the Lenvatinib Monotherapy Safety Set, the incidence of Grade 5 events was similar (0.4%).

Incidences of hepatotoxicity in the Indication Safety Set compared to the Lenvatinib Monotherapy Safety Set were 3.1% vs. 1.7% for SAEs, 1.1% vs. 0.8% for discontinuations, 8.5% vs 3.1% for dose interruptions and 4.3% vs. 2.1% for dose reductions.

QT Prolongation

The overall incidence of QT prolongation events is similar in the Indication and Lenvatinib Monotherapy Safety Sets (6.5% and 4.8%). Grade 3 events were reported at a higher incidence in the Indication Safety Set (2.8%) than in the Lenvatinib Monotherapy Safety Set (1.1%). In the Indication Safety Set, 8 subjects (2.8%) had cardiac-related TEAEs that were associated with QT prolongation events: 4 subjects had Grade 2 QT prolongation events associated with TEAEs of mild arrhythmias (sinus bradycardia or supra ventricular extrasystole) or mild LV dysfunction, and 4 subjects each had one Grade 3 QT prolongation event associated with atrial fibrillation, myocarditis, cardiomyopathy, or acute cardiac failure. Treatment-emergent AEs leading to discontinuation, interruption, and reduction of lenvatinib were

reported at a similar incidence in the Indication Safety Set (0.3%, 0%, and 0.6%, respectively) and the Lenvatinib Monotherapy Safety Set (0.1%, 0.9%, and 0.3%, respectively.

Arterial Thromboembolic Events

The incidence of arterial thromboembolic events was higher in the lenvatinib plus pembrolizumab arm compared with the sunitinib arm (5.4 and 2.1%, respectively).

The incidence of the CSE arterial thromboembolic events was similar between the lenvatinib plus pembrolizumab arm (5.4%) and the Lenvatinib Monotherapy Safety Set (5.7%); however, a clinically meaningful difference was noted in the incidence for the PTs of acute myocardial infarction and myocardial infarction (all AEs of myocardial infarction were Grade 3 or 4 in the Indication Safety Set).

Table 45 TEAEs by SOC and PT

System Organ Class Preferred Term	Lenv 20 mg + Pembro RCC 1L N=352 n (%)	Sunitinib RCC 1L N=340 n (%)	Lenv 20 mg + Pembro All RCC N=497 n (%)	Lenv 20 mg + Pembro Non-RCC N=215 n (%)	Lenv Monotx 24 mg N=1119 n (%)	Pembro Monotx RSD-A N=2799 n (%)	Pembro Monotx RSD-B N=5884 n (%)
Cardiac disorders	60 (17.0)	36 (10.6)	80 (16.1)	38 (17.7)	201 (18.0)	254 (9.1)	487 (8.3)
Acute myocardial infarction	6 (1.7)	0 (0.0)	6 (1.2)	0 (0.0)	6 (0.5)	8 (0.3)	13 (0.2)
Myocardial infarction	6 (1.7)	1 (0.3)	10 (2.0)	3 (1.4)	9 (0.8)	5 (0.2)	19 (0.3)

Cardiac Dysfunction

The incidence of the CSE of cardiac dysfunction events was similar in the Indication Safety Set (2.6%), the Lenvatinib Monotherapy Safety Set (5.5%) and in the sunitinib arm (2.1%).

Table 46 Overview of CSAEs for Lenvatinib ; cardiac dysfunction events

Cardiac Dysfunction Events

	Lenv 20 mg + Pembro RCC 1L N=352 n (%)	Sunitinib RCC 1L N=340 n[a] (%)	Lenv 20 mg + Pembro All RCC N=497 n (%)	Lenv 20 mg + Pembro Non-RCC N=215 n (%)	Lenv Monotx 24 mg N=1119 n (%)
Subjects with Any Cardiac Dysfunction Events for Lenvatinib	9 (2.6)	7 (2.1)	15 (3.0)	15 (7.0)	62 (5.5)
Worst CTCAE Grade of[b]					
1	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.5)	13 (1.2)
2	3 (0.9)	2 (0.6)	7 (1.4)	8 (3.7)	26 (2.3)
≥ 3	6 (1.7)	4 (1.2)	8 (1.6)	6 (2.8)	23 (2.1)
3	6 (1.7)	4 (1.2)	7 (1.4)	6 (2.8)	18 (1.6)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
5	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	5 (0.4)
Serious CSAEs	4 (1.1)	3 (0.9)	6 (1.2)	6 (2.8)	19 (1.7)
CSAEs Leading to Discontinuation of Lenvatinib/Sunitinib	4 (1.1)	2 (0.6)	4 (0.8)	2 (0.9)	6 (0.5)
CSAEs Leading to Study Drug Modification[c]	1 (0.3)	2 (0.6)	4 (0.8)	7 (3.3)	22 (2.0)

Grade 3 cardiac dysfunction events were congestive cardiac failure, cardiomyopathy, ejection fraction decreased, left ventricular dysfunction and stress cardiomyopathy reported in 1 subject each and cardiac failure reported in 2 subjects in the lenvatinib plus pembrolizumab arm; A review of the 6 subjects with Grade 3 cardiac dysfunction events in the Indication Safety Set indicated that the majority of the subjects had pre-existing risk factors: the subject with stress cardiomyopathy had multiple pericardial tumor lesions along with a reduced ejection fraction (30%) reported on Day 3; the subject with left ventricular dysfunction had this condition at Baseline; the subject with congestive cardiac failure had baseline aortic valve incompetence, stenosis, and replacement with left bundle branch block; the subject with acute cardiac failure had a pre-existing condition of atrial fibrillation and had an associated TEAE of QT prolongation. One subject with cardiac failure had concurrent Grade 3 myocarditis.

AEOSI for pembrolizumab

Adverse Events of Special Interest (AEOSI) are categories comprised of groups of PTs developed by the MAH during the pembrolizumab monotherapy program to assess the frequency of immune-mediated events considered by the MAH to be causally related to pembrolizumab.

The overall incidence of AEOSI was higher in the Indication Safety Set (60.8%) than in the Pembrolizumab Monotherapy (RSD-A and RSD-B) Safety Sets (21.4% and 25.1%, respectively). The majority of AEOSI events were Grade 1 and 2; however higher incidences of AEOSI in the Indication Safety Set were also observed for Grade ≥3 (14.8% vs 6.5%), serious AEOSI (12.5% vs 6.5%) and AEOSI leading to discontinuation of pembrolizumab (10.2% vs 3.9% for the Indication Safety Set vs the Pembrolizumab Monotherapy RSD-B Safety Set, respectively; see Table 47). In the lenvatinib plus pembrolizumab arm, the incidence of Grade ≥3 AEOSI was 14.8%, consisting primarily of Grade 3 events (12.8%). Five subjects (1.4%) had Grade 4 AEOSI; these were immune-hepatitis, acute pancreatitis, pneumonitis, severe skin reactions (PT toxic epidermal necrolysis), and type 1 diabetes mellitus (PT diabetic ketoacidosis). Two subjects (0.4%) had Grade 5 AEOSI: myocarditis, nephritis, pneumonitis, and hepatitis in 1 subject, and myasthenic syndrome in the other subject.

The higher incidence of all-grade AEOSI in the Indication Safety Set was primarily driven by hypothyroidism (47.2%, 8.5%, and 11.1%, respectively). Further AEOSI with an increased incidence in the Indication Safety Set compared to the Pembrolizumab Monotherapy (RSD-A and RSD-B) Safety Sets were hyperthyroidism (8.0%, 3.4%, and 4.2%, respectively), adrenal insufficiency (5.1%, 0.8%, and 0.8%), severe skin reactions (5.1%, 1.4%, and 1.6%), and pancreatitis (2.8%, 0.3%, and 0.3%). [- Numerically higher incidences in the Indication Safety set were also reported for AEOSIs of colitis (2.6%, 1.7%, 1.1%), hepatitis (2.0%, 0.7%, 0.5%), myocarditis (1.1% vs. 0%, 0%), and nephritis (1.7%, 0.3%, 0.4%). Pneumonitis was reported for 5.4%, 3.4%, and 4.5% of subjects, incidences of Grade ≥3 pneumonitis events were 2.0%, 1.3% and 1.5%. -]

Table 47 Overview of Adverse Events of Special Interest for Pembrolizumab by Safety Set

Subjects With at Least 1 of the Following:	**Indication N=352 n (%)**	**All RCC N=497 n (%)**	**Non-RCC N=215 n (%)**	**Pembro Monotx RSD-A N=2799 n (%)**	**Pembro Monotx RSD-B N=5884 n (%)**
Any AEOSI	214 (60.8)	292 (58.8)	121 (56.3)	599 (21.4)	1474 (25.1)
AEOSI With Worst CTCAE Grade[a] of					
1	33 (9.4)	47 (9.5)	14 (6.5)	153 (5.5)	367 (6.2)
2	129 (36.6)	175 (35.2)	81 (37.7)	290 (10.4)	726 (12.3)
≥3	52 (14.8)	70 (14.1)	26 (12.1)	156 (5.6)	381 (6.5)
3	45 (12.8)	62 (12.5)	24 (11.2)	135 (4.8)	325 (5.5)
4	5 (1.4)	6 (1.2)	2 (0.9)	17 (0.6)	45 (0.8)
5	2 (0.6)	2 (0.4)	0	4 (0.1)	11 (0.2)
Serious AEOSI	44 (12.5)	55 (11.1)	18 (8.4)	163 (5.8)	381 (6.5)
AEOSI Leading to Discontinuation of Pembro	36 (10.2)	47 (9.5)	12 (5.6)	85 (3.0)	232 (3.9)
AEOSI Leading to Drug Interruption of Pembro	38 (10.8)	50 (10.1)	23 (10.7)	NA	NA

Percentages are based on the total number of subjects in the relevant safety set.For each row category, a subject with 2 or more AEOSI events in that category is counted only once. Adverse events were graded using CTCAE version 4.03.
a: Subjects with 2 or more of the same AEOSI reported were counted only once in the worst CTCAE grade.

Table 48 Adverse Events of Special Interest for Pembrolizumab With Preferred Terms Reported for the Indication Safety Set, Overall and Severe Incidence by Safety Set

AEOSI Category Preferred Term:	Indication N=352		All RCC N=497		Non-RCC N=215		Pembro Monotx RSD-A N=2799		Pembro Monotx RSD-B N=5884	
	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)
Subjects With Any AEOSI	214 (60.8)	52 (14.8)	292 (58.8)	70 (14.1)	121 (56.3)	26 (12.1)	599 (21.4)	156 (5.6)	1474 (25.1)	381 (6.5)
Subjects With Any TEAE in the AEOSI category of:										
Adrenal Insufficiency Events	18 (5.1)	4 (1.1)	27 (5.4)	6 (1.2)	11 (5.1)	4 (1.9)	22 (0.8)	10 (0.4)	47 (0.8)	23 (0.4)
Adrenal insufficiency	17 (4.8)	4 (1.1)	26 (5.2)	6 (1.2)	11 (5.1)	4 (1.9)	20 (0.7)	8 (0.3)	42 (0.7)	18 (0.3)
Secondary adrenocortical insufficiency	1 (0.3)	0	1 (0.2)	0	0	0	1 (<0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Colitis events	9 (2.6)	4 (1.1)	17 (3.4)	9 (1.8)	12 (5.6)	3 (1.4)	48 (1.7)	32 (1.1)	110 (1.9)	67 (1.1)
Colitis	5 (1.4)	2 (0.6)	11 (2.2)	5 (1.0)	11 (5.1)	3 (1.4)	45 (1.6)	31 (1.1)	95 (1.6)	59 (1.0)
Enterocolitis	2 (0.6)	1 (0.3)	2 (0.4)	1 (0.2)	0	0	1 (<0.1)	1 (<0.1)	8 (0.1)	4 (0.1)
Colitis microscopic	1 (0.3)	0	1 (0.2)	0	0	0	2 (0.1)	0	4 (0.1)	1 (<0.1)
Immune-mediated enterocolitis	1 (0.3)	1 (0.3)	3 (0.6)	3 (0.6)	1 (0.5)	0	0	0	3 (0.1)	2 (<0.1)
Encephalitis events	2 (0.6)	2 (0.6)	2 (0.4)	2 (0.4)	0	0	1 (<0.1)	1 (<0.1)	3 (0.1)	2 (<0.1)
Encephalitis	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	0	0	1 (<0.1)	1 (<0.1)	3 (0.1)	2 (<0.1)
Noninfective encephalitis	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	0	0	0	0	0	0
Hepatitis Events	7 (2.0)	5 (1.4)	9 (1.8)	6 (1.2)	2 (0.9)	1 (0.5)	19 (0.7)	14 (0.5)	56 (1.0)	44 (0.7)
Immune-mediated hepatitis	4 (1.1)	4 (1.1)	5 (1.0)	5 (1.0)	0	0	0	0	1 (<0.1)	1 (<0.1)
Drug-induced liver injury	2 (0.6)	0	2 (0.4)	0	0	0	2 (0.1)	2 (0.1)	6 (0.1)	6 (0.1)
Autoimmune hepatitis	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	1 (0.5)	0	12 (0.4)	8 (0.3)	25 (0.4)	20 (0.3)
Hyperthyroidism Events	28 (8.0)	0	34 (6.8)	0	14 (6.5)	0	96 (3.4)	4 (0.1)	247 (4.2)	7 (0.1)

AEOSI Category Preferred Term:	Indication N=352		All RCC N=497		Non-RCC N=215		Pembro Monotx RSD-A N=2799		Pembro Monotx RSD-B N=5884	
	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)
Hyperthyroidism	28 (8.0)	0	34 (6.8)	0	14 (6.5)	0	96 (3.4)	4 (0.1)	247 (4.2)	7 (0.1)
Hypophysitis Events	3 (0.9)	2 (0.6)	3 (0.6)	2 (0.4)	1 (0.5)	1 (0.5)	17 (0.6)	9 (0.3)	36 (0.6)	20 (0.3)
Hypophysitis	2 (0.6)	1 (0.3)	2 (0.4)	1 (0.2)	0	0	9 (0.3)	4 (0.1)	22 (0.4)	11 (0.2)
Hypopituitarism	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	1 (0.5)	1 (0.5)	8 (0.3)	5 (0.2)	14 (0.2)	9 (0.2)
Hypothyroidism Events	166 (47.2)	5 (1.4)	224 (45.1)	5 (1.0)	96 (44.7)	1 (0.5)	237 (8.5)	3 (0.1)	652 (11.1)	7 (0.1)
Hypothyroidism	166 (47.2)	5 (1.4)	224 (45.1)	5 (1.0)	96 (44.7)	1 (0.5)	236 (8.4)	3 (0.1)	651 (11.1)	7 (0.1)
Infusion Reactions Events	5 (1.4)	1 (0.3)	10 (2.0)	1 (0.2)	1 (0.5)	0	70 (2.5)	6 (0.2)	138 (2.3)	14 (0.2)
Infusion related reaction	4 (1.1)	1 (0.3)	4 (0.8)	1 (0.2)	0	0	29 (1.0)	0	56 (1.0)	0
Infusion related hypersensitivity	1 (0.3)	0	1 (0.2)	0	0	0	0	0	0	0
Myasthenic Syndrome Events	1 (0.3)	1 (0.3)	2 (0.4)	2 (0.4)	0	0	2 (0.1)	1 (<0.1)	3 (0.1)	1 (<0.1)
Myasthenic syndrome	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	0	0	2 (0.1)	1 (<0.1)	2 (<0.1)	1 (<0.1)
Myocarditis Events	4 (1.1)	3 (0.9)	4 (0.8)	3 (0.6)	0	0	0	0	5 (0.1)	5 (0.1)
Myocarditis	4 (1.1)	3 (0.9)	4 (0.8)	3 (0.6)	0	0	0	0	5 (0.1)	5 (0.1)
Myositis Events	3 (0.9)	2 (0.6)	4 (0.8)	3 (0.6)	1 (0.5)	1 (0.5)	11 (0.4)	1 (<0.1)	19 (0.3)	4 (0.1)
Myositis	2 (0.6)	1 (0.3)	3 (0.6)	2 (0.4)	0	0	7 (0.3)	0	13 (0.2)	2 (<0.1)
Immune-mediated myositis	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	0	0	0	0	0	0
Nephritis Events	6 (1.7)	4 (1.1)	8 (1.6)	4 (0.8)	3 (1.4)	2 (0.9)	9 (0.3)	5 (0.2)	23 (0.4)	16 (0.3)
Nephritis	5 (1.4)	3 (0.9)	5 (1.0)	3 (0.6)	1 (0.5)	0	0	0	3 (0.1)	2 (<0.1)

AEOSI Category Preferred Term:	Indication N=352		All RCC N=497		Non-RCC N=215		Pembro Monotx RSD-A N=2799		Pembro Monotx RSD-B N=5884	
	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)
Nephrotic syndrome	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	0	0	0	0	1 (<0.1)	1 (<0.1)
Pancreatitis Events	10 (2.8)	6 (1.7)	15 (3.0)	7 (1.4)	8 (3.7)	5 (2.3)	9 (0.3)	6 (0.2)	18 (0.3)	11 (0.2)
Pancreatitis	9 (2.6)	5 (1.4)	12 (2.4)	6 (1.2)	6 (2.8)	4 (1.9)	7 (0.3)	4 (0.1)	14 (0.2)	7 (0.1)
Immune-mediated pancreatitis	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	0	0	0	0	0	0
Pancreatitis acute	1 (0.3)	1 (0.3)	3 (0.6)	1 (0.2)	2 (0.9)	1 (0.5)	1 (<0.1)	1 (<0.1)	4 (0.1)	3 (0.1)
Pneumonitis Events	19 (5.4)	7 (2.0)	21 (4.2)	9 (1.8)	8 (3.7)	3 (1.4)	94 (3.4)	36 (1.3)	264 (4.5)	91 (1.5)
Pneumonitis	18 (5.1)	7 (2.0)	20 (4.0)	9 (1.8)	5 (2.3)	2 (0.9)	87 (3.1)	34 (1.2)	242 (4.1)	83 (1.4)
Interstitial lung disease	1 (0.3)	0	1 (0.2)	0	0	0	7 (0.3)	2 (0.1)	22 (0.4)	8 (0.1)
Severe Skin Reactions Events	18 (5.1)	18 (5.1)	25 (5.0)	23 (4.6)	11 (5.1)	9 (4.2)	39 (1.4)	30 (1.1)	97 (1.6)	75 (1.3)
Rash	13 (3.7)	13 (3.7)	14 (2.8)	14 (2.8)	0	0	11 (0.4)	11 (0.4)	30 (0.5)	30 (0.5)
Rash maculo-papular	4 (1.1)	4 (1.1)	6 (1.2)	6 (1.2)	5 (2.3)	5 (2.3)	7 (0.3)	7 (0.3)	16 (0.3)	16 (0.3)
Erythema multiforme	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	0	0	3 (0.1)	1 (<0.1)	5 (0.1)	3 (0.1)
Pruritus	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	1 (0.5)	1 (0.5)	4 (0.1)	4 (0.1)	12 (0.2)	12 (0.2)
Toxic epidermal necrolysis	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	0	0	0	0	0	0
Toxic skin eruption	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	1 (0.5)	0	1 (<0.1)	0	2 (<0.1)	1 (<0.1)
Thyroiditis Events	2 (0.6)	0	2 (0.4)	0	6 (2.8)	0	16 (0.6)	0	58 (1.0)	1 (<0.1)
Thyroiditis	2 (0.6)	0	2 (0.4)	0	5 (2.3)	0	11 (0.4)	0	41 (0.7)	1 (<0.1)

AEOSI Category Preferred Term:	Indication N=352		All RCC N=497		Non-RCC N=215		Pembro Monotx RSD-A N=2799		Pembro Monotx RSD-B N=5884	
	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)
Type 1 Diabetes Mellitus Events	2 (0.6)	1 (0.3)	2 (0.4)	1 (0.2)	0	0	6 (0.2)	5 (0.2)	20 (0.3)	19 (0.3)
Type 1 diabetes mellitus	2 (0.6)	0	2 (0.4)	0	0	0	5 (0.2)	3 (0.1)	16 (0.3)	13 (0.2)
Diabetic ketoacidosis	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	0	0	2 (0.1)	2 (0.1)	9 (0.2)	9 (0.2)
Uveitis Events	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	0	0	14 (0.5)	1 (<0.1)	21 (0.4)	2 (<0.1)

Percentages are based on the total number of subjects in the relevant safety set.

Subjects with 2 or more TEAEs reported in the same special interest category or PT were counted only once in the worst CTCAE grade.

Adverse event terms were coded using MedDRA version 23.0.

Adverse events were graded using CTCAE version 4.03.

Data cutoff date: 28 Aug 2020 for Study 307; for all other studies, the clinical cutoff dates specified in ISS SAP version 2.0 were used.

1L = first line, AEOSI = adverse event of special interest, CTCAE = Common Terminology Criteria for Adverse Events, Lenv = lenvatinib, MedDRA = Medical Dictionary for Regulatory Activities, Monotx = monotherapy, Pembro = pembrolizumab, PT = preferred term, Q3W = once every 3 weeks, QD = once daily, RCC = renal cell carcinoma, RSD = Reference Safety Dataset, TEAE = treatment emergent adverse event.

Hypothyroidism

TEAEs of hypothyroidism were reported for a higher proportion of subjects in the Indication Safety Set (47.2%) than in the Pembrolizumab Monotherapy (RSD-A or RSD-B) Safety Sets (8.5%, and 11.1%, respectively). In the Indication Safety Set, most of the events of hypothyroidism (97.0%) were Grade 1 or 2. The remaining 5 events were all Grade 3. The incidence of drug discontinuation due to hypothyroidism was low in both the Indication Safety Set and the Pembrolizumab Monotherapy (RSD-A and RSD-B) Safety Sets (0.6%, <0.1%, and <0.1%, respectively).

Hyperthyroidism

TEAEs of hyperthyroidism were reported for a higher proportion of subjects in the Indication Safety Set (8.0%) than in the Pembrolizumab Monotherapy (RSD-A or RSD-B) Safety Sets (3.4%, and 4.2%, respectively); the same was also observed for treatment-related TEAEs (6.3%, 2.9%, and 3.7%, respectively). All hyperthyroidism events in the Indication Safety Set were Grade 1 and 2 with no Grade ≥3 events. In the Indication Safety Set, hyperthyroidism did not lead to drug discontinuation and led to pembrolizumab interruption in only 2 subjects (0.6%).

Adrenal Insufficiency

TEAEs of adrenal insufficiency were reported for a higher proportion of subjects in the Indication Safety Set (5.1.%) than in the Pembrolizumab Monotherapy Safety Sets (0.8%). Adrenal insufficiency events in the Indication Safety Set were mostly Grade 1 or 2 (14 of 18 subjects). The remaining 4 events were all Grade 3 (1.1% in the Indication Safety Set and 0.3% in the Pembrolizumab Monotherapy Safety Sets).

Of the 18 subjects, 14 had prior nephrectomy/adrenalectomy and another subject had preexisting pituitary adenoma with secondary adrenocortical insufficiency. Adrenal insufficiency was managed with drug discontinuation of pembrolizumab (1 subject [0.3%]) and drug interruption (5 subjects [1.4%]), systemic corticosteroids as appropriate, and standard medical care as per the protocol.

Severe Skin Reactions

Severe skin reaction AEOSI in the Indication Safety Set were mostly Grade 3 (4.8%) with 1 Grade 4 (0.3%) event, and were reported at a higher incidence than that in the Pembrolizumab Monotherapy (RSD-A and RSD-B) Safety Sets (Grade 3: 1.1% and 1.3%, respectively; Grade 4: 0% and 0%). The incidence of severe skin reaction events leading to drug discontinuation was low in both the Indication Safety Set and the Pembrolizumab Monotherapy (RSD-A and RSD-B) Safety Sets (1.4%, 0.1%, and 0.2%). The event led to drug interruption in 6 subjects (1.7%) in the Indication Safety Set.

Pancreatitis

The overall pancreatitis incidence in the Indication Safety Set was higher than that in the Pembrolizumab Monotherapy (RSD-A and RSD-B) Safety Sets (2.8%, 0.3%, and 0.3%, respectively). In the Indication Safety Set, the events were Grade 2 in 4 subjects, Grade 3 in 5 subjects, and Grade 4 in 1 subject (1.1%, 1.4%, and 0.3%, respectively); respective incidences for Grade 2, 3 and 4 events in the Pembrolizumab Monotherapy RSD-A Safety Set were lower (0.1%, 0.2%, and 0.0%). The incidence of pancreatitis leading to discontinuation of pembrolizumab was 0.9% in the Indication Safety Set and 0.1% in both Pembrolizumab Monotherapy Safety Sets. Drug interruption due to the events occurred in 5 subjects (1.4%) in the Indication Safety Set.

In the Indication Safety Set, SAEs of pancreatitis (including acute pancreatitis and immune-mediated pancreatitis) were reported for 7 (2.0%) subjects. The majority of subjects reporting pancreatitis SAEs had pre-existing hyperlipidemia and elevated triglycerides as well as obesity (BMI over 30).

Of note, pancreatitis is also a known ADR for lenvatinib.

Myocarditis

The incidence of myocarditis was 1.1% in the Indication Safety Set with 4 events: 1 Grade 1 (0.3%), 2 Grade 3 (0.6%), and 1 Grade 5 (0.3%). The incidence of Grade ≥3 myocarditis was lower for Pembrolizumab Monotherapy (0.1% in RSD-B).

Laboratory findings

Hematology

Overall, the incidence of Grade 3 and 4 hematology laboratory results in the Indication Safety Set was low (≤5%), similar to that in the Lenvatinib Monotherapy Safety Set and higher in the sunitinib arm. Grade 3 events of INR increased were reported in 3% of subjects (compared to 0.8% in the Lenvatinib Monotherapy Safety Set and 1.3% in the sunitinib arm).

Table 49 Increase From Baseline in CTCAE Grade of at Least 1 for Hematology Tests of Grade 3 or Higher by Safety Set

Hematology Parameter **Worst Postbaseline Grade**	**Indication** **N=352** **n (%)**	**Sunitinib** **N=340** **n (%)**	**All RCC** **N=497** **n (%)**	**Non-RCC** **N=215** **n (%)**	**Lenv Monotx** **N=1119** **n (%)**

Hemoglobin Decreased, m[a]	349	333	493	208	1065
Grade 3, n (%)	12 (3.4)	26 (7.8)	17 (3.4)	7 (3.4)	20 (1.9)
Grade 4, n (%)	0	0	0	0	0
Platelet Count Decreased, m[a]	348	333	492	208	1060
Grade 3, n (%)	6 (1.7)	36 (10.8)	6 (1.2)	4 (1.9)	20 (1.9)
Grade 4, n (%)	1 (0.3)	8 (2.4)	1 (0.2)	0	2 (0.2)
White Blood Cells Decreased, m[a]	349	333	493	208	1064
Grade 3, n (%)	2 (0.6)	27 (8.1)	2 (0.4)	5 (2.4)	7 (0.7)
Grade 4, n (%)	0	1 (0.3)	0	1 (0.5)	1 (0.1)
Neutrophil Count Decreased, m[a]	348	333	492	208	1057
Grade 3, n (%)	10 (2.9)	49 (14.7)	13 (2.6)	6 (2.9)	14 (1.3)
Grade 4, n (%)	5 (1.4)	5 (1.5)	5 (1.0)	3 (1.4)	4 (0.4)
INR increased, m[a]	99	80	169	139	372
Grade 3, n (%)	3 (3.0)	1 (1.3)	4 (2.4)	3 (2.2)	3 (0.8)
Grade 4, n (%)	0	0	0	0	0

Grade 3, Grade 4 = the number of subjects with an increase of at least 1 CTCAE grade from baseline to the worst postbaseline value that is Grade 3 or 4.

Laboratory Results were graded using CTCAE version 4.03.

a: 'm' indicates the number of subjects with both nonmissing baseline and at least 1 postbaseline result in the relevant safety set; this number is used to calculate the percentages within each laboratory test.

Clinical chemistry

A summary of chemistry parameters is presented in the following table:

Table 50 Laboratory Results: Increase from Baseline in CTCAE Grade of at Least 1, All Grades and Grades 3 or 4

	Lenv 20 mg + Pembro RCC 1L N=352 n (%)	Sunitinib RCC 1L N=340 n (%)	Lenv 20 mg + Pembro All RCC N=497 n (%)	Lenv 20 mg + Pembro Non-RCC N=215 n (%)	Lenv Monotx 24 mg N=1119 n (%)
Blood cholesterol increased					
Grade 3 or 4, n (%)	17 (4.9)	3 (0.9)	25 (5.2)	8 (3.9)	17 (3.0)
Blood triglycerides increased					
Grade 3 or 4, n (%)	50 (14.6)	50 (15.1)	73 (15.2)	14 (6.9)	---
Blood glucose increased					
Grade 3 or 4, n (%)	25 (7.2)	11 (3.3)	38 (7.8)	13 (6.2)	---
Blood potassium decreased					
Grade 3 or 4, n (%)	15 (4.3)	2 (0.6)	18 (3.7)	20 (9.6)	49 (4.6)
Blood potassium increased					

Grade 3 or 4, n (%)	31 (8.9)	21 (6.3)	40 (8.1)	2 (1.0)	10 (0.9)
Blood sodium decreased					
Grade 3 or 4, n (%)	41 (11.7)	29 (8.7)	57 (11.6)	32 (15.3)	71 (6.6)
Lipase increased					
Grade 3 or 4, n (%)	117 (33.8)	93 (28.0)	148 (30.3)	32 (15.8)	41 (5.6)
Grade 3, n (%)	75 (21.7)	71 (21.4)	93 (19.1)	19 (9.4)	29 (4.0)
Grade 4, n (%)	42 (12.1)	22 (6.6)	55 (11.3)	13 (6.4)	12 (1.7)
Serum amylase increased					
Grade 3 or 4, n (%)	59 (17.1)	29 (8.8)	74 (15.2)	13 (6.4)	23 (3.1)
Grade 3, n (%)	47 (13.6)	23 (6.9)	62 (12.7)	11 (5.4)	22 (2.9)
Grade 4, n (%)	12 (3.5)	6 (1.8)	12 (2.5)	2 (1.0)	1 (0.1)
Alanine aminotransferase increased					
Grade 3 or 4, n (%)	25 (7.2)	12 (3.6)	28 (5.7)	11 (5.3)	36 (3.4)
Grade 3, n (%)	22 (6.3)	12 (3.6)	25 (5.1)	11 (5.3)	32 (3.0)
Grade 4, n (%)	3 (0.9)	0 (0.0)	3 (0.6)	0 (0.0)	4 (0.4)
Alkaline phosphatase increased					
Grade 3 or 4, n (%)	14 (4.0)	3 (0.9)	16 (3.2)	9 (4.3)	16 (1.5)
Aspartate aminotransferase increased					
Grade 3 or 4, n (%)	26 (7.4)	10 (3.0)	29 (5.9)	18 (8.6)	31 (2.9)
Grade 3, n (%)	21 (6.0)	10 (3.0)	23 (4.7)	16 (7.7)	28 (2.6)
Grade 4, n (%)	5 (1.4)	0 (0.0)	6 (1.2)	2 (1.0)	3 (0.3)
Blood bilirubin increased					
Grade 3 or 4, n (%)	5 (1.4)	3 (0.9)	8 (1.6)	9 (4.3)	10 (0.9)
Creatinine increased					
Grade 3 or 4, n (%)	19 (5.4)	8 (2.4)	22 (4.5)	10 (4.8)	20 (1.9)
Grade 3, n (%)	16 (4.6)	8 (2.4)	19 (3.9)	9 (4.3)	20 (1.9)
Grade 4, n (%)	3 (0.9)	0 (0.0)	3 (0.6)	1 (0.5)	0 (0.0)

Urinalysis - Proteinuria

Proteinuria is a CSE for lenvatinib, incidences were similar between the Lenvatinib Safety Sets but lower in the sunitinib arm. In the Integrated Safety Set, the majority of proteinuria TEAEs (29.5%) were effectively managed with dose interruptions (7.7%) or reductions (10.2%); few subjects (n=6, 1.7%) had proteinuria events leading to discontinuation of lenvatinib treatment.

Table 51 Proteinuria events excerpt from Overview of CSAEs for Lenvatinib

Proteinuria Events

	Lenv 20 mg + Pembro RCC 1L N=352 n (%)	Sunitinib RCC 1L N=340 n[a] (%)	Lenv 20 mg + Pembro All RCC N=497 n (%)	Lenv 20 mg + Pembro Non-RCC N=215 n (%)	Lenv Monotx 24 mg N=1119 n (%)
Subjects with Any Proteinuria Events for Lenvatinib	104 (29.5)	43 (12.6)	164 (33.0)	73 (34.0)	395 (35.3)
Worst CTCAE Grade of[b]					
1	20 (5.7)	19 (5.6)	50 (10.1)	23 (10.7)	106 (9.5)
2	57 (16.2)	14 (4.1)	74 (14.9)	36 (16.7)	188 (16.8)
≥ 3	27 (7.7)	10 (2.9)	40 (8.0)	14 (6.5)	100 (8.9)
3	27 (7.7)	10 (2.9)	40 (8.0)	14 (6.5)	100 (8.9)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Serious CSAEs	1 (0.3)	0 (0.0)	1 (0.2)	1 (0.5)	9 (0.8)
CSAEs Leading to Discontinuation of Lenvatinib/Sunitinib	6 (1.7)	0 (0.0)	9 (1.8)	2 (0.9)	17 (1.5)
CSAEs Leading to Study Drug Modification[c]	44 (12.5)	13 (3.8)	68 (13.7)	31 (14.4)	170 (15.2)
Dose Reduction of Lenvatinib/Sunitinib	36 (10.2)	5 (1.5)	50 (10.1)	19 (8.8)	80 (7.1)
Drug Interruption of Lenvatinib/Sunitinib	27 (7.7)	11 (3.2)	46 (9.3)	24 (11.2)	147 (13.1)

Safety in special populations

Safety by age and sex, baseline renal function and baseline hypertension status are presented below. With regard to race or geographic region (Western Europe and North America vs Rest of World), no meaningful and consistent differences among subgroups were observed for the AE profile of lenvatinib plus pembrolizumab (data not copied). Safety by baseline hepatic function and body weight (<60 kg and ≥60 kg) are not meaningful due to numerical imbalances in subgroups.

Age

In the Indication Safety Set, the median duration of treatment with lenvatinib plus pembrolizumab decreased with age: 18.33 months in the <65 years subgroup, 16.64 months in the ≥65 to <75 subgroup, and 14.09 months in the ≥75 years subgroup. Median dose intensity and received dose as a percentage of planned starting dose also declined with age. A similar, but less pronounced pattern was also observed in the Lenvatinib Monotherapy Safety Set.

The incidence of Grade ≥3 TEAEs and Grade ≥3 related TEAEs was higher in the older age subgroups than in the <65 years age subgroup in the Indication Safety Set. Increases were also partly observed in the other Safety Sets, however less consistent (see Table 52). In the Indication Safety Set, there was also an increase in SAEs and fatal SAEs with higher age, which was not observed or less pronounced in the Monotherapy Safety Sets.

Consistent with the duration of treatment, the incidence of TEAEs leading to discontinuation of any study drug was higher in the older aged subgroups than in the <65 years age subgroup for the Indication Safety Set. A trend towards numerically higher discontinuations rates for elderly was evident in the Lenvatinib Monotherapy Safety Set and the Pembrolizumab Monotherapy Safety Sets as well. The rates of discontinuations of both drugs in the Indication Safety Set were similar to the rate of discontinuation in the sunitinib arm.

Data for subjects with an age of ≥75 years are considered less reliable given the limited numbers in the Indication Safety Set (n=45) and the sunitinib arm (n=25).

Table 52 Overview of Incidence of TEAEs by Age Subgroup

	Age (years)	Indication N=352 n (%)	Sunitinib N=340 n (%)	All RCC N=497 n (%)	Non-RCC N=215 n (%)	Lenv Monotx N=1119 n (%)	Pembro Monotx RSD-B N=5884 n (%)
Number of subjects in each subgroup	**<65**	193	215	281	90	700	3385
	≥65 to <75	114	100	161	100	321	1737
	≥75	45	25	55	25	98	762
Any TEAE	**<65**	193 (100)	211 (98.1)	281 (100)	90 (100)	692 (98.9)	3268 (96.5)
	≥65 to <75	114 (100)	100 (100)	161 (100)	100 (100)	319 (99.4)	1678 (96.6)
	≥75	44 (97.8)	24 (96.0)	54 (98.2)	25 (100)	97 (99.0)	744 (97.6)
Related[a] TEAEs	**<65**	189 (97.9)	195 (90.7)	276 (98.2)	88 (97.8)	660 (94.3)	2367 (69.9)
	≥65 to <75	109 (95.6)	96 (96.0)	156 (96.9)	95 (95.0)	303 (94.4)	1226 (70.6)
	≥75	43 (95.6)	22 (88.0)	53 (96.4)	23 (92.0)	97 (99.0)	543 (71.3)
Grade[b] ≥3 TEAEs	**<65**	149 (77.2)	150 (69.8)	224 (79.7)	82 (91.1)	542 (77.4)	1505 (44.5)
	≥65 to <75	101 (88.6)	72 (72.0)	142 (88.2)	87 (87.0)	273 (85.0)	891 (51.3)
	≥75	40 (88.9)	22 (88.0)	49 (89.1)	24 (96.0)	84 (85.7)	433 (56.8)
Related[a] Grade[b] ≥3 TEAEs	**<65**	123 (63.7)	115 (53.5)	177 (63.0)	62 (68.9)	418 (59.7)	457 (13.5)
	≥65 to <75	93 (81.6)	66 (66.0)	126 (78.3)	70 (70.0)	230 (71.7)	311 (17.9)

	Age (years)	Indication N=352 n (%)	Sunitinib N=340 n (%)	All RCC N=497 n (%)	Non-RCC N=215 n (%)	Lenv Monotx N=1119 n (%)	Pembro Monotx RSD-B N=5884 n (%)
	≥75	36 (80.0)	19 (76.0)	44 (80.0)	17 (68.0)	76 (77.6)	147 (19.3)
Any SAE[c]	**<65**	89 (46.1)	64 (29.8)	132 (47.0)	50 (55.6)	370 (52.9)	1182 (34.9)
	≥65 to <75	68 (59.6)	36 (36.0)	90 (55.9)	60 (60.0)	183 (57.0)	719 (41.4)
	≥75	21 (46.7)	13 (52.0)	29 (52.7)	22 (88.0)	60 (61.2)	365 (47.9)
Fatal SAEs	**<65**	5 (2.6)	7 (3.3)	10 (3.6)	4 (4.4)	57 (8.1)	144 (4.3)
	≥65 to <75	7 (6.1)	2 (2.0)	11 (6.8)	14 (14.0)	28 (8.7)	103 (5.9)
	≥75	3 (6.7)	2 (8.0)	4 (7.3)	5 (20.0)	12 (12.2)	65 (8.5)
Nonfatal SAEs	**<65**	89 (46.1)	62 (28.8)	131 (46.6)	50 (55.6)	353 (50.4)	1095 (32.3)
	≥65 to <75	66 (57.9)	36 (36.0)	86 (53.4)	57 (57.0)	169 (52.6)	670 (38.6)
	≥75	21 (46.7)	13 (52.0)	29 (52.7)	22 (88.0)	58 (59.2)	336 (44.1)
Discontinuation[d]	**<65**	57 (29.5)	24 (11.2)	73 (26.0)	23 (25.6)	172 (24.6)	399 (11.8)
	≥65 to <75	49 (43.0)	18 (18.0)	64 (39.8)	42 (42.0)	93 (29.0)	246 (14.2)
	≥75	25 (55.6)	7 (28.0)	29 (52.7)	10 (40.0)	34 (34.7)	145 (19.0)
Of Lenv[e]	**<65**	35 (18.1)	NA	47 (16.7)	20 (22.2)	172 (24.6)	NA
	≥65 to <75	35 (30.7)	NA	47 (29.2)	39 (39.0)	93 (29.0)	NA
	≥75	20 (44.4)	NA	24 (43.6)	10 (40.0)	34 (34.7)	NA
Of Pembro[f]	**<65**	42 (21.8)	NA	55 (19.6)	21 (23.3)	NA	399 (11.8)
	≥65 to <75	39 (34.2)	NA	50 (31.1)	32 (32.0)	NA	246 (14.2)

	Age (years)	Indication N=352 n (%)	Sunitinib N=340 n (%)	All RCC N=497 n (%)	Non-RCC N=215 n (%)	Lenv Monotx N=1119 n (%)	Pembro Monotx RSD-B N=5884 n (%)
	≥75	20 (44.4)	NA	24 (43.6)	10 (40.0)	NA	145 (19.0)
Of Both Drugs[g]	**<65**	16 (8.3)	NA	24 (8.5)	16 (17.8)	NA	NA
	≥65 to <75	19 (16.7)	NA	25 (15.5)	26 (26.0)	NA	NA
	≥75	12 (26.7)	NA	15 (27.3)	9 (36.0)	NA	NA
Dose Reduction of Lenv or Sunitinib	**<65**	125 (64.8)	99 (46.0)	182 (64.8)	57 (63.3)	303 (43.3)	NA
	≥65 to <75	88 (77.2)	57 (57.0)	124 (77.0)	70 (70.0)	175 (54.5)	NA
	≥75	29 (64.4)	15 (60.0)	34 (61.8)	15 (60.0)	53 (54.1)	NA
Dose Interruption[d]	**<65**	147 (76.2)	104 (48.4)	219 (77.9)	73 (81.1)	445 (63.6)	799 (23.6)
	≥65 to <75	89 (78.1)	64 (64.0)	129 (80.1)	83 (83.0)	229 (71.3)	473 (27.2)
	≥75	40 (88.9)	15 (60.0)	50 (90.9)	22 (88.0)	83 (84.7)	220 (28.9)
Dose Modification of Lenv or Sunitinib[h]	**<65**	159 (82.4)	140 (65.1)	237 (84.3)	81 (90.0)	490 (70.0)	NA
	≥65 to <75	101 (88.6)	82 (82.0)	144 (89.4)	89 (89.0)	258 (80.4)	NA
	≥75	38 (84.4)	17 (68.0)	48 (87.3)	22 (88.0)	87 (88.8)	NA

a: Adverse events were graded using CTCAE version 4.03.

b: Treatment-related TEAEs include TEAEs that were considered by the Investigator to be related, or possibly/probably related to the study drug or TEAEs with a missing causality on the case report form. A total of 19 events (12 subjects) in the Pembro Monotx RSD-A and 31 events (21 subjects) in the Pembro Monotx RSD-B with missing causality were considered 'related' to study drug.

c: For combination of Lenv 20 mg + Pembro, the SAE follow-up window was 90 days after the last dose for Studies 111 and 115, and 120 days after the last dose date for Study 307. For Lenv Monotx and Pembro Monotx (RSD-A and RSD-B), the window was 30 days and 90 days after the last dose, respectively. d: Lenv or Pembro (or sunitinib). e: Regardless of the action taken for Pembro. f: Regardless of the action taken for Lenv. g: Due to the same AE. h: Dose modification includes dose reduction or drug interruption.

In the Indication Safety Set, events in the most common lenvatinib CSE groups were generally reported at a similar incidence in each of the age subgroups with the following exceptions:

- Proteinuria was reported at a higher frequency in the ≥75 years subgroup (37.8%) than in the <65 years (26.4%) and ≥65 to <75 years (31.6%) subgroups. This subgroup difference was also observed in the Lenvatinib Monotherapy Safety Set and Non RCC Safety Set.

- Renal events were reported at a higher frequency in the subjects ≥65 years (≥75 years subgroup [24.4%] and ≥65 to <75 years subgroup [29.8%]) than in the <65 years age subgroup (17.1%). This subgroup difference was also observed in the Lenvatinib Monotherapy Safety Set and Non RCC Safety Set.

No other meaningful age specific differences were noted.

Table 53 Adverse Event Summary for Elderly Subjects by Age (Safety Analysis Set)

	Age (Years)															
	Lenvatinib + Pembrolizumab								Sunitinib							
	< 65		65-74		75-84		≥ 85		< 65		65-74		75-84		≥ 85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	193		114		43		2		215		100		25		0	
with one or more adverse events	193	(100.0)	114	(100.0)	42	(97.7)	2	(100.0)	211	(98.1)	100	(100.0)	24	(96.0)		
who died	5	(2.6)	7	(6.1)	2	(4.7)	1	(50.0)	7	(3.3)	2	(2.0)	2	(8.0)		
with serious adverse events	89	(46.1)	68	(59.6)	20	(46.5)	1	(50.0)	64	(29.8)	36	(36.0)	13	(52.0)		
discontinued due to an adverse event	57	(29.5)	49	(43.0)	23	(53.5)	2	(100.0)	24	(11.2)	18	(18.0)	7	(28.0)		
CNS (confusion / extrapyramidal)	67	(34.7)	48	(42.1)	19	(44.2)	1	(50.0)	20	(9.3)	19	(19.0)	2	(8.0)		
AE related to falling	23	(11.9)	18	(15.8)	6	(14.0)	0	(0.0)	17	(7.9)	9	(9.0)	4	(16.0)		
CV events	132	(68.4)	80	(70.2)	28	(65.1)	2	(100.0)	101	(47.0)	56	(56.0)	14	(56.0)		
Cerebrovascular events	5	(2.6)	5	(4.4)	0	(0.0)	0	(0.0)	2	(0.9)	3	(3.0)	0	(0.0)		
Infections	117	(60.6)	61	(53.5)	19	(44.2)	0	(0.0)	98	(45.6)	42	(42.0)	8	(32.0)		

Sex

In the Indication Safety Set, the majority of the subjects were male (71.6%). In the sunitinib arm, the incidences of all and related Grade ≥3 related TEAEs, and fatal and nonfatal SAEs were higher in the female subgroup than in the male subgroup. Discontinuations of sunitinib were similar between sexes but dose modifications (dose reductions and interruptions) were higher for females. For all and related Grade ≥3 TEAEs, and nonfatal SAEs, a small trend towards higher incidences in females was also observed in the Indication Safety Set.

Table 54 Overview of Incidence of Treatment Emergent Adverse Events by Sex Subgroup (excerpt)

	Sex	**Indication N=352 n (%)**	**Sunitinib N=340 n (%)**	**All RCC N=497 n (%)**	**Non-RCC N=215 n (%)**	**Lenv Monotx N=1119 n (%)**	**Pembro Monotx RSD-B N=5884 n (%)**
Number of subjects in each subgroup	**Male**	252	260	365	63	554	3887
	Female	100	80	132	152	565	1197
Any TEAE	**Male**	251 (99.6)	255 (98.1)	364 (99.7)	63 (100)	552 (99.6)	3756 (96.6)
	Female	100 (100)	80 (100)	132 (100)	152 (100)	556 (98.4)	1934 (96.8)
Related[a] TEAEs	**Male**	247 (98.0)	240 (92.3)	359 (98.4)	61 (96.8)	529 (95.5)	2714 (69.8)

	Sex	Indication N=352 n (%)	Sunitinib N=340 n (%)	All RCC N=497 n (%)	Non-RCC N=215 n (%)	Lenv Monotx N=1119 n (%)	Pembro Monotx RSD-B N=5884 n (%)
	Female	94 (94.0)	73 (91.3)	126 (95.5)	145 (95.4)	531 (94.0)	1422 (71.2)
Grade[b] ≥3 TEAEs	**Male**	203 (80.6)	175 (67.3)	301 (82.5)	57 (90.5)	440 (79.4)	1894 (48.7)
	Female	87 (87.0)	69 (86.3)	114 (86.4)	136 (89.5)	459 (81.2)	935 (46.8)
Related[a] Grade[b] ≥3 TEAEs	**Male**	176 (69.8)	143 (55.0)	252 (69.0)	41 (65.1)	329 (59.4)	632 (16.3)
	Female	76 (76.0)	57 (71.3)	95 (72.0)	108 (71.1)	395 (69.9)	283 (14.2)
Any SAE[c]	**Male**	123 (48.8)	78 (30.0)	181 (49.6)	40 (63.5)	296 (53.4)	1534 (39.5)
	Female	55 (55.0)	35 (43.8)	70 (53.0)	92 (60.5)	317 (56.1)	732 (36.7)
Fatal SAEs	**Male**	11 (4.4)	7 (2.7)	16 (4.4)	7 (11.1)	49 (8.8)	221 (5.7)
	Female	4 (4.0)	4 (5.0)	9 (6.8)	16 (10.5)	48 (8.5)	91 (4.6)
Nonfatal SAEs	**Male**	121 (48.0)	77 (29.6)	179 (49.0)	39 (61.9)	279 (50.4)	1416 (36.4)
	Female	55 (55.0)	34 (42.5)	67 (50.8)	90 (59.2)	301 (53.3)	685 (34.3)
Discontinuation[d]	**Male**	92 (36.5)	37 (14.2)	120 (32.9)	19 (30.2)	152 (27.4)	529 (13.6)
	Female	39 (39.0)	12 (15.0)	46 (34.8)	56 (36.8)	147 (26.0)	261 (13.1)
Of Lenv[e]	**Male**	62 (24.6)	NA	85 (23.3)	18 (28.6)	152 (27.4)	NA
	Female	28 (28.0)	NA	33 (25.0)	51 (33.6)	147 (26.0)	NA
Of Pembro[f]	**Male**	69 (27.4)	NA	90 (24.7)	17 (27.0)	NA	529 (13.6)
	Female	32 (32.0)	NA	39 (29.5)	46 (30.3)	NA	261 (13.1)
Of Both Drugs[g]	**Male**	30 (11.9)	NA	44 (12.1)	15 (23.8)	NA	NA
	Female	17 (17.0)	NA	20 (15.2)	36 (23.7)	NA	NA

	Sex	Indication N=352 n (%)	Sunitinib N=340 n (%)	All RCC N=497 n (%)	Non-RCC N=215 n (%)	Lenv Monotx N=1119 n (%)	Pembro Monotx RSD-B N=5884 n (%)
Dose Reduction of Lenv or Sunitinib	**Male**	176 (69.8)	121 (46.5)	252 (69.0)	42 (66.7)	239 (43.1)	NA
	Female	66 (66.0)	50 (62.5)	88 (66.7)	100 (65.8)	292 (51.7)	NA
Dose Interruption[d]	**Male**	193 (76.6)	134 (51.5)	288 (78.9)	55 (87.3)	364 (65.7)	986 (25.4)
	Female	83 (83.0)	49 (61.3)	110 (83.3)	123 (80.9)	393 (69.6)	506 (25.3)
Dose Modification of Lenv or Sunitinib[h]	**Male**	213 (84.5)	175 (67.3)	316 (86.6)	58 (92.1)	395 (71.3)	NA
	Female	85 (85.0)	64 (80.0)	113 (85.6)	134 (88.2)	440 (77.9)	NA

a: Adverse events were graded using CTCAE version 4.03. b: Treatment-related TEAEs include TEAEs that were considered by the Investigator to be related, or possibly/probably related to the study drug or TEAEs with a missing causality on the case report form. A total of 19 events (12 subjects) in the Pembro Monotx RSD-A and 31 events (21 subjects) in the Pembro Monotx RSD-B with missing causality were considered 'related' to study drug. c: For combination of Lenv 20 mg + Pembro, the SAE follow-up window was 90 days after the last dose for Studies 111 and 115, and 120 days after the last dose date for Study 307. For Lenv Monotx and Pembro Monotx (RSD-A and RSD-B), the window was 30 days and 90 days after the last dose, respectively. d: Lenv or Pembro (or sunitinib). e: Regardless of the action taken for Pembro. f: Regardless of the action taken for Lenv. g: Due to the same AE. h: Dose modification includes dose reduction or drug interruption.

Baseline renal function

In the Indication Safety Set, the majority of the subjects had a Baseline CrCl ≥60 mL/min (65.1%).

In the Indication Safety Set, the median duration of treatment with lenvatinib plus pembrolizumab was higher in the CrCl ≥60 mL/min subgroup than in the CrCl <60 mL/min subgroup (20.04 months and 11.86 months, respectively).

The incidences of Grade ≥3 TEAEs, Grade ≥3 related TEAEs, fatal SAEs, nonfatal SAEs and discontinuations were higher in the CrCl <60 mL/min subgroup than in the CrCl ≥60 mL/min subgroup for the Indication Safety Set; however this was similarly observed in the sunitinib arm (see Table 55).

In the Indication Safety Set, with the exception of renal events (reported at a higher frequency in the CrCl <60 mL/min subgroup [31.1%] than in the CrCl ≥60 mL/min subgroup [17.5%]), events in the most common lenvatinib CSE groups were reported at a similar incidence in each of the renal function subgroups. No other meaningful renal function-specific differences were noted.

Table 55 Overview of Incidence of Treatment Emergent Adverse Events by Baseline Renal Function Subgroup

	Baseline Renal Function (CrCl)	Indication N=352 n (%)	Sunitinib N=340 n (%)	All RCC N=497 n (%)	Non-RCC N=215 n (%)	Lenv Monotx N=1119 n (%)
Number of subjects in each subgroup	**<60 mL/min**	106	86	137	49	157
	≥60 mL/min	229	242	343	166	933
Any TEAE	**<60 mL/min**	106 (100)	86 (100)	137 (100)	49 (100)	153 (97.5)
	≥60 mL/min	228 (99.6)	238 (98.3)	342 (99.7)	166 (100)	926 (99.2)
Related[a] TEAEs	**<60 mL/min**	103 (97.2)	79 (91.9)	134 (97.8)	44 (89.8)	146 (93.0)
	≥60 mL/min	222 (96.9)	223 (92.1)	335 (97.7)	162 (97.6)	885 (94.9)
Grade[b] ≥3 TEAEs	**<60 mL/min**	94 (88.7)	66 (76.7)	123 (89.8)	46 (93.9)	122 (77.7)
	≥60 mL/min	183 (79.9)	171 (70.7)	279 (81.3)	147 (88.6)	755 (80.9)
Related[a] Grade[b] ≥3 TEAEs	**<60 mL/min**	86 (81.1)	58 (67.4)	111 (81.0)	35 (71.4)	101 (64.3)
	≥60 mL/min	156 (68.1)	135 (55.8)	226 (65.9)	114 (68.7)	605 (64.8)
Any SAE[c]	**<60 mL/min**	62 (58.5)	42 (48.8)	77 (56.2)	31 (63.3)	80 (51.0)
	≥60 mL/min	106 (46.3)	68 (28.1)	164 (47.8)	101 (60.8)	517 (55.4)
Fatal SAEs	**<60 mL/min**	9 (8.5)	5 (5.8)	13 (9.5)	5 (10.2)	20 (12.7)
	≥60 mL/min	4 (1.7)	5 (2.1)	10 (2.9)	18 (10.8)	75 (8.0)
Nonfatal SAEs	**<60 mL/min**	60 (56.6)	42 (48.8)	74 (54.0)	31 (63.3)	72 (45.9)
	≥60 mL/min	106 (46.3)	67 (27.7)	162 (47.2)	98 (59.0)	493 (52.8)
TEAEs Leading to Study Drug						
Discontinuation[d]	**<60 mL/min**	55 (51.9)	23 (26.7)	63 (46.0)	14 (28.6)	42 (26.8)

	Baseline Renal Function (CrCl)	Indication N=352 n (%)	Sunitinib N=340 n (%)	All RCC N=497 n (%)	Non-RCC N=215 n (%)	Lenv Monotx N=1119 n (%)
	≥60 mL/min	71 (31.0)	24 (9.9)	98 (28.6)	61 (36.7)	249 (26.7)

Baseline hypertension status

In the Indication Safety Set, the majority of the subjects had hypertension at Baseline (57.4%).

The incidence of Grade ≥3 TEAEs and Grade ≥3 related TEAEs were slightly higher in the subgroup with hypertension than in the subgroup without hypertension for the Indication Safety Set (similar trend also seen in the sunitinib arm and the Lenvatinib Monotherapy Safety Set) (see Table 56). The incidence of fatal SAEs and non-fatal SAEs was similar between the hypertension subgroups.

The subjects with hypertension at Baseline in the Indication Safety Set had a higher incidence of TEAEs leading to discontinuation of lenvatinib than did the subjects without Baseline hypertension. This difference was not observed in the Lenvatinib Monotherapy Safety Set or in the Non-RCC Safety Set.

Proteinuria was reported more frequently in subjects with Baseline hypertension (33.2%) than those without (24.7%). This difference was also observed in the Non-RCC Safety Set, but not in the Lenvatinib Monotherapy Safety Set. No other notable subgroup differences were identified in the Indication Safety Set.

Table 56 Overview of Incidence of Treatment Emergent Adverse Events by Baseline Hypertension Subgroup

	Baseline Hypertension	Indication N=352 n (%)	Sunitinib N=340 n (%)	All RCC N=497 n (%)	Non-RCC N=215 n (%)	Lenv Monotx N=1119 n (%)
Number of subjects in each subgroup	**Yes**	202	204	303	112	529
	No	150	136	194	103	590
Any TEAE	**Yes**	201 (99.5)	202 (99.0)	302 (99.7)	112 (100)	524 (99.1)
	No	150 (100)	133 (97.8)	194 (100)	103 (100)	584 (99.0)
Related[a] TEAEs	**Yes**	192 (95.0)	190 (93.1)	293 (96.7)	105 (93.8)	498 (94.1)
	No	149 (99.3)	123 (90.4)	192 (99.0)	101 (98.1)	562 (95.3)
Grade[b] ≥3 TEAEs	**Yes**	173 (85.6)	155 (76.0)	259 (85.5)	98 (87.5)	450 (85.1)
	No	117 (78.0)	89 (65.4)	156 (80.4)	95 (92.2)	449 (76.1)

	Baseline Hypertension	Indication N=352 n (%)	Sunitinib N=340 n (%)	All RCC N=497 n (%)	Non-RCC N=215 n (%)	Lenv Monotx N=1119 n (%)
Related[a] Grade[b] ≥3 TEAEs	**Yes**	153 (75.7)	131 (64.2)	219 (72.3)	76 (67.9)	379 (71.6)
	No	99 (66.0)	69 (50.7)	128 (66.0)	73 (70.9)	345 (58.5)
Any SAE[c]	**Yes**	105 (52.0)	72 (35.3)	158 (52.1)	72 (64.3)	305 (57.7)
	No	73 (48.7)	41 (30.1)	93 (47.9)	60 (58.3)	308 (52.2)
Fatal SAEs	**Yes**	10 (5.0)	7 (3.4)	19 (6.3)	13 (11.6)	51 (9.6)
	No	5 (3.3)	4 (2.9)	6 (3.1)	10 (9.7)	46 (7.8)
Nonfatal SAEs	**Yes**	103 (51.0)	70 (34.3)	154 (50.8)	70 (62.5)	288 (54.4)
	No	73 (48.7)	41 (30.1)	92 (47.4)	59 (57.3)	292 (49.5)
TEAEs Leading to Study Drug						
Discontinuation[d]	**Yes**	82 (40.6)	32 (15.7)	113 (37.3)	41 (36.6)	153 (28.9)
	No	49 (32.7)	17 (12.5)	53 (27.3)	34 (33.0)	146 (24.7)
Of Lenv[e]	**Yes**	62 (30.7)	NA	87 (28.7)	36 (32.1)	153 (28.9)
	No	28 (18.7)	NA	31 (16.0)	33 (32.0)	146 (24.7)
Of Pembro[f]	**Yes**	63 (31.2)	NA	88 (29.0)	33 (29.5)	NA
	No	38 (25.3)	NA	41 (21.1)	30 (29.1)	NA
Of Both Drugs[g]	**Yes**	33 (16.3)	NA	48 (15.8)	24 (21.4)	NA
	No	14 (9.3)	NA	16 (8.2)	27 (26.2)	NA

Safety related to drug-drug interactions and other interactions

No drug interactions are expected between pembrolizumab and lenvatinib because of different metabolic pathways. Pembrolizumab is a monoclonal antibody and is primarily catabolized like other proteins, while lenvatinib is metabolized by enzymatic (cytochrome P450 3A and aldehyde oxidase) and nonenzymatic processes. Therefore, no dedicated DDI studies have been performed.

Discontinuation due to adverse events

Discontinuations

The types of TEAEs resulting in discontinuation of study drug in the lenvatinib plus pembrolizumab arm were consistent with previous experience with each individual study drug. The median time to discontinuation in the lenvatinib plus pembrolizumab arm was almost double at 8.97 months than that in the sunitinib arm (4.57 months). The number of subjects who discontinued all study drugs due to TEAEs was comparable in both arms (13.4% and 14.4% in the lenvatinib plus pembrolizumab and sunitinib arms, respectively).

Table 57 Discontinuation of study drugs

Subjects With at Least 1 of the Following:	**Indication N=352 n (%)**	**Sunitinib N=340 n (%)**	**All RCC N=497 n (%)**	**Non-RCC N=215 n (%)**	**Lenv Monotx N=1119 n (%)**	**Pembro Monotx RSD-A N=2799 n (%)**	**Pembro Monotx RSD-B N=5884 n (%)**
TEAEs Leading to Discontinuation of ***d***	131 (37.2)	49 (14.4)	166 (33.4)	75 (34.9)	299 (26.7)	334 (11.9)	790 (13.4)
Lenv ***e***	90 (25.6)	NA	118 (23.7)	69 (32.1)	299 (26.7)	NA	NA
Pembro ***f***	101 (28.7)	NA	129 (26.0)	63 (29.3)	NA	334 (11.9)	790 (13.4)
Both Lenv and Pembro ***g***	47 (13.4)	NA	64 (12.9)	51 (23.7)	NA	NA	NA

d: Lenv or Pembro (or sunitinib).

e: Drug discontinuation for Lenv, regardless of the action taken for Pembro.

f: Drug discontinuation for Pembro, regardless of the action taken for Lenv.

g: Drug discontinuation for both Lenv and Pembro occurred at the same time due to the same AE.

In the Indication Safety Set, 13.4% of subjects had TEAEs that led to treatment discontinuation of both lenvatinib and pembrolizumab, which was similar to that in the All RCC Safety Set (12.9%) and lower than that in the Non-RCC Safety Set (23.7%).

The TEAEs that led to discontinuation of study drug in more than 1 subject were as follows:

- acute kidney injury (2 subjects; 1 Grade 4 and 1 Grade 3 TEAE, both related to study drug),
- pneumonitis (2 subjects; 1 Grade 4 and 1 Grade 3 TEAE, both related to study drug),
- proteinuria (2 subjects; 1 Grade 3 and 1 Grade 2 TEAE, both related to study drug), and
- rash (2 subjects; both Grade 3 and related to study drug).

All other TEAEs that led to discontinuation of both study drugs in the Indication Safety Set were reported for 1 subject each.

The incidence of TEAEs that led to discontinuation of lenvatinib, regardless of the action taken with pembrolizumab, was similar in the Indication Safety Set (25.6%) and in the Lenvatinib Monotherapy Safety Set (26.7%). In the Indication Safety Set, for following SOCs incidences ≥2% were reported: cardiac disorders (4.5%), renal and urinary disorders (3.4%), nervous system disorders (2.8%), skin and subcutaneous tissue disorders (2.8%), and gastrointestinal disorders (2.3%). The TEAEs that most commonly (≥0.9% of subjects) led to discontinuation of lenvatinib were proteinuria (1.7%), rash (including rash maculo-papular and rash papular) (1.5%), diarrhea (1.4%), myocardial infarction (1.1%), acute myocardial infarction (1.1%), and acute kidney injury (0.9%).

Incidences of TEAEs leading to treatment discontinuation of pembrolizumab, regardless of the action taken with lenvatinib, were 28.7% in the Indication Safety Set and higher than that in the Pembrolizumab Monotherapy Safety Sets (RSD-A: 11.9%; RSD-B: 13.4%). In the Indication Safety Set, for following SOCs incidences ≥2% were reported: investigations (4.3%); gastrointestinal disorders (3.4%); respiratory, thoracic and mediastinal disorders (3.4%); skin and subcutaneous tissue disorders (3.4%); and renal and urinary disorders (2.8%). The TEAEs that most frequently (>1% of subjects) led to discontinuation of pembrolizumab were pneumonitis (2.8%), rash (including rash maculo-papular and papular) (2.3%), diarrhea (1.1%), and alanine aminotransferase (ALT) increased (1.1%).

The number of subjects who discontinued lenvatinib **or** pembrolizumab due to TEAEs was 37.2% in the lenvatinib plus pembrolizumab arm. For following SOCs incidences ≥2% were reported: cardiac disorders (5.1% [n=18; including 9 myocardial infarction, 2 acute coronary syndrome and 2 myocarditis]), gastrointestinal disorders (4.8%), investigations (4.8%), renal and urinary disorders (4.8%), skin and subcutaneous tissue disorders (4.3%), and respiratory, thoracic and mediastinal disorders (3.7%).

The TEAEs that most commonly (≥1% of subjects) led to discontinuation of either study drug in the Indication Safety Set were pneumonitis (2.8%), rash (including rash maculo-papular and papular) (2.6%), (acute) myocardial infarction (2.6%), diarrhoea (2.3%), proteinuria (1.7%), acute kidney injury (1.1%), renal failure (1.1%), and ALT increased (1.1%).

Table 58 TEAEs Leading to Study Drug Discontinuation of Lenvatinib or Pembrolizumab by Decreasing Frequency of Preferred Term; ISS Safety Set

Preferred Term (or Grouped Term) Preferred Term	Lenv 20 mg + Pembro RCC 1L N=352 n (%)
Subjects with any TEAEs Leading to Study Drug Discontinuation of Lenvatinib or Pembrolizumab	127 (36.1)
Pneumonitis	10 (2.8)
Myocardial infarction	9 (2.6)
Acute myocardial infarction	5 (1.4)
Myocardial infarction	4 (1.1)
Rash	9 (2.6)
Rash	7 (2.0)
Rash maculo-papular	1 (0.3)
Rash papular	1 (0.3)
Diarrhoea	8 (2.3)
Proteinuria	6 (1.7)
Acute kidney injury	4 (1.1)
Alanine aminotransferase increased	4 (1.1)
Renal failure	4 (1.1)
Aspartate aminotransferase increased	3 (0.9)
Musculoskeletal pain	3 (0.9)

- AEs Resulting in Discontinuation of Sunitinib

In the sunitinib arm, 14.4% of subjects experienced TEAEs leading to discontinuation of sunitinib. The most common TEAEs leading to discontinuation in 3 of subjects (0.9% each) were nausea, asthenia, fatigue, acute kidney injury, and metastases to central nervous system.

Dose modification

Table 59 Dose Modification (Reduction or Interruption) of study drugs

Subjects With at Least 1 of the Following:	Indication N=352 n (%)	Sunitinib N=340 n (%)	All RCC N=497 n (%)	Non-RCC N=215 n (%)	Lenv Monotx N=1119 n (%)	Pembro Monotx RSD-A N=2799 n (%)	Pembro Monotx RSD-B N=5884 n (%)
TEAEs Leading to Dose **Reduction** of Lenv or Sunitinib	242 (68.8)	171 (50.3)	340 (68.4)	142 (66.0)	531 (47.5)	NA	NA
TEAEs Leading to Drug **Interruption** [d] of	276 (78.4)	183 (53.8)	398 (80.1)	178 (82.8)	757 (67.6)	622 (22.2)	1492 (25.4)
Lenv [e]	257 (73.0)	NA	374 (75.3)	173 (80.5)	757 (67.6)	NA	NA
Pembro [f]	194 (55.1)	NA	269 (54.1)	116 (54.0)	NA	622 (22.2)	1492 (25.4)
Both Lenv and Pembro [g]	138 (39.2)	NA	192 (38.6)	93 (43.3)	NA	NA	NA

TEAEs Leading to Dose **Modification** [h] of Lenv or Sunitinib	298 (84.7)	239 (70.3)	429 (86.3)	192 (89.3)	835 (74.6)	NA	NA

d: Lenv or Pembro (or sunitinib). ***e***: Drug interruption for Lenv, regardless of the action taken for Pembro. ***f***: Drug interruption for Pembro, regardless of the action taken for Lenv. ***g***: Drug interruption for both Lenv and Pembro occurred at the same time due to the same AE. ***h***: Dose modification includes dose reduction or drug interruption.

AEs Resulting in Dose **Modification** (Reduction or Interruption) of **Lenvatinib**

A dose reduction guideline for lenvatinib was specified for management of treatment-related toxicity in the lenvatinib and pembrolizumab combination studies and in the studies that comprised the Lenvatinib Monotherapy Safety Set. In the Indication Safety Set, 84.7% of subjects had TEAEs leading to a lenvatinib dose modification (dose interruption or reduction), 73.0% had TEAEs leading to a dose interruption, and 68.8% had TEAEs leading to a dose reduction.

The incidence of TEAEs leading to a dose reduction of lenvatinib was higher in the Indication Safety Set (68.8%) than in the Lenvatinib Monotherapy Safety Set (47.5%) [and higher than in the sunitinib arm 50.3%]. The TEAEs that most frequently led to a lenvatinib dose reduction (occurring in ≥5% of subjects) were diarrhea (15.9%), hypertension (11.6%), proteinuria (10.2%), PPES (8.8%), decreased appetite (7.7%), and nausea (5.1%).

The incidence of TEAEs leading to a dose interruption of lenvatinib was similar in the Indication (73.0%) and Lenvatinib Monotherapy (67.6%) Safety Sets [and higher than in the sunitinib arm 53.8%]. The TEAEs that most frequently led to a lenvatinib dose interruption (occurring in ≥5% of subjects) were diarrhea (17.6%), hypertension (8.2%), proteinuria (7.7%), asthenia (6.3%), increased lipase (5.4%), and fatigue (5.1%).

Table 60 Treatment Emergent Adverse Events Leading to Dose Modification (Reduction or Interruption) of Lenvatinib in 2% or More of Subjects by Preferred Term and Safety Set

Preferred Term	**Indication N=352 n (%)**	**All RCC N=497 n (%)**	**Non-RCC N=215 n (%)**	**Lenv Monotx N=1119 n (%)**
Subjects With Any TEAEs Leading to Dose Modification of Lenvatinib[a]	298 (84.7)	429 (86.3)	192 (89.3)	835 (74.6)
Diarrhoea	90 (25.6)	127 (25.6)	50 (23.3)	175 (15.6)
Hypertension	56 (15.9)	80 (16.1)	46 (21.4)	192 (17.2)
Proteinuria	44 (12.5)	68 (13.7)	31 (14.4)	166 (14.8)
Decreased appetite	41 (11.6)	54 (10.9)	37 (17.2)	112 (10.0)
Palmar-plantar erythrodysaesthesia syndrome	37 (10.5)	53 (10.7)	20 (9.3)	88 (7.9)
Asthenia	32 (9.1)	33 (6.6)	13 (6.0)	72 (6.4)
Fatigue	31 (8.8)	65 (13.1)	49 (22.8)	150 (13.4)
Nausea	30 (8.5)	48 (9.7)	25 (11.6)	103 (9.2)
Lipase increased	23 (6.5)	28 (5.6)	11 (5.1)	16 (1.4)
Stomatitis	22 (6.3)	31 (6.2)	17 (7.9)	59 (5.3)

Preferred Term	Indication N=352 n (%)	All RCC N=497 n (%)	Non-RCC N=215 n (%)	Lenv Monotx N=1119 n (%)
Vomiting	21 (6.0)	28 (5.6)	24 (11.2)	77 (6.9)
Alanine aminotransferase increased	19 (5.4)	22 (4.4)	12 (5.6)	19 (1.7)
Amylase increased	19 (5.4)	23 (4.6)	3 (1.4)	10 (0.9)
Rash	18 (5.1)	18 (3.6)	2 (0.9)	12 (1.1)
Weight decreased	16 (4.5)	21 (4.2)	18 (8.4)	105 (9.4)
Abdominal pain	15 (4.3)	23 (4.6)	9 (4.2)	52 (4.6)
Aspartate aminotransferase increased	14 (4.0)	16 (3.2)	10 (4.7)	14 (1.3)
Blood creatinine increased	12 (3.4)	14 (2.8)	2 (0.9)	13 (1.2)
Pyrexia	11 (3.1)	12 (2.4)	2 (0.9)	10 (0.9)
Arthralgia	10 (2.8)	15 (3.0)	14 (6.5)	33 (2.9)
Hyponatraemia	10 (2.8)	13 (2.6)	8 (3.7)	9 (0.8)
Dyspnoea	9 (2.6)	15 (3.0)	6 (2.8)	19 (1.7)
Hypothyroidism	9 (2.6)	9 (1.8)	5 (2.3)	13 (1.2)
Myalgia	9 (2.6)	13 (2.6)	6 (2.8)	19 (1.7)
Headache	8 (2.3)	13 (2.6)	8 (3.7)	37 (3.3)
Hyperkalaemia	7 (2.0)	8 (1.6)	0	1 (0.1)
Neutrophil count decreased	7 (2.0)	8 (1.6)	2 (0.9)	5 (0.4)
Pancreatitis	7 (2.0)	10 (2.0)	4 (1.9)	6 (0.5)
Platelet count decreased	7 (2.0)	7 (1.4)	3 (1.4)	16 (1.4)
Pneumonia	7 (2.0)	11 (2.2)	4 (1.9)	29 (2.6)

Preferred terms are included in this table if the relevant frequency was ≥2% in the Indication Safety Set.Percentages are based on the total number of subjects in the relevant safety set.MedDRA PTs "Neoplasm Progression," "Malignant Neoplasm Progression," and "Disease Progression," which are unrelated to the study drug are excluded.Subjects with 2 or more TEAEs in the same PT were counted only once for that PT.a: Dose modification includes drug interruption or dose reduction. Dose modification of lenvatinib, regardless of action taken for pembrolizumab.

- AEs Resulting in Dose Modification of Sunitinib

In the sunitinib arm, 70.3% of subjects experienced TEAEs leading to dose modification (reduction or interruption) of sunitinib. The most common TEAEs (≥5% of subjects) leading to dose modification of sunitinib were palmar-plantar erythrodysaesthesia syndrome (12.6%), platelet count decreased (10%), thrombocytopenia (7.1%), neutrophil count decreased (6.8%), neutropenia (6.2%), diarrhoea (8.2%), fatigue (8.2%), and stomatitis (6.2%).

AEs Resulting in Treatment Interruption of **Pembrolizumab**

Per protocol, dose reductions of pembrolizumab were not permitted.

The overall incidence of TEAEs leading to a dose interruption of pembrolizumab in the Indication Safety Set (55.1%) was higher than that in the Pembrolizumab Monotherapy Safety Sets (22.2% for RSD-A and 25.4% for RSD-B). The TEAEs that most frequently led to a pembrolizumab dose interruption (occurring in ≥5% of subjects) in the Indication Safety Set were diarrhea (10.2%) and increased lipase (5.1%).

Table 61 TEAEs Leading to Dose Interruption of Pembrolizumab in ⩾2% of Subjects by PT and Safety Set

Preferred Term	**Indication N=352 n (%)**	**All RCC N=497 n (%)**	**Non-RCC N=215 n (%)**	**Pembro Monotx RSD-A N=2799 n (%)**	**Pembro Monotx RSD-B N=5884 n (%)**
Subjects With Any TEAEs Leading to Drug Interruption of Pembrolizumab[a]	194 (55.1)	269 (54.1)	116 (54.0)	622 (22.2)	1492 (25.4)
Diarrhoea	36 (10.2)	53 (10.7)	19 (8.8)	45 (1.6)	112 (1.9)
Lipase increased	18 (5.1)	20 (4.0)	8 (3.7)	0	5 (0.1)
Asthenia	16 (4.5)	16 (3.2)	11 (5.1)	10 (0.4)	20 (0.3)
Amylase increased	14 (4.0)	19 (3.8)	3 (1.4)	2 (0.1)	6 (0.1)
Alanine aminotransferase increased	12 (3.4)	15 (3.0)	4 (1.9)	28 (1.0)	73 (1.2)
Hypertension	11 (3.1)	12 (2.4)	4 (1.9)	4 (0.1)	5 (0.1)
Aspartate aminotransferase increased	9 (2.6)	12 (2.4)	3 (1.4)	28 (1.0)	62 (1.1)
Decreased appetite	9 (2.6)	10 (2.0)	11 (5.1)	14 (0.5)	30 (0.5)
Fatigue	9 (2.6)	16 (3.2)	17 (7.9)	27 (1.0)	56 (1.0)
Proteinuria	8 (2.3)	12 (2.4)	4 (1.9)	1 (<0.1)	3 (0.1)
Blood creatinine increased	7 (2.0)	9 (1.8)	2 (0.9)	8 (0.3)	17 (0.3)
Myalgia	7 (2.0)	8 (1.6)	2 (0.9)	8 (0.3)	13 (0.2)
Rash	7 (2.0)	7 (1.4)	2 (0.9)	16 (0.6)	47 (0.8)

a: Drug interruption of Pembro, regardless of action taken for Lenv.

Post marketing experience

The safety profile of lenvatinib and pembrolizumab is summarized in the respective Periodic Safety Update Reports (PSURs) and product information.

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

The primary safety data in support of the new indication of lenvatinib plus pembrolizumab for the first-line treatment of patients with advanced RCC derive from the open-label, phase 3 **Study 307** (KEYNOTE-581). As of the data cutoff date of 28 Aug 2020, 352 subjects were enrolled in Arm B to receive a starting dose of 200 mg pembrolizumab every 3 weeks and 20 mg lenvatinib once daily (QD) (Indication Safety Set) and 340 subjects were enrolled in Arm B to receive sunitib 50 mg QD (Sunitinib Safety Set).

In the All RCC Safety Set (N=497), lenvatinib + pembrolizumab safety data were pooled from Study 307 and Study 111 from patients with advanced RCC, regardless of prior anticancer therapy. The Non-RCC Safety Set describes lenvatinib + pembrolizumab safety data from 215 subjects in non-RCC cohorts from Study 111 and 115.

To enable a relative characterization of the combination safety profile, further safety data are presented for lenvatinib and pembrolizumab as monotherapy. The Lenvatinib Monotherapy Safety Set comprised 1119 subjects with a lenvatinib starting dose level of 24 mg QD from 11 Studies. The largest Pembrolizumab Monotherapy Safety Set (RSD-B) included 5884 subjects from studies of melanoma, NSCLC, cHL, urothelial cancer, and HNSCC in EU-approved indications.

At the time of data cutoff, the median duration of treatment with lenvatinib plus pembrolizumab in the Indication Safety Set was 17.00 months which was comparable to the All RCC Safety Set (15.4 months) and longer than the median treatment duration with sunitinib (7.84 months). The median treatment duration with lenvatinib plus pembrolizumab in the Indication Safety Set was 3 times longer than with each of the monotherapies: 5.55 months for lenvatinib and 4.86 months for pembrolizumab (in RSD-B).

A dose reduction guideline for lenvatinib was specified for management of treatment-related toxicity in the lenvatinib and pembrolizumab combination studies and in the studies that comprised the Lenvatinib Monotherapy Safety Set. In the Indication Safety Set, the median percentage of the planned dose of lenvatinib received was 69.65% and the median dose intensity was 13.93 mg per day. In the Lenvatinib Monotherapy Safety Set, where subjects received a higher starting dose of lenvatinib (24 mg), the median percentage of planned dose and the median dose intensity were higher (83.61% and 20.07 mg per day, respectively). This was in line with a higher incidence of Treatment Emergent Adverse Events (TEAEs) leading to a dose reduction of lenvatinib in the Indication Safety Set (68.8%) than in the Lenvatinib Monotherapy Safety Set (47.5%).

The analysis of a **summary of adverse events** revealed an unfavourable toxicity profile for lenvatinib plus pembrolizumab compared to sunitinib, based on between-treatment arm differences in terms of Grade ≥3 and related Grade ≥3 TEAEs (82.4% vs 71.8% and 71.6% vs. 58.8%), non-fatal SAEs (50.0% vs 32.6%), and TEAEs leading to discontinuation of either lenvatinib or pembrolizumab (37.2% vs 14.4%). The incidence of TEAEs leading to discontinuation of all study drugs was similar in the lenvatinib plus pembrolizumab and sunitinib arms (13.4% vs 14.4% of subjects). TEAEs leading to dose reduction of lenvatinib and dose interruption of either study drug in the lenvatinib plus pembrolizumab arm occurred more frequently than dose reductions or interruptions in the sunitib arm (68.8% vs. 50.3% and 78.4% vs. 53.8%, respectively). Adjusted by drug exposure, the rates of Grade ≥3 TEAEs was comparable at 1.95 and 2.06 per SY but remained numerically higher for SAEs (0.72 vs 0.55 per SY) in the lenvatinib plus pembrolizumab and sunitinib arms, respectively.

The incidences of most TEAEs categories were similar between the Indication Safety Set and the Lenvatinib Monotherapy Safety Set, including any TEAEs (99.7% and 99.0%, respectively), treatment-related TEAEs (96.9% and 94.7%), Grade ≥3 TEAEs (82.4% and 80.3%), nonfatal SAEs (50.0% and 51.8%), and fatal AEs (4.3% and 8.7%). The rate of related Grade ≥3 TEAEs was numerically higher in the Indication Safety Set compared to the Lenvatinib Monotherapy Safety Set (71.6% and 64.7%), mainly driven by Grade 4 events (11.6% and 4.7%). Adjusted by drug exposure, incidences for all TEAEs

categories were numerically lower in the Indication Safety Set compared to the Lenvatinib Monotherapy Safety Set.

The comparison of the Indication Safety Set with pembrolizumab monotherapy demonstrated considerably lower incidences for pembrolizumab monotherapy across all TEAEs categories.

Nearly all subjects in both the lenvatinib plus pembrolizumab and sunitinib arms had at least 1 TEAE (99.7% vs 89.5%) and related TEAE (96.9% vs 92.1%). In the Indication Safety Set, the **most common AEs** (occurring in >30% of subjects) were diarrhea (61.4%), hypertension (55.4%), hypothyroidism (47.2%), decreased appetite (40.3%), fatigue (40.1%), nausea (35.8%), and stomatitis (34.7%).

Most commonly reported AEs for KN-581 lenvatinib+pembrolizumab treatment were consistent with the safety pattern found in the non-RCC 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.

For sunitinib, the most commonly reported TEAEs (>30%) were diarrhea (49.4%), hypertension (41.5%), stomatitis (38.5%), PPE (palmar-plantar erythrodysaesthesia) syndrome (37.4%), fatigue (36.8%), nausea (33.2%), and decreased appetite (30.9%).

The incidence of treatment-related TEAEs in the Indication Safety Set were generally consistent with that in the Lenvatinib Monotherapy or Pembrolizumab Monotherapy Safety Set (RSD-B), with the exceptions of diarrhea (54.5%, 45.4%, and 10.7%), hypothyroidism (42.6%, 11.1%, and 9.6%), increased amylase (15.1%, 0.9%, and 0.2%) and increased lipase (14.2%, 2.8%, and 0.3%, respectively).

The majority of patients experienced **Grade ≥3 AEs** (82.4% vs 71.8% in the lenvatinib plus pembrolizumab and sunitinib arm, respectively). The most common Grade 3 TEAEs (≥5% of subjects in either arm) in lenvatinib plus pembrolizumab and sunitinib arms, respectively, were: hypertension (27.6% vs 18.8%), diarrhea (9.7% vs 5.0%), weight decreased (8.0% vs 0.3%), proteinuria (7.7% vs 2.9%), amylase increased (7.4% vs 2.1%), lipase increased (7.1% vs 6.2%), and asthenia (5.4% vs 4.4%). Grade 4 TEAEs occurred in 14.8% of subjects in the combination arm and 9.4% of subjects in the sunitinib arm. The only Grade 4 TEAEs that occurred in 1% or more of subjects in the combination or sunitinib arms, respectively, were lipase increased (5.7% vs 2.6%) and amylase increased (1.7% vs 0.9%).

The incidence and type of Grade 3 and Grade 4 TEAEs observed in the Indication Safety Set were generally consistent with one or more monotherapy safety sets except for the following TEAEs: increased lipase and increased amylase, QT prolongation, pancreatitis, increased ALT and increased AST, adrenal insufficiency, acute myocardial infarction and myocardial infarction, rash, and renal failure.

Nonfatal SAEs were reported in 50.0% and 32.6% of subjects in the lenvatinib plus pembrolizumab and sunitinib arms, respectively. SAEs that occurred at a higher incidence in subjects in the lenvatinib plus pembrolizumab arm compared with the sunitinib arm, respectively, were: diarrhea (3.4% vs 1.2%), pneumonitis (2.6% vs 0%), vomiting (2.8% vs 0.9%), acute kidney injury (2.3% vs 1.2%), hypertension (2.3% vs 0.6%), adrenal insufficiency (2.0% vs 0%), myocardial infarction (1.7% vs 0.3%), acute

myocardial infarction (1.4% vs 0%), immune-mediated hepatitis and lipase increased (1.1% vs 0% for both), renal failure (1.1% vs 0.6%), and pancreatitis (1.7% vs 0%).

Diarrhea was the only SAE that occurred at a >2% higher incidence in the Indication Safety Set compared to the Lenvatinib Monotherapy and Pembrolizumab Monotherapy Safety Sets (3.4% vs 1.2% and 1.0%); however, numerically higher incidences of nonfatal SAEs in the Indication Safety Set compared to the Monotherapy Safety Sets were reported also for numerous other PTs.

The incidence of **fatal AEs**, excluding 'malignant neoplasm progression', was 4.3% in the Indication Safety Set, 3.2% in the sunitinib arm, 8.7% in the Lenvatinib Monotherapy Safety Set, and 5.3% in the Pembrolizumab Monotherapy RSD-B Safety Sets, indicating that there is no increased risk of fatal AEs with combination therapy.

AEs Leading to Treatment Discontinuation or Dose Modification: 13.4% of subjects discontinued both study drugs due to TEAEs in the lenvatinib plus pembrolizumab arms. The TEAEs that led to discontinuation of both study drugs in more than 1 subject were acute kidney injury, pneumonitis, proteinuria, and rash. 37.2% of subjects discontinued either lenvatinib or pembrolizumab due to TEAEs. 5.1% of patients discontinued study drug due to cardiac disorders including 9 patients with myocardial infarction (including also acute myocardial infarction), 2 patients with acute coronary syndrome and 2 patients with myocarditis. TEAEs that most commonly (≥1% of subjects) led to discontinuation of study drugs in the Indication Safety Set were pneumonitis (2.8%), rash (including rash maculo-papular and papular) (2.6%), (acute) myocardial infarction (2.6%), diarrhoea (2.3%), proteinuria (1.7%), acute kidney injury (1.1%), renal failure (1.1%), and ALT increased (1.1%).

Treatment discontinuation rates for lenvatinib due to TEAEs were similar for both the Indication (25.6%) and Lenvatinib Monotherapy (26.7%) Safety Sets and were substantially lower than the rates for dose reductions (68.8% and 47.5%) and interruptions (73.0% and 67.6%). These findings indicate that the majority of TEAEs can be managed with lenvatinib dose modifications rather than with lenvatinib discontinuation. Most common TEAEs leading to dose modification (reduction or interruption) of lenvatinib in ≥10% of subjects in the Indication Safety Set were diarrhoea (25.6%), hypertension (15.9%), proteinuria (12.5%), decreased appetite (11.6%), and PPES (10.5%). Incidences of TEAEs leading to treatment discontinuation of pembrolizumab, regardless of the action taken with lenvatinib, were 28.7% in the Indication Safety Set and higher than that in the Pembrolizumab Monotherapy Safety Sets (RSD-B: 13.4%). Per protocol, dose reductions of pembrolizumab were not permitted. Dose interruptions were also higher in the Indication Safety Set (55.1%) than in the Pembrolizumab Monotherapy Safety Sets (25.4% for RSD-B). Most common TEAEs leading to dose interruption of pembrolizumab in ≥5% of subjects in the Indication Safety Set were diarrhoea (10.2%) and lipase increased (5.1%).

(**AEOSI**) are defined categories to assess the frequency of immune-mediated events and infusion-related reactions considered by the MAH to be causally **related to pembrolizumab**. The overall incidence of AEOSI was higher in the Indication Safety Set (60.8%) than in the Pembrolizumab Monotherapy Safety Sets) (25.1% for RSD-B). The majority of AEOSI events were Grade 1 and 2; however higher incidences of AEOSI in the Indication Safety Set were also observed for Grade ≥3 (14.8% vs 6.5%), serious AEOSI (12.5% vs 6.5%) and AEOSI leading to discontinuation of pembrolizumab (10.2% vs 3.9% for the Indication Safety Set vs the Pembrolizumab Monotherapy RSD-B Safety Set, respectively). The higher incidence of all-grade AEOSI in the Indication Safety Set was primarily driven by hypothyroidism (47.2% vs 11.1%). Further AEOSI with an increased incidence in the Indication Safety Set compared to the Pembrolizumab Monotherapy were hyperthyroidism (8.0% vs 4.2%), adrenal insufficiency (5.1% vs 0.8%), severe skin reactions (5.1% vs 1.6%), and pancreatitis (2.8% vs 0.3%).

Clinically significant events (**CSE**) defined **for lenvatinib** are arterial thromboembolic events, cardiac dysfunction, hypothyroidism, gastrointestinal perforation, fistula formation, hemorrhage, hepatotoxicity, hypertension, hypocalcemia, palmar-plantar erythrodysesthesia syndrome (PPES), posterior reversible encephalopathy syndrome (PRES), proteinuria, QT prolongation, and renal events. The overall incidence of CSEs of all grades, serious CSEs, and CSEs leading to study drug discontinuation were generally similar in the Indication and Lenvatinib Monotherapy Safety Sets. CSE leading to dose reductions were higher in the Indication Safety Set than in the Lenvatinib Monotherapy Safety Sets (33.0% vs. 23.7%).

The incidences of the CSE of hypothyroidism, hepatotoxicity, and renal events were higher in the Indication Safety Set (56.8%, 27.3%, and 22.2%, respectively) than in the Lenvatinib Monotherapy Safety Set (19.8%, 17.5%, and 10.0%). Hypothyroidism, hepatotoxicity, and renal events were primarily low grade (Grade ≥3 TEAEs 1.4%, 9.9% and 5.7%) and remained generally manageable with standard medical care and study drug dose modification. Hypothyroidism is a known adverse drug reaction for both lenvatinib and pembrolizumab. The higher incidence hepatotoxicity with the combination was due to increases in the PTs of AST and ALT , which were primarily low-grade and asymptomatic, and the higher incidence with the combination of renal events was associated with a high rate of baseline renal disease in this RCC population. The incidences of the CSE of cardiac dysfunction, arterial thrombotic events, and QT prolongation in the Indication Safety Set were similar to that in the Lenvatinib Monotherapy Safety Set; Of note, a clinically meaningful difference was noted in the incidence for the PTs of acute myocardial infarction and myocardial infarction (3.4% in the Indication Safety Set vs 1.3% in the Lenvatinib Monotherapy Safety Set); however, myocardial infarction is a known ADR for lenvatinib and the increase was also associated with a higher cardiovascular risk in the RCC population.

In terms of laboratory findings, for hematology and urinalysis parameters, the overall pattern of shifts from baseline in grade was similar in the Indication and Lenvatinib Monotherapy Safety Sets. In the Indication Monotherapy Safety Set, the most common laboratory abnormality (≥10%) with a shift from baseline to Grade 3 or 4 events were reported for lipase increased (33.8% of subjects), amylase increased (17.1%), triglycerides increased (14.6%) and sodium decreased (11.7%).

Safety profile by subgroups

Age: In the Indication Safety Set, an age-dependent increase in toxicity can be observed which was overall more pronounced than in the other Safety Sets higher incidences in the older age subgroups than in the <65 years age subgroup were reported for Grade ≥3 TEAEs (all and related), SAEs, fatal SAEs and TEAEs leading to discontinuations. In the ≥65 to <75 years age group 43.0% of subjects and more than half of the patients (55.6%) in the ≥75 years age group discontinued either lenvatinib or pembrolizumab, compared to 29.5% in the younger age group <65 years. Differences by age were especially notable for clinically significant events of proteinuria and renal events. Data for subjects with an age of ≥75 years are limited due to the small patient numbers in the Indication Safety Set (n=45).

Baseline renal function: In the Indication Safety Set, the majority of the subjects had a Baseline CrCl ≥60 mL/min (65.1%). An unfavourable safety profile were observed in the CrCl <60 mL/min subgroup compared to the CrCl ≥60 mL/min subgroup regarding Grade ≥3 TEAEs, Grade ≥3 related TEAEs, fatal SAEs, nonfatal SAEs and discontinuations; however this was similarly observed in the sunitinib arm.

Baseline hypertension status: The incidence of Grade ≥3 TEAEs (all and related) and TEAEs leading to discontinuation of lenvatinib were slightly higher in the subgroup with hypertension (= 57.4% of subjects in the Indication Safety Set) than in the subgroup without hypertension for the Indication Safety Set. Proteinuria was reported with the largest difference (33.2% in subjects with baseline hypertension vs 24.7% for subjects without).

Gender: In the Indication Safety Set, the majority of the subjects were male (71.6%). Small numerical trends towards higher incidences in females than in males were observed for Grade ≥3 TEAEs (all and

related), nonfatal SAEs and dose interruptions of either drug. In comparison, larger gender differences were reported in the sunitinib arm.

With regard to race or geographic region (Western Europe and North America vs Rest of World), no meaningful and consistent differences among subgroups were observed for the AE profile of lenvatinib plus pembrolizumab.

2.5.2. Conclusions on clinical safety

The safety profile of the combination of lenvatinib and pembrolizumab in patients with renal cancer is overall unfavourable compared with sunitinib; however, the pattern of observed AEs is generally consistent with what would be expected from the addition of the two individual drugs with different, but partly also overlapping toxicity profiles. No new safety signals were identified. The tolerability of the combined regimen appears worse with increasing age.

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

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 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.

Pharmacovigilance plan

No new additional pharmacovigilance activities were identified. Routine pharmacovigilance activities remain sufficient to mitigate the risks for Keytruda in all approved indications.

Risk minimisation measures

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		
Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and endocrinopathies)	Routine risk minimisation measures: • 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 Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire for spontaneous postmarketing reports of all adverse events
	Additional risk minimisation measures: Patient educational materials	Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

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: • 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. No additional risk minimisation measures warranted	Routine pharmacovigilance activities Additional pharmacovigilance including: • 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: • 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. No additional risk minimisation measures warranted	Routine pharmacovigilance activities Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

No new additional risk minimisations activities were identified.

2.7. Update of the Product information

As a consequence of this variation, sections 4.1, 4.2, 4.8, and 5.1 of the SmPC are being updated to extend the indication in order to include in combination with lenvatinib first line treatment of adults with advanced renal cell carcinoma (RCC). The Package Leaflet (PL) is 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 MAH and has been found acceptable for the following reasons:

The Applicant justified that the amendments to the SmPC, which will be reflected in the package leaflet are limited in this submission. The changes will affect the following presentations "Keytruda 50 mg powder for concentrate for solution for infusion" and "Keytruda 25 mg/mL concentrate for solution for

infusion", and will cover a new indication: new combination for pembrolizumab with lenvatinib for first line treatment of renal cell carcinoma (RCC).

The applicant claimed that the combination treatment in section 1 of the package leaflet already exists for the pembrolizumab/axitinib combination and that just changes in section 4 are foreseen related to the inclusion of side effects for the new combination pembrolizumab/lenvatinib.

Due to the minor changes of the content, the key safety messages are not affected and the design and layout seems not to be changed remarkable.

Therefore, the justification is acceptable to carry out neither a full or an abridged user testing.

2.7.2. Additional monitoring

Pursuant to Article 23(3) of Regulation No (EU) 726/2004, Keytruda (pembrolizumab) has been removed from the additional monitoring list with the renewal procedure five years after the Union reference date.

3. Benefit-Risk Balance

The MAH is seeking an extension of indication to include first line treatment of advanced or metastatic renal cell carcinoma (RCC) as combination therapy of pembrolizumab together with lenvatinib based on the results of the Interim Analysis (IA3) from the pivotal study, KN581. This is an ongoing, Phase 3, randomized, open-label, multicenter, global study, to evaluate the efficacy and safety of pembrolizumab in combination with lenvatinib or lenvatinib in combination with everolimus versus sunitinib in previously untreated subjects with advanced/metastatic RCC.

3.1. Therapeutic Context

3.1.1. Disease or condition

Renal cell carcinoma (RCC) represents the sixth most common cancer in men and the eighth most common cancer in women, accounting for 3%-4% of all adult malignancies in the US (Siegel et al. CA A Cancer J Clin. 2019). In 2020, an estimated 138,611 new cases of kidney cancer were expected to be diagnosed in Europe with approximately 54,054 people expected to die from the disease (GLOBOCAN, 2020). Clear cell renal cell carcinoma (ccRCC) is the most common type of kidney cancer, comprising 80-90% of all kidney tumours (2020 European Association of Urology [EAU] RCC guidelines).

3.1.2. Available therapies and unmet medical need

In the EU, the following agents targeting the VEGF/VEGFR signaling pathway are approved for the 1L treatment of advanced RCC: sunitinib, pazopanib, bevacizumab + IFNα, tivozanib and cabozantinib (in patients who are considered to be intermediate and poor risk).

In addition to agents that target VEGFR and VEGF, other approved agents for advanced RCC include the mTOR inhibitor temsirolimus for patients considered to be poor risk (per the MSKCC risk category) in the 1L setting and the mTOR inhibitor everolimus

Recently, the combination of nivolumab + ipilimumab was approved in the EU for use in treatment-naïve patients with advanced RCC who were considered to be intermediate or poor risk per the IMDC criteria. In addition, the combinations of avelumab + axitinib, pembrolizumab + axitinib and nivolumab + cabozantinib

have also been approved by EMA for the 1L treatment of adult patients with advanced RCC.

In spite of recent additions to the (systemic) treatment armamentarium, both (median) progression-free survival (PFS) and OS for patients with advanced RCC are still rather limited, especially for patients in the intermediate and poor risk groups. There thus remains an unmet medical need.

3.1.3. Main clinical studies

The application is based upon the interim analysis 3 of KEYNOTE-581 Study, an ongoing, Phase 3, randomized, multicenter, active-controlled, 3 arms, open-label clinical study in first line adult patients with advanced renal cell carcinoma (RCC), comparing the combination of pembrolizumab 200mg Q3W + lenvatinib 20 mg PO QD or lenvatinib + everolimus with sunitinib 50 mg QD 4 weeks on 2 weeks off.

The primary objectives of the study was to compare the PFS per RECIST 1.1 by IIR in participants treated with pembrolizumab + lenvatinib vs sunitinib. OS, ORR, safety and tolerability profile of pembrolizumab + lenvatinib, PFS2 and PFS by investigator assessment, PROs, and PK assessments were secondary objectives.

A total of 1069 subjects were randomized in a 1:1:1 ratio, of whom 355 were allocated to receive lenvatinib plus pembrolizumab, 357 subjects were allocated to receive lenvatinib plus everolimus, and 357 subjects were allocated to receive sunitinib, in the 1L setting.

The application is based upon the interim analysis 3 (final analysis for PFS, interim analysis for OS). Updated result for OS have been provided during the procedure.

3.2. Favourable effects

A statistically significant benefit in PFS has been observed. Median PFS assessed by IIR was 23.9 months for lenvatinib plus pembrolizumab compared with 9.2 months for sunitinib (HR=0.39, [95% CI: 0.32, 0.49], nominal P<0.0001);

A benefit in OS has been observed for pembrolizumab + lenvatinib over sunitinib (HR 0.66 (95% CI: 0.49, 0.88), P=0.0049);

Objective response rate based on IIR assessment were observed in 71.0% (95% CI 66.3, 75.7) of the patients treated with the combination compared to 36.1% (95% CI 31.2, 41.1) in the control arm. The median DOR in responders was 25.8 months (95% CI: 22.1, 27.9) in the lenvatinib plus pembrolizumab arm and 14.6 months (95% CI: 9.4, 16.7) in the sunitinib arm.

3.3. Uncertainties and limitations about favourable effects

The OS data are currently immature to allow for the informative analyses in the key subgroups, in particular IMDC and MSKCC favourable prognosis subgroupswhile the updated analysis in the overall population supports benefit, with HR of 0.72 (0.55, 0.93).

The lack of monotherapy experimental arms in study KN-581 hampers the assessment of the contribution of each component of the combination treatment. Indirect comparisons have been provided for monotherapy data (in 2L for lenvatinib monotherapy) and the combination use is supported by mechanistic rationale.

3.4. Unfavourable effects

An unfavourable toxicity profile was observed for lenvatinib plus pembrolizumab compared to sunitinib, based on between-treatment arm differences in terms of Grade ≥3 TEAEs (82.4% vs 71.8%), non-fatal SAEs (50.0% vs 32.6%), and TEAEs leading to discontinuation of either lenvatinib or pembrolizumab (37.2% vs 14.4%). The most common TEAEs (≥ 40%) in the Indication Safety Set were diarrhoea (61.4%), hypertension (55.4%), hypothyroidism (47.2%), decreased appetite (40.3%), and fatigue (40.1%).

The incidences of most TEAEs categories were similar between the Indication Safety Set and the Lenvatinib Monotherapy Safety Set; however numerically higher incidences of related Grade ≥3 TEAEs occurred in the Indication Safety Set compared to the Lenvatinib Monotherapy Safety Set (71.6% and 64.7%), mainly driven by Grade 4 events (11.6% and 4.7%). Clinically significant events (CSEs) of hypothyroidism, hepatotoxicity and renal events were higher in the Indication Safety Set than in the Lenvatinib Monotherapy Safety Set.

The comparison of the Indication Safety Set with Pembrolizumab Monotherapy demonstrated considerably lower incidences for pembrolizumab monotherapy across all TEAEs categories. Incidences of all-grade AEOSIs were 60.8% vs. 25.1%; the higher incidence in the Indication Safety Set was primarily driven by hypothyroidism (47.2% vs 11.1%), but increased rates were also observed for hyperthyroidism, adrenal insufficiency, severe skin reactions, and pancreatitis.

3.5. Uncertainties and limitations about unfavourable effects

Higher incidences in the older age subgroups than in the <65 years age subgroup were reported for Grade ≥3 TEAEs, SAEs, fatal SAEs and TEAEs leading to discontinuations. In the ≥65 to <75 years age group, 43.0% of subjects and more than half of the patients (55.6%) in the ≥75 years age group discontinued either lenvatinib or pembrolizumab, compared to 29.5% in the younger age group <65 years; however, data for subjects with an age of ≥75 years are limited due to the small patient numbers in the Indication Safety Set (n=45).

More subjects experienced myocardial infarction in the Indication Safety Set than in the Lenvatinib Monotherapy Safety Set (3.4% vs. 1.3%, respectively); however these increases were also associated with higher cardiovascular risk factors in the RCC population.

3.6. Effects Table

Table 62 Effects Table for the combination of lenvatinib plus pembrolizumab for the first-line treatment of patients with advanced RCC (data cut-off: 28 Aug 2020)

Effect	Short description	Unit	Pembro+ Lenvatinib	Sunitinib	Uncertainties / Strength of evidence
Favourable Effects					
PFS per RECIST1.1 by IIR (ITT)	PFS defined as the time from the date of randomization to the date of the first documentation of disease progression or death (whichever occurred first).	Months HR (95% CI)	23.9 vs 9.3 HR=0.39, (95% CI: 0.32, 0.49, P<0.0001)		Primary Endpoint ITT: statistically significant OS data from IA31 too immature to assess the B/R in all relevant subgroups
OS (ITT)	OS, defined as the	Months HR	NR vs NR		

Effect	Short description	Unit	Pembro+ Lenvatinib	Sunitinib	Uncertainties / Strength of evidence
	time from the date of randomization to the date of death from any cause.	(95% CI)	HR of 0.66 (95% CI: 0.49, 0.88, P=0.0049)		
ORR per RECIST 1.1 by IIR (ITT)	ORR, defined as the proportion of subjects who had best confirmed overall response of complete response or partial response	%	71.0	36.1	
			Odds ratio: 4.35 (3.16, 5.97)		
Unfavourable Effects					
AE summary			Lenvatinib/ Pembro arm (n=352)	**Sunitinib** arm (n=340)	
	Drug-related AE incidence	%	96.9	92.1	Toxicity profile of combination therapy compares unfavourable with sunitib;
	G3-5 AE	%	82.4	71.8	
	SAEs	%	50.6	33.2	
	Fatal AEs	%	4.3	3.2	
	discontinuation of any drug due to AE	%	37.2	14.4	
			Lenvatinib/ Pembro arm (n=352)	**Pembro** mono RSD B (n=5994)	Overall, pattern of observed AEs of the combination as expected for the addition of the two individual drugs with higher incidences of multiple PTs compared to either Monotherapy Safety Set;
AEOSI	**all**	%	60.8	25.1	
	hypothyroidism	%	47.2	11.1	
	hyperthyroidism	%	8.0	4.2	
	adrenal insufficiency (including secondary adrenocortical insufficiency)	%	5.1	0.8	
	severe skin reactions (including rash, Rash maculo-papular, Erythema multiforme, Pruritus, Toxic epidermal necrolysis, Toxic skin eruption)	%	5.1	1.6	
	Pancreatitis (including Immune-mediated pancreatitis and Pancreatitis acute)	%	2.8	0.3	
			Lenvatinib/ Pembro arm (n=352)	**Lenvatinib** mono (n=1119)	
CSE	**all**	%	94.0	86.9	
	hypothyroidism	%	56.8	19.8	
	hepatotoxicity	%	27.3	17.5	
	renal events	%	22.2	10.0	

Abbreviations: NR: not reached; ORR: objective response rate; Note: The primary efficacy endpoint is PFS

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The combination of pembrolizumab and lenvatinib demonstrated superiority vs sunitinib in PFS in patients with advanced RCC, supported by an advantage in terms of OS and ORR.

For 1L treatment of subjects with advanced RCC, the overall safety profile of pembrolizumab + lenvatinib compares less favourable to sunitinib. In KEYNOTE-581, a higher rate of all adverse event categories (particularly grade 3-5 AES, SAEs and drug discontinuations due to TEAEs) was observed for the combination of pembrolizumab with lenvatinib. A higher rate of dose adjustments (dose reductions, interruptions) and discontinuation due to AEs was observed in the combination arm, also based on exposure-adjusted rates.

3.7.2. Balance of benefits and risks

The combination of pembrolizumab and lenvatinib demonstrated superiority vs sunitinib in PFS in patients with advanced RCC, supported by an advantage in terms of OS and ORR.

For 1L treatment of subjects with advanced RCC, the overall safety profile of pembrolizumab + lenvatinib compares less favourable to sunitinib. In Study 307/KEYNOTE-581, a higher rate of all adverse event categories (particularly grade 3-5 AES, SAEs and drug discontinuations due to TEAEs) was observed for the combination of pembrolizumab with lenvatinib.

A higher rate of dose adjustments (dose reductions, interruptions) and discontinuation due to AEs was observed in the combination arm, also based on exposure-adjusted rates.

The benefits of the combination treatment are considered to outweigh the risks in the overall population.

3.7.3. Additional considerations on the benefit-risk balance

None

3.8. Conclusions

The overall B/R of lenvatinib in combination with pembrolizumab is positive.

The MAH is recommended to submit the final OS analysis (including analyses/KM plots from favourable prognosis subgroups) from the E7080-G000-307/KEYNOTE 581 study which is comparing the efficacy and safety of pembrolizumab in combination with lenvatinib and lenvatinib plus everolimus vs. sunitinib monotherapy as a first-Line treatment of patients with advanced RCC.

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 Keytruda in combination with lenvatinib first line treatment of adults with advanced renal cell carcinoma (RCC); 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 32.1 of the RMP has also been submitted.

Amendments to the marketing authorisation

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