14 October 2021
EMA/621560/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kisplyx

International non-proprietary name: lenvatinib

Procedure No. EMEA/H/C/004224/II/0045

Note

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

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List of abbreviations

Abbreviation	Definition
1L	First-line
2L	Second-line
ADA	Antidrug antibody
AE	Adverse event
AEOSI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
BICR	Blinded independent central review
ccRCC	Clear cell renal cell carcinoma
CD8	Cluster of differentiation 8
cHL	Chronic Hodgkin's lymphoma
CI	Confidence interval
CHMP	Committee for Medicinal Products for Human Use
CPS	Combined positive score
DFG-out	Asparagine-phenylalanine-glycine out
DOR	Duration of response
EC50	Half maximal effective concentration
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
EU	European Union
FDA	US Food and Drug Administration
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
FoxP3	Forkhead box P3
HNSCC	Head and neck squamous cell carcinoma
HR	Hazard ratio
IA	Interim analysis
IFNα-2b	Interferon alpha 2b
IFNγ	Interferon gamma

Abbreviation	Definition
IgG4	Immunoglobulin G4
IL-2	Interleukin 2
ITT	Intent-to-treat
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
KM	Kaplan-Meier
MSI-H	Microsatellite instability-high
MSKCC	Memorial Sloan Kettering Cancer Center
mTOR	Mammalian target of rapamycin
NCCN	National Comprehensive Cancer Network
nccRCC	Nonclear cell renal cell carcinoma
NSCLC	Nonsmall cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death 1
PDGFR-β	Platelet-derived growth factor receptor beta
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival
PK	Pharmacokinetics
RCC	Renal cell carcinoma
RECIST 1.1	Response Evaluation Criteria in Solid Tumours version 1.1
RSD	Reference Safety Dataset
RTK	Receptor tyrosine kinase
SAE	Serious adverse event
SAWP	Scientific Advice Working Party
TILs	Tumour infiltrating lymphocyte
TNFα	Tumour necrosis factor alpha
TKI	Tyrosine kinase inhibitor
US	United States
VEGFR	Vascular endothelial growth factor receptor

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eisai GmbH submitted to the European Medicines Agency on 10 March 2021 an application for a variation.

The following variation was requested:

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

Extension of indication to include Kisplyx in combination with pembrolizumab as first line treatment of adults with advanced renal cell carcinoma (RCC); as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 14.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder took the opportunity to update the list of local representatives in the Package Leaflet.

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/0427/2020 and P/0210/2020 on the agreement of a paediatric investigation plan (PIP).

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

Two PIPs are agreed for lenvatinib including a PIP with a deferral and waiver for the treatment of follicular thyroid cancer, papillary thyroid cancer, and osteosarcoma, agreed on 28 May 2013 (P/0125/2013, EMEA-001119-PIP02-12) and a PIP with a deferral and waiver for the treatment of all conditions included in the category of malignant neoplasms except haematopoietic and lymphoid tissue neoplasms, papillary thyroid cancer, follicular thyroid cancer and osteosarcoma, agreed on 16 June 2020 (P/0210/2020, EMEA-001119-PIP03-19).

This Type II variation for the addition of a new therapeutic indication is supported by EMEA-001119-PIP03-19. All of the dates of completion for the agreed clinical studies within this PIP have been deferred and the date of initiation have not been determined by the PDCO. Based on this no partial compliance check is required for the purposes of this submission.

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 Marketing Authorization Holder (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

Scientific advices have been sought by the MAH for Kisplyx pertaining to clinical aspects of the dossier: 1 April 2016 (EMEA/H/SA/3261/1/2016/II), 18 October 2018 (EMEA/H/SA/3261/1/FU/1/2018/II).

1.2. Steps taken for the assessment of the product

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

Rapporteur: Karin Janssen van Doorn

Timetable	Actual dates
Submission date	10 March 2021
Start of procedure:	27 March 2021
CHMP Rapporteur Assessment Report	25 May 2021
PRAC Rapporteur Assessment Report	28 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	25 August 2021
CHMP members comments	6 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	08 October 2021
Opinion	14 October 2021

2. Scientific discussion

2.1. Introduction

This application concerns an extension of indication to include the first-line combination treatment with lenvatinib and pembrolizumab of adult patients with advanced or metastatic renal cell carcinoma (RCC).

The approved indication is:

Kisplyx is indicated for the treatment of adults with advanced renal cell carcinoma (RCC):

- in combination with pembrolizumab, as first-line treatment (see section 5.1).

2.1.1. Problem statement

Disease or condition

Worldwide, kidney cancer is the 14th most common cancer, and is the 9th most frequently diagnosed cancer in men and 14th in women (World Cancer Research Fund, 2020). Renal cell carcinoma is the most common type of kidney cancer, constituting the majority of primary renal neoplasms. Most cases of RCC (70%–80%) are classified as clear-cell tumours.

State the claimed therapeutic indication

The proposed new indication for Kisplyx in this procedure is:

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

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

Epidemiology

Renal cell carcinoma is the most common type of kidney cancer, constituting the majority of primary renal neoplasms. Most cases of RCC (70%–80%) are classified as clear-cell tumours.

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

Biologic features

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).

Approximately 2%-3% of all RCCs are hereditary and several autosomal dominant syndromes are described, each with a distinct genetic basis and phenotype, the most common one being von Hippel–Lindau (VHL) disease (Escudier et al. An Oncol. 2019).

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

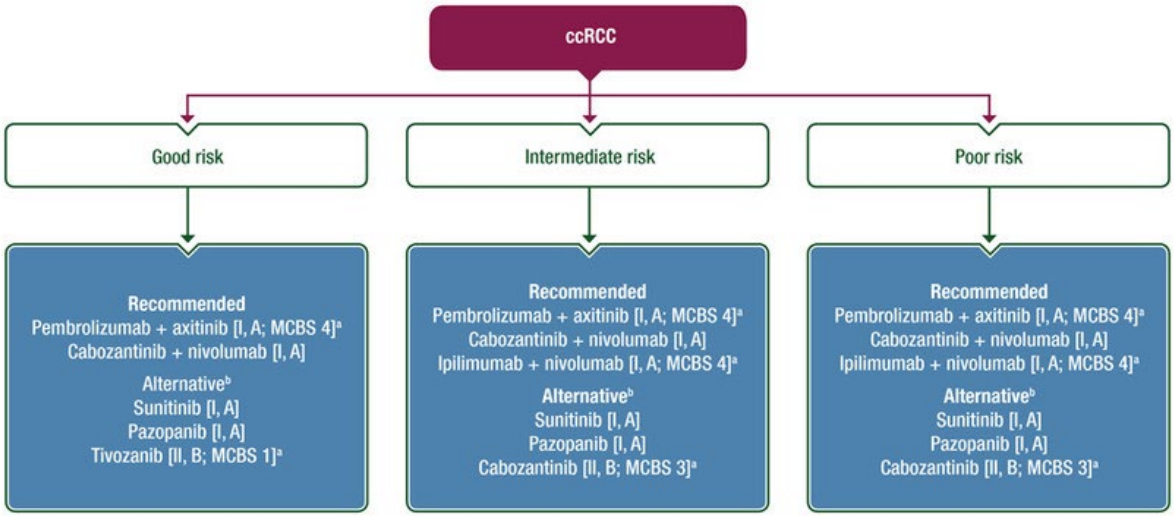
Renal cell carcinoma generally resists both traditional chemotherapy and radiation therapy. Surgical resection can be curative for patients presenting with localized disease. However, one third of patients present with regional or distant metastases and the 5-year survival rate for metastatic disease is approximately 12%.

Cytokine based immunotherapy was the standard of care for advanced RCC until developments in the understanding of the pathogenesis and molecular biology of RCC led to the identification of angiogenesis as a key factor in the development of RCC. This led to a shift from predominantly cytokine-based treatment options to the use of targeted agents, including those targeted against VEGF/receptors of VEGF (VEGFR), and mammalian target of rapamycin (mTOR).

New treatment approach for patients with treatment naïve advanced RCC consisted of single agent VEGFR tyrosine kinase inhibitors (TKIs), pazopanib, and sunitinib. This approach improved clinical outcomes and expanded treatment options.

Several immune checkpoint inhibitor combinations have demonstrated a survival advantage in advanced RCC and standard, globally approved 1L therapy has changed to include nivolumab plus ipilimumab (for International Metastatic Renal Cell Carcinoma Database Consortium [IMDC] intermediate or poor risk disease), axitinib plus avelumab, axitinib plus pembrolizumab, and cabozantinib plus nivolumab (National Comprehensive Cancer Network [NCCN], 2021). All of the pivotal studies that support these indications included sunitinib as the comparator arm, since sunitinib was standard of care at the time they were initiated and conducted.

As of 2020, the ESMO guidelines include combination of cabozantinib and nivolumab, which is now recommended as front-line therapy for advanced disease. This is based on data from the CheckMate 9ER study, which compared programmed cell death protein 1 (PD-1) inhibitors plus vascular endothelial growth factor (VEGF) tyrosine kinase inhibitors (TKIs) versus sunitinib in the front-line setting. Results showed a significant overall survival advantage (OS) for cabozantinib and nivolumab at interim analysis (18.1 months median follow-up) [(hazard ratio (HR) 0.60; 95% confidence interval (CI) 0.40-0.89; P<0.001). Reponses rates and progression-free survival (PFS) also significantly favoured the combination (56% versus 27% and HR 0.51, 95% CI 0.41-0.64, respectively).



a. ESMO-MCBS scores for new therapies/indications approved by the EMA since 1 January 2016. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee.
b. Where recommended treatment not available or contraindicated.
ccRCC, clear cell renal cell carcinoma; EMA, European Medicines Agency; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; MCBS, Magnitude of Clinical Benefit Scale.

Figure 1 2020 ESMO recommendation systemic first-line treatment of clear cell renal cell carcinoma (ccRCC)

Approved or recommended first-line treatments for advanced RCC

Approved Drug	Target	Study Treatment	N	ORR	Median PFS (months)	Median OS (months)	Median Survival Follow-up (months)
Sunitinib (TKI) SUTENT SmPC, 2020 SUTENT USPI, 2020 Motzer, et al., 2009	VEGFR 1-2-3, PDGFR, c-Kit, FLT3	Sunitinib Interferon alfa	375 375	27.5% 5.3% *P*<0.001	10.9 5.1 *P*<0.000001	26.4 21.8 NS; HR=0.821; *P*=0.051	Not reported
Pazopanib (TKI) Sternberg, et al., 2010; Sternberg, et al., 2013	VEGFR 1-2-3, PDGFR, c-Kit	Pazopanib Placebo	155 78	32% 4%	11.1 2.8 HR=0.40; *P*<0.0001	22.9 20.5 NS; HR=0.91	Not reported
Cabozantinib (TKI)[a] CABOMETYX SmPC, 2020 CABOMETYX USPI, 2021	MET, RET, VEGFR-2	Cabozantinib Sunitinib	79 78	20% 9%	8.6 5.3 HR=0.48; *P*=0.0008	54% had OS events 60% had OS events HR=0.80	Not reported
Ipilimumab plus nivolumab[b] (CTLA-4 plus PD-1) Motzer, et al., 2018	CTLA-4 plus PD-1	Ipilimumab plus nivolumab Sunitinib	550 546	41.6% 26.5% *P*<0.001	11.6 8.4 HR=0.82; *P*=0.03	Not reached 26.0 HR=0.63; *P*<0.001	25.2
Pembrolizumab plus axitinib (PD-1 plus TKI) Rini, et al., 2019	PD-1 plus VEGF 1-2-3	Pembrolizumab plus axitinib Sunitinib	432 429	59.3% 35.7% *P*<0.001	15.1 11.1 HR=0.69; *P*<0.001	Not reached in either arm. OS rate at 12 months 89.9% 78.3% HR=0.53; *P*<0.0001	12.8

Approved Drug	Target	Study Treatment	N	ORR	Median PFS (months)	Median OS (months)	Median Survival Follow-up (months)
Avelumab plus axitinib (PD-L1 plus TKI) Motzer, et al., 2019	PD-L1 plus VEGF 1-2-3	Avelumab plus axitinib Sunitinib	442 444	51.4% 25.7%	13.8 8.4 HR=0.69; *P*<0.001	Not reported	11.6 10.7
Bevacizumab plus interferon alfa (VEGF plus cytokine) AVASTIN SmPC, 2021 AVASTIN USPI, 2020	VEGF 1-2-3 plus interferon alpha receptor	Bevacizumab + interferon alfa Placebo + interferon alfa	327 322	30% 12% *P*<0.0001	10.2 5.4 HR=0.60; *P*<0.0001	23 21 NS; HR=0.86	Not reported
Temsirolimus (mTOR inhibitor)[c] TORISEL SmPC, 2020 TORISEL USPI, 2018 Kwitkowski, et al., 2010	mTOR	Temsirolimus Interferon alfa	209 207	8.6% 4.8% *P*=0.1232	5.5 3.1 HR=0.66; *P*<0.0001	10.9 7.3 HR=0.73; *P*=0.0078	17.0 16.3
Cabozantinib plus nivolumab (TKI plus PD-1) CABOMETYX USPI, 2021	MET, RET, VEGFR-2 plus PD-1	Cabozantinib + nivolumab Sunitinib	323 328	55.7% 27.1% *P*<0.0001	16.6 8.3 HR=0.51; *P*<0.0001	Not reached Not reached HR=0.60; *P*=0.0010	Not reported

c-Kit = tyrosine protein kinase KIT, CTLA-4 = cytotoxic T-lymphocyte-associated protein 4, EMA = European Medicines Agency, FLT3 = fms-related kinase 3, HR = hazard ratio, IMDC = International Metastatic RCC Database Consortium, mAb = monoclonal antibody, MET = hepatocyte growth factor receptor, mTOR = mammalian target of rapamycin, NE = not estimable, NS = no statistically significant difference, ORR = objective response rate, OS = overall survival, PD-1 = programmed death 1, PD-L1 = programmed death ligand 1, PDGFR = platelet-derived growth factor receptor, PFS = progression-free survival, RCC = renal cell carcinoma, RET = RET proto oncogene, TKI = tyrosine kinase inhibitor, VEGF = vascular endothelial growth factor, VEGFR = vascular endothelial growth factor receptor.

All agents listed in this table are approved in both the EMA and FDA except cabozantinib plus nivolumab, which as of 27 Jan 2021 is only approved by the FDA.

a: All subjects were required to have intermediate or poor risk disease as defined by IMDC risk categories.

b: Indicated for the treatment of patients with intersmediate or poor-risk, previously untreated advanced RCC.

c: All subjects had at least 3 of 6 prognostic risk factors (<1 year from time of initial RCC diagnosis to randomization, Karnofsky performance status of 60 or 70, hemoglobin <lower limit of normal, corrected calcium >10 mg/dl, lactate dehydrogenase >1.5 times the upper limit of normal, >1 metastatic organ site).

2.1.2. About the product

Lenvatinib

Lenvatinib is a Tyrosine Kinase Inhibitor (TKI) active against both VEGFR, VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4) and FGFR, FGFR1, 2, 3, and 4. Lenvatinib also inhibits other Receptors Tyrosine Kinases (RTKs) that have been implicated in pathogenic angiogenesis, tumour growth, and cancer progression in addition to their normal cellular functions, including the platelet-derived growth factor receptor α (PDGFRα), KIT, and RET.

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

Pembrolizumab

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between the Programmed cell death protein 1 (PD-1) and its ligands, PD-L1 and PD-L2.

Pembrolizumab has been approved in the EU a 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

Rationale for the combination of lenvatinib and pembrolizumab in RCC

Renal cell carcinoma is a highly vascularized tumour, and VEGF is a crucial regulator of both physiologic and pathologic angiogenesis; increased expression of VEGF is associated with a poor prognosis (Ferrara, et al., 2003; Posadas, et al., 2013). Accumulated evidence also suggests that FGF and its receptor tyrosine kinase, FGFR, play a role in angiogenesis and contribute to the aggressiveness of RCC (Cross and Claesson-Welsh, 2001; Lieu, et al., 2011; Limaverde-Sousa, et al., 2014). Therefore, the blocking of not only VEGFRs but also FGFRs may be important for antiangiogenesis (Hojjat-Farsangi, 2014). In addition, FGF induced angiogenesis has been reported to be involved in resistance to anti VEGF/VEGFR therapy; therefore, inhibition of FGF may decrease the rate of drug resistance (Dieci, et al., 2013; Stjepanovic and Capdevila, 2014).

Renal cell carcinoma is also considered an immunogenic tumour, as evidenced by the use of cytokine-based immunotherapy, which affords long-term durable response in some patients. Upregulation of the anti-programmed cell death 1 (PD-1) receptor on tumour-infiltrating lymphocytes and its ligand PD-L1 on tumour cells, is associated with poor prognosis (Hsieh, et al., 2018).

The immune-modulating effect of lenvatinib may result in a potent combination effect with PD-1/L1 signal inhibitors. Thus, the effect of combining lenvatinib with an anti- PD-1 mAb (a surrogate for pembrolizumab) was investigated. The combination was tested in 4 murine tumour isograft models and showed significant tumour growth inhibition compared with control. Significantly longer survival was observed in the RAG murine tumour isograft model (Study M18018), and a significant increase in the population of activated cytotoxic T cells was observed in the CT26 murine tumour isograft model, in groups treated with the combination compared with the respective monotherapy groups (Kato, et al., 2019). Treatment was well tolerated, and severe body weight loss was not observed (data on file).

Combinations involving PD-1 checkpoint inhibitors have become effective therapies in several malignancies such as non-small cell lung cancer, RCC, and endometrial carcinoma (Schmidt, 2019). Lenvatinib in combination with pembrolizumab was examined in the multi cohort Phase 1b/2 Study E7080 A001 111/KEYNOTE 146 (hereafter referred to as Study 111/KN-146), a multicenter, open-label study that was designed to evaluate the safety, tolerability, and antitumour activity of lenvatinib plus pembrolizumab in patients with advanced RCC, endometrial carcinoma, melanoma, squamous cell carcinoma of the head and neck (SCCHN), non–small-cell lung cancer (NSCLC), and urothelial carcinoma. 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). The RP2D, 20 mg daily, was evaluated for efficacy and safety in the Phase 2 portion. Across cohorts, ORRs (per immune related RECIST 1.1 by investigator assessment) ranged from 25% to 70%, with the most favourable responses seen among patients with RCC, EC, and melanoma (Taylor, et al., 2020). 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). These efficacy data were compelling, showing significant tumour reduction with durable responses in treatment naïve and previously treated subjects. Moreover, adverse events (AEs) were manageable with dose interruptions and dose reductions, and there were no new safety signals for either lenvatinib or pembrolizumab. Based on these data, the lenvatinib plus pembrolizumab development

program was expanded, which currently consists of 16 Phase 2 and Phase 3 registration studies in a range of indications. Lenvatinib 20 mg QD (starting dosage) plus pembrolizumab 200 mg Q3W were the RP2D for lenvatinib in combination with pembrolizumab in Study 111, and thus were used in Study 307 and have been implemented as the recommended starting dosages across the program

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

01 Apr 2016	Scientific Advice (Study 307 design) EMEA/H/SA/3261/1/2016/II
18 Oct 2018	Scientific Advice (interim analyses) EMEA/H/SA/3261/1/FU/1/2018/II
20 Jan 2021	Rapporteur/Co-rapporteur/EMA To discuss the topline data of Study 307/KN581 and the new indication filing.

In the Scientific Advice from 01 April 2016, the CHMP pointed the risk of underestimating PFS (and ORR) in the lenvatinib + pembrolizumab arm (arm B) vs. arms A and C should be taken into consideration. It was also noted that PFS was be determined using irRECIST for Arm B only as an exploratory endpoint, but the Applicant may also consider including also irRECIST for arms A and C for comparison. In a subsequent amendment to the Study 307 protocol (ie amendment 7), the exporatory objective to assess PFS by irRECIST has been removed from the protocol.

The proposed stratification factors, geographic region and MSKCC prognostic risk model (alternatively IMDC could be considered), were considered acceptable. MSKCC prognostic risk model was employed as stratification factor (in addition to geographic location) and in the analysis the IMDC was programmatically derived and included in the subgroup analyses.

The evidence to support the contribution of components was discussed in the Scientific Advice from 18 Oct 2018. It acknowledged the Applicant's intention to demonstrate the contribution of each agent based on cross-study comparisons of the efficacy data for the lenvatinib monotherapy in 2L and pembrolizumab monotherapy in 1L, compared to the combination of lenvatinib and pembrolizumab in 1L. The CHMP noted that it was presumed that the patient population influences the likelihood of OR; therefore, cross study comparisons also of this parameter were not straightforward. Furthermore ORR is generally seen as a marker of pharmacodynamic activity and not as a clinical benefit per se; however, showing convincing additive effects on ORR are generally accepted as supportive of combination use.

CHMP pointed out that a randomised comparison, even of ORR rather than relevant time to event endpoints would be preferred and that eventually the contribution of components would be a review issue, dependent on the actual ORR observed in Study 307.

Regulatory concerns regarding the dissemination of results in case of positive IA findings in the US were discussed. A submission to FDA may in itself trigger anticipation regarding efficacy of the combination. This could affect the behaviour of investigators and patients still on therapy in this open-label trial and ultimately the conclusions of the study.

During the pre-submission meeting with the Rappoterur/Co-rapporteur/EMA, there was an agreement on the data to be submitted. Updated OS data were agreed to be provided during the review procedure.

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 this submission for lenvatinib in combination with pembrolizumab, 4 in vivo primary pharmacodynamics studies were conducted with lenvatinib, rat anti-murine programmed cell death 1 (PD-1) monoclonal antibody (mAb), clone RMP1-14, as a surrogate antibody for pembrolizumab, and the combination of lenvatinib with anti-PD-1 mAb. The following in vivo primary pharmacodynamic studies were conducted:

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

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

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

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

2.2.2. Pharmacology

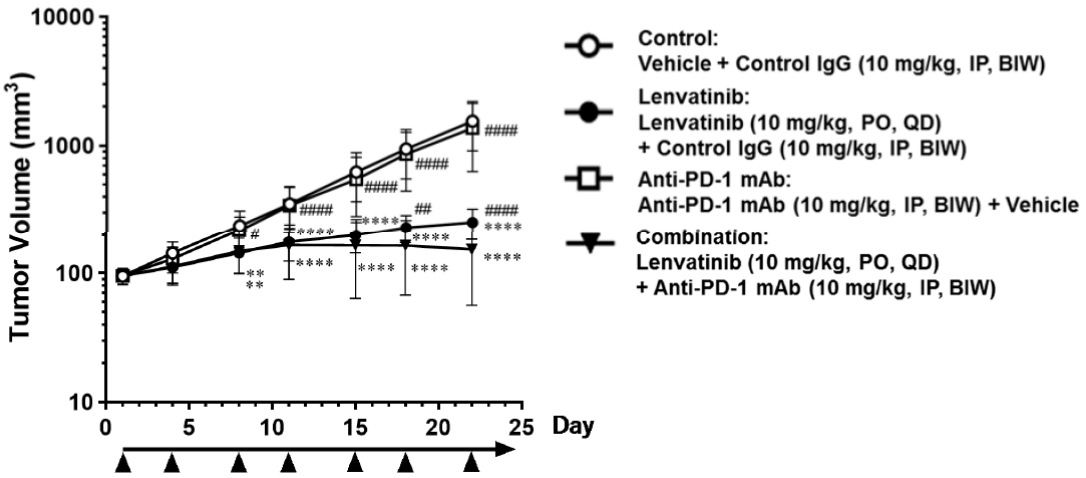
Primary pharmacodynamic studies

In vivo pharmacodynamics

1) Antitumour 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 totalling 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.

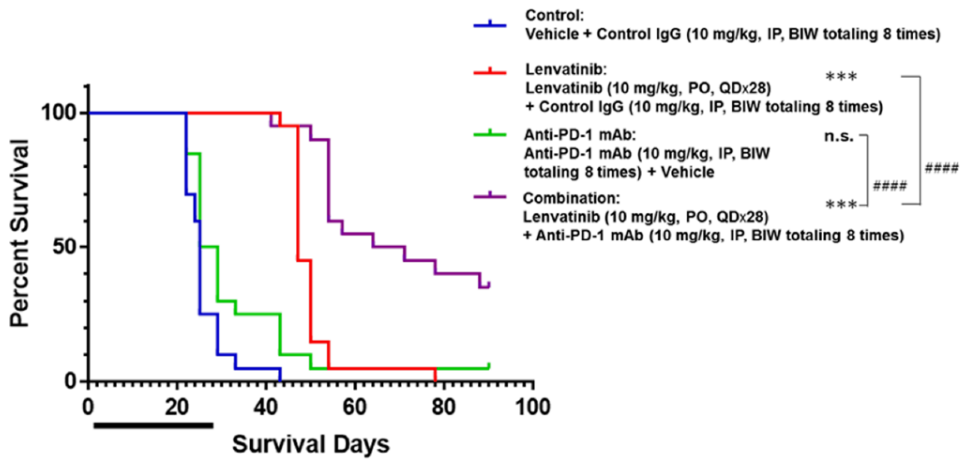


Each point represents the mean ±SD of 20 animals. Horizontal arrow signifies the dosing period for lenvatinib. The ▲ signifies the dosing day of anti-PD-1 mAb or control IgG. BIW = twice per week, IgG = immunoglobulin G, mAb = monoclonal antibody, QD = once daily, RCC = renal cell carcinoma. $^{**}P<0.01$, $^{****}P<0.0001$ 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 Antitumour Activity of Lenvatinib in Combination With Anti-PD-1 mAb Against the RAG Murine RCC Isografts

The 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 antitumour 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.



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

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

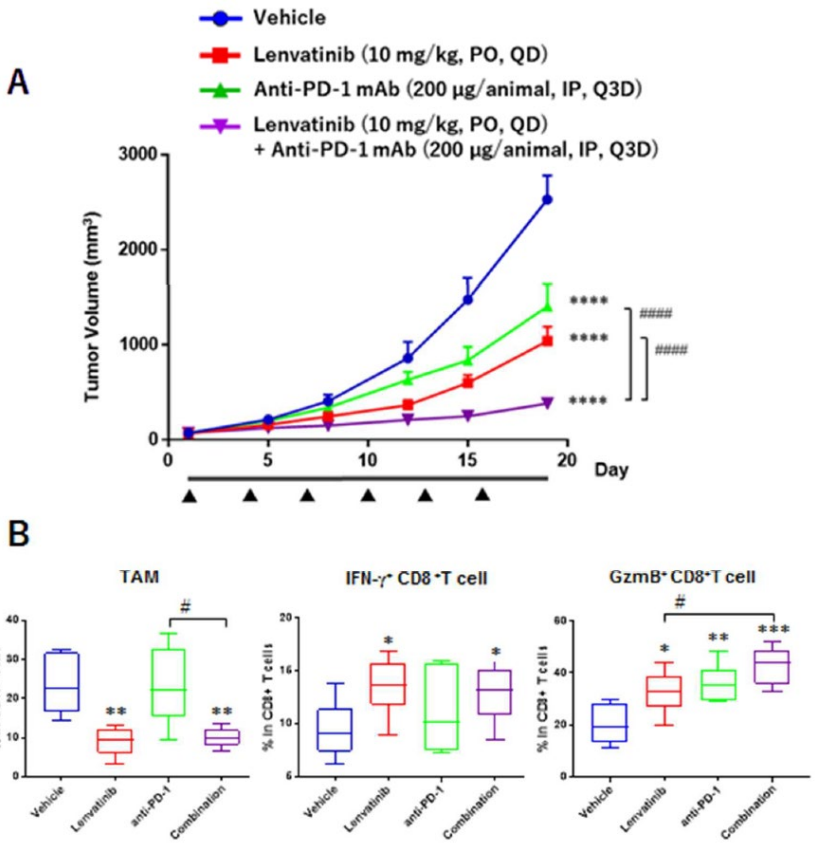
Antitumour activity of lenvatinib in combination with anti-PD-1 mAb was also evaluated in the CT26 murine colon carcinoma isografts in syngeneic immunocompetent BALB/cAnNCrlCrlj mice and athymic CAnN.Cg-Foxn1nu/CrlCrlj mice (Kato et al. 2019). Here more extensive studies have been performed.

CT26 cells were inoculated in syngeneic immunocompetent BALB/cAnNCrlCrlj mice (7-week old females. When tumour 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 5.2.3 demonstrates lenvatinib (10 mg/kg) monotherapy and anti-PD-1 mAb (200 µg/animal) monotherapy showed Tumour Growth Inhibition (TGI) compared with the vehicle control. In addition, antitumour 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 tumours 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.

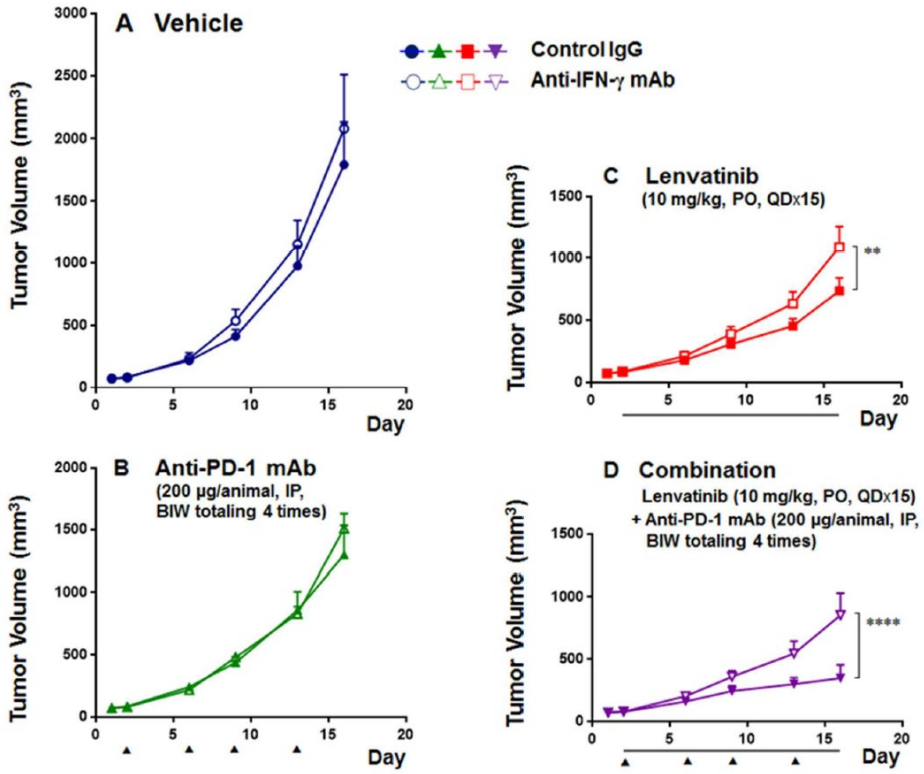
Therefore, lenvatinib could modulate the Tumour Microenviroment (TME) by decreasing the immunosuppressive TAM population and the increasing activated cytotoxic T cell population. Here no significant difference could be demonstrated between the TAM suppression and cytotoxic T-cell activation of lenvatinib 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). Source: Kato, et al., 2019.

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

The antitumour activity of lenvatinib monotherapy and the combination therapy was also decreased in mice injected with anti-IFN-γ mAb, whereas the antitumour 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 antitumour 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). Source: Kato, et al., 2019.

Figure 5 Effects of Prior and Concomitant Injection of IFN-γ Neutralizing Antibody on the Antitumour 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 safety pharmacology studies were conducted.

2.2.3. 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.

2.2.4. 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.

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; $AUC_{(0-24)}$) 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.

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 ($AUC_{(0-14d)}$) 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 $AUC_{(0-tau)}$ are ≥ 19-fold and ≥ 74-fold compared to exposures at the human dose of 10 mg/kg and 200 mg, respectively.

2.2.5. Ecotoxicity/environmental risk assessment

It was previously concluded that "The findings of the nonclinical studies indicate that by general comparison of the responses observed with the extremely low environmental exposure". Based on previous environmental risk assessments (ERA), lenvatinib has not been identified as a PBT (persistent, bioaccumulative and toxic) or a vPvB substance (very persistent and bioaccumulative) and there are no environmental concerns expected for lenvatinib.

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

for all combinations. In conclusion, lenvatinib is unlikely to represent a risk for the environment when used in accordance with the Summary of Product Characteristics.

2.2.6. Discussion on non-clinical aspects

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

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

The new nonclinical studies conducted with lenvatinib investigated the antitumour activity of lenvatinib and the combination of lenvatinib with an anti-PD-1 mAb (used as a surrogate antibody for pembrolizumab), in murine tumour isograft models of RCC, HCC, colon carcinoma and lung carcinoma. In addition, the immunomodulatory activity of lenvatinib in murine tumour isograft models using immunocompetent mice and athymic mice was investigated to determine the effects of lenvatinib on the host immune systems in the tumour microenvironment.

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

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

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

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

No new PK or toxicology studies were conducted with lenvatinib or pembrolizumab to support this submission, which is considered acceptable based on the available clinical data on lenvatinib and pembrolizumab. Because pembrolizumab was well tolerated in chronic toxicity studies, the potential of a toxicologic interaction with lenvatinib is considered low. The clinical adverse effect profiles of both agents

have been well characterized in the various clinical trials conducted with each agent. In addition, the efficacy, safety and tolerability of lenvatinib in combination with pembrolizumab is being evaluated in completed/ongoing clinical studies (Study 111/KN-146 and KEYNOTE-523 Phase 1b studies in subjects with solid tumours including EC, Study 307/KN-581 Phase 3 in advanced RCC, Study 309/KN-775 Phase 3 study in subjects with EC).

The applicant provided additional data for the ERA regarding the prevalence of the disease population targeted by the first line RCC, as well as for different combinations of indications. Based on the updated data submitted in this application, the new indication does not lead to a significant increase in environmental exposure further to the use of lenvatinib. Considering the above data, lenvatinib is not expected to pose a risk to the environment.

2.2.7. Conclusion on the non-clinical aspects

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

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.

Based on the updated data submitted in this application, the new indication does not lead to a significant increase in environmental exposure further to the use of lenvatinib. Considering the above data, lenvatinib is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- **Tabular overview of clinical studies**

Study ID (Status)	Indication	Number of Study Centers (Locations)	Study Starta / 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 (Ongoing)	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 geographic region and MSKCC prognostic groups	Arm A: LENV 18 mg, PO, QD plus EVER 5 mg PO, QD 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)	Final PFS analysis: 1047/321	Final PFS analysis: Approximately 582 PFS events (as determined by IIR) 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 2014b	Phase 1b/2, open-label, multicenter with Treatment and Extension Phases. Phase 1b: dose escalation in sequential	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	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

Study ID (Status)	Indication	Number of Study Centers (Locations)	Study Starta / 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
				cohorts to determine MTD and RP2D Phase 2: randomized (1:1:1); stratified by hemoglobin level and corrected serum calcium	mg, PO QD; EVER 10 mg, PO, QD Continuous, 28-day cycles		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

Clinical pharmacology data pertaining to the existing licenses are contained in the original lenvatinib Marketing Authorization Application.

The current application concerns the combination of lenvatinib plus pembrolizumab for the first-line treatment of patients with advanced RCC based on efficacy and safety data for the combination from the Phase 3 Study 307. In addition to the studies supporting the proposed indication, the applicant mentions that newly completed studies were carried out to evaluate the effect of intrinsic factors and for drug-drug interactions.

Updated clinical pharmacology data are included in the following studies:

- Study 307; lenvatinib and pembrolizumab combination in subjects with RCC
- E7080-A001-010; in subjects with either renal or hepatic impairment and matched healthy controls.
- E7080-A001-109; in subjects with solid tumours to determine the effect of lenvatinib on the pharmacokinetics (PK) of midazolam (a cytochrome P450 3A4 [CYP3A4] substrate)
- Population PK analysis of lenvatinib on pooled data from several studies, including PK/safety analyses from Study 307/Arm B data.
- The observed pembrolizumab and incidence rate of anti-drug antibodies of pembrolizumab in combination with lenvatinib in Study 307 Arm B were summarized and compared with historical rates from pembrolizumab monotherapy

Bioanalytical methods

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

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

A sensitive, specific, and reproducible method was developed and validated for the determination of lenvatinib (free base concentration) in human plasma (sodium heparinized) and was previously reported in DTC and HCC indications and are not discussed.

Study 307

Plasma samples from study 307 were analyzed for lenvatinib. The results from the calibration standards and quality control samples demonstrated acceptable performance of the method for all reported concentrations and met acceptance criteria for incurred sample reproducibility. 670 out of 701 (95.58%) samples for lenvatinib met the acceptance criteria.

Immunogenicity assays and strategy used for the detection and characterisation of Anti-drug Antibody (ADA) against Pembrolizumab

The samples were assayed for anti-pembrolizumab antibodies presence using a validated electrochemiluminescence (ECL) immunoassay on the MesoScale Discovery (MSD) platform. Bioanalysis of pembrolizumab ADA was carried out using the standard 3-tiered assay approach that consisted of screening (Tier 1), confirmation (Tier 2) and antibody titer assessment (Tier 3). Only Tier 2 confirmed ADA positive samples were moved to Tier 3 and reported with a titer value and a neutralizing antibody (NAb) result.

Pembrolizumab could interfere with the antibody assays at concentrations above the drug tolerance level (DTL). Therefore, an integrated evaluation of pembrolizumab ADA results and pembrolizumab serum

concentration was created for interpretation of immunogenicity results. A flow chart of the ADA sample analysis is given in the figure below.

The DTL for the ADA assay, executed at the vendor PPD, is 124 µg/mL.

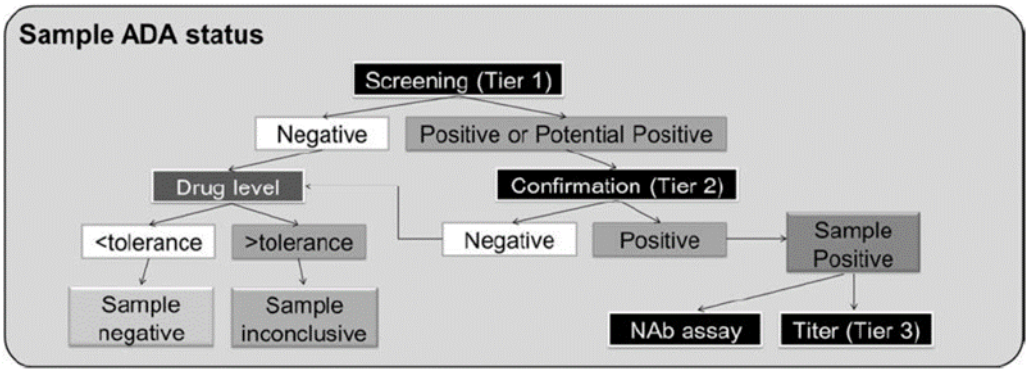


Figure 6 Flow Chart of ADA Sample Analysis

Tier 2 confirmed ADA positive samples were also characterized for neutralizing capacity using a neutralizing antibody (NAb) assay based on the ability of ADA to block (neutralize) the critical first step in the pharmacological action of pembrolizumab, which is binding to PD-1, it's in vivo target.

The neutralizing assay was a validated ligand binding ECL assay, with an assay cut point of 1% false positives. The assay employed, next to the acid dissociation step, a purification step to further reduce the influence of remaining drug in the study serum sample.

The flow chart followed for the ADA subject analysis is presented in the figure below:

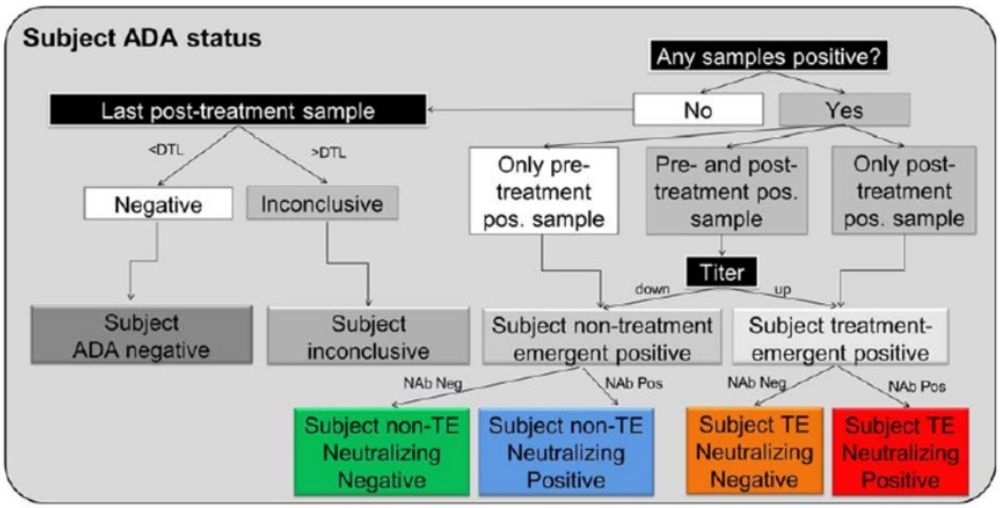


Figure 7 Flow Chart of ADA Subject Analysis

It should be noted that the subject with pre-treatment and postdose sample positive in the confirmatory assay for antibodies against pembrolizumab is considered subject treatment-emergent positive if an increase in titer ≥ 2 fold of baseline is observed (treatment-boosted positive).

An immunogenicity evaluation of pembrolizumab combination therapy with lenvatinib in subjects with advanced RCC has been performed using data from Eisai Study E7080-G000-307 (Study 307) / KEYNOTE-581. For pembrolizumab combination therapy, ADA samples were available from 343 subjects. A subset of the subjects was not assessable for drug-induced immunogenicity because the subjects were not treated with pembrolizumab or only a pre-treatment ADA sample was available (N=11). The

remaining 332 subjects were assessable for drug-induced immunogenicity analysis. On those assessable subjects, 18 subjects were found inconclusive, i.e. subjects with no positive ADA samples present and the drug concentration in the last sample above the drug tolerance level. A listing of all the ADA samples has been presented.

Absorption, Distribution, Elimination

No new Absorption, distribution and Elimination data have been submitted in this application. The data provided on protein binding (study E7080-A001-010) are not new since they were submitted in a previous worksharing procedure (WS1607) in 2019 (see below). The information on lenvatinib absorption, distribution, metabolism and elimination is unchanged from the original DTC (Lenvima) and RCC (Kisplyx) indications.

Special populations

E7080-A001-010

During review of the initial Marketing Authorisation Applications, the applicant was requested to provide the results from the Multicenter Phase 1 Study in Healthy Subjects and Subjects with Either Hepatic or Renal Impairment to Obtain Plasma To Assess In Vitro Lenvatinib Protein Binding (Study E7080-A001-010). This commitment was captured as Measure 010 in the Post-Authorisation Measures for Lenvima and Measure 005 for Kisplyx.

The primary objective of this multicenter parallel-group study was to obtain plasma from subjects with mild, moderate, or severe hepatic or renal impairment, as well as healthy subjects for use in in-vitro protein binding studies in order to define correctly the dose-adjustment in patients with severe hepatic and renal impairment and determine unbound drug concentration.

Lenvatinib plasma protein binding results are similar to previously reported ex-vivo and in-vitro studies conducted by equilibrium dialysis, and unbound plasma protein binding of lenvatinib correlated with serum albumin and alpha-1-acid glycoprotein concentrations regardless of the degree of hepatic or renal impairment. No new safety concerns were identified during this study. There is therefore no impact on the benefit and risk conclusions based on the results of Study E7080-A001-010 and the benefit-risk balance of Lenvima-Kisplyx remains positive.

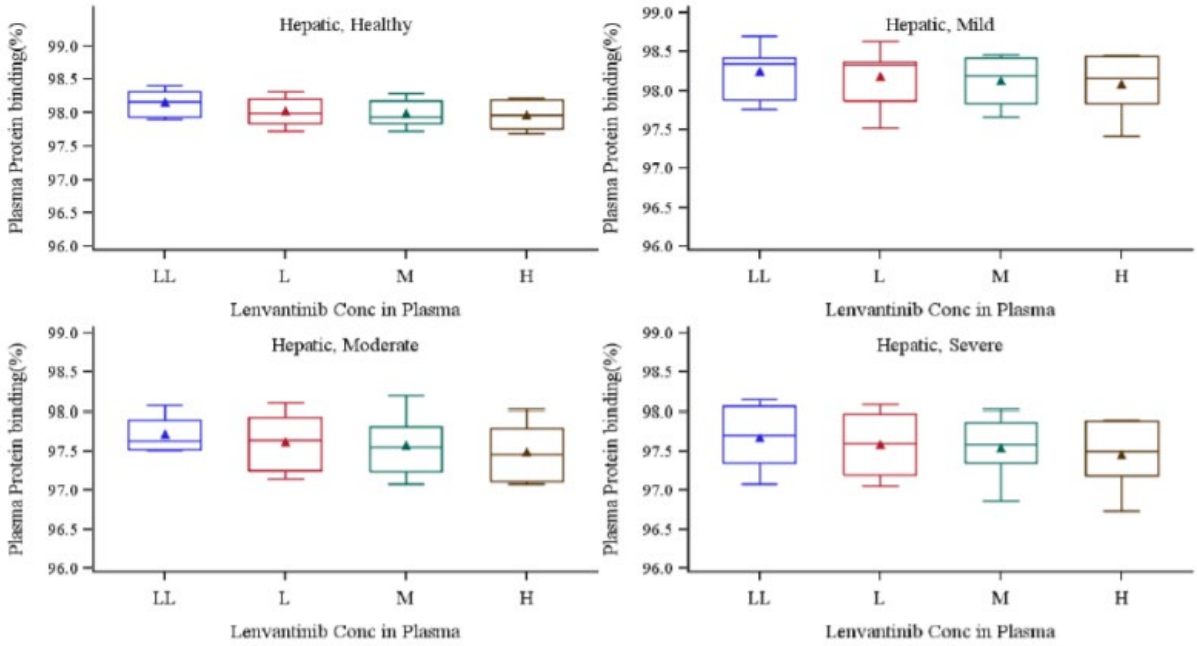


Figure 8 Plasma Protein Binding Versus Lenvatinib Concentrations by Hepatic Impairment Status – Safety Analysis Set

From E7080-A001-010, it can be concluded that plasma protein binding in both hepatically and renally impaired subjects was similar to the respective matched healthy subjects and no concentration dependency was observed for lenvatinib binding in plasma. Lenvatinib plasma protein binding ranged from 98.0% to 98.4% in renally impaired subjects; 97.5% to 98.2% in hepatically impaired subjects; and 98.0% to 98.2% in matched healthy control subjects.

Pharmacokinetic interaction studies

Study E7080-A001-109

During the review of initial MAAs, it was requested that the applicant investigates the potential of lenvatinib for CYP3A4 inhibition/induction (study 109) in a drug-drug interaction study. The commitment was captured as Measure 006 from the Post-Authorisation Measures for Lenvima and Measure 003 for Kisplyx.

In order to fulfil the commitment, Eisai herein submitted in 2018 the results of the finalised Phase 1 study E7080-A001-109, to determine DDI of lenvatinib (E7080) and midazolam, a CYP3A4 substrate, in subjects with advanced solid tumours (Study Title - An Open-Label Phase 1 Study to Determine the Effect of Lenvatinib (E7080) on the Pharmacokinetics of Midazolam, a CYP3A4 Substrate, in Subjects With Advanced Solid Tumours).

The primary objective of the study was to determine the effect of lenvatinib on cytochrome P450 3A4 (CYP3A4) activity by using midazolam as a probe. The secondary objective was to assess the safety of lenvatinib when co-administered with midazolam to subjects with advanced solid tumours.

The study was a multi-center, open-label, non-randomised, Phase 1 study conducted in 3 phases: a pre-treatment Phase, a Treatment Phase, and an Extension Phase as depicted in the figure below. The pre-randomization phase comprised 2 periods, screening and baseline. Subjects who completed the Pre-randomization Phase entered the Treatment Phase.

In the Treatment Phase, all subjects received lenvatinib once daily (QD) in 28-day cycles and 3 single doses of midazolam, 1 each on Days −3, 1, and 14 of Cycle 1.

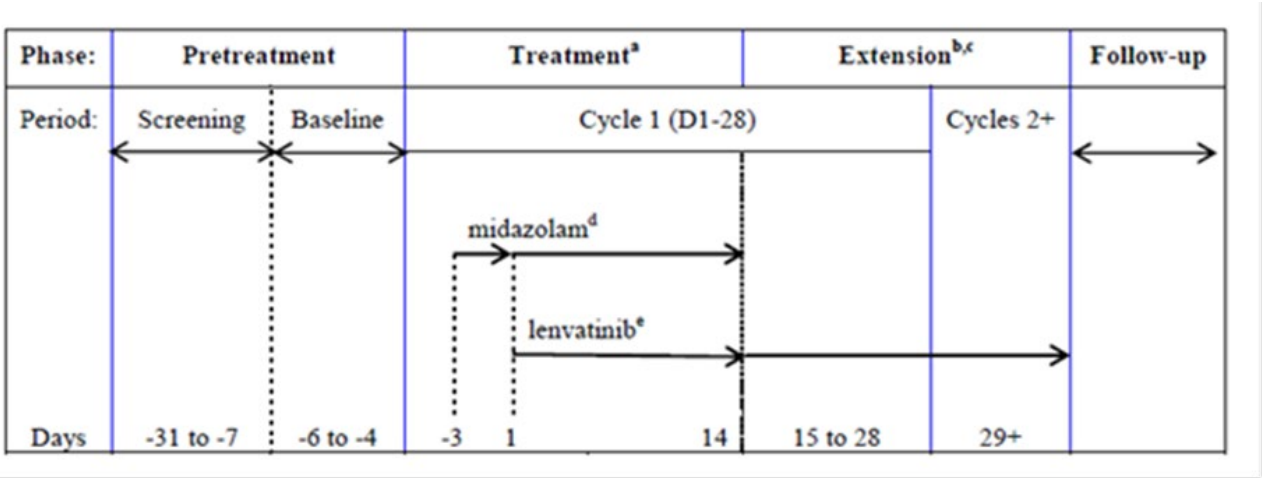


Figure 9 Study design for E7080-A001-109

Test Treatment, Dose, Mode of Administration, and Batch Numbers

Lenvatinib

- 4-mg and 10-mg oral capsules
- Dose: 24 mg (two 10-mg and one 4-mg capsule) once daily
- Mode of administration: oral
- Batch numbers: 10 mg: P22012ZZA; 4 mg: P22011ZZA, P34007ZZA

Midazolam

- 2 mg/mL syrup
- Dose: 4 mg
- Mode of administration: oral
- Batch number: 559339A

Blood samples (2 mL per time point) for PK assessment of midazolam and its metabolite 1'-OH midazolam were collected on C1D -3, C1D1 and C1D14, at predose (0 hour), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, and 24 hours after the midazolam dose.

Pharmacokinetic parameters included area under the concentration time curve (AUC), maximum drug concentration (Cmax,), time to maximum concentration (tmax), terminal elimination half-life (t½), apparent clearance (CL/F), and apparent volume of distribution (Vz/F).

Table 1 Geometric Means and Ratios for AUC and Cmax of Midazolam and 1' OH Midazolam on Cycle 1 Day 1 and Day 14 (with Lenvatinib) versus Day -3 (without Lenvatinib), by Time Point – Pharmacokinetic Analysis Set

Analyte PK Parameter	Test Day	Reference Day (-3) (Midazolam Alone)		Test Day (1 or 14) (Midazolam + Lenvatinib)		GM Ratio (Test Day vs Reference)
		n[a]	Geometric Mean	n[a]	Geometric Mean	
Midazolam						
C_{max} (ng/mL)	Day 1	28	24.729	28	21.323	0.862
	Day 14	19	24.104	19	24.755	1.027
$AUC_{(0-24)}$ (ng•h/mL)	Day 1	27	89.904	27	82.192	0.914
	Day 14	19	88.302	19	101.367	1.148
1□-OH Midazolam						
C_{max} (ng/mL)	Day 1	28	9.039	28	9.539	1.055
	Day 14	19	8.757	19	8.235	0.940
$AUC_{(0-24)}$ (ng•h/mL)	Day 1	20	33.844	20	37.911	1.120
	Day 14	14	30.806	14	36.925	1.199

Reference Day: Cycle 1 Day -3 (C1D-3) (midazolam alone).
Test Days: Cycle 1 Day 1 (C1D1) (midazolam + single-dose lenvatinib); Cycle 1 Day 14 (C1D14) (midazolam + multiple-dose lenvatinib [at steady-state]).
Last sampling time point was 24 hours after administration.
$AUC_{(0-24)}$ = area under the concentration × time curve from time 0 to 24 hours after midazolam dose;
C_{max} = maximum drug concentration; GM = geometric mean; PK = pharmacokinetic.
The ratios are based on natural log scale data and converted back to the original scale.
Midazolam based on C1D-3 assessments. Lenvatinib + midazolam based on assessments on C1D1 and C1D14.
Subject 10031014 took a known potent CYP3A4 inducer/inhibitor (exclusion criterion no. 5) and was excluded from the analysis.
a: Number of subjects in the Pharmacokinetic Analysis Set at specified time point.

The mean PBPK model-predicted midazolam AUCR with lenvatinib was 1.18, which is in agreement with the observed mean AUCR of 1.14 from this clinical study, confirming that there is no clinically relevant effect of lenvatinib on the PK of midazolam.

Study 307 - E7080-G000-307/KEYNOTE-581

Study 307 determined the efficacy and safety of lenvatinib plus everolimus (Arm A) or pembrolizumab (Arm B) versus the control arm of sunitinib (Arm C).

One of the secondary objectives of this study was to summarize serum concentrations of pembrolizumab obtained from subjects with advanced renal cell carcinoma (RCC) following administration of pembrolizumab (200 mg pembrolizumab Q3W) in combination with lenvatinib (Eisai Study 307 /KEYNOTE-581) and to compare observed pembrolizumab PK data in Eisai Study 307 / KEYNOTE-581 with reference pembrolizumab model (TDPK model based) predicted PK.

PK analysis for pembrolizumab was reported in pembrolizumab (MK-3475) PK analysis report HOPE307-PembroPK. Over the course of clinical development of pembrolizumab, PK has been robustly characterized. 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 as indicated in the pembrolizumab USPI and EU SmPC. This model is used as the reference PK model to support pembrolizumab submissions across indications worldwide.

Table 2 Overview of Pembrolizumab Cohorts Included in Eisai 307 / KEYNOTE581 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

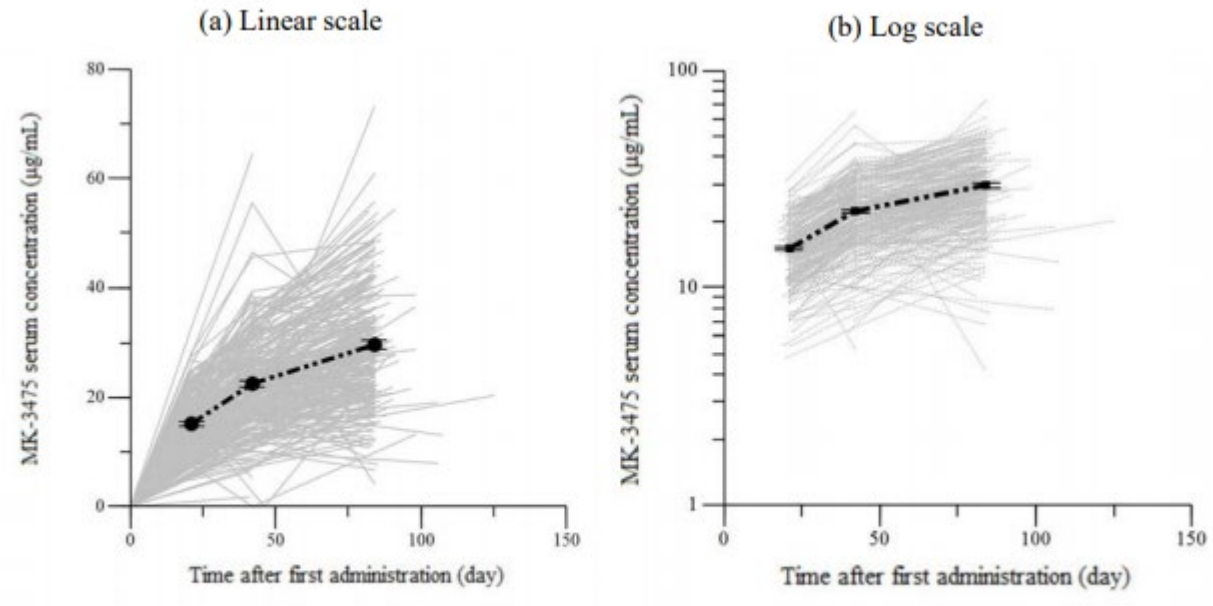
PK sampling schedule in Eisai Study 307 / KEYNOTE-581, Arm B: Pre-dose pembrolizumab serum concentrations (Ctrough) were obtained within 24 hours prior to dosing at cycles 1, 2, 3, 5 and during the off-treatment visit after pembrolizumab discontinuation. Post-dose serum concentrations (Cmax) were drawn within approximately 30 minutes after the end of the infusion in cycle 1 and cycle 2.

Table 3 Summary Statistics of Pembrolizumab Pre-dose (Ctrough) and Post-dose (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



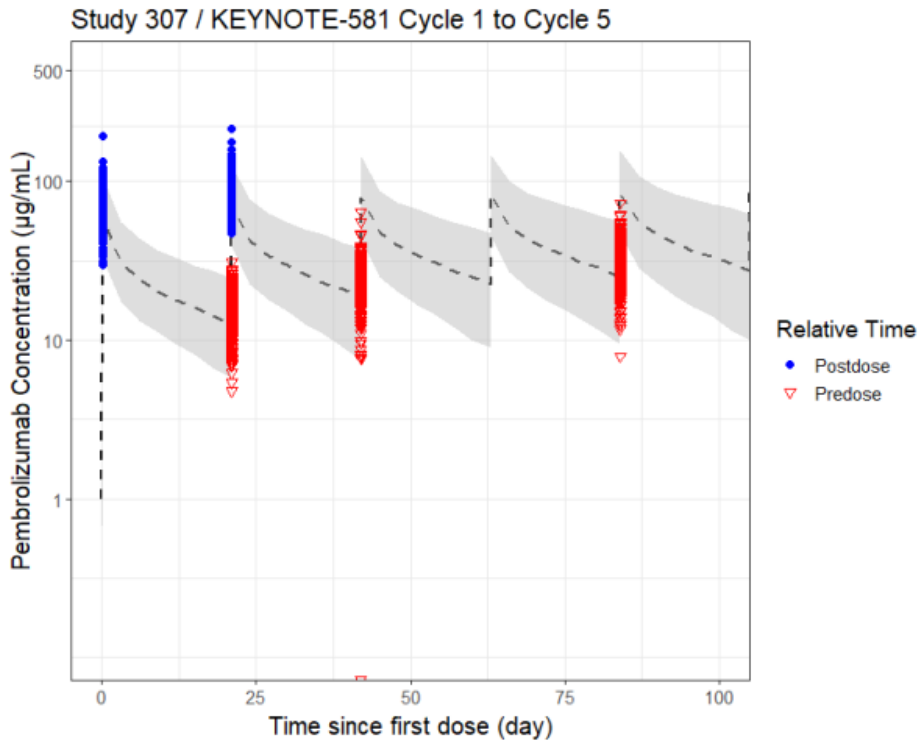
Note: Grey lines represent individual concentration observations. Black dashed lines represent arithmetic mean concentrations and error bars are associated +/- SE. Actual times were used for this analysis.

Data Source – 05NHKJ: adpcpem

Figure 10. Individual and Arithmetic Mean Pre-dose 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

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. This model is used as the reference PK model to support pembrolizumab submissions across indications worldwide.

Observed pembrolizumab concentration data in Study 307 Arm B are overlaid on the simulated profile using the reference model as shown in the figure below. The majority of the observed pembrolizumab serum concentration values are contained within the boundaries of the predicted interval using the reference PK model, which indicate that pembrolizumab data from study are consistent with the historical monotherapy data.



Symbols are individual observed data (nominal time) from Study 307 / KEYNOTE-581 200 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.

Data Source Data Source – 05NHKJ: adpcpem

Figure 11 Observed Pembrolizumab Concentration Data in Eisai Study 307 / KEYNOTE-581 Subjects Receiving 200 mg Q3W Pembrolizumab in Combination with 20 mg QD Lenvatinib with Reference Model-Predicted Pharmacokinetic Profile for Pembrolizumab 200 mg Q3W Dose Regimen (Log-Linear Scale)

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 observed pembrolizumab concentration data in Study 307 Arm B from subjects with advanced RCC following administration of 200 mg every 3 weeks (Q3W) pembrolizumab therapy in combination with 20 mg once daily (QD) lenvatinib are consistent and within the range of simulated monotherapy pembrolizumab PK profiles using the reference population PK model created using data from 2993 subjects administered with pembrolizumab monotherapy regimen.

The population PK of lenvatinib when co-administered with pembrolizumab has been characterised in study CPMS-E7080-012R-LP:

CPMS-E7080-012R-LP

The objectives of the population PK analysis of lenvatinib is 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.

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) Lenvatinib + Pembrolizumab First-Line Advanced Renal Cell Carcinoma 2.7 Clinical Written and Tabular Summaries 2.7.2 Summary of Clinical Pharmacology Studies Eisai CONFIDENTIAL Page 15 of 27 > upper limit of normal (ULN) on CL/F, CYP3A4 inhibitors on CL/F, and capsule formulation on relative bioavailability. In the current analysis, due to the large dataset which resulted in a very long run time Ka, D1, F1rel, V3/F and effect of healthy subjects and CYP3A4 inhibitors on CL/F, which all were similar to those from many previous PK analyses, were fixed to those from the recent PK analysis and only effects of albumin, ALP and tumour type were re-evaluated in the PK model in addition to co-medication effect of everolimus and pembrolizumab (categorical) or area under the concentration × time curve (AUC) of everolimus on CL/F.Estimation of model parameters was performed using first order conditional estimation method with interaction (FOCEI).

PK analysis for lenvatinib

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, however, in these cases none was found to be significant. Population PK parameter estimates from the final model are presented in the table below:

Table 4 Population Pharmacokinetic Parameter Estimates of Lenvatinib

Parameter	NONMEM Estimates		
	Point Estimate	%RSE	95% Confidence Interval
$CL/F\ [L/h] = \Theta_{CL} * (WGT/74.7)^{0.75} * \Theta_{INHIB}^{INHIB} * \Theta_{ALP}^{ALP} * \Theta_{ALB}^{ALB} * \Theta_{HV}^{HV} * \Theta_{HCC}^{HCC} * \Theta_{RCC}^{RCC}$			
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

The DTC population was found to have similar lenvatinib CL/F to that in patients with other cancer types excluding RCC and HCC. 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 HCC population was found to have a 12.7% lower lenvatinib CL/F compared with patients with DTC and other cancer types excluding RCC. The

magnitude of each effect is within the inter-subject variability for CL/F (%CV = 34.2 %) and hence of no clinical relevance. These effects are consistent with those from a recent analysis (CPMS-E7080-013R).

Individual lenvatinib CL/F and AUC for RCC subjects receiving lenvatinib 20 mg in combination with pembrolizumab (Arm B) in Study 307 are summarized in **Table 5**. 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 (**Table 6**), confirming the non-clinically relevant effect of pembrolizumab co-administration on lenvatinib exposure. The median values and range of CL/F and AUC for Asian (Japanese + Chinese + other Asian) and Japanese populations are comparable with overall population who received lenvatinib 20 mg in combination with pembrolizumab (Arm B) in Study 307.

Table 5 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

Table 6 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

The median values and range of CL/F and AUC for Asian (Japanese + Chinese + other Asian) and Japanese populations are comparable with overall population received lenvatinib 20 mg in combination with pembrolizumab (Arm B) in study 307.

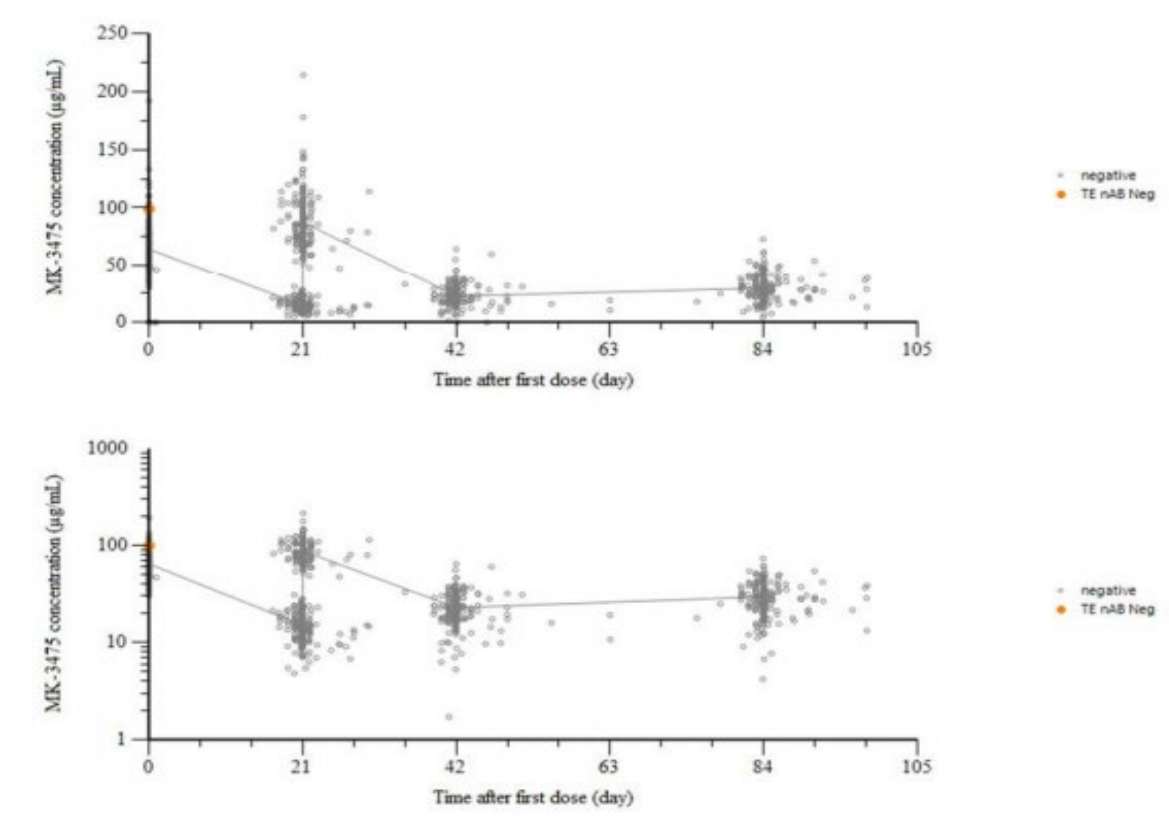


Figure 12 Effect of ADA on on Pembrolizumab Exposure after Pembrolizumab Combination Therapy, 200 mg MK-3475 Q3W, in Combination with Lenvatinib (Eisai Study 307 / KEYNOTE-581)

The evaluation has confirmed the assessment that pembrolizumab combination therapy with lenvatinib in subjects with advanced RCC, has a limited potential to elicit the formation of ADA and that there is no impact on pembrolizumab exposure in the cases where ADA formation occurs.

The observed incidence of treatment emergent ADA 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. The treatment emergent positive subject had no antibodies with neutralizing capacity.

This is consistent with the low immunogenicity incidence after pembrolizumab monotherapy of prior immunogenicity evaluations.

2.3.3. Pharmacodynamics

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 the USPI and EU SmPC.

This low rate of immunogenicity has been shown to be consistent across tumour type and no clinical consequences have been observed in the subjects with a positive immunogenicity reading.

Immunogenicity evaluation for study 307

For pembrolizumab combination therapy, ADA samples were available from 343 subjects. A subset of the subjects was not assessable for drug-induced immunogenicity because the subjects were not treated with pembrolizumab or only a pre-treatment ADA sample was available (N=11). The remaining 332 subjects were assessable for drug-induced immunogenicity analysis.

Table 7 Overview of Subjects Included in the Immunogenicity Analysis after Pembrolizumab Combination Therapy, 200 mg MK-3475 Q3W, in Combination with Lenvatinib (Eisai Study 307 / KEYNOTE-581)

Study	Indication	Subjects		
		Subjects Providing ADA Samples	Subjects Dosed with Pembrolizumab	Assessable Subjects Subjects Dosed with Pembrolizumab and Post Treatment Samples
Pembrolizumab Combination Therapy				
Eisai Study 307 / KEYNOTE-581	Advanced renal cell carcinoma (RCC)	343	343	332

The table below presents an overview of the immunogenicity status of all assessable subjects.

To evaluate immunogenicity, the overall immunogenicity was defined as the proportion of emergent positive subjects to the total number of evaluable subjects (treatment emergent positive, non-treatment emergent positive and negative immunogenicity status).

Table 8 Overview of the immunogenicity status Study 307

Solid tumors	
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

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.

Impact on pembrolizumab exposure

The effect of ADA on pembrolizumab levels, for the subjects with ADA positive samples, is compared with the subjects treated with the same regimen that only have ADA negative samples. For the ADA positive

subject, the pembrolizumab exposure was comparable to that for other subjects treated with the same regimen.

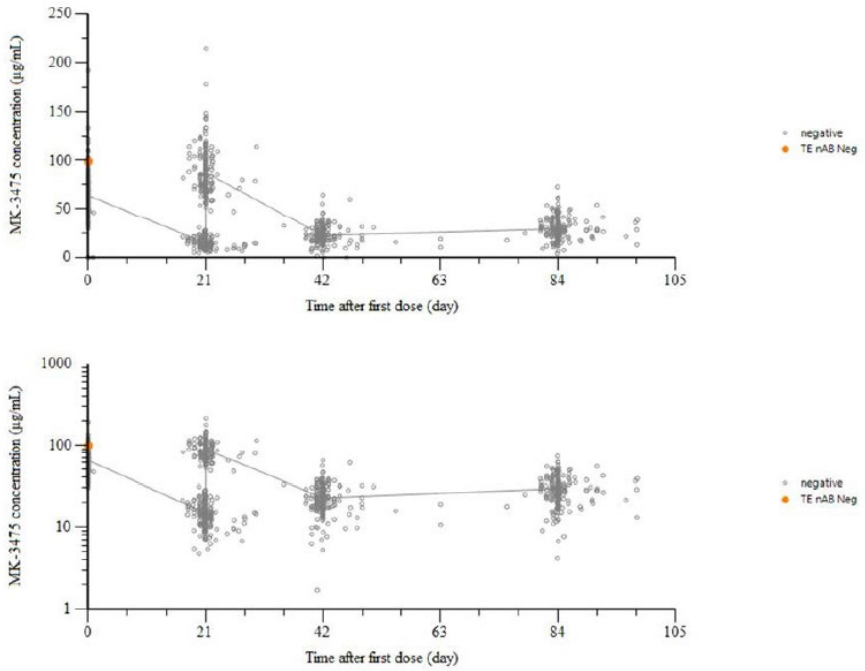


Figure 13 Effect of ADA on Pembrolizumab Exposure after Pembrolizumab Combination Therapy, 200 mg MK-3475 Q3W, in Combination with Lenvatinib (Eisai Study 307 / KEYNOTE-581)

Impact of ADA on pembrolizumab safety and efficacy

There was one ADA positive sample from one patient for whom no neutralising activity was detected.

The evaluation has confirmed the assessment that pembrolizumab combination therapy with lenvatinib in subjects with advanced RCC has a limited potential to elicit the formation of ADA and that there is no impact on pembrolizumab exposure in the cases where ADA formation occurs. This is consistent with the low immunogenicity incidence after pembrolizumab monotherapy of prior immunogenicity evaluations.

2.3.4. PK/PD modelling

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 9 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

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 10 **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/Study 307.

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).

Predose pembrolizumab serum concentrations (Ctrough) were obtained within 24 hours prior to dosing at cycles 1, 2, 3, 5 and and during the off-treatment visit after pembrolizumab discontinuation. Postdose 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.

It is already demonstrated that RCC subjects had 14.6 % lower oral clearance than that in subjects with other types of tumour excluding HCC. It is agreed that the magnitude of the effect is within the inter-subject variability for CL/F and that therefore the difference is of no clinical relevance.

Based on the PK results of study 307 and POP PK analysis based on pooled PK data from the 21 studies, including Study 307, a change in the PK information of the Kisplyx SmPC is not justified.

The information on special populations is unchanged from the original DTC (Lenvima) and RCC (Kisplyx) indications.

Given the divergent metabolic pathways for both compounds, no DDI is expected on pembrolizumab and lenvatinib when administered in combination with each other. 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.

Pembrolizumab combination therapy with lenvatinib in subjects with advanced RCC, has a limited potential to elicit the formation of ADA and that there is no impact on pembrolizumab exposure in the cases where ADA formation occurs.

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 E7080-A001-111/KEYNOTE 146

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 tumour 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).

The Phase 1b dose-finding portion of the study using a dose de-escalation strategy with a 3+3 design.

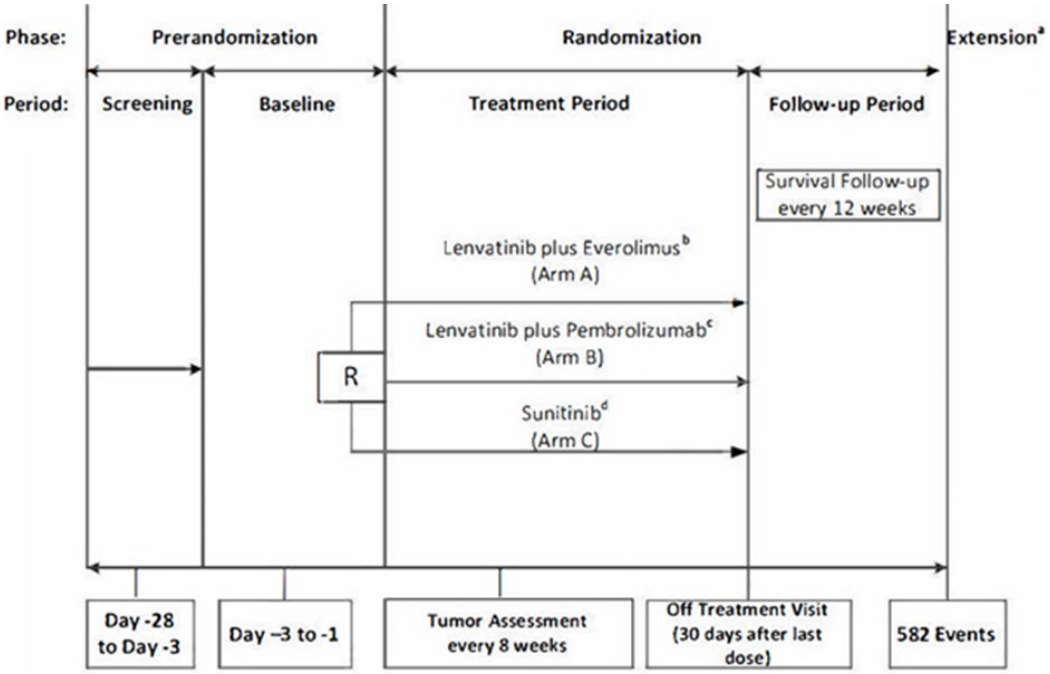
Per protocol, in Phase 1b of this study, if ≥2 subjects at a dose level experienced dose-limiting toxicity (DLT), the study proceeded with enrollment at the next lower dose level. The MTD was confirmed if ≤ 3 of the 10 evaluable subjects in a dose level experienced DLTs during the first 3 weeks of treatment (Cycle 1). The study began with 3 subjects 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. Both subjects had a dose reduction to 20 mg QD and continued to receive study treatment. Ten subjects were subsequently enrolled in the lenvatinib 20 mg/day + pembrolizumab 200 mg dose level and no DLTs were reported.

Based on these data, the lenvatinib 20 mg QD (starting dosage) plus pembrolizumab 200 mg Q3W has been implemented as the recommend dose across the lenvatinib plus pembrolizumab combination program (with the exception of hepatocellular carcinoma), that currently consists of 13 Phase 2 and Phase 3 registration studies in a range of indications. Lenvatinib 20 mg QD plus pembrolizumab 200 mg Q3W are also the approved dosages for the treatment of patients with advanced EC (in those countries where this indication is currently approved).

2.4.2. Main study

Title of Study

E7080-G000-307 / KEYNOTE 581 (CLEAR): 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



R = Randomization. a:Extension Phase includes a Treatment and Follow-up Period. All subjects still on treatment at the end of the Randomization Phase will enter the Extension Phase and continue to receive the same study treatment they received in the Randomization Phase. b:lenvatinib 18 mg plus everolimus 5 mg given orally once daily (Arm A). c:Lenvatinib 20 mg once daily plus pembrolizumab 200 mg intravenously every 3 weeks (Arm B).d:Sunitinib 50 mg once daily on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2; Arm C).

Figure 14 Study Design for Study 307

Methods

At the time of Data Cut-Off, the study randomized 1,069 subjects with advanced RCC in total. A total of 355 subjects 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.

Study participants

Key inclusion criteria

- 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 computerized 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.
- Male or female subjects age ≥18 years (or any age greater than 18 years of age if that age is considered to be an adult per the local jurisdiction) at the time of informed consent
- Karnofsky Performance Status (KPS) of ≥70.

Key exclusion criteria

- Subjects who have received any systemic anticancer therapy for RCC, including anti-VEGF therapy, or any systemic investigational anticancer 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 CNS metastases are not eligible unless they have completed local therapy (eg, whole brain radiation therapy [WBRT], surgery or radiosurgery) and have discontinued the use of corticosteroids for this indication for at least 4 weeks before starting treatment in this study. Any signs (eg, radiologic) or symptoms of CNS metastases must be stable for at least 4 weeks before starting study treatment.
- Prior radiation therapy within 21 days prior to start of study treatment with the exception of palliative radiotherapy to bone lesions, which is allowed if completed 2 weeks prior to study treatment start.
- Subjects with proteinuria >1+ on urine dipstick testing will undergo 24-h urine collection for quantitative assessment of proteinuria. Subjects with urine protein ≥1 g/24 h will be ineligible
- Fasting total cholesterol >300 mg/dL (or >7.75 mmol/L) and/or fasting triglycerides level >2.5×ULN. NOTE: these subjects can be included after initiation or adjustment of lipid lowering medication.
- Uncontrolled diabetes as defined by fasting glucose >1.5×ULN. Note: these subjects can be included after initiation or adjustment of glucose-lowering medication.
- Prolongation of QTc interval to >480 ms.
- Subjects who have not recovered adequately from any toxicity and/or complications from major surgery prior to starting therapy.
- Gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of lenvatinib, everolimus, and/or sunitinib.
- Bleeding or thrombotic disorders or subjects at risk for severe hemorrhage. The degree of tumour invasion/infiltration of major blood vessels should be considered because of the potential risk of severe hemorrhage associated with tumour shrinkage/necrosis following lenvatinib therapy.
- Clinically significant hemoptysis or tumour 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: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction, cerebrovascular accident (CVA), or cardiac arrhythmia associated with hemodynamic instability.
- The following is also excluded:
- Left ventricular ejection fraction (LVEF) below the institutional normal range as determined by MUGA or echocardiogram.
- 17. Subjects known to be positive for Human Immunodeficiency Virus (HIV).
- 18. Known active Hepatitis B (eg, HBsAg reactive) or Hepatitis C (eg, HCV RNA [qualitative] is
- detected).

Treatments

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

- **Arm A:** lenvatinib 18 mg orally (PO) QD + everolimus 5 mg PO QD in each 21-day cycle
- **Arm B:** lenvatinib 20 mg PO QD + pembrolizumab 200 mg intravenously (IV) every 3 weeks (Q3W) in each 21-day cycle
- **Arm C:** sunitinib 50 mg PO QD was given for 4 weeks on, then 2 weeks off (Schedule 4/2)

Treatment continued until unacceptable toxicity or disease progression as determined by the investigator and confirmed by independent radiologic review committee (IRC) using Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST 1.1). Administration of lenvatinib with pembrolizumab was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit. Pembrolizumab was continued for a maximum of 24 months; however, treatment with lenvatinib could be continued beyond 24 months.

Objectives

Primary Objective

- The primary objective of the study is to demonstrate that lenvatinib in combination with everolimus (Arm A) or pembrolizumab (Arm B) is superior compared to sunitinib alone (Arm C) in improving progression-free survival (PFS) (by independent imaging review [IIR] using Response Evaluation Criteria in Solid Tumours [RECIST 1.1]) as first-line treatment in subjects with advanced renal cell carcinoma (RCC).

Secondary Objectives

- To compare objective response rate (ORR) by IIR using RECIST 1.1 of subjects treated with lenvatinib in combination with everolimus or pembrolizumab versus sunitinib.
- To compare overall survival (OS) 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 Index-Disease-Related Symptoms (FKSI-DRS), the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-30, and the European Quality of Life (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 v.1.1
- To characterize the population pharmacokinetics (PK) of lenvatinib when co-administered with everolimus or pembrolizumab.
- To compare the PK of pembrolizumab from this study to historical data.
- To characterize the population PK of everolimus when co-administered 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] + partial response [PR] + stable disease [SD]) and clinical benefit rate (CBR) (CR, PR + durable SD) 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 tumour and blood biomarkers and clinical outcome measures including antitumour activity of study treatment.

Outcomes/endpoints

Primary Endpoint

Progression-free survival (PFS) by independent review was defined as the time from the date of randomization to the date of the first documentation of disease progression as determined by IIR using RECIST 1.1 or death (whichever occurs first).

Secondary Endpoints

- Objective response rate (ORR) is defined as the proportion of subjects who have best overall response of CR or PR as determined by IIR using RECIST 1.1.

- Overall survival (OS) is 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 will be censored at the date the subject was last known alive, or date of data cutoff, whichever occurs first.

Other Secondary endpoints

Safety will be assessed summarizing the incidence of treatment-emergent adverse events (TEAEs) and SAEs together with all other safety parameters.

Proportion of subjects who discontinued treatment due to toxicity is defined as the proportion of subjects who discontinue study treatment due to treatment-emergent adverse events (TEAEs).

Time to treatment failure due to toxicity is defined as the time from the date of first dose to the date that a subject discontinues study treatment due to TEAEs.

Health-Related Quality of Life (HRQoL) will be assessed 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) QLQ-C30 and the European Quality of Life (EuroQOL) EQ-5D-3L instruments.

PFS on next-line of therapy (PFS2) is defined as the time from randomization to disease progression on next-line of treatment, or death from any cause, (whichever occurs first).

Progression-free survival (PFS) by investigator assessment is 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 v.1.1 or death (whichever occurs first).

Model-predicted clearance and AUC for lenvatinib in Arms A and B.

Model-predicted clearance and AUC for everolimus in Arm A.

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.

- Duration of response (DOR) is defined as the time from the date a response was first documented until the date of the first documentation of disease progression or date of death from any case.

- Disease control rate is the proportion of subjects who have best overall response of CR or PR or SD. Stable disease must be achieved at ≥7 weeks after randomization to be considered best overall response.

- Clinical benefit rate is the proportion of subjects who have best overall response of CR or PR or durable SD (duration of SD ≥ 23 weeks after randomization).

- Blood and tumour biomarkers will be assessed for identifying potential correlation with clinical outcomes-related endpoints.

Sample size

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

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% is assumed in the sample size calculation.

Since the study was testing more than one comparison for the primary and secondary endpoints, the graphical approach was used for testing multiple hypotheses. For the two PFS comparisons (one for each test arm), the sponsor chose to split the total alpha of 0.0499 (2-sided), as initial allocations, 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.

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 were expected to be observed in Arms A and C, a total of 388 PFS events is 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 is approximately 70% at the initial assigned α = 0.0049, and would at least 90% when 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 is to be performed at the 80% information fraction and a Lan-DeMets spending function with O'Brien-Fleming boundary used between the interim and final analysis of PFS.

Assuming an average enrollment rate of 31 subjects per month, the interim and final analysis of PFS would occur approximately 38 and 45 months (34-month enrollment period) after the first subject had been 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 would 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 would increase to at least 80% when the OS testing between Arms B and C is significant and both PFS testings are significant, and vice versa.

The assumptions that are used for the OS power calculations were: 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 enrollment, the final analysis of OS was expected to occur approximately 69 months after the first subject is randomly assigned to treatment.

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 will 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.

Randomisation

Subjects were to be assigned to treatments based on a computer-generated randomization scheme that were reviewed and approved by an independent statistician. Randomization was to be performed centrally by an interactive voice and web response system (IxRS).

Stratification

The randomization was based on the following stratification factors:

- Geographic region: Region 1(Western Europe and North America); Region 2 (rest of the world)

- Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic groups: favorable, intermediate, and poor risk

Blinding (masking)

The study was open-label to sites and investigators and was blinded to MAH clinical, biostatistics, and ICL personnel. The data integrity of Study 307 was maintained by 1) the Data Integrity Protection Plan, which detailed the masking procedures throughout the study conduct, and 2) the Operational and Communication Plans, which specified the operational and communication procedures that were followed during conduct of each of the interim analyses.

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 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 priorization described below.

Table 11 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 tumour 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 tumour assessment prior to or on the date of new anticancer treatment.
- If a subject missed two or more tumour assessments before PD or death (No. 7), the subject will be censored on the date of the last adequate tumour 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:

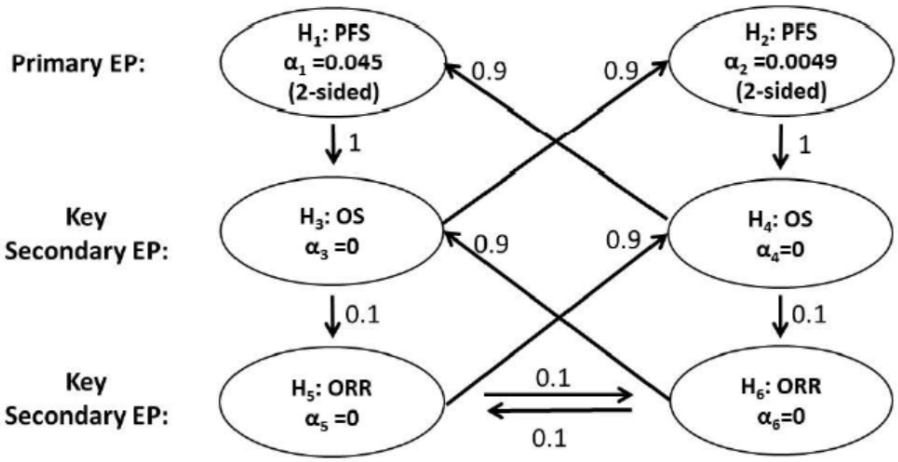
Overall Survival (OS) was planned to be compared between lenvatinib + everolimus (Arm A) vs. sunitinib alone (Arm C) and lenvatinib + pembrolizumab (Arm B) vs. sunitinib alone (Arm C) using the stratified logrank test with geographic region (Western Europe and North America vs. Other) and MSKCC prognostic 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.

Multiplicity

To adjust for multiplicity and control the overall FWER, the graphical approach of Maurer and Bretz (Maurer et al., 2013) will be used in the primary endpoint of PFS and the key secondary efficacy endpoints (OS and ORR). No multiplicity adjustment will be made for other secondary endpoint analyses. An α of 0.0001 will be subtracted from the total α of 0.05 to account for the interim analysis of ORR from Arm B. Figure below shows the initial α- allocation (the remaining α of 0.0499) for each hypothesis and the graphical approach for multiple analyses of PFS, OS, and ORR.

If the null hypothesis of PFS is rejected at the initial allocated alpha level 0.045 for H1 (or 0.0049 for H2), this alpha of 0.045 (or 0.0049) will be reallocated to the tests with the corresponding weights as shown in Figure 15. The initial weights for reallocation from each hypothesis to the others are represented by the numbers next to the arrows (eg, if H1 and H3 are positive, 90% alpha will be reallocated to H2, and 10% to H5). An alpha level 0.045 is assigned to H1 to increase the successful rate of H1 test so that this alpha can be re-allocated to other hypothesis tests. When alpha is re-allocated as planned for all hypotheses, the PFS tests H1 and H2 will both have 90% power, OS tests H3 and H4 will both have 80% power, and

the ORR tests H5 and H6 will both have more than 95% power



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 15 Graphical Approach to Control Familywise Error Rate for Testing

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.

Table 12 Efficacy Boundaries and Properties for OS H3 and OS H4 (LDPocock Spending function) when PFS Tests 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.

Interim analysis

The interim efficacy analyses were planned to be conducted by an independent statistical group that has no other responsibilities for the study. The safety monitoring was planned to be conducted by the independent DMC and only the DMC was planned to have access to data with treatment information.

The frequency of the safety reviews was planned to be defined in the DMC charter. The recommendation whether to stop the trial for safety reasons had to be reached by the DMC based on its review of safety data with treatment information. The function and membership of the DMC was planned to be described in the DMC charter.

Interim analyses of PFS, OS, and ORR were planned. The timing of each analysis are summarized in table 13 below.

Table 13 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.

An interim analysis of ORR for the first 88 subjects from the lenvatinib + pembrolizumab arm (Arm B) of this study was planned to be performed. No comparative analysis was planned to be conducted for the interim analysis of ORR; however, an α of 0.0001 will be allocated and deducted from the analyses of PFS. Details outlining how the integrity of study conduct will be maintained are described in a separate operational plan. This interim analysis of ORR will occur after the first 88 subjects treated in Arm B (lenvatinib + pembrolizumab) have completed a median follow-up of 12 months and a minimum DOR follow-up of 6 months.

Results

Participant flow

The patient distribution is described in the below figure and table.

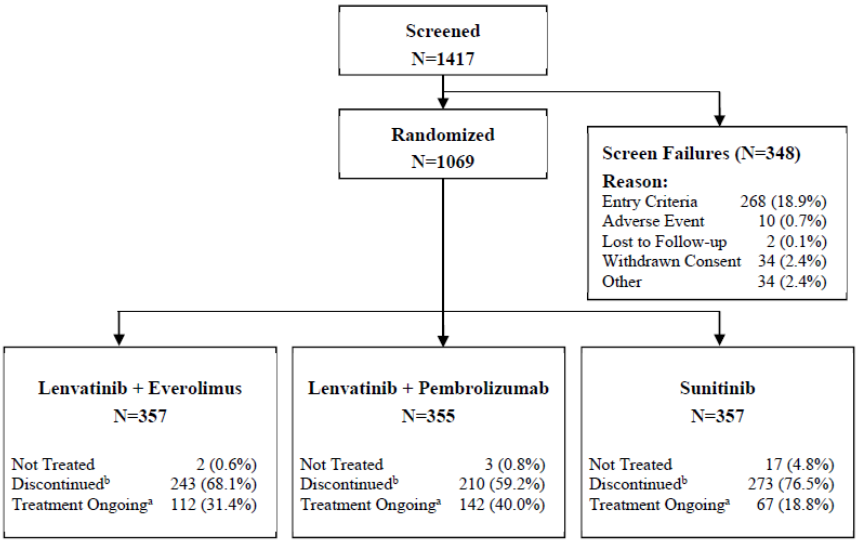


Figure 16 Subject Disposition and Reason for Discontinuation From Study Treatment at IA3 – FAS

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 14 Subject Disposition and Reasons for Discontinuation From Treatment During Randomization Phase at IA3 – FAS

Category	Lenvatinib + Everolimus (N=357) n (%)	Lenvatinib + Pembrolizumab (N=355) n (%)	Sunitinib (N=357) n (%)
Randomized	357 (100)	355 (100)	357 (100)
Not Treated	2 (0.6)	3 (0.8)	17 (4.8)
Treated	355 (99.4)	352 (99.2)	340 (95.2)
Treatment Ongoing at Data Cutoff Date[a]	112 (31.4)	142 (40.0)	67 (18.8)
On Both Study Drugs	100 (28.0)	60 (16.9)	NA
On Lenvatinib Only	9 (2.5)	78 (22.0)	NA
On Pembrolizumab Only	NA	4 (1.1)	NA
On Everolimus Only	3 (0.8)	NA	NA
Discontinued Treatment[b]	243 (68.1)	210 (59.2)	273 (76.5)
Primary Reason for Discontinuation from Treatment[c]			
Radiological Disease Progression	123 (34.5)	97 (27.3)	174 (48.7)
Clinical Disease Progression	20 (5.6)	19 (5.4)	22 (6.2)
Adverse Event	63 (17.6)	60 (16.9)	41 (11.5)
Subject Choice	29 (8.1)	17 (4.8)	23 (6.4)
Lost to Follow-up	0 (0.0)	0 (0.0)	1 (0.3)
Withdrawal of Consent	4 (1.1)	4 (1.1)	9 (2.5)
Other	4 (1.1)	13 (3.7)	3 (0.8)
Completed 35 Cycles of Pembrolizumab	NA	7 (2.0)	NA
Ongoing in Study at Data Cutoff Date[d]	220 (61.6)	254 (71.5)	222 (62.2)
Discontinued Treatment but Remained in Survival Follow-up at Data Cutoff Date	107 (30.0)	112 (31.5)	153 (42.9)
Discontinued from Study[e]	137 (38.4)	101 (28.5)	135 (37.8)
Reason for Discontinuation from Study			
Death	120 (33.6)	80 (22.5)	101 (28.3)
Lost to Follow-up	6 (1.7)	7 (2.0)	6 (1.7)
Withdrawal of Consent	11 (3.1)	14 (3.9)	28 (7.8)

Data cutoff date: 28 Aug 2020.

eCRF = electronic case report form; IA3 = interim analysis 3; NA = not applicable.
a: Treatment ongoing is based on data available in the database at the time of data cutoff. Subjects with sunitinib or at least 1 study drug in combination therapy are deemed to have 'treatment ongoing' in absence of an off-treatment visit, or with a:treatment ongoing at data cutoff in the subject disposition (Randomization Phase) page of the eCRF.
b: Treatment discontinuation includes subjects who discontinued sunitinib or both study drugs in combination therapy.
c: As reported on the Subject Disposition electronic case report form. d: 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. e: Discontinued from study refers to subjects who were no longer followed up for survival as of the cutoff date.

Recruitment

Enrolment in Study 307 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 after 365 PFS events had been observed for the comparison between lenvatinib plus pembrolizumab and sunitinib and 396 PFS events had been observed for the comparison between lenvatinib plus everolimus and sunitinib.

Conduct of the study

Protocol amendments

The original protocol (v1.0) was approved on 22 Jun 2016. There were 7 protocol amendments.

Amendment 01 (26 Sep 2016)

- 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 the EMA.
- Characterization of the population PK of pembrolizumab was added as an exploratory objective.
- Exclusion Criterion 19 was changed, and Exclusion Criterion 20 was added to clarify the exclusion of subjects with a history of (non-infectious) pneumonitis requiring steroid treatment and exclusion of subjects with current pneumonitis.

Amendment 02 (03 Feb 2017)

- Assessment of PFS based on investigator assessment per RECIST 1.1 was added as a secondary objective/endpoint as requested by the regulatory authorities.
- Exclusion Criterion 13 was adapted for the study indication (ie, carotid artery reference was deleted).
- Exclusion Criterion 27 was added to capture "known intolerance to any of the study drugs (or any of the excipients)," as requested by the regulatory authorities.
- Dose modification guidelines for holding treatment for pneumonitis were amended from "Grade 3 to 4" to "Grade 3 to 4 or Recurrent 2."
- Pregnancy assessment was added to the Follow-up Period, as requested by the regulatory authorities.
- As requested by the regulatory authorities, 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."
- PK and PK/PD related exploratory objectives were recategorized from exploratory to secondary, and the following secondary endpoints were added as requested by the regulatory authorities:
    - 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.

Amendment 03 (10 Jan 2018)

- Exclusion Criterion 15 was revised to change cardiovascular impairment window from 6 months to 12 months, as requested by the EMA.
- Dose modification guidelines for pembrolizumab were updated.
- Guidelines for the management of proteinuria, hypertension and hemorrhage were revised.

Amendment 04 (30 Jun 2018)

- Planned enrolment was increased to 1050 subjects (approximately 350 subjects per arm) to address slow enrolment in the first 12 months and high loss of PFS event rate and provide adequate power for intergroup comparisons of OS. The planned number of investigational sites was increased to 200 to accommodate the delay in study enrollment.
- The estimated duration of the Study Randomization Period was increased to 43 months (29-month enrolment period; 14-month Follow-up Period). The total study period was increased to 53 months.
- Specific conditions under which subjects in Arm B could receive retreatment with pembrolizumab with or without lenvatinib, referred to as the Second Course Phase, after discontinuation or completion of pembrolizumab in this study were added.
- 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.
- Exclusion Criterion 28 was added to exclude subjects who had had an allogenic tissue/solid organ transplant in accordance with current pembrolizumab label.
- Management of proteinuria section was updated to include to clarify that lenvatinib/sunitinib must be discontinued in the event of nephrotic syndrome, to align with guidance in the current lenvatinib global investigator brochure (IB).
- Two interim analyses were added:
  - 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.
  - A planned interim analysis of OS was added to be performed at the time of the primary analysis for PFS.
- For the primary analysis of PFS, α was decreased to 0.0499 for all comparisons, due to the addition of an interim analysis to which an α of 0.0001 was allocated.
- For the multiplicity adjustment, the P value thresholds for the primary analysis of PFS were changed because of the addition of an interim analysis.

Amendment 05 (19 Dec 2018)

- Removed the second course retreatment phase option for pembrolizumab at the assessors' request following the EU member states Voluntary Harmonisation Procedure regulatory authority review.
- Updated interim analysis of ORR and DOR to clarify that the results may be considered for an early submission in regions outside of EMA jurisdiction.

Amendment 06 (10 Sep 2019)

- Added of interim analysis of PFS and ORR

- Added of interim analysis of OS
- Updated multiplicity adjustment strategy for efficacy

Amendment 07 (06 Aug 2020)

- Removal of the exploratory objective to assess PFS using immune-related RECIST in subjects treated with lenvatinib in combination with pembrolizumab

Protocol deviations

Overall, the rate of major protocol deviations was low, and the incidence and nature of the protocol deviations were balanced across the treatment arms; therefore, there was no impact on the overall conclusions of the study. The categories for the major protocol deviations are summarized below.

Table 15 Summary of Major Protocol Deviations - FAS

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.

Of the major protocol deviations described above, 1 subject in the sunitinib arm, who missed more than 1 consecutive tumour assessment scans leading to censoring of PFS event per IIR, was associated with coronavirus 19 (COVID-19).

Site Closure Due to Non-Compliance:

Site 2906 was initiated on 29 May 2017 and enrolled a total of 11 subjects. Due to significant compliance issues, the enrollment was halted on 16 April 2018 and alternative arrangements for the care of 4 ongoing subjects was put in place. A total of 3 subjects (2 with major protocol deviations and 1 who discontinued the study due to subject choice before receiving study drug) from this site were excluded from the PP analysis set; no other sensitivity analysis was considered necessary.

Baseline data

Demographic and Other Baseline Characteristics

Baseline demographics were generally balanced across the treatment arms. Most subjects were male, white, overweight with a KPS score ≥80 at study entry. Overall, the age of subjects ranged from 29 to 88 years, with a median age of 62.0 years.

Table 16 Demographic and Baseline Characteristics FAS

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 (%)				

Category	Lenvatinib + Everolimus (N=357)	Lenvatinib + Pembrolizumab (N=355)	Sunitinib (N=357)	Total (N=1069)
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.

Disease History and Characteristics

Table 17 Disease History and Characteristics at Study Entry – FAS

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)

Parameter	Lenvatinib + Everolimus (N=357)	Lenvatinib + Pembrolizumab (N=355)	Sunitinib (N=357)	Total (N=1069)
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.

Overall, 53.1% of subjects had Stage IV disease at initial diagnosis. Most subjects had metastatic disease at study entry, with predominantly 2 metastatic organs/sites (37.6%); the most common metastatic site at baseline was lung (67.8%). Subject randomization was stratified by MSKCC prognostic group; most subjects (63.8%) were in the intermediate risk prognostic group. International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk group was derived programmatically and was not a stratification factor; most subjects (55.8%) were in the intermediate risk group, and there was a numerically higher proportion of subjects in the IMDC favourable risk group in the sunitinib arm. Overall, tumours were PD-L1 positive for 342 subjects (32.0%) and PD-L1 negative for 333 subjects (31.2%), while PD-L1 status was not available for 394 subjects (36.9%).

Prior Therapy

None of the subjects enrolled had received prior systemic anticancer therapy for RCC. The proportion of subjects who had a prior nephrectomy and those who received prior radiotherapy was balanced across the treatment arms. Overall, most subjects (74.6%) had undergone prior nephrectomy and 12.5% of subjects had received prior radiotherapy.

Numbers analysed

The full analysis set (FAS) was the primary analysis set used for efficacy analyses and the safety set was used for the safety analyses. The FAS consisted of 355 subjects randomly assigned to lenvatinib plus pembrolizumab, 357 to lenvatinib plus everolimus, and 357 to sunitinib. In total, 22 of these subjects did not receive study drug: 3 in the lenvatinib plus pembrolizumab arm, 2 in the lenvatinib plus everolimus arm, and 17 in the sunitinib arm.

Therefore, the Safety Analysis Set included 352 subjects treated with lenvatinib plus pembrolizumab, 355 subjects treated with lenvatinib plus everolimus, and 340 subjects treated with sunitinib.

Table 18 Analysis sets

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.

Treatment duration

Table 19 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

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

Primary objective: 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]). The P value was less than the pre specified P value boundary of 0.0411 and the null hypothesis was rejected. 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.

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 20 Progression-Free Survival at IA3 – Independent Imaging Review

	Lenvatinib + Pembrolizumab (N = 355)	Sunitinib (N = 357)
Subjects with Events, n (%)	160 (45.1)	205 (57.4)
Progressive Disease	145 (40.8)	196 (54.9)
Death	15 (4.2)	9 (2.5)
Censored, n (%)	195 (54.9)	152 (42.6)
No Baseline Tumor Assessment	0 (0.0)	1 (0.3)
No Adequate Postbaseline Tumor Assessment	6 (1.7)	22 (6.2)
No Progression and Alive at the Time of Data Cutoff	146 (41.1)	52 (14.6)
New Anticancer Treatment Started	37 (10.4)	71 (19.9)
Death or Progression after More than One Missing Assessment	6 (1.7)	6 (1.7)
Progression-Free Survival (months)[a]		
Median (95% CI)	23.9 (20.8, 27.7)	9.2 (6.0, 11.0)
Q1 (95% CI)	10.9 (8.7, 12.3)	4.2 (3.7, 5.5)
Q3 (95% CI)	NE (NE, NE)	22.1 (18.2, 25.8)
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]	0.39 (0.32, 0.49)	
Stratified Log-rank Test P value[c]	<0.0001	
Progression-Free Survival Rate (%) (95% CI) at[d]		
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)
Follow-Up Time for Progression-Free Survival (months)[a,e]		
Median (95% CI)	22.3 (21.1, 25.6)	16.6 (13.1, 18.5)
Q1 (95% CI)	14.9 (13.1, 16.6)	5.5 (4.9, 7.4)
Q3 (95% CI)	27.6 (27.1, 29.3)	27.5 (25.7, 29.4)

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, RECIST = Response Evaluation Criteria in Solid Tumours.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: Progression-free survival rate and 95% CIs are calculated using Kaplan-Meier product-limit method and Greenwood Formula.e: Estimates for progression-free survival follow-up time are calculated in the same way as the Kaplan-Meier estimate of PFS but with the meaning of 'censor' and 'event' status indicator reversed.

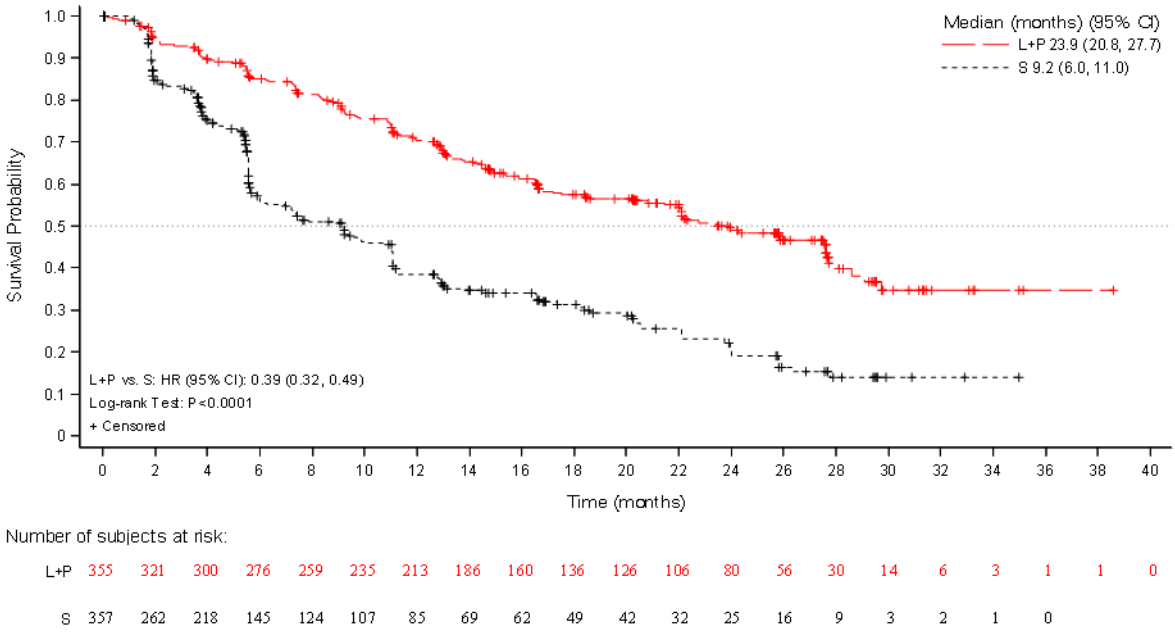


Figure 17 Kaplan-Meier Plot of Progression-Free Survival by Independent Imaging Review Using RECIST 1.1 – FAS

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 Tumours, 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.

Table 21 Progression-Free Survival at IA3 Treating All PD/Death as Events per EMA Guidance – Independent Imaging Review

	Lenvatinib + Pembrolizumab (N = 355)	Sunitinib (N = 357)
Subjects with Events, n (%)	180 (50.7)	232 (65.0)
Progressive Disease	149 (42.0)	200 (56.0)
Death	31 (8.7)	32 (9.0)
Censored, n (%)	175 (49.3)	125 (35.0)
No Baseline Tumor Assessment	0 (0.0)	1 (0.3)
No Adequate Postbaseline Tumor Assessment	6 (1.7)	23 (6.4)
No Progression and Alive at the Time of Data Cutoff	169 (47.6)	101 (28.3)
Progression-Free Survival (months)[a]		
Median (95% CI)	22.1 (18.4, 25.9)	9.2 (7.0, 11.0)
Q1 (95% CI)	9.7 (8.5, 11.9)	4.2 (3.7, 5.5)
Q3 (95% CI)	NE (31.9, NE)	20.5 (17.6, 24.0)
Stratified Hazard Ratio (95% CI)[b,c]	0.41 (0.33, 0.50)	
Stratified Log-rank Test P value[c]	<0.0001	
Progression-Free Survival Rate (%) (95% CI) at[d]		
6 Months	84.7 (80.4, 88.1)	57.6 (51.9, 62.9)
12 Months	69.9 (64.7, 74.5)	38.5 (32.9, 44.1)
18 Months	56.4 (50.7, 61.7)	30.3 (24.8, 35.9)
24 Months	46.1 (40.1, 51.9)	19.3 (14.3, 25.0)
Follow-Up Time for Progression-Free Survival (months)[a,e]		
Median (95% CI)	25.6 (23.5, 25.8)	18.7 (16.6, 25.7)
Q1 (95% CI)	16.6 (16.2, 20.2)	10.9 (5.9, 13.0)
Q3 (95% CI)	28.1 (27.6, 29.5)	27.9 (26.9, 29.5)

Percentages are based on the total number of subjects in the Full Analysis Set within the relevant treatment group. Per EMA guidance, the actual reported date of progression by independent imaging review or death regardless of missing assessments, or use of new anti-cancer therapy were used for analysis. NE = Not Estimable; PD = Progressive Disease. 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 Hazards 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: Progression-Free survival rate and 95% CIs are calculated using Kaplan-Meier product-limit method and Greenwood Formula.e: Estimates for PFS follow-up time are calculated in the same way as the Kaplan-Meier estimate of PFS but with the meaning of 'censor' and 'event' status indicator reversed.

Secondary objective: 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 (see below).

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;. OS rates at Months 12, 18, and 24 were higher in the lenvatinib plus pembrolizumab arm (91.4%, 87.1%, and 79.2%, respectively) than the sunitinib arm (80.2%, 74.4%, and 70.4%, respectively).

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.

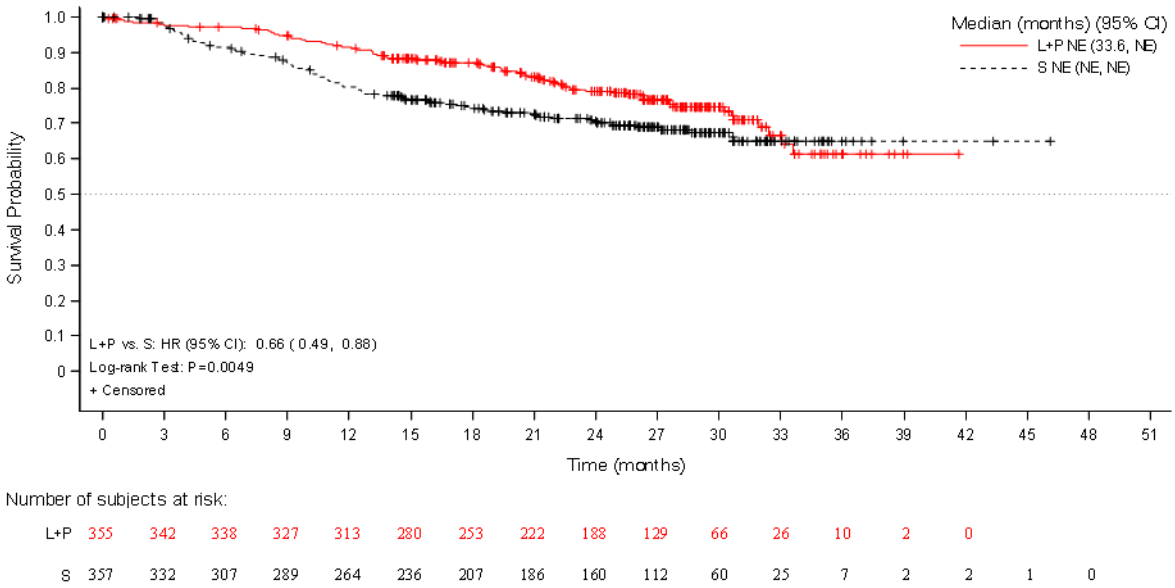
Table 22 Overall Survival at IA3 – Full Analysis Set

	Lenvatinib + Pembrolizumab (N = 355)	Sunitinib (N = 357)
Death, n (%)	80 (22.5)	101 (28.3)

	Lenvatinib + Pembrolizumab (N = 355)	Sunitinib (N = 357)
Censored, n (%)	275 (77.5)	256 (71.7)
Lost to Follow-Up	7 (2.0)	6 (1.7)
Withdrawal of Consent	14 (3.9)	28 (7.8)
Alive	254 (71.5)	222 (62.2)
Overall Survival (months)[a]		
Median (95% CI)	NE (33.6, NE)	NE (NE, NE)
Q1 (95% CI)	27.8 (22.9, 32.4)	17.6 (12.4, 24.0)
Q3 (95% CI)	NE (NE, NE)	NE (NE, NE)
Lenvatinib + Pembrolizumab vs Sunitinib		
Stratified Hazard Ratio (95% CI)[b,c]	0.66 (0.49, 0.88)	
Stratified Log-rank Test P value[c]	0.0049	
Overall Survival Rate (%) (95% CI) at[d]		
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)
36 Months	61.2 (49.8, 70.8)	65.0 (58.2, 70.9)
Duration of Survival Follow-Up (months)[a,e]		
Median (95% CI)	26.7 (25.9, 27.4)	26.3 (25.4, 27.2)
Q1 (95% CI)	21.0 (19.0, 22.3)	19.3 (16.9, 21.3)
Q3 (95% CI)	30.0 (29.1, 30.8)	30.0 (29.1, 30.9)

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.

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 18 Kaplan-Meier Plot of Overall Survival – Full Analysis Set

Objective Response Rate and Duration of Response

Table 23 Summary of Objective Response When Confirmation of Response Required at IA3 – Independent Imaging Review, per RECIST 1.1 – FAS

	Lenvatinib + Pembrolizumab (N = 355)	Sunitinib (N = 357)
Best Overall Response, n (%)		
Complete Response (CR)	57 (16.1)	15 (4.2)
Partial Response (PR)	195 (54.9)	114 (31.9)
Stable Disease (SD)	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 Postbaseline Tumor Assessment	12 (3.4)	38 (10.6)
>=1 Lesions NE	1 (0.3)	2 (0.6)
Early SD (SD < 7 Weeks)	3 (0.8)	1 (0.3)
Objective Response Rate (CR + PR), n (%)	252 (71.0)	129 (36.1)
95% CI[a]	(66.3, 75.7)	(31.2, 41.1)
Lenvatinib + Pembrolizumab vs Sunitinib		
Difference (%) (95% CI)[a]	34.9 (28.0, 41.7)	
Odds Ratio (95% CI)[b]	4.35 (3.16, 5.97)	
P value[b]	<0.0001	
Time to First Objective Response (months)		
Subjects with Objective Response		
n	252	129
Mean (SD)	3.30 (2.635)	3.36 (2.600)
Median	1.94	1.94
Q1, Q3	1.87, 3.75	1.87, 3.71
Min, Max	1.41, 18.50	1.61, 16.62
Duration of Objective Response (months)[c]		
Subjects with Objective Response		
n	252	129
Median (95% CI)	25.8 (22.1, 27.9)	14.6 (9.4, 16.7)
Q1 (95% CI)	12.8 (10.1, 14.7)	7.4 (3.8, 9.1)
Q3 (95% CI)	NE (NE, NE)	24.0 (19.0, NE)
Range (Min, Max)	(1.64+, 36.76+)	(1.64+, 33.15+)

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. Stable disease must be ≥7 weeks after randomization. Durable stable disease must be ≥23 weeks after randomization. Time to first objective response (months) = (date of first objective response – date of randomization + 1) × 12 / 365.25, for subjects with best overall response of CR/PR. It is censored for subjects without best overall response of CR/PR. Duration of objective response (months) = '(Date of PD/Death or Censor Date – Date of First Objective Response + 1) × 12 / 365.25, for subjects with objective response. CI = confidence interval, CR = complete response, IxRS = interactive voice and web response system, NE = not estimable, PD = progressive disease, PR = partial response, Q = quartile, RECIST = Response Evaluation Criteria in Solid Tumours, SD = standard deviation.a: 95% CI is constructed using the method of Normal Approximation.b: Odds Ratio and nominal P value are calculated using the Cochran–Mantel–Haenszel method, stratified by IxRS stratification factors.c: Quartiles are estimated by Kaplan–Meier method, and the 95% CIs are estimated with a generalized Brookmeyer and Crowley method.+: indicates the time is censored.

Confirmed ORR per RECIST 1.1, as assessed by IIR in the lenvatinib plus pembrolizumab arm was higher the ORR in the sunitinib arm (71.0% and 36.1%, respectively).

The odds ratio (OR) was 4.35 (95% CI: 3.16, 5.97; nominal P<0.0001) in favor of lenvatinib plus pembrolizumab. These data were consistent with the final analysis of ORR performed at IA2 (DCO 15 Nov 2019). The proportion of subjects who achieved a confirmed CR from lenvatinib plus pembrolizumab was approximately four times higher than from sunitinib (16.1% and 4.2%, respectively).

Responses occurred early, with a median time to first objective response in the lenvatinib plus pembrolizumab arm of 1.94 months.

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.

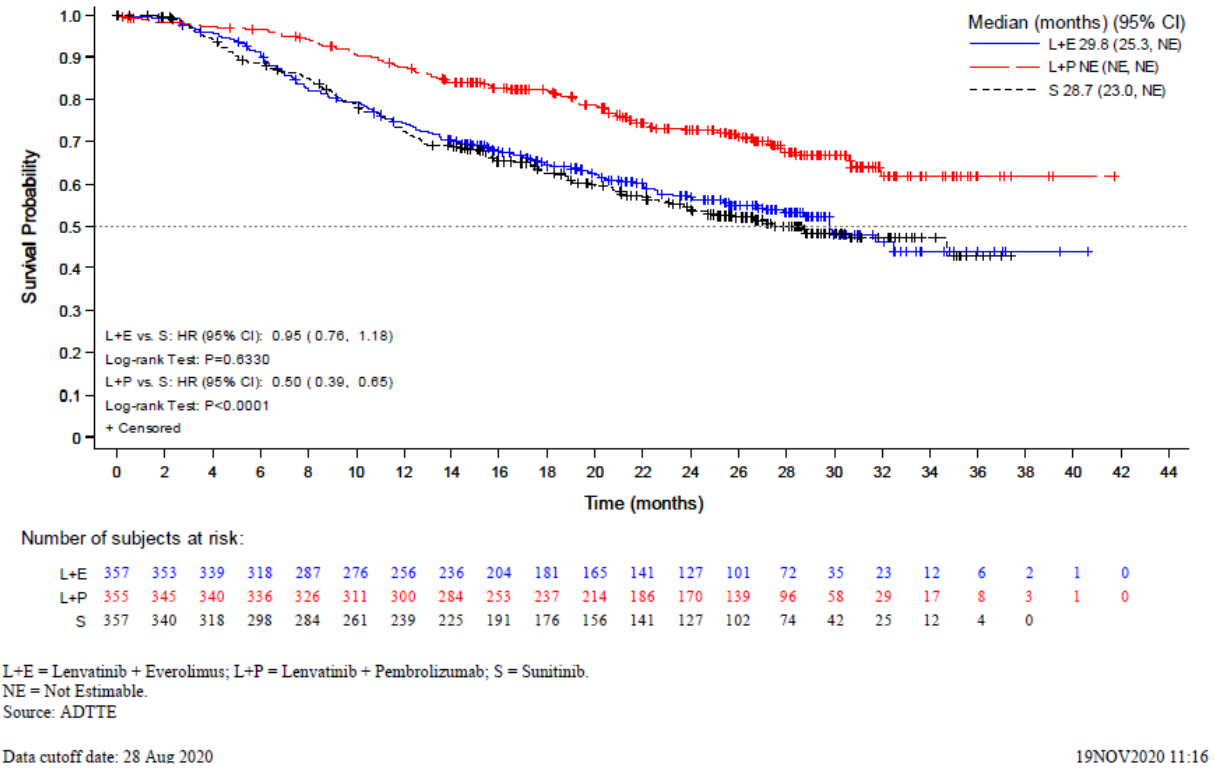
Progression-Free Survival on Next-Line of Therapy (PFS2)

Table 24 Summary of Anticancer Medications During Survival Follow-Up at IA3 – Full Analysis Set

	Lenvatinib + Pembrolizumab (N = 355) n (%)	Sunitinib (N = 357) n (%)
Subjects Started Study Treatment	352 (99.2)	340 (95.2)
Subjects Discontinued Study Treatment	210 (59.2)	273 (76.5)
Subjects Received Any Subsequent Systemic Anticancer Medication during Survival Follow-Up by Type	117 (33.0)	206 (57.7)
Anti-VEGF Therapy	108 (30.4)	120 (33.6)
PD-1/PD-L1 Checkpoint Inhibitor[a]	29 (8.2)	154 (43.1)
MTOR Inhibitor	6 (1.7)	17 (4.8)
CTLA-4 Inhibitor[a]	6 (1.7)	18 (5.0)
Other	12 (3.4)	20 (5.6)
Duration of First Anticancer Regimen during Survival Follow-Up (months)		
n	116	200
Mean (SD)	6.84 (5.953)	8.65 (7.281)
Median	5.16	6.82
Q1, Q3	2.10, 9.53	2.87, 13.52
Min, Max	0.10, 30.23	0.03, 30.72

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. Subjects with 2 or more anticancer medications may be counted in multiple categories.Medications were coded using WHO Drug Dictionary Version WHODDMAR20B3G.
a: Mapping/coding is based on verbatim = XmAb20717, which is a bi-specific antibody for PD-1 and CTLA-4.

CTLA-4 = cytotoxic T-lymphocyte-associated protein 4, Max = maximum, Min = minimum, MTOR = mammalian target of rapamycin, NA = not applicable, PD-1/PD-L1 = programmed cell death/programmed cell death ligand-1, Q = quartile, SD = standard deviation, VEGF = vascular endothelial growth factor, WHO = World Health Organization.



L+E = Lenvatinib + Everolimus; L+P = Lenvatinib + Pembrolizumab; S = Sunitinib.
NE = Not Estimable.
Source: ADTTE

Data cutoff date: 28 Aug 2020 19NOV2020 11:16

Figure 19 Kaplan-Meier Plot of Progression-Free Survival on Next-Line of Therapy (PFS2) Full Analysis Set

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

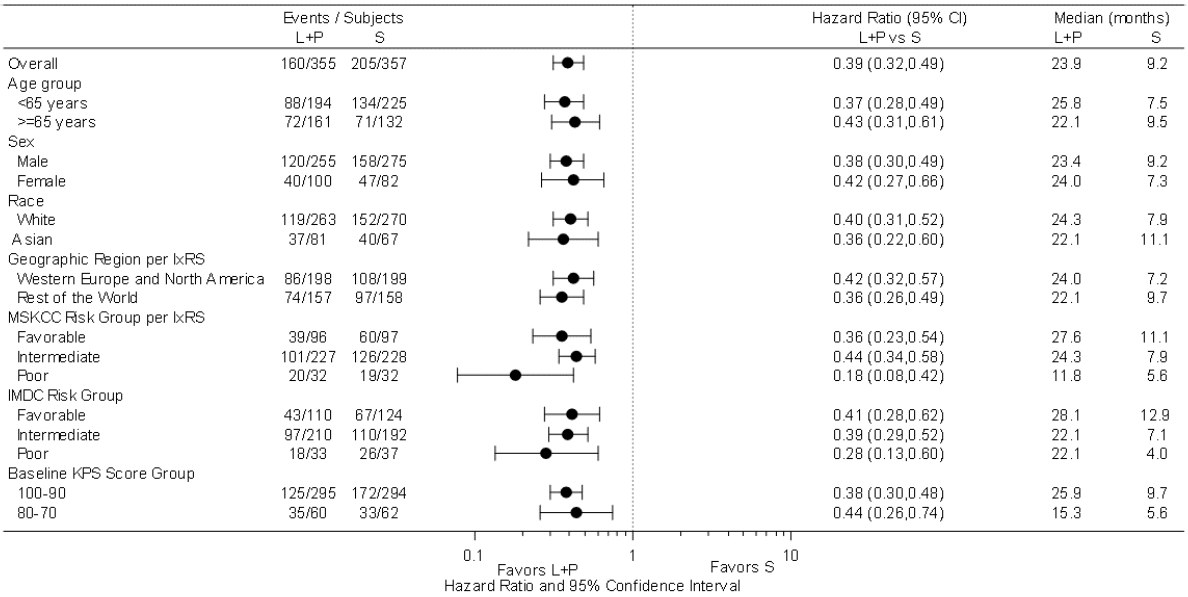
With Cancer–Core 30 (EORTC QLQ-C30), and the EQ-5D-3L with the associated Visual Analogue Scale (EQ-VAS).

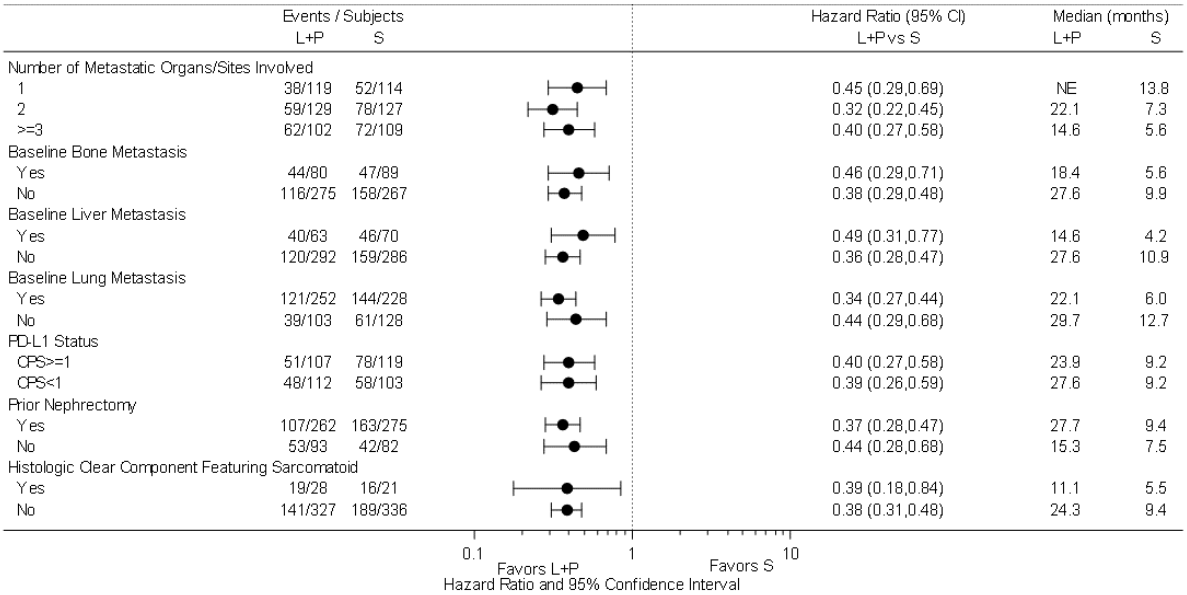
With a mean follow-up time of 46 weeks from baseline, the longitudinal analysis of changes from baseline favored lenvatinib plus pembrolizumab for many scales, and the difference was significant for the EORTC QLQ-C30 physical functioning scale as well as for symptoms of fatigue, dyspnea, and constipation. 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 with 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), diarrhea (6 weeks longer).

Ancillary analyses

Subgroup analyses

Progression free survival by subgroups



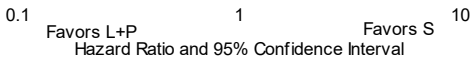


Data cutoff date: 28 Aug 2020. CPS = combined positive score, CSR = clinical study report, IMDC = International Metastatic Renal Cell Carcinoma Database Consortium, IxRS = interactive voice and web response system, KPS = Karnofsky Performance Status, MSKCC = Memorial Sloan-Kettering Cancer Center, L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

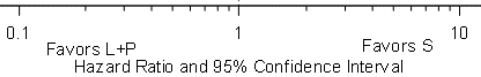
Figure 20 Forest Plot of Hazard Ratio for Lenvatinib plus Pembrolizumab vs Sunitinib in Progression-Free Survival Based on Independent Imaging Review, per RECIST 1.1 – FAS

Overall survival by subgroups

	Events / Subjects L + P	Events / Subjects S	Hazard Ratio (95% CI) L+P vs S	Median (months) L+P	Median (months) S
Number of Metastatic Organs/Sites Involved					
1	15/119	18/114	0.75 (0.38,1.50)	NE	NE
2	22/129	37/127	0.46 (0.27,0.78)	NE	NE
>=3	43/102	44/109	0.76 (0.49,1.17)	32.4	30.6
Baseline Bone Metastasis					
Yes	29/80	39/89	0.62 (0.38,1.02)	32.4	28.6
No	51/275	62/267	0.69 (0.47,1.00)	NE	NE
Baseline Liver Metastasis					
Yes	25/63	28/70	0.89 (0.51,1.57)	31.9	30.6
No	55/292	73/286	0.58 (0.41,0.83)	NE	NE
Baseline Lung Metastasis					
Yes	65/252	68/228	0.63 (0.45,0.89)	NE	NE
No	15/103	33/128	0.58 (0.31,1.07)	NE	NE
PD-L1 Status					
CPS>=1	28/107	36/119	0.76 (0.46,1.27)	NE	NE
CPS<1	21/112	31/103	0.50 (0.28,0.89)	NE	NE
Prior Nephrectomy					
Yes	50/262	66/275	0.71 (0.49,1.03)	NE	NE
No	30/93	35/82	0.52 (0.31,0.86)	33.1	24.0
Histologic Clear Component Featuring Sarcomatoid					
Yes	9/28	7/21	0.91 (0.32,2.58)	NE	NE
No	71/327	94/336	0.64 (0.47,0.87)	NE	NE



	Events / Subjects L + P	Events / Subjects S	Hazard Ratio (95% CI) L+P vs S	Median (months) L+P	Median (months) S
Overall	80/355	101/357	0.66 (0.49,0.88)	NE	NE
Age group					
<65 years	41/194	57/225	0.63 (0.41,0.95)	NE	NE
>=65 years	39/161	44/132	0.61 (0.40,0.95)	NE	NE
Sex					
Male	59/255	71/275	0.70 (0.49,0.99)	NE	NE
Female	21/100	30/82	0.54 (0.30,0.94)	NE	NE
Race					
White	63/263	80/270	0.67 (0.48,0.93)	NE	NE
Asian	15/81	13/67	0.65 (0.28,1.54)	NE	NE
Geographic Region per IxRS					
Western Europe and North America	46/198	57/199	0.68 (0.46,1.00)	NE	NE
Rest of the World	34/157	44/158	0.63 (0.40,0.99)	NE	NE
MSKCC Risk Group per IxRS					
Favorable	11/96	13/97	0.86 (0.38,1.92)	NE	NE
Intermediate	57/227	73/228	0.66 (0.47,0.94)	NE	NE
Poor	12/32	15/32	0.50 (0.23,1.08)	NE	16.5
IMDC Risk Group					
Favorable	14/110	15/124	1.15 (0.55,2.40)	NE	NE
Intermediate	56/210	60/192	0.72 (0.50,1.05)	NE	NE
Poor	10/33	25/37	0.30 (0.14,0.64)	NE	10.4
Baseline KPS Score Group					
100-90	62/295	72/294	0.73 (0.52,1.03)	NE	NE
80-70	18/60	29/62	0.48 (0.26,0.87)	NE	17.9

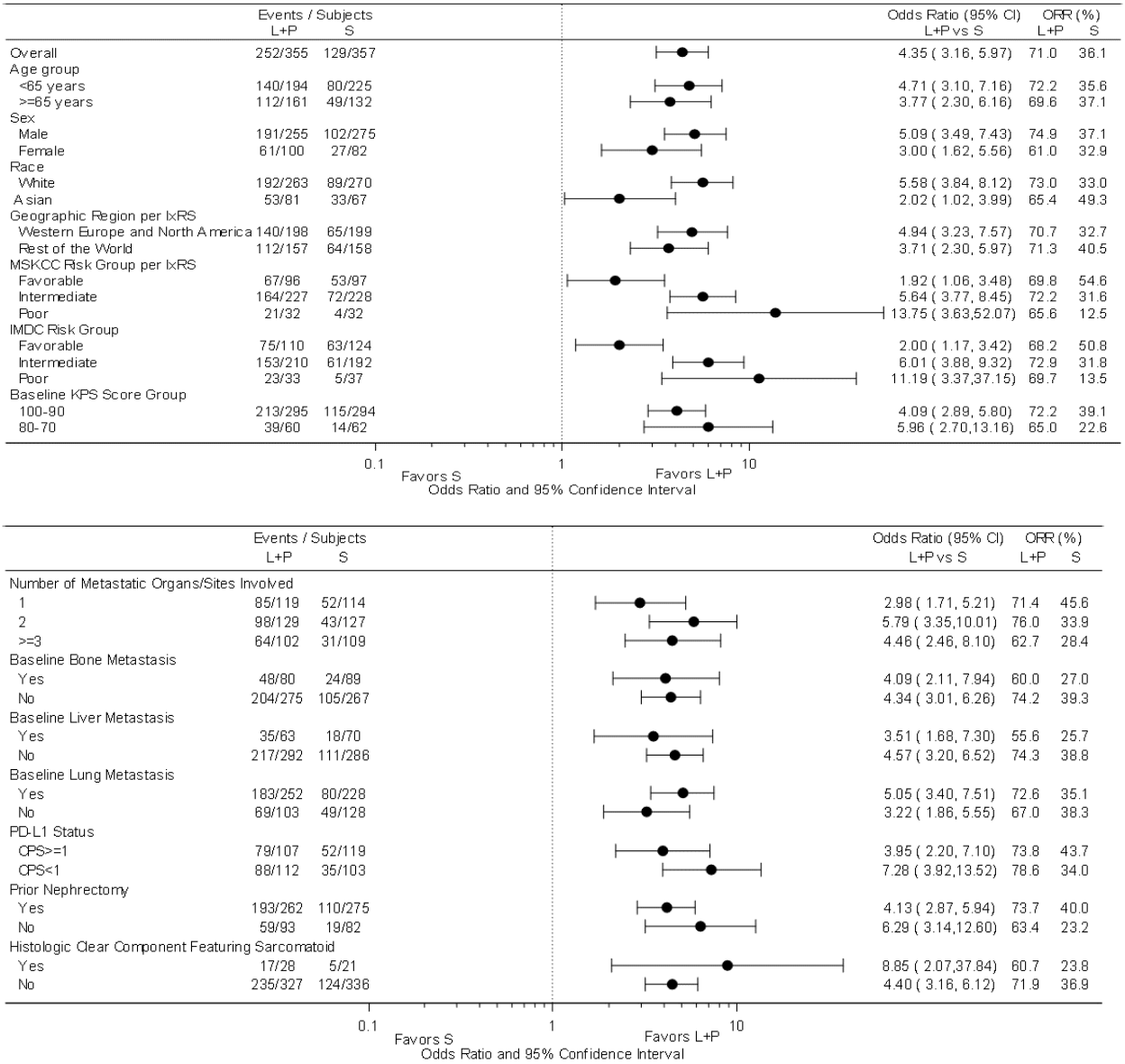


Data cutoff date: 28 Aug 2020. CPS = combined positive score, CSR = clinical study report, IMDC = International Metastatic Renal Cell Carcinoma Database Consortium, IxRS = interactive voice and web response system, KPS = Karnofsky Performance Status, MSKCC = Memorial Sloan-Kettering Cancer Center, L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

Figure 21 Forest Plot of Hazard Ratio for Lenvatinib plus Pembrolizumab vs Sunitinib in Overall Survival – FAS

Objective Response Rate by Subgroups

Table 25 Forest Plot of Odds Ratio for Lenvatinib plus Pembrolizumab vs Sunitinib in Objective Response Rate Based on Independent Imaging Review, per RECIST 1.1 – FAS



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, L = lenvatinib, MSKCC = Memorial Sloan-Kettering Cancer Center, ORR = objective response rate, P = pembrolizumab, PD-L1 = programmed cell death ligand-1, RECIST 1.1 = Response Evaluation Criteria in Solid Tumours, 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.

UPDATED DATA

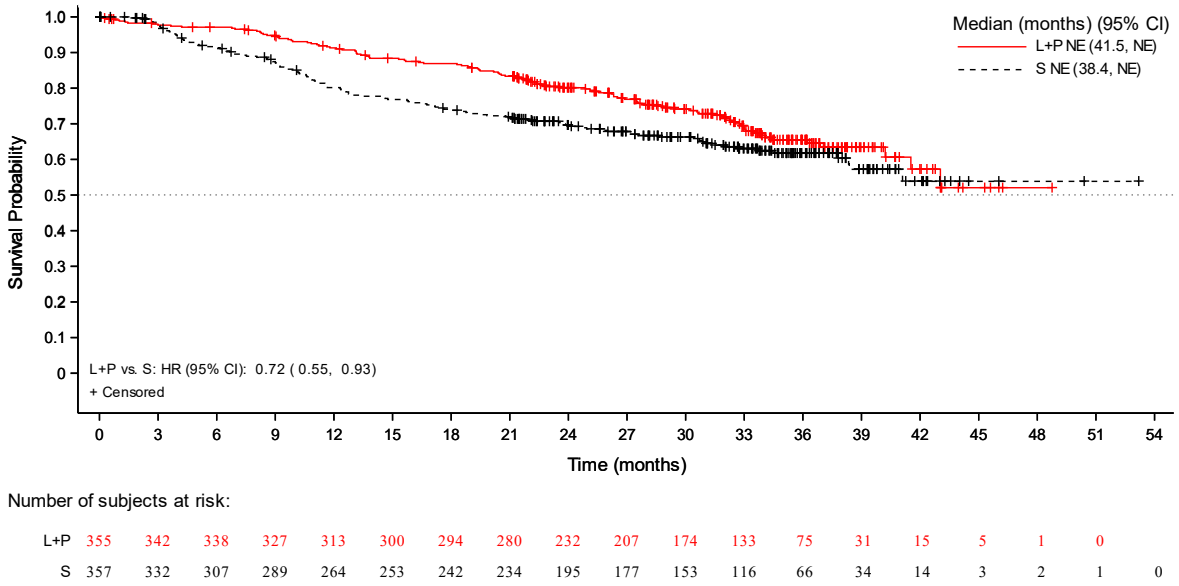
Study 307/KEYNOTE-581 OS follow-up report for the lenvatinib plus pembrolizumab and sunitinib arms, with a data cutoff (DCO) of 31 Mar 2021 and a median duration of OS follow-up of approximately 33

months in each arm (approximately 7 months additional follow up from the DCO for the primary analysis [interim analysis 3, IA3] on 28 Aug 2020) has been provided by MAH.

Table 26 Summary of Overall Survival at Primary Analysis (DCO 28 Aug 2020) and OS Follow-Up Analysis (DCO 31 Mar 2021)

	Primary Analysis		**OS Follow-Up Analysis**	
	Lenvatinib + Pembrolizumab (N=355)	**Sunitinib (N=357)**	**Lenvatinib + Pembrolizumab (N=355)**	**Sunitinib (N=357)**
Deaths, n (%)	80 (22.5)	101 (28.3)	105 (29.6)	122 (34.2)
Median OS (months)	NR	NR	NR	NR
95% CI for Median OS	(33.6, NE)[a]	(NE, NE)[a]	(41.5, NE)	(38.4, NE)
Lenvatinib + Pembrolizumab vs Sunitinib				
Stratified HR (95% CI)[a,b]	0.66 (0.49, 0.88)		0.72 (0.55, 0.93)	
Stratified Log-rank Test *P* value[c]	0.0049		NA	
OS Rate (95% CI)[c] at				
12 months	91.4 (87.9, 93.9)	80.2 (75.5, 84.1)	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)	86.9 (82.9, 90.1)	73.8 (68.7, 78.2)
24 months	79.2 (74.1, 83.3)	70.4 (65.0, 75.2)	80.2 (75.5, 84.1)	69.7 (64.4, 74.3)
Median Follow-Up Time for OS (months; 95% CI)	26.7 (25.9, 27.4)	26.3 (25.4, 27.2)	33.7 (32.8, 34.4)	33.4 (32.5, 34.1)

NA = not applicable, NE = not evaluable, NR = not reached, OS = overall survival a: Hazard ratio is based on a Cox Proportional Hazards Model including treatment group as a factor; Efron method is used for ties.
b: 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.
c: Overall survival rate and 95% CIs are calculated using Kaplan-Meier product-limit method and Greenwood Formula. Data cutoff date: 28 Aug 2020 for Study 307 Primary Analysis and 31 Mar 2021 for OS Follow-up.

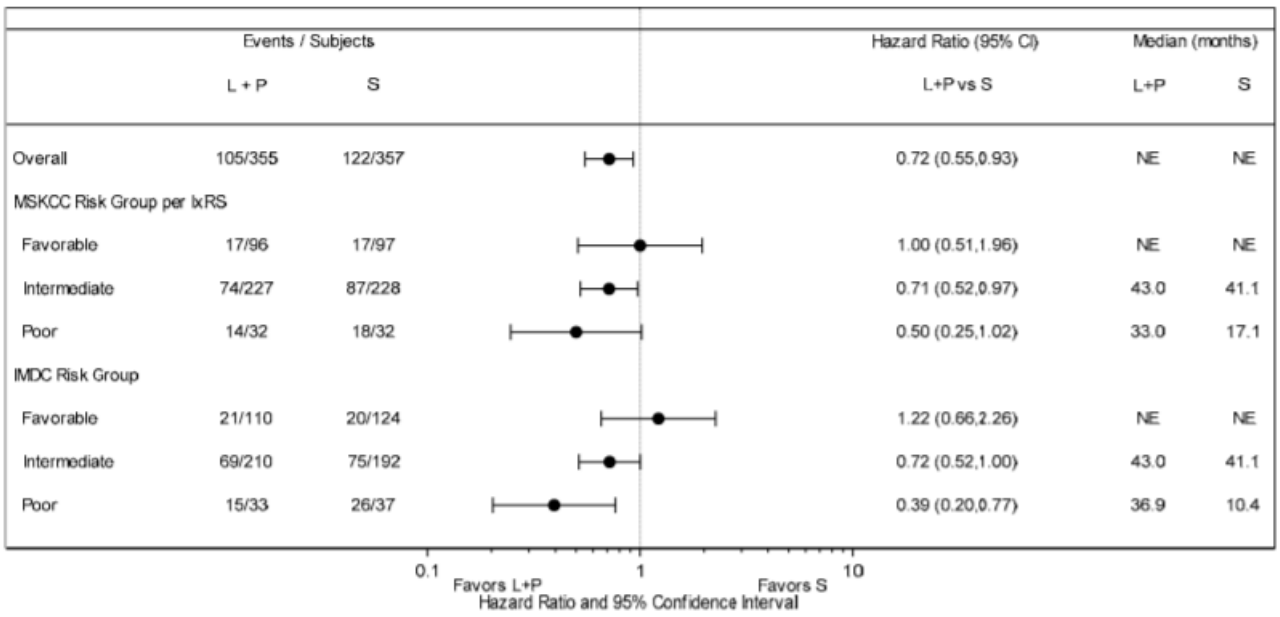


Number of subjects at risk:

L+P	355	342	338	327	313	300	294	280	232	207	174	133	75	31	15	5	1	0
S	357	332	307	289	264	253	242	234	195	177	153	116	66	34	14	3	2	1	0

Data cutoff date: 31 Mar 2021; Full analysis set

Figure 22 Kaplan-Meier Plot of Overall Survival at Follow-up Analysis



Data cutoff date: 31 March 2021.

If a stratification factor is itself a subgroup, this factor is removed from the stratified analysis. The subgroups/strata with sample size less than 5% of the treatment group are not displayed.

IMDC = International Metastatic Renal Cell Carcinoma Database Consortium, IxRS = interactive voice and web response system, L+P = lenvatinib + pembrolizumab, MSKCC = Memorial Sloan-Kettering Cancer Center, NE = not estimable, S = sunitinib.

Source: ADTTE.

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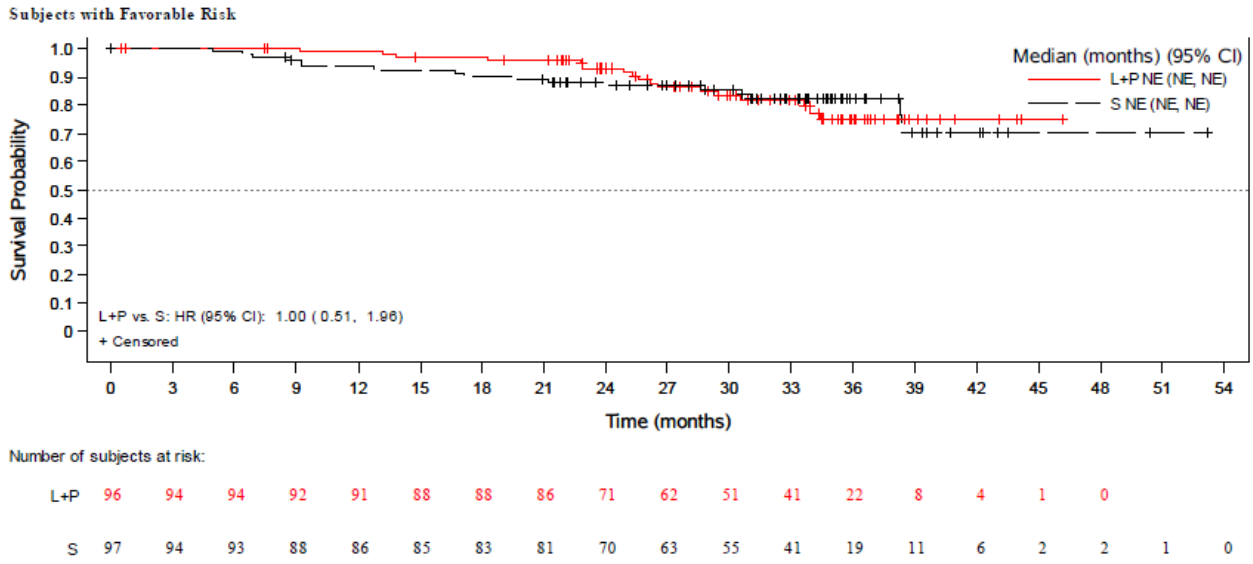
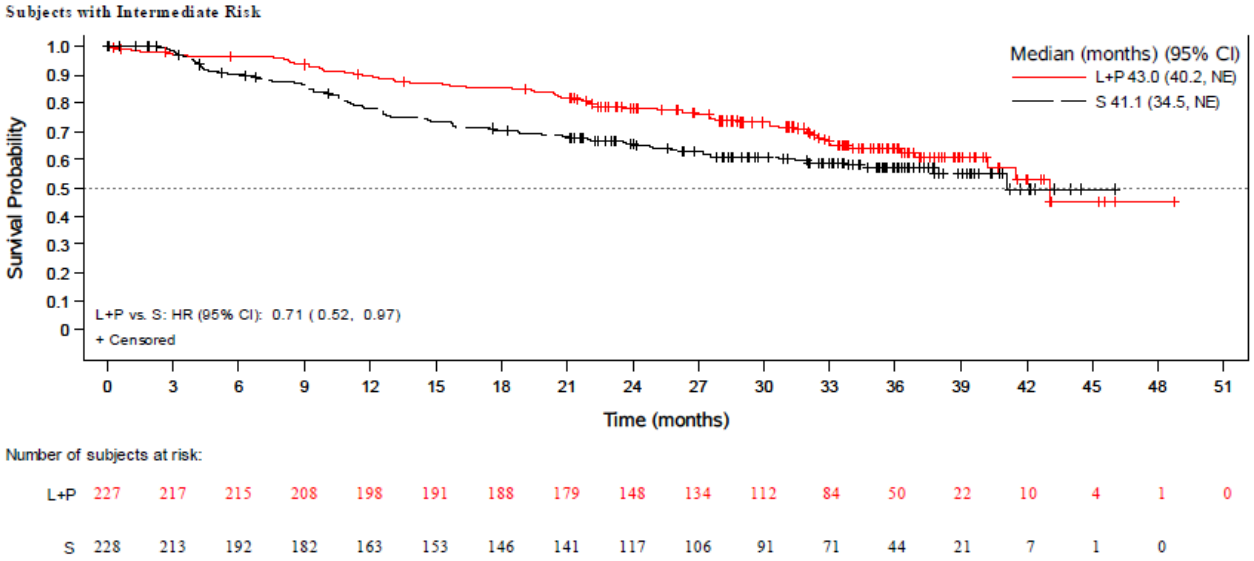
Figure 23 Forest Plot of Hazard Ratio for Lenvatinib + Pembrolizumab vs Sunitinib in Overall Survival – Full Analysis Set



L+P = Lenvatinib + Pembrolizumab; S = Sunitinib.
NE = Not Estimable.
If a stratification factor is itself a subgroup, this factor is removed from the stratified analysis.
Quartiles are estimated by Kaplan-Meier method, and the 95% CIs are estimated with a generalized Brookmeyer and Crowley method.
Hazard ratio is based on a Cox Proportional Hazards Model including treatment group as a factor; Efron method is used for ties and 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.
Source: ADTTE

Figure 24 Kaplan-Meier Plot of Overall Survival as of Data Cutoff Date on 31 March 2021 Full Analysis Set - Subjects with MSKCC Favorable Risk at Baseline per IxRSSummary of main study(ies)

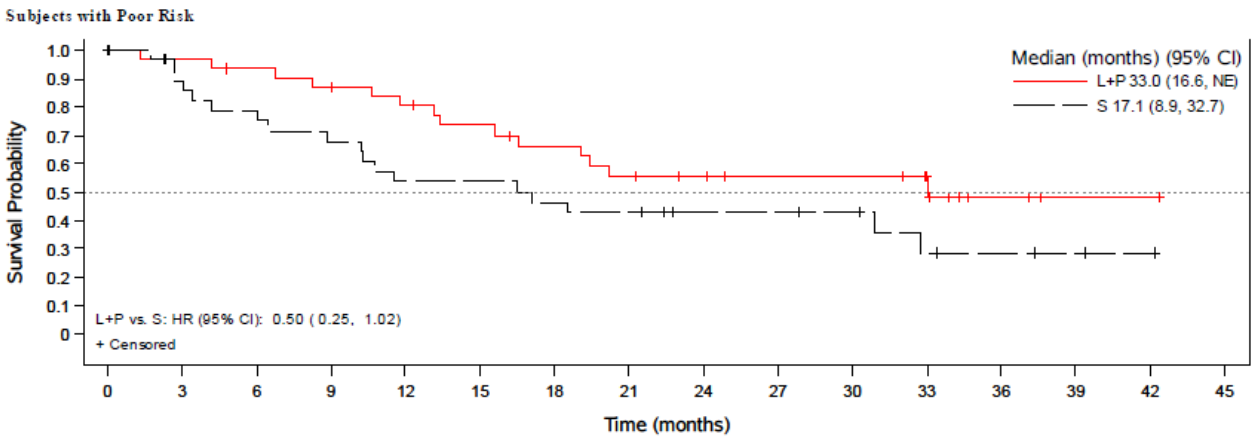


Number of subjects at risk:

L+P	227	217	215	208	198	191	188	179	148	134	112	84	50	22	10	4	1	0
S	228	213	192	182	163	153	146	141	117	106	91	71	44	21	7	1	0	

L+P = Lenvatinib + Pembrolizumab; S = Sunitinib.
NE = Not Estimable.
If a stratification factor is itself a subgroup, this factor is removed from the stratified analysis.
Quartiles are estimated by Kaplan-Meier method, and the 95% CIs are estimated with a generalized Brookmeyer and Crowley method.
Hazard ratio is based on a Cox Proportional Hazards Model including treatment group as a factor; Efron method is used for ties and 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.
Source: ADTTE

Figure 25 Kaplan-Meier Plot of Overall Survival as of Data Cutoff Date on 31 March 2021Full Analysis Set - Subjects with MSKCC Intermediate Risk at Baseline per IxRS

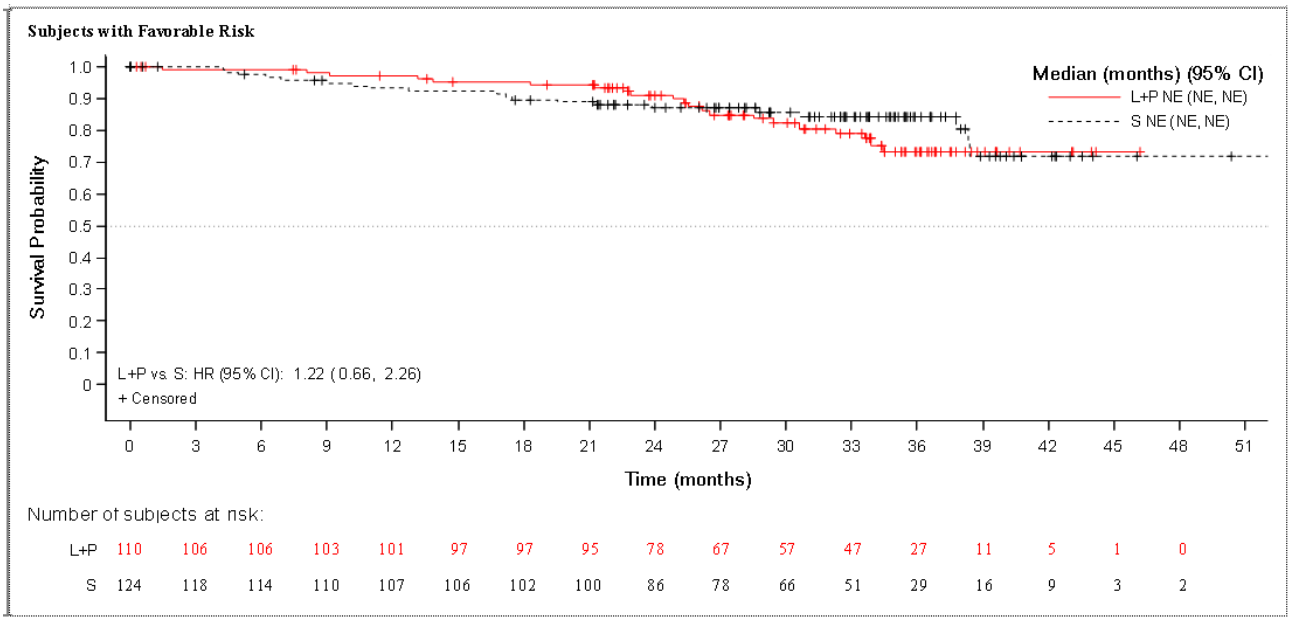


Number of subjects at risk:

L+P	32	31	29	27	24	21	18	15	13	11	11	8	3	1	1	0	
S	32	25	22	19	15	15	13	12	8	8	7	4	3	2	1	0	

L+P = Lenvatinib + Pembrolizumab; S = Sunitinib.
NE = Not Estimable.
If a stratification factor is itself a subgroup, this factor is removed from the stratified analysis.
Quartiles are estimated by Kaplan-Meier method, and the 95% CIs are estimated with a generalized Brookmeyer and Crowley method.
Hazard ratio is based on a Cox Proportional Hazards Model including treatment group as a factor; Efron method is used for ties and 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.
Source: ADTTE

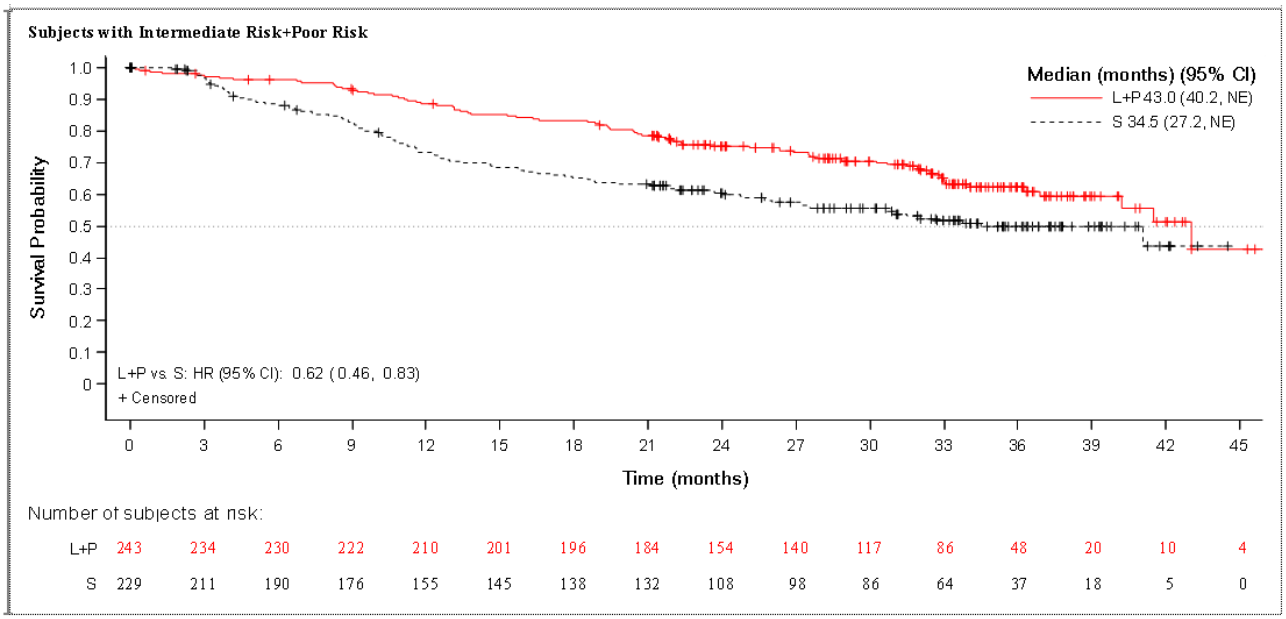
Figure 26 Kaplan-Meier Plot of Overall Survival as of Data Cutoff Date on 31 March 2021Full Analysis Set - Subjects with MSKCC Poor Risk at Baseline per IxRS



L+P = Lenvatinib + Pembrolizumab; S = Sunitinib.
Quartiles are estimated by Kaplan-Meier method, and the 95% CIs are estimated with a generalized Brookmeyer and Crowley method.
Hazard ratio is based on a Cox Proportional Hazards Model including treatment group as a factor; Efron method is used for ies. 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.

Data cutoff date: 31 Mar 2021; Full analysis set.

Figure 27 Kaplan-Meier Plot of Overall Survival - Subjects with IMDC Favorable Risk at OS Follow-Up DCO 31 March 2021



L+P = Lenvatinib + Pembrolizumab; S = Sunitinib.
Quartiles are estimated by Kaplan-Meier method, and the 95% CIs are estimated with a generalized Brookmeyer and Crowley method.
Hazard ratio is based on a Cox Proportional Hazards Model including treatment group as a factor; Efron method is used for ies. 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.

Data cutoff date: 31 Mar 2021; Full analysis set.

Figure 28 Kaplan-Meier Plot of Overall Survival - -Subjects with IMDC Intermediate/Poor Risk at OS Follow-Up DCO 31 March 20217

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable, see supportive studies.

Clinical studies in special populations

Not applicable

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).

A Multicenter, Open-label, Randomized, Phase 3 Trial to **C**ompare the Efficacy and Safety of **L**envatinib in Combination with **E**verolimus or Pembrolizumab Versus Sunitinib Alone in First-Line Treatment of Subjects with **A**dvanced **R**enal Cell Carcinoma (**CLEAR**).		
Study identifier	Study Protocol Number:	E7080-G000-307 / KEYNOTE 581
	IND Number:	124564
	EudraCT Number:	2016-000916-14
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.	

A Multicenter, Open-label, Randomized, Phase 3 Trial to **C**ompare the Efficacy and Safety of **L**envatinib in Combination with **E**verolimus or Pembrolizumab Versus Sunitinib Alone in First-Line Treatment of Subjects with **A**dvanced **R**enal Cell Carcinoma (**CLEAR**).			
	Hypothesis: ORR of lenvatinib plus pembrolizumab is superior to sunitinib alone.		
Treatment 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, update data cut-off (95% CI)[a]	NE (41.5, NE)	NE (38.4, NE)

A Multicenter, Open-label, Randomized, Phase 3 Trial to **C**ompare the Efficacy and Safety of **L**envatinib in Combination with **E**verolimus or Pembrolizumab Versus Sunitinib Alone in First-Line Treatment of Subjects with **A**dvanced **R**enal Cell Carcinoma (**CLEAR**).			
	Stratified HR vs Sunitinib (95% CI)[b,c]	0.72 (0.55, 0.93)	-
	Stratified Log-rank Test *P* value vs Sunitinib[c]	NA	-
	Overall Survival Rate, **%** (95% CI)		
	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)
	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)	-
	Odds Ratio vs Sunitinib (95% CI)[e]	4.35 (3.16, 5.97)	-
	P value vs Sunitinib[e]	<0.0001	-
	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. e.Odds Ratio and nominal P value are calculated using the Cochran–Mantel–Haenszel method, stratified by IxRS stratification factors. At the earlier pre-specified final analysis of ORR (median follow-up time of 17.3 months), statistically significant superiority was achieved for ORR comparing lenvatinib plus pembrolizumab with sunitinib (odds ratio: 3.84 [95% CI: 2.81, 5.26], P value <0.0001).		

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable, see supportive studies.

Clinical studies in special populations

Not applicable

Supportive studies

To establish the contribution of the individual components pembrolizumab and lenvantinib to the pembro+lenvatinib regimen in 1L advanced RCC, Keynote-581/Study307 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 27.

Comparison and Analyses of Results Across Studies - Assessment of the Contribution of Components

Comparison of key features of Study 307 versus Study 205 and KEYNOTE-427

A major difference in entry criteria between Study 307 and KN-427 versus Study 205 is that both Study 307 and KN-427 recruited subjects receiving 1L systemic therapy for RCC, while Study 205 enrolled subjects that had received 1 prior VEGF-targeted treatment.

Lenvatinib was administered at different doses in Study 307 and Study 205; the RP2D of lenvatinib in combination with pembrolizumab 200 mg in Study 111 (20 mg QD) is lower than the monotherapy dosage used in Study 205 (24 mg QD), however, this is unlikely to account for the difference in activity observed with the combination. Pembrolizumab was administered at a dose of 200 mg in both Study 307 and KN-427.

Table 27 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 tumour assessment	Q8W			At Week 12, Q6W until Week 54, then Q12W until EOS

	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)

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 Tumours, TL = target lesion, VEGF = vascular endothelial growth factor. a:Sunitinib was administered on a schedule of 4 weeks on then 2 weeks off.

Extent of exposure

Table 28 Subject Disposition and Reasons for Discontinuation from Study Treatment Across Study 307, Study 205, and KEYNOTE 427

	Combination Therapy		**Monotherapy**	
	Study 307 (RCC-1L)		Study 205 (RCC-2L+)	**KEYNOTE-427 (RCC-1L)**
Number of subjects (%)	**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)**
Treatment Ongoing at Cutoff Date[a]	**142 (40.0)**	**67 (18.8)**	**7 (13.5)**	**0**
Both Study Drugs	60 (16.9)	NA	NA	NA
Lenvatinib only	78 (22.0)	NA	7 (13.5)	NA
Pembrolizumab only	4 (1.1)	NA	NA	0
Discontinued Treatment[b]	210 (59.2)	273 (76.5)	45 (86.5)	110 (100)
Primary Reason(s) for Discontinuation from Treatment				
Radiological Disease Progression	97 (27.3)	174 (48.7)	29 (55.8)	53 (48.2)
Adverse Event	60 (16.9)	41 (11.5)	11 (21.2)	24 (21.8)
Clinical Disease Progression	19 (5.4)	22 (6.2)	3 (5.8)	6 (5.5)
Subject Choice	17 (4.8)	23 (6.4)	0	NA
Withdrawal by Subject	4 (1.1)	9 (2.5)	0	2 (1.8)
Lost to Follow-up	0 (0.0)	1 (0.3)	0	NA
Completed 35 Doses (Approximately 2 years) of Pembrolizumab Treatment	NA	NA	NA	20 (18.2)
Non-study Anticancer Therapy	NA	NA	NA	2 (1.8)

Number of subjects (%)	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)
Withdrawal by Parent/Guardian	NA	NA	NA	1 (0.9)
Physician Decision	NA	NA	NA	1 (0.9)
Complete Response	NA	NA	NA	1 (0.9)
Other	13 (3.7)	3 (0.8)	2 (3.8)[c]	NA

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

1L = first line, 2L+ = second line or greater, CSR = Clinical Study Report, NA = not applicable, RCC = renal cell carcinoma. a:Treatment ongoing is based on data available in database at the time of data cutoff. Subjects with sunitinib or at least one study drug in combination therapy are deemed to have 'treatment ongoing' in absence of an off treatment visit, or with a treatment ongoing at data cutoff in the subject disposition (Randomization Phase) page of electronic case report form.b:Treatment Discontinuation includes subjects who discontinue sunitinib or both study drugs in combination therapy.c:Includes reasons of "Clinical progression", "Death due to clinical progression", "Investigator decision", "Palliative radiotherapy", or "withdrawn due to poor compliance".

Table 29 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.

Key Demographics, Baseline and Disease Characteristics

Table 30 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 (%)				

	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)**
<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 (%)				
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

	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)**

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.

Comparison of Efficacy Across Trials: Objective Response Rate and Duration of Response

Table 31 Summary of Tumour 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+)**	**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)**
Best Overall Response, n (%)				
Complete Response	57 (16.1)	15 (4.2)	1 (1.9)	4 (3.6)
Partial Response	195 (54.9)	114 (31.9)	17 (32.7)	36 (32.7)
Stable Disease	68 (19.2)	136 (38.1)	NA	35 (31.8)
Progressive Disease	19 (5.4)	50 (14.0)	NA	33 (30.0)
Unknown/Not Evaluable	16 (4.5)	42 (11.8)	-	-
No Baseline Tumour Assessment	0 (0.0)	1 (0.3)	-	-
No Post-baseline Tumour 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]	-	-	-	2 (1.8)

	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)**
Objective Response Rate (CR + PR), n (%)	252 (71.0)	129 (36.1)	18 (34.6)	40 (36.4)
95% CI	(66.3, 75.7)[b]	(31.2, 41.1)[b]	(22.0, 49.1)[c]	(27.4, 46.1)[c]
Lenvatinib + Pembrolizumab vs Sunitinib				
Difference (%) (95% CI)[b]	34.9 (28.0, 41.7)		NA	NA
Odds ratio (95% CI)[e]	4.35 (3.16, 5.97)		NA	NA
P value[e]	<0.0001		NA	NA
Duration of Objective Response (months)				
Median (95% CI)	25.8 (22.1, 27.9)[f]	14.6 (9.4, 16.7)[f]	9.2[f] (7.2, 14.8)[f]	18.9 (7.1, NE)
Range (Min, Max)	(1.64+, 36.76+)	(1.64+, 33.15+)	(0.95+, 14.78)	NA

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

1L = first line, 2L+ = second line or greater, BICR = blinded independent central review, CR = complete response, CSR = Clinical Study Report, IxRS = interactive voice and web response system, n = number of subjects, max = maximum, min = minimum, NA = not applicable, NE = not evaluable, PR = partial response, RCC = renal cell carcinoma, 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:95% CIs were constructed using the method of Clopper and Pearson.d:Based on binomial exact confidence interval method for binomial data.e:Odds Ratio and nominal *P* value are calculated using the Cochran-Mantel-Haenszel method, stratified by IxRS stratification factors.f:. The median and quartiles were estimated using Kaplan-Meier method. 95% CI was from a generalized Brookmeyer and Crowley method.

Comparison of Efficacy Across Trials: Progression-Free Survival

Table 32 Summary of Progression-Free Survival 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+)	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)
Subjects with PFS events, n (%)	160 (45.1)	205 (57.4)	33 (63.5)	80 (72.7)

Median PFS (months)	23.9	9.2	9.0[a]	7.1
95% CI for Median PFS	(20.8, 27.7)	(6.0, 11.0)	(5.6, 10.2)[a]	(5.6, 11.0)
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]	NA
Lenvatinib + Pembrolizumab vs Sunitinib				
Stratified HR (95% CI)[b,c]	0.39 (0.32, 0.49)		NA	NA
Stratified Log-rank Test *P* value[c]	<0.0001		NA	NA
Progression-Free Survival Rate (%) (95% CI)[d] at				
6 months	84.9 (80.6, 88.3)	57.0 (51.1, 62.5)	63.5 (47.9, 75.6)	58.0 (48.0, 66.7)
12 months	70.6 (65.3, 75.2)	38.4 (32.4, 44.3)	32.2 (18.5, 46.8)	37.6 (28.2, 46.9)
18 months	57.4 (51.5, 62.8)	31.2 (25.4, 37.2)	NA	26.7 (18.4, 35.8)
24 months	48.9 (42.7, 54.9)	20.7 (15.0, 26.9)	NA	22.3 (14.6, 31.0)

Data cutoff date: 28 Aug 2020 for Study 307, 24 Feb 2020 for KEYNOTE-427 and 13 Jun 2014 for Study 205.1L = 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 Tumours.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.

Comparison of Efficacy Across Trials: Overall Survival

Table 33 Summary of Overall Survival 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)
Deaths, n (%)	80 (22.5)	101 (28.3)	26 (50.0)	48 (43.6)
Median OS (months)	NR	NR	18.4	NR
95% CI for Median OS	(33.6, NE)[a]	(NE, NE)[a]	(13.3, NE)[a]	(31.2, NE)
Lenvatinib + Pembrolizumab vs Sunitinib				
Stratified HR (95% CI)[b,c]	0.66 (0.49, 0.88)		NA	NA

Stratified Log-rank Test *P* value[c]	0.0049		NA	NA
OS Rate (95% CI)[d] at				
3 months	NA	NA	96.2 (85.5, 99.0)	97.3 (91.8, 99.1)
6 months	NA	NA	86.5 (73.8, 93.3)	92.7 (86.0, 96.3)
9 months	NA	NA	80.8 (67.2, 89.2)	NA
12 months	91.4 (87.9, 93.9)	80.2 (75.5, 84.1)	71.1 (56.7, 81.5)	88.2 (80.5, 93.0)
18 months	87.1 (83.1, 90.3)	74.4 (69.3, 78.8)	54.3 (38.9, 67.4)	80.0 (71.2,86.3)
24 months	79.2 (74.1, 83.3)	70.4 (65.0, 75.2)	NA	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]	17.8 (16.0, 21.1)[a]	34.2 (NA)[e]

Data cutoff date: 28 Aug 2020 for Study 307, 24 Feb 2020 for KEYNOTE-427 and 13 Jun 2014 for Study 205.1L = first line, 2L+ = second line or greater, CI = confidence interval, CSR = Clinical Study Report, HR hazard ratio, IxRS = interactive voice and web response system, MSKCC = Memorial Sloan-Kettering Cancer Center, NA = not applicable, NE = not evaluable, NR = not reached, OS = overall survival, RCC = renal cell carcinoma.a:For Study 307, 95% CIs are estimated with a generalized Brookmeyer and Crowley method. For Study 205, 95% CIs are based on the Greenwood formula.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:Overall survival rate and 95% CIs are calculated using Kaplan-Meier product-limit method and Greenwood Formula.E;Follow-up duration is defined as the time from first dose to the date of death or the database cutoff date if the subject is still alive.

2.4.3. Discussion on clinical efficacy

The current application concerns lenvatinib in combination with pembrolizumab for adults with advanced renal cell carcinoma (RCC) as first-line treatment.

Design and conduct of clinical studies

The pivotal study 307 is an multicentre, randomized, open-label, 3 arm Phase 3 study.

The study randomized 1,069 subjects with advanced RCC in total. A total of 355 subjects were randomized 1:1:1 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. Arm A of the study (lenvatinib and everolimus) is not part of the current submission. The ITT population includes 355 subjects in lenvatinib and pembrolizumab (arm B) and 357 subjects in the sunitinib arm (arm C). Three subjects (0.8%) in arm B ad 17 (4.8%) subjects in arm C were not treated.

Study participants included adult male and female subjects with advanced RCC with without prior systemic anti-cancer therapy. To be included, patients should have had a KPS of ≥70, histologically or cytologically confirmed diagnosis of advanced RCC with clear-cell subtype component and no evidence of significant cardiovascular impairment within 12 months prior study. Subjects were stratified by geographic region (Western Europe and North America or rest of the world) and MSKCC prognostic group

(favorable, intermediate, and poor risk). The IMDC risk group was derived programmatically and was not a stratification factor.

Sunitinib is considered to be an acceptable comparator in the target population as the study started inclusion 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.

The MAH bases the lenvatinib dose selection on the phase 1b/2 E7080-A001-111/KEYNOTE 146 study. No DLT as defined by the protocol were observed at 20 mg lenvatinib dose level (in combination with 200 mg pembrolizumab Q3W). The overall rate of dose reductions and interruptions due to TEAE was overall high (67% of patients) with 20 mg lenvatinib in combination with pembrolizumab (Study 111 CSR).

The primary objective of Study 307 was to demonstrate that lenvatinib plus everolimus or lenvatinib plus pembrolizumab is superior to sunitinib alone in improving PFS (by independent imaging review using RECIST version 1.1). OS, ORR, DoR, and safety were secondary outcomes. PFS as primary objective is considered appropriate since OS is defined as a secondary objective.

All efficacy analyses were to be carried out using the treatment arm as randomised (intent to treat). Overall, the statistical analyses are considered appropriate and the sample size calculations can be endorsed.

Seven amendments have been done since the original protocol. The amendments were done to clarify inclusion/exclusion criteria or to adapt the HA requests. The amendment 4 increased the planned enrolment to 1050 subjects from 735 initially planned to address slow enrolment and provide adequate power for OS comparisons. Amendment 7 has been performed to exclude the assessment of PFS and ORR based on irRECIST in arm B. The amendment was issued three weeks before 28 Aug 2020 (data cutoff for the final PFS analysis and second interim analysis of OS; interim analysis 3 [IA3]).

Efficacy data and additional analyses

The data cutoff for the primary analysis occurred on 28 August 2020. Median duration of follow-up for PFS was 22.3 months for lenvatinib and pembrolizumab combination and 16.6 months for sunitinib;

At the time of DCO study treatment was ongoing for 40% in lenvatinib and pembrolizumab arm and 18.8 for sunitinib arm.

Baseline demographics were generally balanced across the treatment arms. Most subjects were male, white, overweight with a favourable KPS score ≥80 at study entry. The median age was 62.0 years. The baseline distribution of European patients are not available since the grouping was based on Western Europe and North America and the rest of the world.

The majority of patients had intermediate and favourable risk as per MSKCC at baseline, with less than 10% of patients having poor risk. Approximately one third of patients had either combined positive score (CPS)≥1, <1 or unknown status each. All but one patient had clear cell carcinoma histology subtype, and 49 patients had clear cell RCC with sarcomatoid features: 28 (7.9%) in lenvatinib + pembrolizumab arm and 21 (5,9%) in sunitinib arm. Except for International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) poor risk group (9.3% in lenvatinib arm and 10,4% in sunitinib arm), the disease baseline characteristics were generally balanced between arm B and arm C of 307 study.

Primary endpoint: PFS

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 (Figure 5.4. 3). 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.

Key secondary endpoint-Overall survival

Median OS was not reached at the time of DCO. Lenvatinib plus pembrolizumab treatment resulted in higher and statistically significant OS rates compared with sunitinib alone.

The OS HR of 0.66 (95% CI: 0.49, 0.88) represents a statistically significant reduction in the risk of death for lenvatinib plus pembrolizumab compared with sunitinib. The P value was less than the pre specified P value boundary of 0.0161 and the null hypothesis was rejected.

The separation of KM curves appears to occur early after 3 months from randomization. No clear separation is observed before 3 months. Extensive censoring after approximately month 12 can be observed.

The data are immature with about 20-30% events; however, a clear separation of the curves over time is apparent. Since median OS was not reached, there is an uncertainty in interpretation of the OS results.

In the subgroup analysis DCO 28 August 2020, OS HRs for most subgroups favored (HR < 1) lenvatinib and pembrolizumab vs sunitinib with the exception of favourable IMDC risk groups.

In the initial data package, the OS data for all subgroups were immature as median OS was not reached for several subgroup in both arms. Updated data for OS were submitted during the procedure (see Conclusion of Clinical Efficacy).

Key secondary endpoint-Objective response rate

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

PFS2 In the lenvatinib and pembrolizumab arm, the most frequent systemic (30.4%) anticancer therapy administered after study drug were VEGF inhibitors; 8.2% patients received checkpoint inhibitors. In the sunitinib arm, 33.6% of the patients received a VEGF inhibitor and 43.1% received checkpoint inhibitors.

The PFS2 did not reach the median in the lenvatinib+pembrolizumab arm; the PFS2 analysis favors lenvatinib and pembrolizumab when compared with sunitinib (HR=0.50, 95% CI: 0.39-0.65). The immaturity of the data and the different anti-cancer treatments used as second line contributes to an uncertainty in interpretation of the PFS2.

The mPFS, OS, ORR and mDOR were favourable in the lenvatinib and pembrolizumab arm compared with sunitinib, independently of the PD-L1 tumour expression (CPS≥1, <1 or unknown status).

There was low incidence of treatment emergent ADA in evaluable subjects based on a pooled analysis (pembrolizumab combination therapy) in subjects with advanced RCC.

Contribution of each component in the combination regimen

The clinical trial design of the study 307 is lacking a monotherapy arm, testing the combination lenvatinib and pembrolizumab against either lenvatinib and pembrolizumab alone. This leads to uncertainties when it comes to reaching a conclusion on the contribution of each agent to the combination. The MAH has provided cross trial comparisons.

To justify the contribution of lenvatinib the MAH provided results from study 205. This is a completed, multicenter, open-label, Phase 1b/2 study of lenvatinib administered alone and in combination with everolimus in subjects with unresectable advanced or metastatic RCC (predominantly clear-cell) following 1 prior VEGF-targeted treatment. The results of this trial led to approval of lenvatinib in combination with everolimus in RCC as 2L, after failure of VEGF targeted therapy.

To assess the contribution of pembrolizumab, the MAH summarised results from study KN-427 (an ongoing, multicenter, single arm, open-label, Phase 2 study of the safety and efficacy of pembrolizumab (200 mg Q3W) in adults with 1L locally advanced or metastatic RCC.

A precise quantitative assessment of the contribution of each component of the pembrolizumab+lenvatinib combination cannot be established. However 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. Numerically higher PFS, OS and ORR were observed in lenvatinib and pembrolizumab arm in study 307 than in study 205 or in study KN-427.

2.4.4. Conclusions on the clinical efficacy

The combination of lenvatinib and pembrolizumab in patients with RCC as first line therapy demonstrated superiority with regard to PFS over sunitinib therapy. This is supported by the ORR results. In addition, there is an OS survival improvement observed with HR of 0.66 (95% CI: 0.49, 0.88). However, OS data are still immature and mOS was not reached in key subgroups. An updated OS analysis with the data cut-off date of 31 March 2021 was provided: HR for OS was 0.72 (0.55, 0.93), in line with the IA3 results.

Study 307 lacked monotherapy controls, hampering the assessment of contribution of components to the lenvatinib and pembrolizumab combination. Cross-trial comparisons have been provided however 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 34**).

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 34 **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 35).

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

Table 35 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 first dose + 1).
b: Received dose as percentage of planned starting dose = 100 × dose intensity (mg/day)/planned starting dose (20 mg/day

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 36 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

AEs were defined as any unfavorable and unintended change in a physical sign(s) or symptom(s), or a clinically significant laboratory change occurring in a subject during clinical study participation, regardless of its relationship to study drug or if due to progression of disease (PD).

In Study 307, 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. However, if PD led to an untoward medical occurrence (eg, increased pain, pleural effusion), the medical occurrence itself was recorded as an AE.

The analysis of AEs was based on TEAEs, which were considered any of the following:

- An AE that emerged during treatment (up to 30 days after the subject's last dose of study drug), having been absent at pretreatment (Baseline).
- An AE that reemerged during treatment or up to 30 days following the last dose of study drug, having been present at pretreatment (Baseline), but stopped before treatment.
- An AE that worsened in severity during treatment or up to 30 days following last dose of study drug relative to the pretreatment state, when the AE was continuing.

SAEs were defined as any AE that resulted in death or was otherwise life threatening, that required inpatient hospitalization or prolongation of a hospitalization, that resulted in persistent or significant disability/incapacity, that resulted in a congenital anomaly/birth defect or which was an important medical event that could jeopardize the subject or required medical or surgical intervention to prevent any of the outcomes listed above.

SAEs were collected through the termination visit and for 30 days (lenvatinib monotherapy studies), 90 days (Studies 111 and 115, and pembrolizumab monotherapy studies), or 120 days (Study 307) after the last dose of study drug (or 30 days following the last dose if the subject initiated new anticancer therapy, whichever is earlier). All were followed to resolution or, if resolution was unlikely, to stabilization.

Adverse event summary

An overview of adverse event profile is provided in Table 37:

Table 37 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 38 Table:

Table 38 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)
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 39 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)
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)

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 (%)
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)
Hypertriglyceridemia	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)
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)
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)
Hypophosphatemia	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 diarrhoea (61.4%), hypertension (55.4%), hypothyroidism (47.2%), decreased appetite (40.3%), fatigue (40.1%), nausea (35.8%), and stomatitis (34.7%) (**Table 39**).

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 diarrhoea (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: diarrhoea, 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 diarrhoea, hypothyroidism, increased lipase, increase amylase, increased blood creatinine, increased ALT and AST, hyperthyroidism, hypertriglyceridemia, hypercholesterolemia, rash and maculopapular rash, hyperkalaemia, and hypophosphatemia.

- **Treatment-related all grade AEs**

Table 40 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 41 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:

- Diarrhoea (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 cut-off date.

Grade ≥3 Adverse Events

Table 42 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 sunitinib, 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 43).

Table 43 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
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)

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 (%)	
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)
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

The Applicant provided a tabular summary of adverse reactions which were used to update section 4.8, and more in particular the column with pembrolizumab/lenvatinib combination therapy in RCC (SmPC Table 4). Pooling comprised of 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.

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 diarrhoea (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: diarrhoea (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 44 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

[Methodology: 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 haemorrhage, 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. Haemorrhagic events is a CSE for lenvatinib and this subject experienced

subarachnoid haemorrhage 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 45 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 46 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 47 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 because of their clinical relevance.

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 48 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 49 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)

Percentages are based on the total number of subjects in the corresponding safety set. For each row category, a subject with 2 or more adverse events in that category is counted only once.
a: Indicates the number of subjects who had events on sunitinib which are considered CSAEs for lenvatinib. b: If a subject had more than one CSAE, 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.
Data cutoff date: 28 Aug 2020

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 tumour 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 Sponsor during the pembrolizumab monotherapy program to assess the frequency of immune-mediated events considered by the Sponsor 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 51). 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 50 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 51 Adverse Events of Special Interest for Pembrolizumab With Preferred Terms Reported for the Indication Safety Set, Overall and Severe Incidence by Safety Set

	Indication N=352		**All RCC N=497**		**Non-RCC N=215**		**Pembro Monotx RSD-A N=2799**		**Pembro Monotx RSD-B N=5884**	
AEOSI Category Preferred Term:	**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)
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)

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 (%)
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)
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)
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)
Vogt-Koyanagi-Harada disease	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	0	0	0	0	0	0

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 52 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 53 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

In the Indication Safety Set, a total of 19.0% (65/343) of subjects had a shift in urine dipstick protein from negative or trace at Baseline to 3+ during treatment. A shift in score from negative or trace at Baseline to 4+ during treatment occurred for an additional 5.2% (18/343) of subjects. A similar shift pattern was observed in the lenvatinib Monotherapy SS with 13.2% (139/1049) of subjects having a shift from negative or trace at Baseline to 3+ during treatment and 5.2% (55/1049) of subjects having negative or trace at Baseline to 4+ during treatment.

The AE data were consistent with the laboratory data, although more subjects in all safety sets reported proteinuria as a TEAE than had shifts in urine dipstick protein from a score of negative or trace at Baseline to 3+ or 4+ during treatment. 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 (1.7%) had proteinuria events leading to discontinuation of lenvatinib treatment.

2.5.1.1. Vital Signs

In the Indication Safety Set, a shift from Grade 0 or from Grade 1 hypertension at Baseline to a worst postbaseline of Grade 3 during treatment was observed for 6.3% of subjects for Grade 0 and 24.1% of subjects for Grade 1. These findings were similar to those in the lenvatinib Monotherapy SS (8.4% and 21.8%, respectively) No such data are available for the Pembrolizumab Monotherapy SSs.

In the Indication Safety Set, the incidence of hypertension reported as a TEAE was 55.4% and that of hypotension was 6.8%. These results are similar to those in the lenvatinib Monotherapy SS (60.1% for hypertension and 7.8% for hypotension); however, the incidences are higher than those observed in the Pembrolizumab Monotherapy RSD-A (3.8% for hypertension and 2.4% for hypotension) and RSD-B (5.0% for hypertension and 2.8% for hypotension) Safety Sets.

In the Indication Safety Set, 1 subject (0.3%) had a TEAE of hypertension that led to the discontinuation of lenvatinib; this was similar to the incidence of hypertension leading to discontinuation in the lenvatinib Monotherapy SS (15 subjects [1.3%]).

2.5.1.2. ECG

In the Indication Safety Set, shifts in ECG findings from normal at Baseline to abnormal, clinically significant postbaseline were observed in 7.0% of subjects and shifts from abnormal, not clinically significant to abnormal, clinically significant were observed in 5.8% of subjects. Corresponding shifts were similar for the lenvatinib Monotherapy SS (5.6% and 4.5%, respectively).

2.5.1.3. QTc

In the Indication Safety Set, there were no clinically relevant differences in shifts in Karnofsky Performance Status scores from Baseline to worst postbaseline KPS score.

Echocardiogram data were consistent in the Indication and lenvatinib Monotherapy SSs. In the Indication Safety Set, most subjects had a normal LVEF value at Baseline, with no postbaseline shift (89.2% [74/83]). Only 3 subjects (3.6%) had a worsening shift in LVEF from normal at Baseline to mild dysfunction, 2 subjects (2.4%) to moderate dysfunction, and 3 subjects (3.6%) to severe dysfunction postbaseline.

In the Indication Safety Set, the median change (decrease) from Baseline in LVEF was -2.0% (range: -32% to 13%), similar to results in the lenvatinib Monotherapy SS (-5.0% [range: -54% to 19%]). Likewise, the percentage of subjects with a worst postbaseline LVEF less than 50% was similar in the Indication (10.6%) and Lenvatinib Monotherapy (11.3%) Safety Sets.

The TEAEs of "ejection fraction decreased" were reported for 1 subject (0.3%) in the Indication Safety Set, 37 subjects (3.3%) in the lenvatinib Monotherapy SS and 6 subjects (2.8%) in the Non-RCC Safety Set, indicating that there likely is no increased risk of decreased LVEF with combination therapy.

Safety in special populations

2.5.1.4. Pregnancy & Lactation

No pregnancies have been reported with lenvatinib plus pembrolizumab in the treatment of RCC as of the data cutoff date (28 Aug 2020) for Study 307. However. Based on their MoA it is generally accepted that both lenvatinib and pembrolizumab will have fetotoxic properties that will likely lead to in-utero harm.

Lenvatinib was embryotoxic and teratogenic when administered to rats and rabbits, and while animal reproduction studies have not been conducted with pembrolizumab, blockade of programmed death-ligand 1 (PD-L1) signalling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss.

This data and consequences for treatment are clearly noted in both Kisplyx and Keytruda product's SmPCs.

2.5.1.5. Subgroup analysis: Age

Safety and exposure were evaluated for the age subgroups <65, ≥65 to <75, and ≥75 years, with the majority of Indication SSsubjects being <65 years of age (54.8%) and the ≥75 years of age subgroup being relatively small which implies caution should be needed when interpreting results in this advanced age group.

Median treatment duration, dose intensity and percentage received dose based on the planned starting dose also decreased with increasing age, an observation that was also shared in the lenvatinib Monotherapy SS. An overview of TEAE occurrence in the age subgroups for all SSs is shown in Table 55.

Table 54 Overview of Incidence of Treatment Emergent Adverse Events 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)
	≥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)

	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	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)
	≥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

Percentages are based on the total number of subjects in the relevant safety set. MedDRA preferred terms 'Neoplasm Progression,' 'Malignant Neoplasm Progression,' and 'Disease Progression,' which are unrelated. For each row category, subjects with 2 or more AEs in that category were counted only once. A subject 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. 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, AE = adverse event, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CTCAE = Common Terminology Criteria for Adverse Events, Lenv = lenvatinib, MedDRA = Medical Dictionary for Regulatory Activities, Monotx = monotherapy, NA = not applicable, Pembro = pembrolizumab, Q3W = once every 3 weeks, QD = once daily, RCC = renal cell carcinoma, RSD = Reference Safety Dataset, SAE = serious adverse event, 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/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.

As can be seen in **Table 55** the incidence of Grade ≥3 TEAEs was higher in the older age subgroups than in the <65 years age subgroup in the Indication Safety Set and in both the lenvatinib Monotherapy SS as well as in the pembrolizumab Monotherapy RSD-B SS.

The incidence of deaths was also higher in the older subgroups for both the Indication and pembrolizumab Monotherapy SSs, but not for the lenvatinib Monotherapy SS.

Consistent with the duration of treatment, the incidence of TEAEs leading to discontinuation of any study drug was higher in 1 or both of the older aged subgroups than in the <65 years age subgroup for the Indication SSS and lenvatinib Monotherapy SS but not for the pembrolizumab Monotherapy SSs, though a trend in this direction seems to be visible there too. Discontinuations of each investigated therapy taken alone were similar to that observed with discontinuations overall.

The incidence of dose reductions and interruptions for lenvatinib was higher in 1 or both of the older aged subgroups than in the <65 years age subgroup for the Indication Safety Set and the Lenvatinib Monotherapy Safety Set. Note that pembrolizumab was not dose reduced as per the study protocols

Lastly, the incidence of dose modifications was more common in the 2 older age subgroups than in the <65 years age subgroup in the Lenvatinib Monotherapy Safety Set.

Overall lenvatinib CSEs were reported in similar incidence in the various age subgroups in the associated safety sets with the exception of proteinuria and renal events, both of which occurred more frequently in the older subgroups. This latter observation was seen in both the Indication as well as the lenvatinib Monotherapy SSs.

Subgroup analysis: Sex

In the Indication Safety Set, the majority of the subjects were male (71.6%), whereas these percentages were 49.51%, 59.27% and 66.06% in the lenvatinib, pembrolizumab RSD-A and pembrolizumab RSD-B subgroups. Given the rather large intergroup inbalance in male:female ratios, any interpretations of this subanalysis should be done with caution.

Overall, the most obvious difference noted was that the incidence of Grade ≥3 related TEAEs being higher in the female subgroup than in the male subgroup in the lenvatinib Monotherapy Safety Set while being similar between sexes in the Indication SS and pembrolizumab Monotherapy SSs.

In the Indication Safety Set, the incidence of diarrhea was higher in male subjects (66.7%) than female subjects (48.0%), which was not observed in the monotherapy safety sets or the Non-RCC Safety Set.

Regarding lenvatinib CSEs, for the overall population these were all reported at a similar incidence within each sex subgroup for both Indication and lenvatinib Monotherapy SSs.

Subgroup analysis: Race

Overall the incidence of TEAEs, related TEAEs, and Grade ≥3 TEAEs were similar between the race subgroups in the Indication SS, which itself was consistent with that in the lenvatinib Monotherapy SS . The incidence of SAEs and non-fatal SAEs was similar between the race subgroups in the Indication Safety Set and the monotherapy safety sets. Of note is the fact that the incidence of fatal SAEs was lower in the Asian Race subgroup than in the White Race subgroup in the Indication Safety Set, as well as the All RCC and Non-RCC Safety Sets, but not in the Lenvatinib Monotherapy Safety Set. No major differences in TEAE incidences were evident in the Indication SS between White and Asian subsets, a part for:

- PPES (17.3% and 64.2% respectively) and proteinuria (and 22.7% and 55.6%), which were also seen in the lenvatinib Monotherapy SS .

- fatigue (46.5% and 23.5%, respectively), nausea (41.9% and 14.8%), arthralgia (31.9% and 14.8%), vomiting (27.3% and 18.5%), asthenia (25.8% and 3.7%), cough (23.8% and 6.2%), and dyspnea (18.8% and 1.2%); all of which, save for asthenia, were not seen in the lenvatinib Monotherapy SS .

Lenvatinib CSEs did not show any disparity between Asian and White subsets, a part for hypothyroidism which was reported with a 14,9% higher incidence by the former subset. This latter difference was however not replicated in the lenvatinib Monotherapy SS.

Subgroup analysis: Baseline Renal Function

Two creatine clearance subgroups were defined for this analysis: CrCl ≥60 mL/min and CrCl <60 mL/min, the former of which encompassed 65.1% of the Indication SSsubjects.

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, the former of which was about 69% longer compared to the latter. This was in contrast to the lenvatinib Monotherapy SS where both subgroups' median treatment duration was broadly similar. It should be noted that in the Indication SS the CrCl ≥60 mL/min subgroup median dose intensity and received dose as a percentage of planned starting dose were 18.6% and 11.43% higher, respectively, than in the lower CrCl group.

The incidences of TEAEs and related TEAEs were similar between the renal function subgroups in the Indication SS, which was consistent with the lenvatinib Monotherapy SS . The incidences of Grade ≥3 TEAEs and Grade ≥3 related TEAEs were however higher in the CrCl <60 mL/min subgroup for the Indication Safety Set whereas they were similar between the renal function subgroups in the lenvatinib Monotherapy SS as well as the Non-RCC Safety Set.

The incidences of fatal SAEs and nonfatal SAEs were higher in the CrCl <60 mL/min subgroup than in the CrCl ≥60 mL/min subgroup for the Indication Safety Set but were again similar between the renal function subgroups in the lenvatinib Monotherapy SS as well as in the Non-RCC SS. The subjects in the Indication Safety Set in the CrCl <60 mL/min subgroup had a higher incidence of discontinuation of lenvatinib, pembrolizumab, and both drugs than in the CrCl ≥60 mL/min subgroup.

Finally, in the Indication SS, events in the most common lenvatinib CSE groups were reported at a similar incidence in each of the renal function subgroup, which was also true of the lenvatinib Monotherapy SS, save for renal events which were reported at a 13.6% higher frequency in the CrCl <60 mL/min subgroup.

Subgroup analysis: Baseline Hepatic Function

Due to the imbalance in hepatic function subgroups (330 subjects with Normal (no CTCAE Grade 1 AST, ALT, and bilirubin) function vs 22 subjects with abnormal funtion), comparisons regarding TEAEs in the Indication SS are considered not meaningful.

Subgroup analysis: Baseline Hypertension

In the Indication SS 57.4% of subjects had hypertension, and the overall TEAEs, related TEAEs, non-fatal SAEs and fatal SAEs was similar between the hypertension and no hypertension subgroups. The incidence of Grade ≥3 TEAEs and Grade ≥3 related TEAEs were slightly higher in the former group and this was also noted in the lenvatinib Monotherapy SS.

In contrast, 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 SS.

Outcomes in the all-RCC ss were wholly consistent with the findings in the Indication SS.***Subgroup analysis: Geographic Region***

Safety and exposure were evaluated for the geographic regions Western Europe and North America verus Rest of World, and in the Indication SS the median duration of treatment with lenvatinib plus pembrolizumab was similar for both geographic regions (6% difference only).

Overall, there was no major difference between TEAE incidence between subgroups and this was consistent across all SSs. TEAEs leading to lenvatinib discontinuation occurred less in the WE/NA group compared to the ROW group, though strangely this finding was opposite in the lenvatinib Monotherapy SS

On the other hand, incidences of TEAEs leading to lenvatinib dose reduction were similar between the Indication SSsubgroups, whereas these incidences were lower in the WE/NA subgroups of the lenvatninb Monotherapy SS.

Overall study drug interruption due to TEAEs was also higher in the WE/NA subgroups of the lenvatninb Monotherapy SS, whereas they were similar to the ROW subgroups in all the other SSs.

Safety related to drug-drug interactions and other interactions

Since 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, no pharmacokinetic drug interaction is expected between both.

Discontinuation due to adverse events

In total 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%). It was also similar to the rate of such events in the sunitinib SS (14.4%).

TEAEs leading 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)
- Rash (2 subjects; both Grade 3 and related to study drug)

The Incidence of TEAEs leading to treatment discontinuation of lenvatinib, regardless of the action taken with pembrolizumab, was similar in the Indication Safety Set (25.6%) and in the lenvatinib Monotherapy SS (26.7%). The incidences of each of these events in the Indication Safety Set were all less than 2%.

The incidence of treatment-emergent AEs leading to treatment discontinuation of pembrolizumab, regardless of the action taken with lenvatinib, in the Indication Safety Set (28.7%) was higher than that in the Pembrolizumab Monotherapy Safety Sets (RSD-A: 11.9%; RSD-B: 13.4%). The most frequently reported event in the Indication Safety Set was pneumonitis (2.8%). The incidences of other events leading to discontinuation of pembrolizumab were all less than 2%.

Dose alterations due to AEs

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. This was in contrast to the sunitinib SS where these latter two numbers were 53.8% and 50.3% respectively.

The incidence of TEAEs leading to such dose reduction of lenvatinib was higher in the Indication Safety Set (68.8%) than in the lenvatinib Monotherapy SS (47.5%) and a similar trend was observed for treatment-related TEAEs leading to lenvatinib interruption or reduction.

TEAEs that most frequently leading 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 again a similar trend was observed for treatment related TEAEs leading to lenvatinib dose reduction.

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%).

Regarding pembrolizumab, the overall incidence of TEAEs leading to a dose interruption in the Indication Safety Set (55.1%) was higher than 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%).

Overall Conclusions on discontinuations and dose modifications

TEAE-caused treatment discontinuation rates for lenvatinib were similar in both Indication (25.6%) and Lenvatinib Monotherapy (26.7%) Safety Sets. Moreover, they were substantially lower than the rates for dose reductions (68.8% and 47.5% in the Indication and lenvatinib Monotherapy SSs, respectively) and interruptions (73.0% and 67.6).

Hence, these findings indicate that the majority of TEAEs can be managed with lenvatinib dose modifications rather than with lenvatinib discontinuation according to the prespecified dose modification

Post marketing experience

Both lenvatinib and pembrolizumab have a safety profile which is well-known and summarized in the respective Periodic Safety Update Reports and product information.

No revocation or withdrawal of lenvatinib or pembrolizumab or registration for safety reasons has occurred in any country.

2.5.2. Discussion on clinical safety

In support of the safety of the novel combination therapy consisting of oral QD lenvatinib and IV Q3W pembrolizumab in the context of 1L advanced RCC, the Applicant submitted the results of the E7080-G000-307/KEYNOTE 581 CLEAR trial, wherein the aforementioned combination is compared to the, treatment of oral sunitinib in a 4/2 schedule.

Note that the E7080-G000-307/KEYNOTE 581 CLEAR trial also included a lenvatinib + everolimus investigative arm, but in light of the investigative subject of this particular procedure this arm was considered of negligible interest and as such any results thereof are not discussed.

As of data cut-off date 352 subjects were enrolled 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 sunitinib 50 mg QD (Sunitinib Safety Set).

In addition to the comparison with the preferred treatment regimen the Applicant also discussed the safety findings in contrast to the aggregated safety results from lenvatinib and pembrolizumab monotherapy studies in a variety of indications. Additionally, supportive safety data was also available from other studies using the investigative combination in RCC and non-RCC indications.

When adjust for exposure time the median duration of exposure of the lenvatinib and pembrolizumab combination was about 2.2 times longer than sunitininband the safety profiles between sunitinib and the investigative combination became more similar than initially observed, though observed difference in safety outcomes still remains.

The most common TEAEs, occurring in over 30% of subjects, were generally similar between both treatment arms a part for hypothyroidism which was only common in the lenvatinib + pembrolizumab arm and PPE syndrome which was only common in the sunitinib arm. When comparing to the aggregated lenvatinib and pembrolizumab monotherapy data TEAE outcomes and incidences were generally consistent, and for those known safety effects that had an imbalance to the detriment of the combination treatment (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%); increased lipase (14.2%, 2.8%, and 0.3%)) any excess incidence was mostly due to low grade (≤2) events.

Overall severe events (Grade ≥3) occurred with a +/- 10% higher incidence in the investigative combination treatment in absolute terms, which was also reflected in individual event incidences, but when adjusted for exposure the rates were similar in both treatment arms (1.95 versus 2.06 per SY overall), save for SAEs (0.72 vs 0.55 per SY, respectively).

Non-fatal STEAEs had, in absolute terms, a higher incidence in the lenvatinib plus pembrolizumab arm(50%) then in the sunitinib (32.6%), and this difference remained pronounced after adjustment for exposure (0.68 versus 0.51 per SY). On the other hand, fatal TEAEs were reported in similar absolute overall incidence rates between both lenvatinib and sunitinib arms, 7.7% versus 6.8%, as well as in exposure-adjusted rates (0.04/SY versus 0.03/SY). When compared to the aggregated monotherapy data of lenvatinib and pembrolizumab fatal TEAEs were respectively similar and less numerous in the combination treatment safety set, both in absolute and exposure adjusted terms, and no clustering of fatalities was apparent.

Despite the seemingly worse SAE profile in the combination treatment there were nonetheless not more treatment discontinuations noted (13.4% versus 14.4%) and importantly there were no TEAEs identified that led to cluster discontinuations (= more than 2 subjects). Moreover, this observation also held when comparing discontinuation rates with the aggregated lenvatinib and pembrolizumab monotherapy data. Dose reductions or interruptions occurred more frequently in the lenvatinib + pembrolizumab arm, but given that there was no significant difference in discontinuation rates versus the monotherapy comparator data this indicates that dose management of the combination treatment is sufficient to allow patients to continue treatment in case of (S)TEAEs.

Adverse Events of Special Interest (AEOSIs) for pembrolizumab occurred in twice as many subjects in the lenvatinib plus pembrolizumab arm compared to the sunitinib arm, and similarly a small increase of these events compared to pembrolizumab monotherapy data was also seen. Nonetheless, AEOSIs were overall low Grade (≤2), consistent with the known safety profile for pembrolizumab and no new immune events were noted. One notable exception to the known safety profile was the heightened incidence of low-grade hypothyroidism. Hypothyroidism is a known adverse drug reaction for both lenvatinib and pembrolizumab and the unexpected higher incidence could be due to the combination of that two risk profiles.

Overall the observed CSEs for lenvatinib differ in overall incidence compared to the sunitinib arm by 94% versus 85% and the observed lenvatinib CSE profile was congruent with the known safety profile of the drug.

When comparing CSEs with the lenvatinib monotherapy set most were similar a part for hypothyroidism, renal events, and hepatotoxicity that were higher, although the difference was mostly due to low grade (≤2) events. The higher incidence of renal events was an expected observation in this patient population due to the underlying disease versus the indication-independent aggregated monotherapy set. As for hepatotoxicity events, no clustering or patterning was apparent.

Overall, the combination profile as observed in the CLEAR study 307 matched the profile seen in other RCC studies and non-RCC indications. No new safety signals were observed compared to lenvatinib and pembrolizumab monotherapy safety profiles, although worsening of the overlapping toxicity (e.g. hypothyroidism).

The incidence of TEAEs leading to lenvatinib dose reduction of was higher in the Indication Safety Set (68.8%) than in the lenvatinib Monotherapy SS (47.5%) and a similar trend was observed for treatment-related TEAEs leading to lenvatinib interruption or reduction. The most frequently TEAEs leading to a lenvatinib dose reduction (occurring in ≥5% of subjects) were diarrhoea (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 combination (73.0%) and Lenvatinib Monotherapy (67.6%) Safety Sets and again a similar trend was observed for treatment-related TEAEs leading to lenvatinib dose reduction. The TEAEs that most frequently led to a lenvatinib dose interruption (occurring in ≥5% of subjects) were diarrhoea (17.6%), hypertension (8.2%), proteinuria (7.7%), asthenia (6.3%), increased lipase (5.4%), and fatigue (5.1%).

In the combination arm dose reductions were observed in 70.7% vs 53.2% in the sunitinib arm in Study 307. Dose interruptions were observed in 67.9% in the combination vs 53.2% in the sunitinib arm in Study 307. TEAE leading to lenvatinib dose modifications occurred in 84.7% of the patients. The median average daily lenvatinib dose was 14 mg, while the planned starting dose was 20 mg QD.

Finally, subgroup analysis indicated that increasing age may be related to worse tolerability of the combination treatment as 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. Though there was a lack of data in patients ≥ 75 years of age, noticeable differences were present for the lenvatinib CSEs of proteinuria and renal events within the different age strata.

2.5.3. 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.

2.5.4. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC

and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP endorsed the Risk Management Plan version 14.1 with the following content:

Safety concerns

Table: Summary of the safety concerns

Important identified risks	• Proteinuria and nephrotic syndrome • Renal failure or impairment • Cardiac failure • Posterior reversible encephalopathy syndrome (PRES) • Hepatotoxicity • Haemorrhagic events • Arterial thromboembolic events (ATEs) • QTc prolongation • Hypothyroidism • Gastrointestinal perforation and fistula formation • Non-gastrointestinal fistula formation (any fistula which does not involve the stomach or intestine) and pneumothorax
Important potential risks	• Venous thromboembolic events (VTEs) • Abnormal pregnancy outcome, excretion of lenvatinib in milk • Male and female fertility • Bone and teeth abnormalities in the paediatric population • Impaired wound healing • Interstitial Lung Disease (ILD)-like conditions • Overdose (concomitant everolimus) (RCC)
Missing information	• Use in severe hepatic impairment • Use in severe renal impairment • Long-term use

Pharmacovigilance plan

Table: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones** (required by regulators)	**Due dates**
Category 3 - **Required additional pharmacovigilance activities**				
RCC				
Study 307 Ongoing	Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in combination with Everolimus or Pembrolizumab Versus Sunitinib Alone in First-Line Treatment of Subjects with Advanced Unresectable RCC.	- all important identified and potential risks - continue to characterise/confirm the current safety profile of lenvatinib in combination with everolimus in advanced RCC	The protocol and the data analysis plan for PK/PD should be submitted: Updated protocol: Final report submission:	30 Nov 2016 10 Sep 2019 13 Aug 2021
HCC				
Study E7080-M000-508 (Observational Clinical Study: Category 3)	To characterise hepatic-related toxicity and overall safety profile (SAEs, Grade 3-5 AEs, dose modifications, and discontinuations due to AEs) in real-life conditions in the EU (Western population) in HCC patients, including patients with Child-Pugh B. Overall survival data and detailed baseline characteristics will also be collected.	Hepatotoxicity in HCC patients	Protocol submitted on: Final report submission:	22 Apr 2020 Dec 2029

Risk minimisation measures

Table: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Identified Risks		
Proteinuria and Nephrotic Syndrome	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC sections 4.2 and 4.4 where advice on monitoring urine protein and managing proteinuria or nephrotic syndrome is provided. • PL section 4	Additional pharmacovigilance activities: Study 307.
Renal failure or impairment	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC Sections 4.2 and 4.4 where advice on managing risk factors and managing renal failure or impairment is provided • PL section 4	Additional pharmacovigilance activities: Study 307.
Cardiac failure	Routine risk minimisation measures: • SmPC section 4.8 • SmPC Sections 4.2 and 4.4 where advice on monitoring patients and managing cardiac failure is provided. • PL section 4	Additional pharmacovigilance activities: Study 307.
Posterior reversible encephalopathy syndrome (PRES)	Routine risk minimisation measures: • SmPC Section 4.4 and 4.8 • PL section 4	Additional pharmacovigilance activities: Study 307.
Hepatotoxicity	Routine risk minimisation measures: • SmPC section 4.8 • SmPC Sections 4.2 and 4.4 where advice on monitoring liver function and managing hepatotoxicity is provided. • PL section 4	Additional pharmacovigilance activities: Studies 307, 508.
Haemorrhagic events	Routine risk minimisation measures: • SmPC Sections 4.4 and 4.8	Additional pharmacovigilance activities:

Table: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• PL section 4	Study 307.
Arterial thromboembolic events (ATEs)	Routine risk minimisation measures: • SmPC section 4.8 • SmPC section 4.4 where advice to discontinue in case of ATE is given • PL section 4	Additional pharmacovigilance activities: Study 307.
QTc prolongation	Routine risk minimisation measures: • SmPC section 4.8 • SmPC Sections 4.2 and 4.4 where advice on monitoring electrolytes and managing QT interval prolongation is provided • PL section 4	Additional pharmacovigilance activities: Study 307.
Hypothyroidism	Routine risk minimisation measures: • SmPC section 4.8 • SmPC section 4.4 where advice on monitoring thyroid function is given • PL section 4	Additional pharmacovigilance activities: Study 307.
Gastrointestinal perforation and fistula formation	Routine risk minimisation measures: • SmPC sections 4.4 and 4.8 • Sections 4.2 where recommendations for dose modifications/ withdrawal are provided • PL section 4	Additional pharmacovigilance activities: Study 307.
Non-gastrointestinal fistula formation and Pneumothorax	Routine risk minimisation measures: • SmPC section 4.8 • SmPC section 4.4 where advice that lenvatinib should not be started in patients with fistulae and when to permanently discontinue lenvatinib is given • PL section 4	Additional pharmacovigilance activities: Study 307.
Potential Risks		

Table: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Venous thromboembolic events (VTEs)	Routine risk minimisation measures: • SmPC section 4.8 • PL section 4	Additional pharmacovigilance activities: Study 307.
Abnormal pregnancy outcome, excretion in breast milk	Routine risk minimisation measures: • SmPC section 4.6 • PL section 2	Additional pharmacovigilance activities: None
Male and female fertility	Routine risk minimisation measures: • SmPC section 4.6	Additional pharmacovigilance activities: None
Bone and teeth abnormalities in the paediatric population	Routine risk minimisation measures: • SmPC section 5.3	Additional pharmacovigilance activities: Study 207
Impaired wound healing	No risk minimization measures are recommended at present as there is insufficient clinical evidence to establish this as an identified risk. The need for risk minimization measures will be revisited on review of pharmacovigilance data. Prescription only medicine.	Additional pharmacovigilance activities: Study 307.
Interstitial lung disease (ILD)¬like conditions	Not applicable	Additional pharmacovigilance activities: Study 307.
Overdose (concomitant everolimus)	Routine risk minimisation measures: • SmPC section 4.2 • PL section 2	Additional pharmacovigilance activities: None
Missing information		
Use in severe hepatic impairment	Routine risk minimisation measures: • SmPC section 4.2 • PL section 2	None

Table: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Use in severe renal impairment	Routine risk minimisation measures: • SmPC section 4.2 • PL section 2	None
Long-term use	Not applicable	Additional pharmacovigilance activities: None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1, 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, editorial changes have been made and the list of local representatives in the PL has been revised to amend contact details for the representative(s) of Lituania, Bulgaria, Ungheria, Malta, Estonia, Poland, Croatia, Romania, Ireland, Slovenia, Lettonia, United Kingdom (Northern Ireland).

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons: The proposed changes in the context of this extension of indication do not involve a relevant impact on the PIL.

3. Benefit-Risk Balance

This extension of indication for Kisplyx is for the treatment of adults with advanced renal cell carcinoma (RCC) in combination with pembrolizumab, as first-line treatment based on the results of the Interim Analysis (IA3) from the pivotal study 307. This is an ongoing, Phase 3, randomized, open-label, multicenter, global study, to evaluate the efficacy and safety of lenvatinib in combination with everolimus or pembrolizumab versus sunitinib in previously untreated subjects with advanced/metastatic RCC

3.1. Therapeutic Context

3.1.1. Disease or condition

Worldwide, kidney cancer is the 14th most common cancer, and is the 9th most frequently diagnosed cancer in men and 14th in women (World Cancer Research Fund, 2020). Renal cell carcinoma is the most common type of kidney cancer, constituting the majority of primary renal neoplasms. Most cases of RCC (70%–80%) are classified as clear-cell tumours.

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 combination of avelumab plus axitinib, axitinib plus pembrolizumab, and cabozantinib plus nivolumab 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.

3.1.3. Main clinical studies

The pivotal study 307 (CLEAR)/KEYNOTE-581 is an multicentre, randomized, open-label, 3 arm Phase 3 study. A total of 1069 subjects were randomized 1:1:1, 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. Arm A of the study (lenvatinib and everolimus) is not part of the current submission. The ITT population includes 355 subjects in lenvatinib and pembrolizumab (arm B) and 357 subjects in the sunitinib arm (arm C). Three subjects (0.8%) in arm B ad 17 (4.8%) subjects in arm C were not treated.

The primary objectives of the study were to compare the PFS per RECIST 1.1 by Independent Imaging Review (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.

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

3.2. Favourable effects

A statistically significant benefit in PFS (IRR) has been observed for lenvatinib and pembrolizumab over sunitinib with HR=0.39 (95% CI: 0.32, 0.49, P<0.0001).

A statistically significant benefit in OS has been observed for lenvatinib and pembrolizumab over sunitinib with HR of 0.66 (95% CI: 0.49, 0.88, P=0.0049) at 22,5% of maturity in lenvatinib-pembrolimab arm and 28,3% of maturity in sunitinib arm.

Confirmed ORR per RECIST 1.1, as assessed by IIR in the lenvatinib plus pembrolizumab arm was higher the ORR in the sunitinib arm (71.0% and 36.1%, respectively). The odds ratio (OR) was 4.35 (95% CI: 3.16, 5.97; nominal P<0.0001) in favor of lenvatinib plus pembrolizumab. The median time to response was similar in both arms. 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 subgroups, while 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 307 hinders the assessment of the contribution of each component in the combination treatment. The indirect comparisons have provided for monotherapy data (in 2L for lenvatinib monotherapy) and the combination use is supported by mechanistic rationale.

3.4. Unfavourable effects

In the study 307, nearly all patients in both the lenvatinib + pembrolizumab and the sunitinib arms had at least one TEAE.

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%). TEAE leading to lenvatinib dose modifications occurred in 84.7% of the patients; dose modifications occurred early in the treatment. The median average daily lenvatinib dose was 14 mg, while the planned starting dose was 20 mg QD.

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 discontinuation (In the ≥65 to <75 years age group, 43.0% of subjects). More patients >75 years of age in the combination treatment arm had proteinuria events compared to the other age groups, and generally females experienced more Grade ≥3 events then males. However, given the imbalances in these stratification factors (14.66% and 28.4% of all combination treatment subjects) it is difficult to ascertain whether these observations have any clinical meaning. 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).

Hypothyroidism

Though the higher incidence of low grade events in the combination treatment may be due to an additive effect of both constituent components, it is not clear whether this may potentially lead to an interdependent worsening of the severity in some patients.

Renal events

It is not immediately clear why there was slightly higher incidence of Grade 3 events in the lenvatinib + pembrolizumab treatment group, despite the overall all-grade incidence being similar to the sunitinib one.

Arterial thromboembolic events

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. The difference in overall events between both treatment groups may potentially be caused by the large number of patients with pre-existing risk factors in the former.

3.6. Effects Table

Table 55 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: OS data from IA3too immature to assess the B/R in all relevant subgroups
OS (ITT)	OS, defined as the time from the date of randomization to the date of death from any cause.	Months HR (95% CI)	NR vs NR HR of 0.66 (95% CI: 0.49, 0.88, P=0.0049) in IA3		
ORR per RECIST	ORR, defined as the proportion of	%	71.0	36.1	

Effect	Short description	Unit	Pembro+ Lenvatinib	Sunitinib	Uncertainties / Strength of evidence
1.1 by IIR (ITT)	subjects who had best confirmed overall response of complete response or partial response		Odds ratio: 4.35 (3.16, 5.97)		
Unfavourable Effects					
AE summary			Lenvatinib/ Pembro arm (n=352)	**Sunitinib** arm (n=340)	
	Drug-related AE	%	96.9	92.1	Toxicity profile of combination therapy compares unfavourable with sunitinib;
	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	%	5.1	0.8	
	severe skin reactions	%	5.1	1.6	
	pancreatitis	%	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 superiority of lenvatinib-pembrolizumab treatment over sunitinib was demonstrated for the primary endpoint PFS, supported by differences in terms of ORR. The OS data were still immature at the time of submitted interim analyses,with the maturity reported of 29.6 % in the lenvatinib-pembrolizumab arm and 34.2 % in the sunitinib arm for most recent updated data. Currently available data indicate advantage in OS.

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. The main source of uncertainty, at present, remains the immaturity of OS data in the favourable risk group.

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 Kisplyx in combination with pembrolizumab first line treatment of adults with advanced renal cell carcinoma (RCC); as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 14.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder took the opportunity to make editorial changes and update the list of local representatives in the Package Leaflet.

Amendments to the marketing authorisation

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