25 July 2019
EMA/CHMP/455620/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: pembrolizumab

Procedure No. EMEA/H/C/003820/II/0069

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
BID	Twice daily
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
CR	Complete response
CPS	Combined proportion score
CSR	Clinical Study Report
DCR	Disease control rate
DFG-out	Asparagine-phenylalanine-glycine out
DOR	Duration of response
EC50	Half maximal effective concentration
ECOG	Eastern Cooperative Oncology Group
ESMO	European Society for Medical Oncology
EU	European Union
FDA	US Food and Drug Administration
FoxP3	Forkhead box P3
HNSCC	Head and neck squamous cell carcinoma
HR	Hazard ratio
IA1	Interim analysis 1
IFNα-2b	Interferon alpha 2b
IFNγ	Interferon gamma
IgG4	Immunoglobulin G4
IL-2	Interleukin 2
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
ITT	Intent-to-treat
IV	Intravenous
KEYNOTE(-426)	KN(426)
KM	Kaplan-Meier
KPS	Karnofsk Performance Status
MSI-H	Microsatellite instability-high
MSKCC	Memorial Sloan Kettering Cancer Center
mTOR	Mammalian target of rapamycin
NCCN	National Comprehensive Cancer Network
nccRCC	Non-clear cell renal cell carcinoma
NSCLC	Non-small 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 1 ligand 1
PD-L2	Programmed cell death 1 ligand 2
PFS	Progression-free survival
PK	Pharmacokinetics
PMBCL	Primary mediastinal large B-cell lymphoma
PR	Partial response

Abbreviation	Definition
Q3W	Every 3 weeks
Q6W	Every 6 weeks
Q8W	Every 8 weeks
Q12W	Every 12 weeks
QD	Once daily
RCC	Renal cell carcinoma
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RIP-Tag	Rat insulin promoter-SV40 T/t antigen
RSD	Reference Safety Dataset
RTK	Receptor tyrosine kinase
SAE	Serious adverse event
SAWP	Scientific Advice Working Party
SD	Stable disease
TILs	Tumor infiltrating lymphocyte
TNFα	Tumor necrosis factor alpha
TKI	Tyrosine kinase inhibitor
TPS	Tumor proportion score
TTR	Time to reponse
US	United States
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 9 January 2019 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 first line treatment of advanced or metastatic renal cell carcinoma (RCC) as combination therapy of pembrolizumab together with axitinib based on the results of the first Interim Analysis (IA1) from the pivotal study, KN426, an ongoing, Phase 3, randomized, open-label, multicenter, global study, to evaluate the efficacy and safety of pembrolizumab in combination with axitinib versus sunitinib in previously untreated subjects with advanced/metastatic RCC. It also includes supportive data from KEYNOTE-427 Cohort A (pembrolizumab monotherapy) and a Sponsored Study A4061051 (axitinib monotherapy). As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance.
In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.
The risk management plan (RMP) Version 24.1 is submitted.

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

Information on paediatric requirements

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

At the time of submission of the application, the PIP P/0043/2018 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant 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 advice has been obtained from the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) pertained to clinical aspects of the dossier regarding the design of the Keynote 426/427; Procedure No.: EMEA/H/SA/2437/13/2016/II. Objections were raised regarding the

choice of combination TKI (axitinib) and comparator (sunitinib). The CHMP did not support the proposed use of different TKI as comparator (sunitinib) and backbone treatment (axitinib in combination with pembrolizumab). A pure add-on trial with either sunitinib or axitinib as the comparator and backbone treatment was advised. In addition, the Applicant was advised to consider including a third arm, pembrolizumab monotherapy.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Daniela Melchiorri Co-Rapporteur: Jan Mueller-Berghaus

Timetable	Actual dates
Submission date	9 January 2019
Start of procedure	27 January 2019
CHMP Rapporteur's preliminary assessment report circulated on	25 March 2019
CHMP Co-Rapporteur's preliminary assessment report circulated on	22 March 2019
PRAC Rapporteur's preliminary assessment report circulated on	27 March 2019
PRAC RMP advice and assessment overview adopted by PRAC on	11 April 2019
CHMP Rapporteurs' updated joint assessment report circulated on	19 April 2019
Request for supplementary information adopted by the CHMP on	26 April 2019
MAH's responses submitted to the CHMP on	1 May 2019
CHMP Rapporteurs' preliminary joint assessment report on the MAH's responses circulated on	3 June 2019
2nd Request for supplementary information adopted by the CHMP on	27 June 2019
MAH's responses submitted to the CHMP on	2 July 2019
CHMP Rapporteurs' preliminary joint assessment report on the MAH's responses circulated on	11 July 2019
CHMP Opinion	25 July 2019

2. Scientific discussion

2.1. Introduction

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

Pembrolizumab

Keytruda (pembrolizumab) is a humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and, ultimately, immune rejection. In vitro and in vivo experiences have shown that PD-1 and PD-L1 blockade using a mAb can result in activation of antitumor T cells and subsequent tumor regression. In T-cell activation assays using human donor blood cells, the EC50 was in the range of 0.1 to 0.3 nM. Pembrolizumab also modulates the level of IL-2, TNFα,

IFNγ, and other cytokines. The antibody potentiates existing immune responses in the presence of antigen only; it does not nonspecifically activate T cells. The PD-1 pathway, especially the PD-1 receptor-ligand interaction, represents a major immune-control switch that may be engaged by ligands expressed in the tumor microenvironment to overcome active antitumor-specific T cell immune surveillance.

Keytruda is approved in EU for melanoma, NSCLC (both monotherapy and in combination with chemotherapy), refractory classical Hodgkin lymphoma, urothelial carcinoma, and HNSCC.

Clinical studies are being conducted in these tumor types, as well as in several other advanced solid tumor indications and hematologic malignancies.

Axitinib

Inlyta (axitinib) is an oral, potent and selective tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, VEGFR-2 and VEGFR-3. These receptors are implicated in pathologic angiogenesis, tumour growth, and metastatic progression of cancer. Axitinib has been shown to potently inhibit VEGFR-mediated endothelial cell proliferation and survival. Axitinib inhibited the phosphorylation of VEGFR-2 in xenograft tumour vasculature that expressed the target in vivo and produced tumour growth delay, regression, and inhibition of metastases in many experimental models of cancer

Inlyta is approved in EU for the treatment of advanced RCC after failure of 1 prior treatment with sunitinib or a cytokine.

Renal Cell Carcinoma (RCC)

RCC is the seventh most common cancer in men and the ninth most common in women, accounting for 2% to 4% of all adult malignancies. Approximately 85% of renal tumors are RCC and approximately 70% of these are of clear cell histology. Other less common histologies include papillary, chromophobe, translocation, and collecting duct tumors [NCCN Clinical Practice Guidelines in Oncology: kidney cancer: version 3.2019]. Smoking, obesity and hypertension are established risk factors for RCC. Several hereditary conditions, such as von Hippel-Lindau disease, predispose patients to having an increased risk of developing RCC [NCCN Clinical Practice Guidelines in Oncology: kidney cancer: version 3.2019]. At the initial diagnosis, approximately 65% of patients have localized disease; 16% have regional spread, and 16% have distant metastasis [Siegel RL, et al. Cancer statistics, 2018. CA Cancer J Clin. 2018].

In Europe, the expected number of new cases and deaths from kidney cancer for 2018 is 136,500 and 54,700, respectively [Ferlay J, et al. Eur J Cancer 2018;103:356-87.]. The 5-year survival rate for advanced RCC is still poor, approximately 12% [NCCN Clinical Practice Guidelines in Oncology: kidney cancer: version 3.2019].

Current Therapies for First-Line Advanced RCC

A number of medicines are approved in EU for the first-line treatment of advanced RCC.

According to the main guidelines (RCC: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, update January 2019; NCCN Clinical Practice Guidelines in Oncology: kidney cancer: version 3.2019) tumor histology and risk stratification is important in treatment selection. The Memorial Sloan Kettering Cancer Center (MSKCC) Prognostic Model has been the most widely used until recently to define risk groups of patients by combining five independent prognostic factors for survival (interval from diagnosis to treatment less than 1 year, Karnofski PS<80%, serum lactate dehydrogenase [LDH]>1.5 ULN, corrected serum calcium>ULN and serum hemoglobin<ULN). A prognostic model derived from a population of patients with metastatic RCC treated with VEGF-targeted treatment has been more recently developed, known as International Metastatic RCC Database Consortium (IMDC) score: this model take into consideration six clinical parameters to stratify patients into favourable, intermediate and poor

prognosis groups: interval from diagnosis to treatment less than 1 year, Karnofski PS<80%, corrected serum calcium>ULN, serum hemoglobin<ULN, absolute neutrophil count>ULN and platelets>ULN. The IMDC model has been derived from a retrospective study of 645 patients treated with VEGF-targeted agents (Heng DY, et al. J Clin Oncol 2009), and validated in an independent dataset (Heng DY, et al.Lancet Oncol 2013). The 2-year OS ranges from 75% in the favourable risk group (none of the 6 factors identified) to 7% in the poor-risk group (3 to 6 factors identified).

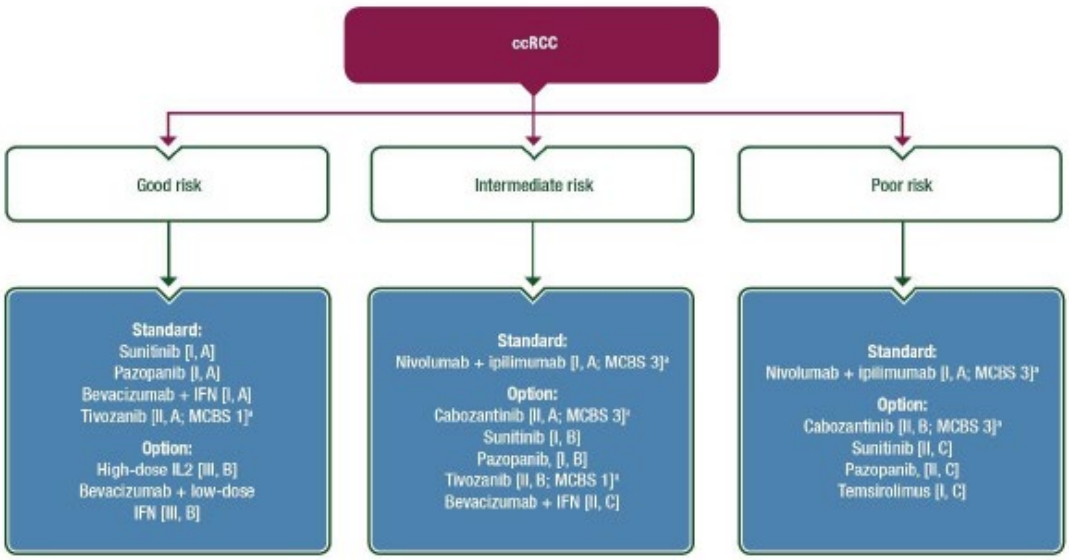
In the EU, the following agents targeting the VEGF/VEGFR signaling pathway are approved for the 1L treatment of advanced RCC: sunitinib, pazopanib, bevacizumab + IFNα, tivozanib and cabozantinib (in patients who are considered to be intermediate and poor risk).

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.

Axitinib and the mTOR inhibitor everolimus, as single agent or in combination with lenvatinib, are approved for patients with advanced RCC who have received prior treatment for their advanced disease. Nivolumab was also approved in the EU for the 2L+ setting after demonstrating a statistically significant and clinically meaningful improvement in OS compared with everolimus in patients who had received 1 or 2 prior anti angiogenic agents; however, this study failed to demonstrate an improvement in PFS.

The current ESMO clinical practice guidelines recommend the following treatments for treatment-naïve patients with advanced RCC:



Axitinib is only approved for the 2L treatment of advanced RCC. In a Phase 3 randomized study of axitinib versus sorafenib in treatment-naïve patients with advanced RCC (N = 288, randomized 2:1), axitinib failed to demonstrate a statistically significant improvement in the primary endpoint of PFS; however, axitinib demonstrated a clinically meaningful improvement in ORR [Hutson TE, et al. Lancet Oncol 2013; Hutson TE, et al., Clin Genitourin Cancer. 2017]. Based on these results, axitinib is considered by the NCCN as a treatment option (category 2B) for advanced RCC patients in the 1L setting [NCCN Clinical Practice Guidelines in Oncology: kidney cancer: version 3.2019].

Approved or Recommended First-Line Treatments for Advanced RCC

Study (N)	Median PFS (mos)/ HR (95% CI, p value)	Median OS (mos)/ HR (95% CI, p value)	ORR (%) (p value)	Reference
Sunitinib vs. IFNα (N = 750)	11.0 vs. 5 / 0.42 (0.32 – 0.54, p<0.001)	26.4 vs. 21.8 / 0.82 (0.67 – 1.00, p=0.051)	31 vs. 6 (p <0.001)	Motzer RC, et al., N Engl J Med. 2007 Motzer RJ, et al., J Clin Oncol. 2009
Pazopanib vs. Placebo (N = 233)[a]	11.1 vs. 2.8 / 0.40 (0.27 – 0.60, p<0.0001)	22.9 vs. 23.5 / 1.01 (0.72 – 1.42)	32 vs. 4	Sternberg CN, et al., J Clin Oncol. 2010 Sternberg CN, et al., Eur J Cancer. 2013
Bevacizumab + IFNα vs. IFNα (N = 649)	10.2 vs. 5.4 / 0.63 (0.52 – 0.75, p=0.0001)	23.3 vs. 21.3 / 0.91 (0.76 – 1.10, p=0.3360)	31 vs. 13 (p=0.0001)	Escudier B, et al., Lancet 2007 Escudier B, et al., J Clin Oncol. 2010
Sunitinib vs. pazopanib (N = 1110)[b]	9.5 vs. 8.4 / 1.05 (0.90 – 1.22)	29.3 vs. 28.4 / 0.91 (0.76 – 1.08, p=0.28)	25 vs. 31 (p=0.03)	Motzer RJ, et al., N Engl J Med. 2013
Temsirolimus vs. IFNα (N = 416)[c]	5.5 vs. 3.1 / NR	10.9 vs. 7.3 / 0.73 (0.58 – 0.92, p=0.008)	8.6 vs. 4.8	Hudes G, et al., N Engl J Med. 2007
Cabozantinib vs. Sunitinib (N = 157)[d]	8.2 vs. 5.6 / 0.66 (0.46 – 0.95, p=0.012)	30.3 vs. 21.8 / 0.80 (0.50 – 1.26)	46 vs. 18	Choueiri TK, et al. J Clin Oncol. 2017
Nivolumab + Ipilimumab vs. Sunitinib (N = 847)[d]	11.6 vs. 8.4 / 0.82 (0.64 – 1.05, p=0.03)[e]	Not reached vs. 26.0 / 0.63 (0.44 - 0.89, p <0.001)[e]	42 vs. 27 (p <0.001)	Motzer RJ, et al., N Engl J Med. 2018
Tivozanib vs sorafenib (N=517)	11.9 v 9.1 / 0.797 (0.639-0.993, p= .042)	29.3 v 28.8 / 1.245 (0.954- 1.624, p=.105)	33.1 vs. 23.3 (p=0.014)	Motzer RJ, et al., J clin Oncol. 2013
Axitinib vs. sorafenib (N = 288)	10.1 vs. 6.5 / 0.77 (0.56 – 1.05, p=0.038)	21.7 vs. 23.3 / 0.995 (0.731 – 1.356, p=0.4883)	32 vs. 15 (p=0.0006)	Hutson TE, et al., Lancet Oncol. 2013 Hutson TE, et al., Clin Genitourin Cancer. 2017

Abbreviations: HR = hazard ratio; IFNα = interferon alpha; mos = months; NR = not reported; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RCC = renal cell carcinoma.

a. Treatment-naïve population.
b. The sunitinib versus pazopanib study used a non-inferiority design which demonstrated that pazopanib was noninferior to sunitinib with the primary endpoint PFS meeting the predefined non-inferiority margin
c. Study enrolled a poor-prognosis population.
d. Data demonstrated in IMDC intermediate and poor risk populations.
e. Reported as 99.1% CI and 99.8% CI for PFS and OS, respectively.

Rationale for the combination of pembrolizumab and axitinib

Angiogenesis is integral to the biology of RCC. As such, anti-angiogenic agents targeting VEGF/VEGFR have substantially improved clinical outcomes in patients with advanced RCC, and are considered among the standard 1L treatment option for advanced RCC.

RCC has long been considered an immune-reactive tumor based on anecdotal reports of spontaneous remissions in advanced RCC patients with evidence of antigen specific lymphocyte infiltration of tumor tissues [Wierecky J, et al. Cancer Res 2006] and the fact that high dose IL-2 could produce durable

long-term responses in a small subset of advanced RCC patients. In RCC, upregulation of the PD-1 receptor on TILs and its ligand PD-L1 on tumors is associated with more aggressive disease and poor prognosis [Pedoeem A, et al. Clin Immunol 2014; Ahmadzadeh M, et al. Blood 2009]. In addition to pro angiogenic functions, VEGF has been shown to have immunosuppressive effects [Johnson BF, et al. Expert Opin Biol Ther 2007] and inhibition of VEGF signaling has been shown to enhance antigen-specific T-cell migration in RCC [Wallin JJ, et al. Nat Commun 2016]. The evidence supports targeting RCC with an immunotherapeutic approach in combination with inhibitors of the VEGF/VEGFR signaling axis.

The clinical activity of an anti-PD-1 agent in advanced RCC was first demonstrated by nivolumab in patients who had received prior anti-angiogenic agents [Motzer RJ, et al. N Engl J Med 2015]. Pembrolizumab has shown clinical efficacy when administered as a monotherapy for the 1L treatment of advanced RCC (Study KEYNOTE-427 - Cohort A). Given the clinical success of targeting the either the VEGFR or PD-1 axis independently, targeting these 2 pathways could provide a significant benefit to patients with advanced RCC. Specifically, KEYNOTE-035 (Study A4061079), which evaluated the combination of axitinib and pembrolizumab in treatment-naive advanced RCC, demonstrated substantial clinical efficacy with an apparently acceptable safety profile.

Based on the scientific rationale of targeting angiogenesis and immune-check point pathways, as well as the promising data from KEYNOTE-035, the combination of pembrolizumab and axitinib was tested in the pivotal Phase 3 KEYNOTE-426 study.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Pembrolizumab is a protein, which is expected to be metabolised in the body and biodegrade in the environment. Thus, according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00), pembrolizumab is exempt from the submission of an Environmental Risk Assessment as the product and excipients do not expect to pose a significant risk to the environment.

2.2.2. Discussion and Conclusion on non-clinical aspects

The applicant did not submit studies for the ERA. According to the guideline, in the case of products containing proteins as active pharmaceutical ingredient(s), the lack of ERA studies is acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The applicant 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 Number Status	Design	Population	Dosage Regimen	Primary Endpoint(s)
KN426 Ongoing; closed for enrollment	Phase 3, open-label, multicenter, global study to evaluate the efficacy and safety of pembrolizumab in combination with axitinib versus sunitinib monotherapy	Treatment-naïve participants with advanced ccRCC	Arm 1: Pembrolizumab 200 mg Q3W + axitinib 5 mg BID Arm 2: Sunitinib 50 mg QD; 4 weeks on and 2 weeks off	OS, PFS
KN427 Ongoing; closed for enrollment	Phase 2, open-label, multicenter, global study to evaluate the efficacy and safety of pembrolizumab	Treatment-naïve participants with advanced ccRCC (Cohort A) or nccRCC (Cohort B)	Pembrolizumab 200 mg Q3W	ORR
A4061051[c] Ongoing, enrollment terminated	Phase 3, randomized, open-label, multicenter study to evaluate the efficacy and safety of axitinib vs sorafenib	Participants with advanced ccRCC who have not received prior systemic first-line therapy	Axitinib 5 mg BID vs Sorafenib 400 mg BID	PFS
KN035 (Study A4061079)[c]	Phase 1b, open-label, dose finding study to evaluate the safety, pharmacokinetics, and pharmacodynamics of axitinib in combination with pembrolizumab	Participants with previously untreated advanced ccRCC	Dose-finding: Axitinib: 5 mg BID[a] + pembrolizumab 2 mg/kg Q3W Dose Expansion Axitinib 5 mg BID[b] + pembrolizumab 2 mg/kg Q3W	Determination of MTD for axitinib Safety

Abbreviations: BID = twice daily; ccRCC = clear cell renal cell carcinoma; KN = KEYNOTE; MTD = maximum tolerated dose; nccRCC = non clear cell renal cell carcinoma; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; Q3W = every 3 weeks; QD = once daily; RCC = renal cell carcinoma.

a. The starting dose of axitinib was 5 mg but could be reduced based on dose-limiting toxicities.
b. The MTD was determined to be 5 mg BID.
c. Sponsored by Pfizer Inc.

2.3.2. Pharmacokinetics

Clinical pharmacology results for the combination therapy of Pembrolizumab together with axitinib, specific to support approval for first line treatment of advanced or metastatic renal cell carcinoma (RCC), are available from the pivotal study KEYNOTE-426 and the Pfizer-sponsored study KEYNOTE-035 (Study A4061079).

The updated clinical pharmacology results specific to this submission include:

- PK data of pembrolizumab at 200 mg Q3W in combination with axitinib at 5 mg BID from KEYNOTE-426.
- A comparison of KN426 observed PK data with reference model (TDPK) predicted PK.
- PK data of axitinib at 5 mg BID alone and in combination with 2 mg/kg Q3W pembrolizumab from KEYNOTE-035.

Pharmacokinetic in target population

Axitinib, as monotherapy, is approved for the treatment of advanced renal cell carcinoma after failure of one prior systemic therapy.

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 axitinib and the predictions from the reference PK model developed with pembrolizumab monotherapy data (KEYNOTE-001, -002, -006, -010, and -024). This analysis is presented in the PK report (Report 052Z0C).

DDI between pembrolizumab and Axitinib are unlikely, considering the divergent metabolic pathways for both compounds. However, axitinib could be considered to have immunomodulatory effects and PK and/or
immunogenicity assessments are planned in cases where pembrolizumab is combined with another agent with potential immunomodulatory effect.
New data related to characterization of pharmacokinetics for the combination of pembrolizumab and axitinib, and a characterization of immunogenicity for pembrolizumab following co-administration with axitinib have been presented in this submission.

Pembrolizumab PK data from KEYNOTE-426 (KN426) study

PK samples were collected and measured for 423 subjects in KN0426 RCC (200 mg Q3W).

PK sample schedule in KN426: Predose pembrolizumab serum concentrations (Ctrough) were obtained within 24 hours prior to dosing at cycles 1, 3, 5 and every 4 cycles (12 weeks) thereafter. Postdose serum concentrations (Cmax) were drawn within approximately 30 minutes after the end of the infusion in cycle 1 and cycle 9.

Phoenix™ WinNonlin® (Version 6.3.0.395) software was used for pharmacokinetic analysis.

Overview of Pembrolizumab Cohorts Included in KN426 PK Analysis

Indication	Arm	Treatment	Number of Subjects providing PK[a]	Data cut off
RCC	1	MK3475 200 mg Q3W + axitinib 5 mg BID	423	24-Aug-2018

[a] number of unique subjects from arm 1 in dataset
Data Source: [052Z0C: analysis-P426pkdm0usfiling0v3.csv]

Summary statistics of the observed pembrolizumab trough (pre-dose) and post-dose concentrations in RCC subjects from KN0426 are presented in the table below:

Summary Statistics of Pembrolizumab Predose (C_{trough}) and Postdose (C_{max}) Serum Concentration Values Following Administration of Multiple I.V. Doses 200 mg Q3W in KN426

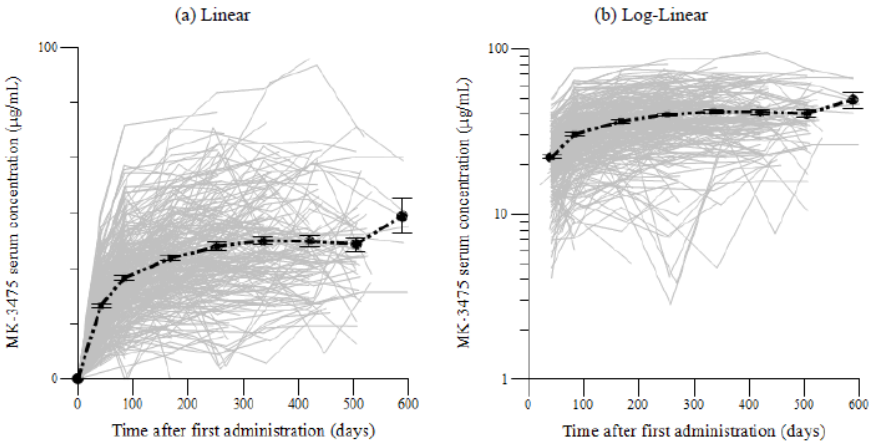
Cycle	NOMTAFD day	N	GM (%CV)	GM (SD)	AM (SD) (µg/mL)	Min	Median	Max
Predose (C_{trough})								
Cycle 3 (Week 6)	42	354	20.4 (43.5)	20.4 (8.4)	22.1 (8.4)	4.07	21.2	50.4
Cycle 5 (Week 12)	84	319	-	-	30.4 (12.3)	0.00	28.8	76.6
Cycle 9 (Week 24)	168	248	-	-	36.4 (13.8)	0.00	35.6	75.7
Cycle 13 (Week 36)	252	205	35.8 (57.5)	35.8 (16.0)	39.9 (16.0)	2.83	37.9	86.4
Cycle 17 (Week 48)	336	142	39.0 (39.2)	39.0 (15.2)	41.7 (15.2)	11.7	39.2	89.5
Cycle 21 (Week 60)	420	90	38.5 (41.7)	38.5 (16.0)	41.5 (16.0)	7.66	39.8	96.8
Cycle 25 (Week 72)	504	48	38.0 (40.6)	38.0 (14.4)	40.6 (14.4)	10.5	38.7	76.2
Cycle 29 (Week 84)	588	7	47.3 (32.5)	47.3 (14.1)	49.2 (14.1)	26.2	48.5	66.9
Postdose (C_{max}) (within 30 min post end of infusion)								
Cycle 1 (Week 0)	0	378	61.2 (28.4)	61.2 (17.8)	63.6 (17.8)	27.3	61.7	152
Cycle 9 (Week 24)	168	240	106 (27.4)	106 (28.9)	110 (28.9)	46.3	108	230

NOMTAFD = Nominal time after first pembrolizumab administration;
GM = Geometric Mean; CV% = Geometric Coefficient of Variation;
SD = Standard Deviation; AM = Arithmetic Mean; - : not applicable;
Results reported for time points with N ≥ 3.

[052Z0C: analysis-P426pkdm0usfiling0v3.csv]

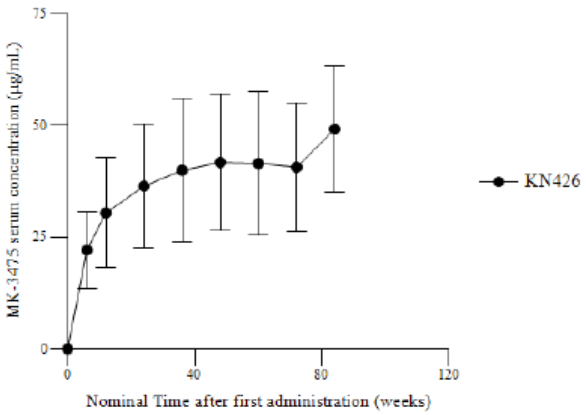
The following figures show the individual and mean predose concentration-time profiles:

Individual and Arithmetic Mean (SE) Pembrolizumab Concentration - Time Profiles Following Multiple I.V. Doses of 200 mg Q3W in Study KN426 (a) Linear scale, (b) Log scale



Note: Grey lines represent individual concentration observations. Black dashed lines represent arithmetic mean concentrations and error bars are associated +/- SE (Standard Error).
Data Source: [052Z0C: analysis-P426pkdm0usfiling0v3.csv]

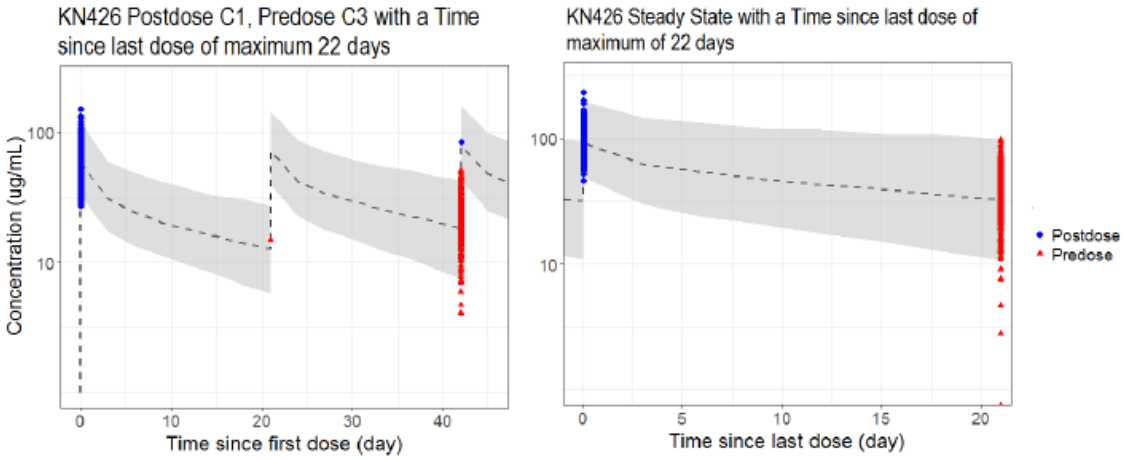
Arithmetic Mean (SD) Pembrolizumab Concentration -Time Profiles Following Multiple I.V. Doses of 200 mg Q3W to Subjects in Study KN426 (Linear scale)



Note: This plot is Arithmetic Mean with Standard Deviation (SD). X-axis unit is in weeks.
Data Source: [052Z0C: analysis-P426pkdm0usfiling0v3.csv]

The observed and predicted pembrolizumab concentration-time profiles following 200 mg Q3W administration at postdose cycle 1 and predose cycle 3 and at steady state with a time since last dose of maximum 22 days are illustrated in the following figure:

Observed Concentration Data with a cut off of 22 days after last dosing of KN426 Subjects Receiving 200 mg Q3W Pembrolizumab with Reference Model-Predicted Pharmacokinetic Profile for 200 mg Q3W Dose Regimen



Postdose cycle1 and cycle 9, predose before cycle 3 dosing and predose at steady state on log scale. Red and blue symbols are individual observed data (nominal time) from subjects with renal cell carcinoma in KN426; 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: [052Z0C: analysis-P426pkdm0usfiling0v3.csv]

Predose pembrolizumab serum concentrations (Ctrough) were obtained within 24 hours prior to dosing at cycles 1, 3, 5 and every 4 cycles (12 weeks) thereafter. Postdose serum concentrations (Cmax) were obtained about 30 minutes after the end of the infusion in cycle 1 and cycle 9.

The observed concentrations in RCC patients treated with Pembrolizumab in combination with Axitinib generally fall within the range of predicted concentrations, both after first dose and at steady state, although some low concentrations don't fall in the 90% PI.

Tabular summaries of descriptive statistics and boxplots comparing observed pembrolizumab concentrations of 200 mg every 3 weeks (Q3W) from participants with RCC in KEYNOTE-426 in combination with axitinib with those obtained with the 200 mg Q3W flat dose for other tumor types in the monotherapy setting were provided as requested. (see below)

Table 6 Summary Statistics of Observed Pembrolizumab Concentrations at 200 mg Q3W in Various Monotherapy Trials (KEYNOTE-024, -045, -052, -055, -087, -158, -164) and in Combination with Axitinib (KEYNOTE-426)

Time point	Dose	Study/ Indication	N	GMCV (µg/mL)	AMSD (µg/mL)	Min (µg/mL)	Median (µg/mL)	Max (µg/mL)
Cycle 1 Postdose	200mg	KN024 NSCLC	147	67.5 (23)	69.27 (16)	36.6	66.8	132
		KN045 UC	247	65.7 (26)	67.93 (18)	33.9	65.9	144
		KN052 UC	298	58 (28)	60.18 (17)	22.8	57.4	148
		KN055 HNSCC	43	56.5 (28)	58.94 (21)	33.1	54.9	162
		KN087 HL	195	60.7 (28)	63.06 (18)	31.2	61.3	183
		KN158 MSIH	90	64.4 (27)	66.65 (18)	31.2	65.2	133
		KN164 MSIH	56	62.2 (28)	64.59 (19)	34.9	61.2	150
		KN426 RCC	378	61.2 (28)	63.58 (18)	27.3	61.7	152
Cycle 8 Predose		KN024 NSCLC	82	30.6 (50)	33.61 (13)	5.26	32.7	64.1
		KN045 UC	104	33.4 (64)	37.83 (17)	1.13	37.5	95.6
		KN052 UC	59	28 (38)	29.86 (10)	8.15	27.9	59.8
		KN055 HNSCC	7	27.8 (41)	29.64 (11)	16.8	24.5	43.3
		KN087 HL	68	43.9 (43)	47.37 (17)	13.9	47.5	92.4
		KN164 MSIH	34	33.6 (43)	36.23 (14)	8.40	33.7	78.8
Cycle 9 Predose		KN426 RCC	248		36.43 (14)	0.00	35.6	75.7

Figure 12 Observed Peak Pembrolizumab Concentrations Post Cycle 1 in Various Monotherapy Trials (KEYNOTE-024, -045, -052, -055, -087, -158, -164) and in the Combination Trial with Axitinib (KEYNOTE-426)

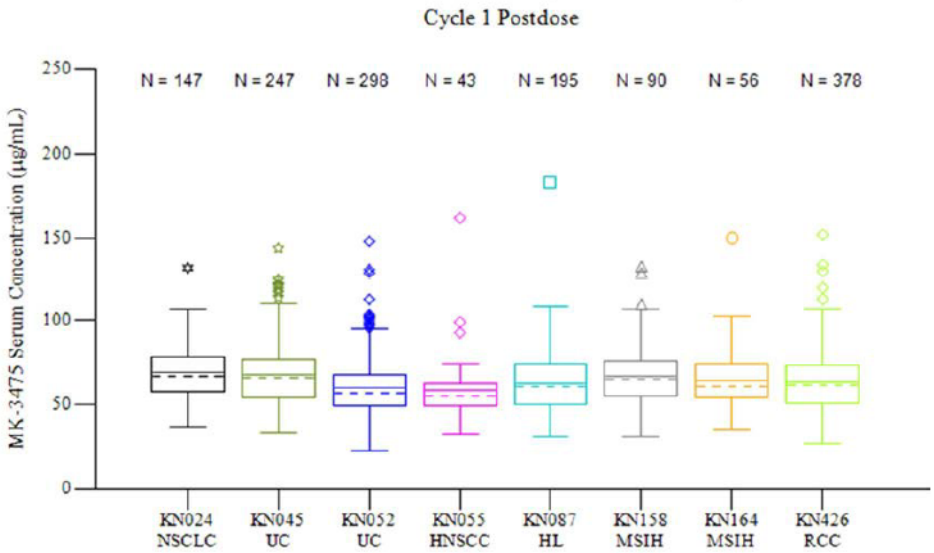
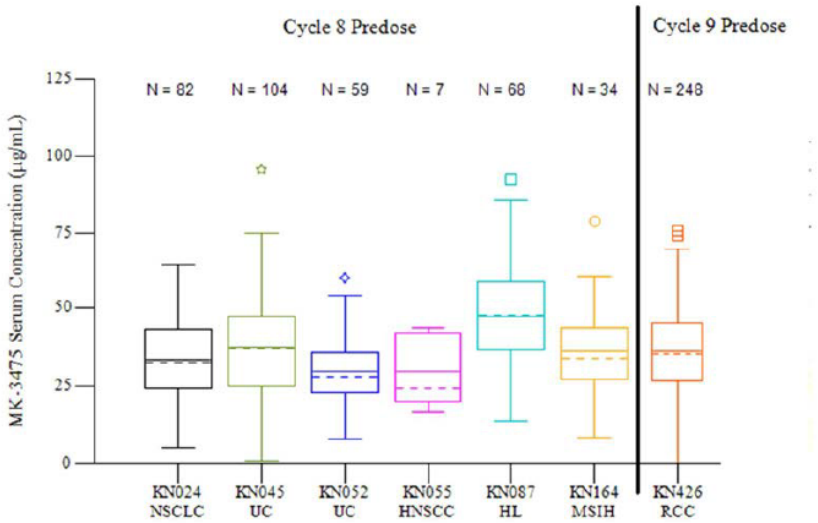


Figure 13 Observed Trough Pembrolizumab Concentrations at Cycle 8 or Cycle 9 Pre-dose in Various Monotherapy Trials (KEYNOTE-024, -045, -052, -055, -087, -158, -164) and in the Combination Trial with Axitinib (KEYNOTE-426)



Axitinib PK data (Alone and in Combination with Pembrolizumab) from KEYNOTE-035 (Study A4061079)

The single sequence DDI assessment in this study was conducted using a 7-day in Lead-in Cycle where daily 5 mg or 3 mg doses of axitinib were to be administered alone for 7 days, with axitinib full PK profile assessment conducted on Day 7 of the Lead-in Cycle. Following the Lead-in Cycle, axitinib was co-administered with MK-3475 continuously, with another axitinib full profile PK assessment conducted on Day 1 of Cycle 7. This design allowed comparison of the multiple dose PK of axitinib administered alone (Lead-in Day 7) to the multiple dose PK of axitinib administered in combination with multiple dose MK-3475 (Cycle 7 Day 1) to assess the potential effect of MK-3475 DDI on axitinib PK.

Summary of Plasma Axitinib Pharmacokinetic Parameters Following Daily 5 mg or 3 mg Oral Doses of Axitinib Alone and in Combination with MK-3475 in Study A4061079

Parameter [Units]	Parameter Summary Statistics[a] by Treatment	
	Axitinib Alone Lead-in Day 7	Axitinib + MK-3475 Cycle 7 Day 1
N	7	7
AUC_{12} [ng·hr/mL]	88.51 (71)	101.3 (63)
AUC_{12}(dn) [ng·hr/mL/mg]	17.70 (71)	21.79 (50)
C_{max} [ng/mL]	23.98 (58)	20.95 (52)
C_{max}(dn) [ng/mL/mg]	4.797 (58)	4.507 (46)
T_{max} [hr]	2.00 (0.00-3.00)	3.00 (1.00-6.00)

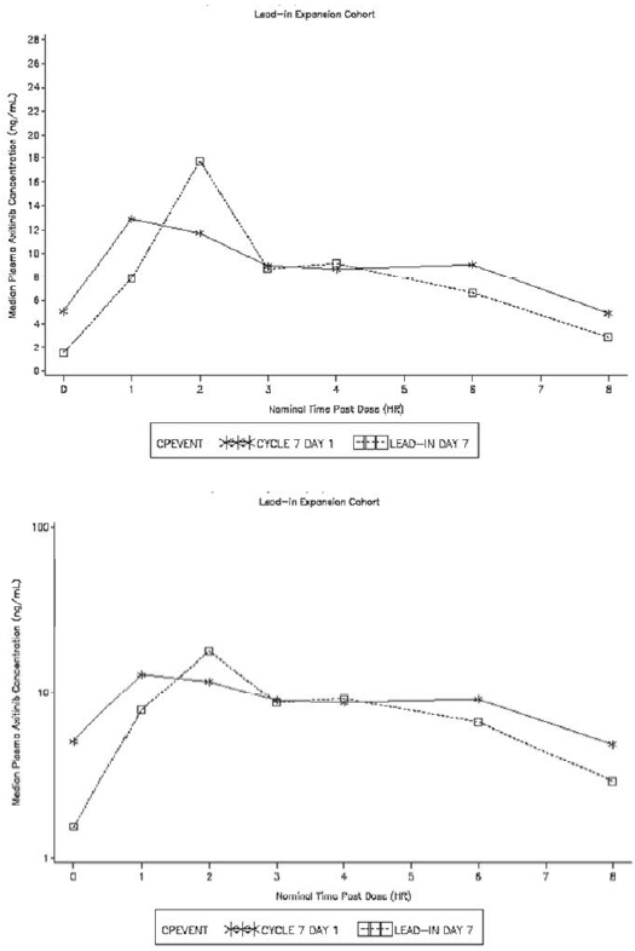
[a] Geometric mean (geometric %CV) for all except: median (range) for T_{max}.
N = Number of subjects contributing to the summary statistics.
Parameters are defined in Table 1.
Source: Table 14.4.3.1

Treatment Comparison For Axitinib Pharmacokinetic Parameters in Study A4061079

Parameter [units]	Axitinib + MK-3475 (Cycle 7 Day 1) (Test)	Axitinib Alone (Lead-in Day 7) (Reference)	Ratio % (Test/Reference)
AUC_{12}(dn) [ng·hr/mL/mg]	21.79	17.70	123.11
C_{max}(dn) [ng/mL/mg]	4.507	4.797	93.95

Source: Table 14.4.3.1

Median axitinib plasma concentration-time profiles were similar when axitinib was administered alone and with MK-3475 dose-normalized AUC12 and Cmax, geometric ratios of 1.23 and 0.94 respectively indicating no clinically meaningful DDI effect.



Upper and lower panels are linear and semi-logarithmic scales, respectively.
Axitinib + MK 3475 (Cycle 7 Day 1) and Axitinib Alone (Lead in Day 7)
Source: [Ref. 5.3.5.4: P1079V01: Figure 14.4.2.2.1] [Ref. 5.3.5.4: P1079V01: Figure 14.4.2.2.2]

Overview of bioanalytical methods and assay validation

Pembrolizumab (MK-3475) Quantification Method Validation

The assay was originally developed and validated at Merck Research Laboratories (Oss, The Netherlands) in September 2010. A full assay validation was performed that evaluated assay performance characteristics typical for validation of ligand binding assay methods.
This first generation validated assay was not used to support quantitative bioanalysis of pembrolizumab concentrations in serum samples collected from clinical studies. This assay served as the foundation for later method transfer validation to the CRO, Intertek (San Diego, CA).
Following transfer of the first generation Oss assay to Intertek, the method underwent refinement and transfer validation in August 2011
The method (2nd generation assay, Report 4020) was used to support bioanalysis of MK-3475 in serum samples from clinical study P001.
This second generation method validated at the CRO Intertek was updated and underwent further validation in May 2013 to become the third generation assay. Method selectivity in normal and disease populations was one of the key performance characteristics investigated during partial re-validation to meet the guidance
requirement to perform selectivity assessments using control samples prepared at the Lower Limit of Quantitation (LLOQ=10 ng/mL).
This third generation method was later transferred and cross-lab validated at a second CRO, PPD (Richmond, VA) to increase the level of automation, increase of sample throughput and reduce variability.
During the continued use of the 3rd generation assay at PPD it was noticed that variability at the LLOQ level of 10 ng/mL prevented the appropriate assessment of the influence of new disease states on the assay. Therefore, it was decided to raise the LLOQ of the assay and change the concentration of the QCs to appropriately span the new range of the assay.
Accuracy and precision of the new QCs were assessed and appeared to be within the already established accuracy and precision. Moreover, due to the logistical difficulties in shipping clinical serum samples collected in China from China to PPD laboratories in USA, the 3rd generation assay at PPD was transferred and cross-validated at Wuxi AppTec laboratories in Shanghai, China.
The validated method at Wuxi is utilized to support Pembrolizumab drug concentration analysis for study protocols where Chinese subjects are enrolled through clinical sites in China.

Pembrolizumab (MK-3475) ADA Method Validation

The ADA assay was originally developed and validated at Merck Research Laboratories (Oss, The Netherlands) in November 2010, with a full assay validation. The assay was transferred to Intertek (San Diego, CA) and underwent method transfer validation in September 2011.
The method was later transferred and re-validated at a second CRO, PPD (Richmond, VA) to perform ADA analysis at the same lab conducting quantitation of pembrolizumab in serum samples.
Due to the logistical difficulties in shipping clinical serum sample out of China for bioanalytical testing, ADA method was fully validated at Wuxi AppTec laboratory in Shanghai, China to perform ADA analysis of samples for studies in which Chinese subjects are enrolled through clinical sites in China.
With method developed at Intertek, the anti-CDR enriched ADA positive control at 250 ng/mL can tolerate up to 25 μg/mL of pembrolizumab. The method at PPD, which includes extended overnight incubation times and optimized acid neutralization timing for further drug tolerance enhancement, can tolerate up to 124 μg/mL drug in an ADA positive control spiked at 250 ng/mL of anti-CDR enriched ADA.
The method used at Wuxi achieved comparable drug tolerance to PPD; the method can tolerate up to 9 μg/mL drug in an ADA positive control spiked at 250 ng/mL of anti-CDR enriched ADA.

Pembrolizumab (MK-3475) Nab Method Validation

The first generation assay was originally developed and validated at Merck's Oss site (The Netherlands) in January 2011. A full assay validation evaluated assay performance characteristics typical for neutralizing ADA assays. The Oss assay method was transferred to the CRO, Intertek (San Diego, CA), and was transfer validated in December 2011. The NAb assay method was redesigned and validated at a second CRO, PPD (Richmond, VA) as a second generation assay. The assay was validated at PPD in September 2016.

This assay was later transfer validated at Wuxi AppTec in Shanghai, China to evaluate neutralizing capacity of samples tested positive for ADA at Wuxi.

Bioanalytical report related to study KEYNOTE-426

Report 054620: *Analysis of Samples Using an ECL Method for the Quantification of MK-3475 in Human Serum.*

This analysis was conducted for Merck Sharp & Dohme Corp. by PPD® Laboratories.

Two thousand eight hundred thirty-nine (2839) original and two thousand seven hundred sixty-five (2765) replicate human serum samples were received frozen and in good condition in 45 shipments from Q2 Solutions (Valencia, California and Bath Gate, United Kingdom) between 21 December 2016 and 06 September 2018. The samples were stored frozen at -80°C ± 10°C and all samples were analyzed within the 1218 days demonstrated long-term storage stability in human serum at -80°C ± 10°C.

The assay used in the analysis of study samples is a quantitative assay designed to quantify MK-3475 in human serum.

A nominal MK-3475 concentration range of 25.0 to 800 ng/mL in 100% human serum was chosen to quantitate samples. The calibration standards ranged from 1.00 to 125 ng/mL, with anchor calibrators at 1.00 and 125 ng/mL after correction for the 1:10 MRD. This assay required a minimum 20 µL human serum aliquot (or more for TECAN use). Calibration standards and quality control samples were prepared using reference. Standards and Certificates of Analysis for these standards are attached to the bioanalytical report.

Analysis of the human serum samples began on 25 April 2017 and was completed on 28 September 2018. Regression equations and correlation coefficients were calculated. The Average Correlation Coefficient was 0.9976. Back-calculated calibration data are found in the following table:

Average Back-calculated Calibration Standards

Run ID /RGTQ	CAL 11* (ng/mL)	CAL 12 (ng/mL)	CAL 13 (ng/mL)	CAL 14 (ng/mL)	CAL 15 (ng/mL)	CAL 16 (ng/mL)	CAL 17 (ng/mL)	CAL 18* (ng/mL)
N	97	98	98	98	98	98	98	98
Theoretical Concentration	1.00	2.50	5.00	10.0	20.0	40.0	80.0	125
Mean	1.00	2.49	5.02	10.0	20.2	40.1	79.7	126
SD	0.0170	0.0693	0.102	0.235	0.457	0.784	1.60	2.48
%CV	1.70	2.78	2.03	2.34	2.27	1.96	2.01	1.97
% Difference from Theoretical	0.238	-0.200	0.307	0.378	0.790	0.267	-0.437	0.548

Legend:
* Denotes anchor calibrators.
a Cal deactivated per SOP.

Precision and accuracy were evaluated by replicate analyses of human serum quality control pools prepared at three concentrations spanning the calibration range. Precision was measured as the percent

coefficient of variation (%CV) of the set of values for each pool. Accuracy was expressed as the percent difference of the mean value for each pool from the theoretical concentration. Inter-assay data are presented in the following table:

Inter-assay Precision and Accuracy

Run ID RGTQ	QC 11 Dil 10 (ng/mL)	QC 12 Dil 10 (ng/mL)	QC 13 Dil 10 (ng/mL)
N	194	192	196
Theoretical Concentration	70.0	150	600
Mean	69.1	151	594
SD	5.46	18.8	39.2
%CV	7.90	12.4	6.60
% Difference from Theoretical	-1.30	0.458	-0.984
Low Limit	56.0	120	480
High Limit	84.0	180	720

Legend:
rcv Replicate coefficient of variation unacceptable.

Report 054622: *Analysis of Samples Using an Electrochemiluminescent (ECL) Method for the Detection of Anti-MK-3475 Antibodies (ADA) in Human*

Human serum samples were analyzed for anti-MK-3475 antibodies in support of Protocol Number MK-3475-426. Two thousand one hundred sixty-six (2166) original and three thousand one hundred sixty-two (3162) replicate human serum samples were received frozen and in good condition from Q2 Solutions (Valencia, California and Bath Gate, United Kingdom) between 21 December 2016 and 06 September 2018. The samples were stored frozen at -80°C ± 10°C. Project samples were analyzed according to the bioanalytical plan and PPD Method ICDIM 201 V 1.02, entitled "An Electrochemiluminescent (ECL) Method for the Detection of Anti-MK-3475 Antibodies in Human Serum," This method employs a three-tiered approach consisting of a screening assay, confirmatory assay, and titration assay.

Sample results are acceptable if the %C.V. between duplicate responses is less than or equal to 20%. A higher %C.V. between duplicate responses is acceptable if the responses for both wells are above the assay cut point or if both responses are below the assay cut point.

Report 054623: *Analysis of Samples Using an Electrochemiluminescent (ECL) Method for the Detection of Anti-MK-3475 Neutralizing Antibodies in Human Serum*

Human serum samples were analyzed to detect anti-MK-3475 neutralizing antibodies (NAb) in support of Protocol Number MK-3475-426.

Two thousand one hundred sixty-six (2166) original and three thousand one hundred sixty-two (3162) replicate human serum samples were received frozen and in good condition in 42 shipments from Q2 Solutions (Valencia, California and Bath Gate, United Kingdom) between 21 December 2016 and 06 September 2018. These samples were first tested in the electro-chemiluminescent immunoassay for the detection of anti-MK-3475 antibodies. Samples that were confirmed to be positive for anti-MK-3475 antibodies were tested for neutralizing capacity. The assay for the detection of neutralizing antibodies to MK-3475 (ICDIM 202 V 2.01) from Protocol MK-3475-426 was assigned the unique PPD project code "RGTS."

All samples from project RGTR which confirmed positive in the ADA immunoassay to date were analyzed for the presence of neutralizing antibodies. Sample analysis was conducted under Project Code "RGTS" using method ICDIM 202 V 2.01.
The NAb assay method, entitled "An ECL Method for the Detection of Anti-MK-3475 Neutralizing Antibodies in Human Serum," was validated under Project Code "RFRI2" and is described under PPD Method ICDIM 202 V 2.01.

Analysis of human serum samples took place in six runs beginning on 19 December 2017 and ending on 28 September 2018. See below in section "Immunogenicity".

2.3.3. Pharmacodynamics

Mechanism of action

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

Primary and secondary pharmacology

Immunogenicity

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

Immunogenicity evaluation for study KEYNOTE-426
For pembrolizumab combination therapy (200 mg pembrolizumab Q3W + 5 mg axitinib BID), ADA samples were available from 434 subjects. A subset of the subjects was not assessable for drug-induced immunogenicity because the subjects were not treated with pembrolizumab (N=12) or only a pre-treatment ADA sample was available (N=16). The remaining 406 subjects were included in the immunogenicity assessment.

Overview of Subjects Included in the Immunogenicity Analysis after Pembrolizumab Combination Therapy, 200 mg Pembrolizumab Q3W + 5 mg Axitinib BID (KN426)

Study	Indication	Subjects		
		Subjects providing ADA Samples	**Subjects Dosed with Pembrolizumab**	**Assessable Subjects** Subjects Dosed with Pembrolizumab and Post Treatment Samples
Pembrolizumab Combination Therapy				
KN426	Renal Cell Carcinoma	434	422	406

Data source [053033: analysis-p426pkada0usfilingv5]

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).

Summary of Subject Immunogenicity Results after Pembrolizumab Combination Therapy, 200 mg Pembrolizumab Q3W + 5 mg Axitinib BID (KN426)

Stratified by treatment	
Immunogenicity status	**Renal Cell Carcinoma 200 mg pembrolizumab Q3W + 5 mg axitinib BID**
Assessable subjects[a]	406
Inconclusive subjects[b]	17
Evaluable subjects[c]	**389**
Negative[d]	358 (92.0%)
Non-Treatment emergent positive[d]	7 (1.8%)
Neutralizing negative	5 (1.3%)
Neutralizing positive	2 (0.5%)
Treatment emergent positive[d]	24 (6.2%)
Neutralizing negative	21 (5.4%)
Neutralizing positive	3 (0.8%)

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.

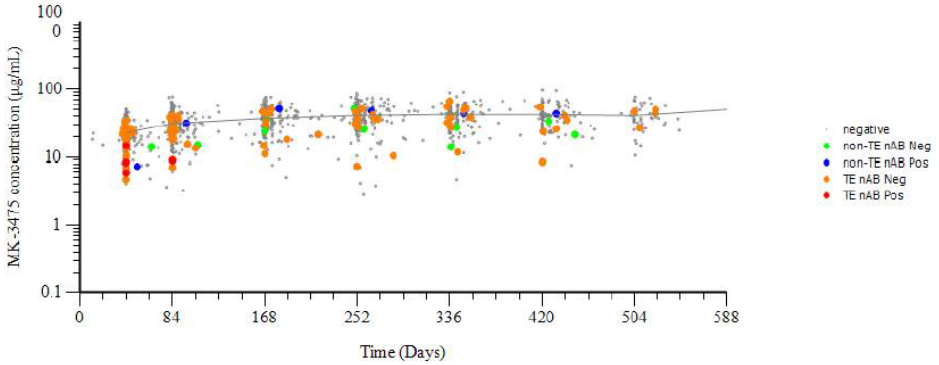
Data source [053033: analysis-p426pkada0usfilingv5]

The observed incidence of treatment emergent ADA in evaluable subjects after pembrolizumab combination therapy is 6.2% (24 out of 389), based on 24 subjects with treatment emergent positive, 7 with non-treatment emergent positive and 358 with negative immunogenicity status. Three of the 24 treatment emergent positive subjects, had antibodies with neutralizing capacity, yielding an incidence of treatment emergent neutralizing positive subjects of 0.8% (3 out of 389).

Impact of ADA 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.

Effect of ADA on Pembrolizumab Exposure, for Subjects Treated with 200 mg Pembrolizumab Q3W + 5 mg Axitinib BID (KN426)



Footnote: Figure includes ADA samples with corresponding PK concentrations. Samples taken > 42 days after last dose (> 2 times the scheduled time) are excluded.

Individual pembrolizumab concentrations for the ADA negative subjects (grey dot), mean value of the negative subjects (grey line), non-treatment emergent neutralizing negative subjects (green dot), non-treatment emergent neutralizing positive subjects (blue dot), treatment emergent neutralizing negative subjects (orange dot), treatment emergent neutralizing positive subjects (red dot).

If a subject is determined to be ADA positive (TE or non-TE, based on one or more positive samples), all data-points belonging to that subject are shown in the color of the corresponding ADA status group.

Data source [053033: analysis-p426pkada0usfilingv5]

For all of the ADA positive subjects, the pembrolizumab exposure was similar to that for other subjects treated with the same regimen.

Impact of ADA on Pembrolizumab Safety

The ADA positive subjects (treatment emergent and non-treatment emergent), were evaluated for potential impact on safety. The safety profile in ADA positive subjects was compared with negative subjects. (see table below)

Overview of Impact of ADA on Adverse Events Incidence after Pembrolizumab Combination Therapy, 200 mg Pembrolizumab Q3W + 5 mg Axitinib BID (KN426)

	negative		non-TE nAB Neg		non-TE nAB Pos		TE nAB Neg		TE nAB Pos	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	358		5		2		21		3	
with one or more adverse events	354	(98.9)	5	(100.0)	2	(100.0)	21	(100.0)	3	(100.0)
with no adverse event	4	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
with drug-related† adverse events	349	(97.5)	4	(80.0)	2	(100.0)	21	(100.0)	3	(100.0)
with toxicity grade 3-5 adverse events	269	(75.1)	4	(80.0)	2	(100.0)	17	(81.0)	3	(100.0)
with toxicity grade 3-5 drug-related adverse events	221	(61.7)	3	(60.0)	2	(100.0)	16	(76.2)	2	(66.7)
with serious adverse events	147	(41.1)	3	(60.0)	1	(50.0)	10	(47.6)	2	(66.7)
with serious drug-related adverse events	84	(23.5)	3	(60.0)	1	(50.0)	6	(28.6)	1	(33.3)
who died	13	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	100	(27.9)	3	(60.0)	2	(100.0)	11	(52.4)	1	(33.3)
discontinued drug due to a drug-related adverse event	81	(22.6)	1	(20.0)	2	(100.0)	9	(42.9)	1	(33.3)
discontinued drug due to a serious adverse event	61	(17.0)	2	(40.0)	1	(50.0)	5	(23.8)	1	(33.3)
discontinued drug due to a serious drug-related adverse event	41	(11.5)	1	(20.0)	1	(50.0)	3	(14.3)	1	(33.3)

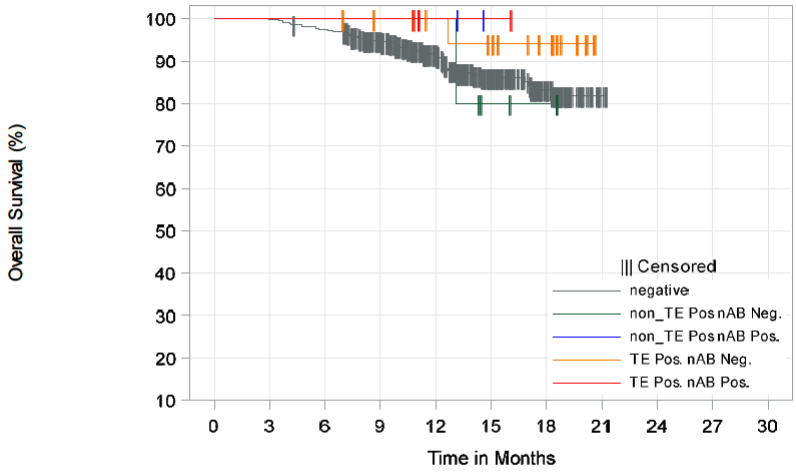
† Determined by the investigator to be related to the drug.
Grades are based on NCI CTCAE version 4.0.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Database Cutoff Date: 24Aug2018.
Subjects with inconclusive ADA results are excluded

Source: [P426V01MK3475: adam-adsl; adae; adbase]

Impact of ADA on Pembrolizumab Efficacy

Only an exploratory impact of ADA on overall survival (OS) over time was visually examined, considering that there are only three subjects with TE Nab positive status. The figure shows that OS was similar across all ADA subgroups.

Kaplan-Meier Estimates of Overall Survival Curves for Subjects Treated with 200 mg Pembrolizumab Q3W + 5 mg Axitinib BID (KN426)



n at risk

negative	358	357	348	298	216	135	66	3	0	0	0
non_TE Pos nAB Neg.	5	5	5	5	5	2	1	0	0	0	0
non_TE Pos nAB Pos.	2	2	2	2	2	0	0	0	0	0	0
TE Pos. nAB Neg.	21	21	21	19	17	15	11	0	0	0	0
TE Pos. nAB Pos.	3	3	3	3	1	1	0	0	0	0	0

Database Cutoff Date: '24AUG2018'd

2.3.4. PK/PD modelling

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

2.3.5. Discussion on clinical pharmacology

Clinical pharmacology results for the combination therapy of Pembrolizumab together with axitinib specific to support approval for first line treatment of advanced or metastatic renal cell carcinoma (RCC), are available from the pivotal study KEYNOTE-426 and the Pfizer-sponsored study KEYNOTE-035 (Study A4061079).

A substantial characterization of the key clinical pharmacology and immunogenicity findings of pembrolizumab as monotherapy have been provided in previous submissions. Axitinib, as monotherapy, is approved for the treatment of advanced renal cell carcinoma after failure of one prior systemic therapy.

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 axitinib 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, 3, 5 and every 4 cycles (12 weeks) thereafter. Postdose serum concentrations (Cmax) were obtained about 30 minutes after the end of the infusion in cycle 1 and cycle 9.

The observed concentrations in RCC patients treated with Pembrolizumab in combination with Axitinib generally fall within the range of predicted concentrations, both after first dose and at steady state, although some low concentrations don't fall in the 90% PI.

As requested, the MAH provided tabular summaries of descriptive statistics and boxplots comparing observed pembrolizumab concentrations of 200 mg every 3 weeks (Q3W) from participants with RCC in KEYNOTE-426 in combination with axitinib with those obtained with the 200 mg Q3W flat dose for other tumor types in the monotherapy setting. These data showed the consistency among exposure obtained in monotherapy with those obtained in combination therapy.

Treatment comparison for axitinib PK parameters (study A4061079) showed that median axitinib plasma concentration-time profiles were comparable when axitinib was administered alone and with pembrolizumab. In addition, comparison of axitinib exposures, as assessed by the PK parameters dose-normalized AUC12 and Cmax, when axitinib was administered alone or in combination, yielded geometric ratios of 1.23 and 0.94 respectively, indicating no clinically meaningful DDI effect.

The exposures observed in this study with or without co-administration of pembrolizumab are within the range of exposures historically observed with axitinib.

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

For pembrolizumab combination therapy (200 mg pembrolizumab Q3W + 5 mg axitinib BID), ADA samples were available from 434 subjects (only 406 subjects were included in the final immunogenicity assessment).

The incidence of treatment-emergent ADA to pembrolizumab in subjects with RCC treated with pembrolizumab in combination with axitinib was ~6% (24 out of 389 total evaluable samples) that is higher compared to the overall incidence in the monotherapy setting (1.8%).

Three out of 24 treatment emergent ADA positive patients had neutralising antibodies against pembrolizumab (0.8%). The percentage of ADA positive patients with neutralising properties is similar with the overall incidence in the monotherapy setting.

There was no evidence of an altered pharmacokinetic or safety profile with anti-pembrolizumab binding or neutralising antibody development.

2.3.6. Conclusions on clinical pharmacology

The observed concentration from KEYNOTE-426 falls within the 90% CI of the model predicted median concentration. Although the number of treatment emergent ADA is higher when pembrolizumab is combined with axitinib, treatment emergent ADA status is not found to alter the PK, efficacy and safety of the combination regimen.

2.4. Clinical efficacy

The proposed indication is based on the results from KEYNOTE-426, an on-going randomized, multi-center, open-label, global phase 3 study investigating pembrolizumab in combination with axitinib vs sunitinib monotherapy as first-line treatment for locally advanced or metastatic RCC.

Data from KEYNOTE-427 (Phase 2 study of pembrolizumab monotherapy in participants with RCC) for participants with clear cell RCC (Cohort A), and the Pfizer-sponsored Study A4061051 (Phase 3 study of axitinib versus sorafenib in treatment-naïve RCC patients) are submitted as supportive with the aim to provide the contribution of each of the components to the efficacy of the pembrolizumab + axitinib regimen, together with the results of the Pfizer sponsored study KEYNOTE-035/A4061079 (Phase 1b of pembrolizumab + axitinib in RCC), which provided the rationale for evaluating pembrolizumab in combination with axitinib in participants with advanced RCC.

2.4.1. Dose response study(ies)

Study KN-035 was a Phase 1b, open label, single-arm, multi-center, multiple-dose, safety, efficacy, PK and pharmacodynamics study of axitinib in combination with pembrolizumab in adult patients with previously untreated advanced RCC. This clinical study comprised of a Dose Finding Phase and a Dose Expansion Phase. In this trial, the axitinib starting dose was 5 mg BID with or without food, i.e. the dose approved for the indication of second-line treatment of adults with advanced RCC. The pembrolizumab starting dose was 2 mg/kg to be administered Q3W.

This study estimated an MTD of axitinib 5 mg BID and pembrolizumab 2 mg/kg intravenously (IV). During the dose-finding phase, there were 3 (27.3%) out of 11 patients who experienced DLTs during the first 2 cycles or 6 weeks post C1D1. One patient had transient ischemic attack (TIA) and two patients were unable to complete ≥75% of planned axitinib dose due to treatment-related toxicity (one due to grade 2/3 headache and the other due to grade 2 headache, fatigue, asthenia, and dehydration).

A total of 52 patients were enrolled into the study from 16 September 2014, including the first 11 patients enrolled in the Dose Finding Phase.

Overall, the combination of axitinib and pembrolizumab was safe and tolerable. No new safety signals were identified with axitinib in combination with pembrolizumab in patients with previously untreated

advanced RCC; the safety profile of either study drug was consistent with the known safety profile when used as single agent.

The most frequently reported AEs such as diarrhea and fatigue were similar to those found in monotherapy trials. No treatment-related deaths during the study was reported.

At the data cut-off date of 31 March 2017, the confirmed ORR was 73.1% (95% CI [59.0, 84.4]), with a best overall response of CR reported for 4 patients and PR reported for 34 patients. The median duration of tumor response was 18.6 months (95% CI [15.1, NR]).The median TTR was 2.8 months (range: 0.7 - 15.2 months).

The median PFS was 20.9 months (15.4, NR) among all the treated patients. The median OS in the current study was not reached at the minimum follow-up period of 17.6 months; the majority of patients [43 (82.7%) patients] were still alive at the time of data cut-off.

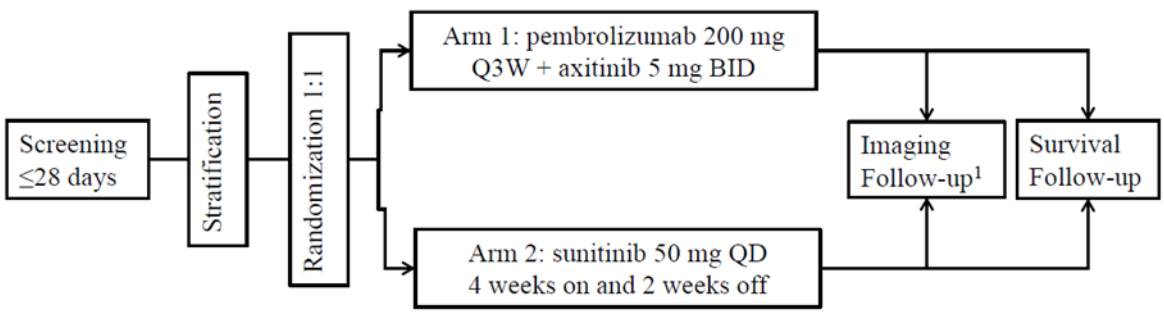
Overall, 48 patients had their tumor tissue evaluated for PD-L1 status. Nine (18.8%) patients had a tumor PD-L1 status positive; 34 (70.8%) patients had a tumor PD-L1 status negative. Four (8.3%) patients had a tumor PD-L1 status of not evaluable, while 1 (2.1%) patient was missing the PD-L1 status. Of the 9 patients with tumor PD-L1 status positive, 8 (88.9%) patients had partial response and 1 (11.1%) had indeterminate response. Of the 34 patients with tumor PD-L1 status negative, 4 (11.8%) patients had complete response, 20 (58.8%) patients had partial response, 6 (17.6%) patients had stable disease, 2 (5.9%) patient had progressive disease, and 2 (5.9%) patients had intermediate response. Of the 4 patients without tumor PD-L1 status available, 3 (75%) patients had PR, and 1 patient had SD, while the patient missing the PD-L1 status had a PR.

Based on these data suggesting the tolerability and anti-tumor efficacy of the combination of axitinib and pembrolizumab, the MAH designed Study KN-426. In this trial, the pembrolizumab dose was 200 mg Q3W. The rational is based on the fact that an integrated body of evidence suggests that 200 mg Q3W is expected to provide similar response to 2 mg/kg Q3W, 10 mg/kg Q3W, and 10 mg/kg Q2W. Exposures for 200 mg Q3W are expected to lie within this range and close to those obtained with the 2 mg/kg Q3W dose.

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

2.4.2. Main study(ies)

A Phase III Randomized, Open-label Study to Evaluate Efficacy and Safety of Pembrolizumab (MK-3475) in Combination with Axitinib versus Sunitinib Monotherapy as a First-line Treatment for Locally Advanced or Metastatic Renal Cell Carcinoma (mRCC) - KEYNOTE-426



Methods

Study participants

Key inclusion criteria were:

- Histologically confirmed diagnosis of RCC with clear cell component with or without sarcomatoid features.
- Locally advanced/metastatic disease, i.e. newly diagnosed stage IV RCC per AJCC or recurrent disease.
- Measurable disease per RECIST 1.1 as assessed by the investigator/site radiologist.
- No prior systemic therapy for advanced RCC.
- KPS ≥70%, as assessed within 10 days prior to randomization.
- Subjects receiving bone resorptive therapy (including but not limited to bisphosphonate or RANK-L inhibitor) must have therapy initiated at least 2 weeks prior to randomization.
- Adequate organ function.

Key exclusion criteria were:

- Major surgery within 4 weeks, radiation therapy within 2 weeks prior to randomization, or has not recovered (i.e., ≤ Grade 1 or at baseline) from AEs due to prior treatment
- Prior treatment with any anti-PD-1, or PD-L1, or PD-L2 agent or an antibody targeting any other immune-regulatory receptors or mechanisms. Examples of such antibodies include (but are not limited to) antibodies against IDO, PD -L1, IL-2R, and GITR.
- Prior systemic anticancer therapy for RCC (e.g., VEGF/VEGFR, chemotherapy, or mTOR-targeting agents).
    - Prior neoadjuvant/adjuvant therapy for RCC was acceptable if completed >12 months prior to randomization.
- Diagnosis of immunodeficiency OR is receiving a systemic steroid therapy exceeding physiologic corticosteroid dose or any other form of immunosuppressive therapy within 7 days prior to randomization, except in the case of central nervous system (CNS) metastases-
- Active autoimmune disease requiring systemic treatment within the past 2 years (i.e., with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs) OR with a documented history of clinically severe autoimmune disease
    - Note: Subjects with vitiligo, Sjögren's syndrome, Type 1 diabetes, or resolved childhood asthma/atopy will not be excluded from the study. Subjects requiring intermittent use of bronchodilators, inhaled steroids, or local steroid injections will not be excluded from the study. Subjects with hypothyroidism, or adrenal or pituitary insufficiency who are stable on hormone replacement will not be excluded from the study.
- Known active CNS metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are radiologically stable, clinically stable and without requirement of steroid treatment for at least 14 days prior to randomization.
- Clinically significant GI abnormality.
- QTc ≥480 msec.

- History of any of the following cardiovascular conditions within 12 months of randomization:
    - myocardial infarction, unstable angina pectoris, cardiac angioplasty or stenting, coronary/peripheral artery bypass graft, Class III or IV congestive heart failure per New York Heart Association criteria, or cerebrovascular accident or transient ischemic attack.
- History of deep vein thrombosis or pulmonary embolism within 6 months of screening.
- Has poorly controlled hypertension defined as systolic blood pressure (SBP) ≥ 150 mm Hg and/or diastolic blood pressure (DBP) ≥ 90 mm Hg.
- Evidence of inadequate wound healing.
- Active bleeding disorder or other history of significant bleeding episodes within 30 days of randomization.
- Hemoptysis within 6 weeks prior to randomization.

Treatments

The study treatments are outlined in the table below:

Treatment	Regimen	Route of Administration	Duration of Treatment	Use in Study
Pembrolizumab + Axitinib				
Pembrolizumab	200 mg Q3W	IV infusion	Up to 35 doses (about 24 months) or until PD is BICR verified or further confirmed by the investigator [a]	Experimental
Axitinib	5 mg BID	PO	Continued treatment until PD is BICR verified or further confirmed by the investigator	Experimental
Sunitinib				
Sunitinib	50 mg QD 4 weeks on, 2 weeks off	PO	Continued treatment until PD is BICR verified or further confirmed by the investigator	Comparator (standard of care)

Abbreviations: BICR = blinded independent central review; BID = twice daily; IV = intravenous; PD = progressive disease; PO = per os/by mouth; QD = once daily; Q3W = every 3 weeks.

a. Subjects in the pembrolizumab+axitinib arm may receive a second course of treatment with an additional 17 doses of pembrolizumab. Details are described in Section 5.8.3 of the study protocol [16.1.1].

Study treatment was to begin on the day of randomization or within 3 days of randomization in the 2 treatment groups. Subsequently, the treatment was to be administered on Day 1 of each treatment cycle. For participants in the pembrolizumab + axitinib group, each treatment cycle was 21 days (+/- 3 days) to correspond with the dosing schedule of pembrolizumab. The first dose of axitinib was to start on the same day when first dose of pembrolizumab was administered or on the following day. For participants in the sunitinib group, each treatment cycle was 42 days.

Pembrolizumab, axitinib, and sunitinib were withheld for drug-related toxicities and severe or life-threatening AEs. The axitinib dose could be adjusted by a dosing interruption with or without dose reduction as indicated. The dose modification could occur independently for the 2 drugs used in the pembrolizumab plus axitinib arm. If axitinib dose reduction from 5 mg BID was required, the next recommended dose levels were 3 mg BID and 2 mg BID. Axitinib was permanently discontinued if subjects could not tolerate 2 mg BID.

Subjects who tolerated axitinib 5 mg BID for 2 consecutive treatment cycles (i.e. 6 weeks) with no > Grade 2 treatment-related AEs to axitinib and with BP well controlled to ≤ 150/90 mm Hg could have axitinib dose increased to 7 mg BID, and further increased to 10 mg BID using the same criteria.

For sunitinib, the study used the label-recommended dose and schedule for RCC (50 mg QD 4 weeks on, 2 weeks off). Dose interruption and/or dose modification in 12.5 -mg increments or decrements was recommended based on individual safety and tolerability, as per label recommendations.

Study treatments continue until progressive disease (PD) is BICR-verified or further confirmed by the investigator, unacceptable adverse events (AEs) or intercurrent illness prevents further administration of treatment, death or withdrawal of consent. For both arms, in the event that a complete response (CR) has been observed in a subject, study treatment may be discontinued at the discretion of the investigator after the CR has been confirmed and after a minimum of 8 cycles of treatment (~24 weeks) in the pembrolizumab plus axitinib arm or 4 cycles of treatment (~24 weeks) in the sunitinib arm have been received. In the combination arm, treatment could continue with one drug if the other had been discontinued due to adverse reactions. Pembrolizumab is administered for a maximum of 35 doses.

Objectives

Primary Objectives:

- To evaluate and compare PFS per RECIST 1.1 as assessed by BICR in participants treated with pembrolizumab + axitinib versus sunitinib.
    - Hypothesis: The combination therapy of pembrolizumab plus axitinib is superior to sunitinib monotherapy with respect to PFS as assessed by BICR per RECIST 1.1.
- To evaluate and compare OS in participants treated with pembrolizumab + axitinib versus sunitinib.
    - Hypothesis: The combination therapy of pembrolizumab plus axitinib is superior to sunitinib monotherapy with respect to OS.

Secondary Objectives:

- To compare ORR and DCR per RECIST 1.1 as assessed by BICR in participants treated with pembrolizumab + axitinib versus sunitinib. DOR per RECIST 1.1 will also be evaluated.
    - Hypothesis: The combination therapy of pembrolizumab plus axitinib is superior to sunitinib monotherapy with respect to ORR as assessed by BICR per RECIST 1.1.
- To evaluate PFS rate per RECIST 1.1 as assessed by BICR at 12, 18, and 24 months based on data adequacy; to evaluate OS rates at 12, 18, and 24 months based on data adequacy.
- To evaluate and compare safety and tolerability profiles in participants treated with

pembrolizumab + axitinib versus sunitinib.

- To compare TTD based on the FKSI-DRS scale in participants treated with pembrolizumab + axitinib versus sunitinib.
- To assess the longitudinal score changes from baseline to 42 weeks as measured by EORTC QLQ-C30 global health status/quality of life scale

In addition, pembrolizumab + axitinib was compared to sunitinib for the following *Exploratory Objectives*:

- To evaluate PFS, ORR, DOR, and DCR per irRECIST as assessed by BICR in participants treated with pembrolizumab + axitinib versus sunitinib.
- To characterize utility in participants using the EQ-5D-3L.
- To characterize the PK of pembrolizumab in participants treated with pembrolizumab + axitinib. To identify molecular (genomic, metabolic and/or proteomic) determinants of response or resistance to pembrolizumab + axitinib treatments in this study, so as to define novel predictive and pharmacodynamic biomarkers and understand the mechanism of action of the pembrolizumab + axitinib combination.

Outcomes/endpoints

Primary endpoints

- Progression-free Survival (PFS) – RECIST 1.1 by Blinded Central Imaging Vendor Review
    - Progression-free survival is defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on BICR or death due to any cause, whichever occurs first.
- Overall Survival (OS)
    - Overall survival is defined as the time from randomization to death due to any cause. Subjects without documented death at the time of the final analysis will be censored at the date of the last follow up.

Secondary endpoints

- Objective Response Rate (ORR) – RECIST 1.1 by BICR
    - Objective response rate is defined as the proportion of the subjects in the analysis population who have a CR or PR per RECIST 1.1.
- Duration of Response (DOR) - RECIST 1.1 by BICR
    - For subjects who demonstrate CR or PR, DOR is defined as the time from first documented evidence of CR or PR per RECIST 1.1 until disease progression per RECIST 1.1 or death due to any cause, whichever occurs first.
- Disease Control Rate (DCR) - RECIST 1.1 by BICR
    - Disease control rate is defined as the percentage of subjects who have achieved CR, PR, or SD of ≥ 6 months based on assessments by BICR per RECIST 1.1.

Sample size

The study was event-driven and planned to randomize approximately 840 subjects with 1:1 ratio into the two treatment groups pembrolizumab plus axitinib and sunitinib.

Both PFS and OS are primary endpoints for this study. For the PFS endpoint, based on a target number of 487 PFS events and one interim analysis at approximately 75% of the target number of events, the study has ~99% power to detect an HR of 0.60 (pembrolizumab+axitinib combination versus sunitinib) at alpha=0.2% (1-sided). The calculation assumes an HSD alpha-spending function with γ=-2 to control the overall Type I error rate for this endpoint at 0.2% (1-sided). The target numbers of PFS events for the first interim and final analysis are projected to occur at 22 and 31 months respectively. The IA1 was triggered when 305 PFS events had accrued and all participants were followed for at least 7 months after randomization. For the OS endpoint, based on a target number of 404 final OS events and 2 interim analyses (with approximately 48% of final OS events at IA1 and 74% of the final OS events at IA2), the study has approximately 80% power to detect an HR of 0.75 at an overall alpha level of 2.3% (1-sided). The calculation assumes that a linear alpha-spending function with a fixed alpha-spending of 0.0001 at IA1 and the rest alpha-spending approximated by an HSD alpha-spending function withγ=-4 to control the overall Type I error rate for this endpoint at 2.3% (1-sided). The target number of OS events is projected to occur at 43 months after the start of the study. The target numbers of OS events for the first and second interim analyses are projected to occur at 22 months and 31 months respectively. The calculations assume an exponential distribution with a median of 13 months for PFS and a median of 33 months for OS for the control group respectively, a yearly dropout rate of 10% for PFS and 1% for OS, and an enrollment of 15 months, with monthly accrual of 40 to 60 patients in the first 3 months and monthly accrual of ~60 patients after the first 3 months. The median PFS and median OS assumptions in the control group are based on emerging data of sunitinib from the CheckMate 214 study.

Randomisation

Treatment randomization occurred centrally using an interactive voice response system/integrated web response system (IVRS/IWRS). Subjects were assigned randomly in a 1:1 ratio to the pembrolizumab plus axitinib combination arm or the sunitinib monotherapy arm.

Prior to randomization subjects will be stratified according to the following factors:

1. International Metastatic RCC Database Consortium (IMDC) risk group: favourable versus intermediate versus poor risk groups

2. Geographic region: North America versus Western Europe versus "Rest of the World".

IMDC risk category for each subject was determined first by assessing 6 risk factors as shown in the table below:

Assessments	Risk Factor
Baseline Karnofsky Performance Status	< 80%
Interval between initial diagnosis of RCC to start of first-line systemic treatment for advanced disease *(note for this study, date of randomization will be used as the start of first-line systemic treatment)*	< 1year
Baseline Hemoglobin	< Lower limit of normal
Baseline Platelet Count	> Upper limit of normal
Baseline Corrected Calcium[1]	> Upper limit of normal
Baseline Neutrophil	> Upper limit of normal
The IMDC risk group is determined by totaling the existing risk factors per subject.	
IMDC Risk Group	**IMDC Category**
Favorable	No risk factors
Intermediate	1 or 2 risk factors
Poor	3 or more risk factors
1. Corrected calcium can be calculated based on the following formula: ***Corrected calcium (mg/dl) = 0.8 × [4.0 - subject's albumin (g/dl)] + subject's calcium (mg/dl)***. A subject's corrected calcium will be compared with the upper limit of normal of institution serum calcium.	

Blinding (masking)

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

Statistical methods

The primary efficacy analysis was performed on Intention-to-Treat (ITT) population.

The non-parametric Kaplan-Meier method was used to estimate the OS and the PFS curve in each treatment group including the PFS rates at 12, 18, and 24 months. The treatment difference in PFS was assessed by the stratified log -rank test. A stratified Cox proportional hazard model with Efron's method of tie handling was used to estimate the magnitude of the treatment difference between the treatment arms. The hazard ratio and its 95% confidence interval from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate was reported. The stratification factors used for randomization was applied to both the stratified log-rank test and the stratified Cox model.

The true date of disease progression was approximated by the date of the first assessment at which PD is objectively documented per RECIST 1.1 by BICR. Death was always considered as a confirmed PD event. Subjects who did not experience a PFS event were censored at the last disease assessment. The censoring rules for primary and sensitivity analyses* are summarized in the following table.

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

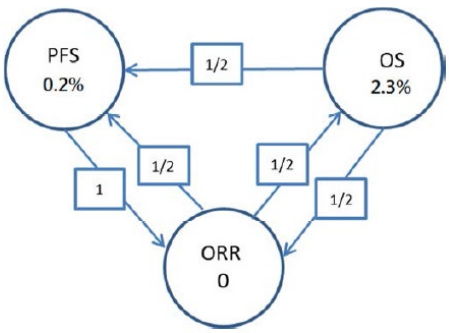
PD = progressive disease; PFS = progression-free survival.

* The Sensitivity analysis was performed for comparison of PFS based on investigator's assessment using primary censoring rule.

Stratified Miettinen and Nurminens method with weights proportional to the stratum size was used for comparison of the objective response rates (ORR) and of the DCR between the treatment arms. A 95% CI for the difference in response rates between the treatment arms was provided. The stratification factors used for randomization were applied to the analysis. Sensitivity analyses were performed to assess ORR and DCR based on investigator's assessment.

The non-parametric Kaplan-Meier method was used to estimate the DOR curve in each treatment group; estimates of the percentage of subjects still in response and 95% CIs at specific duration time points was provided. Sensitivity analyses were performed to assess DOR based on investigator's assessment.

The overall Type I error across the testing of the OS, PFS, and ORR hypotheses was strongly controlled at 2.5% (1-sided) with 0.2% initially allocated to PFS and 2.3% initially allocated to OS. If a hypothesis was rejected, then the corresponding alpha level of that test could be shifted using the graphical approach of Maurer and Bretz (see figure below).



Two interim analyses were planned for OS and one planned interim analysis for PFS for the study. A group sequential approach was used to allocate alpha between the interim and final analyses. The study was considered a success if either PFS or OS is demonstrated to be statistically significant under multiplicity control.

The following table show the strategies for each interim and final analysis in this trial based on model assumptions.

Table 20 Summary of Interim and Final Analyses Strategies

Analysis	Expected Months after Study Start	Hypo-thesis Tested in the Analysis	True Hazard Ratio	n[+]	Infor-mation Fraction	Type I Error (Overall α)	Efficacy Boundary Crossing				Futility Boundary Crossing			
							Nominal α	Z-value	Statistics[‡]	Power[§]	Nominal α	Z-value	Hazard Ratio	Cumulative Type II Error
IA1	22 Months	PFS	0.6	365	0.75	0.20%	0.11%	3.06	0.73	~96.5%	22.1%	-0.77	1.08	<0.01%
						1.35%	0.74%	2.44	0.77	~99.2%	21.8%	-0.78	1.08	<0.01%
						2.5%	1.36%	2.21	0.79	~99.6%	21.6%	-0.79	1.08	<0.01%
		OS	0.75	195	0.48	2.3%	0.01%	3.72	0.59	~4.3%	4.1%	-1.74	1.28	~0.01%
						2.5%	0.01%	3.70	0.59	~4.5%	4.1%	-1.74	1.28	~0.01%
		ORR	-	860	1.0	0.2%	0.2%	2.88	9.4%	>99.9%	-	-	-	-
						1.15%	1.15%	2.27	7.4%	>99.9%				
						2.5%	2.5%	1.96	6.4%	>99.9%				
IA2	31 Months	PFS	0.6	487	1.0	0.2%	0.14%	3.00	0.76	>99.9%	99.8%	3.00	0.76	~3.9%
						1.35%	1.02%	2.32	0.81	>99.9%	98.7%	2.32	0.81	~0.04%
						2.5%	1.95%	2.06	0.83	>99.9%	97.5%	2.06	0.83	~0.02%
		OS	0.75	299	0.74	2.3%	0.78%	2.42	0.76	~52.7%	20.3%	-0.84	1.10	~0.05%
						2.5%	0.92%	2.36	0.76	~55.1%	20.2%	-0.85	1.10	~0.05%
FA	43 Months	OS	0.75	404	1.0	2.3%	2.07%	2.04	0.82	~80.8%	97.7%	2.04	~0.82	~19.2%
						2.5%	2.22%	2.01	0.82	~81.7%	97.5%	2.01	~0.82	~18.3%

[+] n means expected events at the time of corresponding analysis for PFS and OS based on model assumption. In the rare case if PFS events accumulate slower than expected, a minimum of 305 events is required at 22 months to trigger IA1; n means total sample size for ORR.

[‡] The statistics used here are hazard ratio for PFS and OS, and ORR Δ for ORR where ORR Δ = ORR in (pembrolizumab+axitinib group) – ORR in sunitinib group.

[§] The power calculated for OS is cumulative power. For the power calculation, the target ORR in the pembrolizuab+axitinib group and the reference ORR assumed in the sunitinib groups are 55% and 31%, respectively.

For OS, a linear spending function with a fixed alpha spending of 0.0001 at IA1 and the rest alpha spending approximated by a Hwang-Shih-DeCani (HSD) alpha-spending function with gamma parameter (-4) is used to construct Haybittle-Peto type of group sequential boundaries to control the overall Type I error rate for this endpoint at 2.3% or 2.5% (1-sided). Futility spending is done by controlling the probability of crossing the futility bound under the null hypothesis (total of 1-α=97.5%); an HSD alpha-spending function with gamma parameter (-6) is used to construct group sequential boundaries for futility. The Type I error rate to spend at IA2 and FA will be determined by the spending function evaluated at the exact number of deaths at each analysis.

For PFS, an HSD alpha-spending function with gamma parameter (-2), is used to construct group sequential boundaries to control the overall Type I error rate for this endpoint at 0.2%, 1.35% and 2.5% (1-sided). Futility spending is done by controlling the probability of crossing the futility bound under the null hypothesis (total of 1-α=97.5%); an HSD alpha-spending function with gamma parameter (-6) is used to construct group sequential boundaries for futility. The Type I error rate to spend at the interim analysis will be determined by the spending function evaluated at the exact number of PFS events at each analysis.

For ORR, if the testing of ORR hypothesis does not reach statistical significance at interim analysis 1 (IA1), the p-value from the IA1 analysis can be compared to an updated α-level if the null hypothesis for PFS or OS is rejected at a later time.

The MAH planned to update the boundary using the actual number of PFS and of OS events at the interim and final analyses and the same spending function used to derive the design.

The results of the study are based on the IA1 that was performed after enrollment completion, when a minimum of 305 PFS events had accrued and all participants were followed for at least 7 months after randomization.

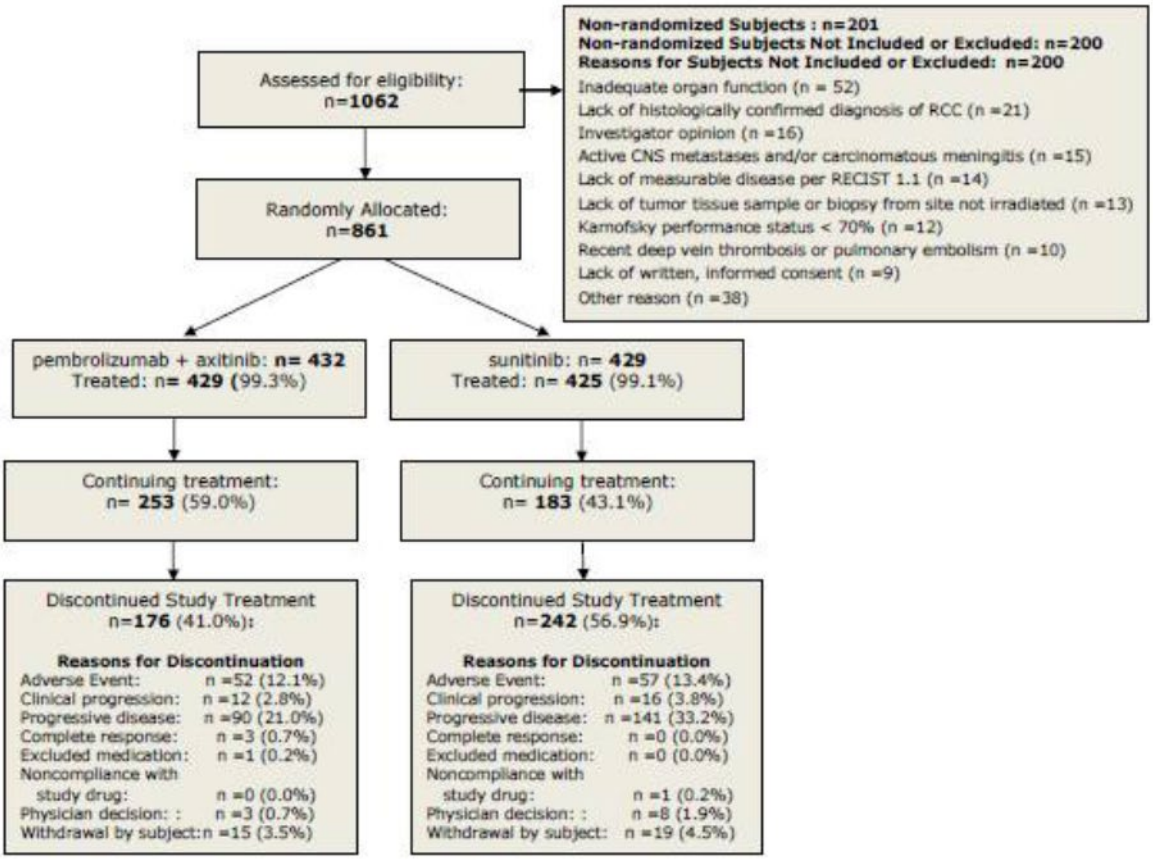
For PRO endpoints no formal hypothesis testing, nominal p-values were provided for treatment comparisons of pembrolizumab + axitinib vs. sunitinib. No multiplicity adjustment was performed. The following table summarizes the planned PRO analyses.

Table 9 Planned Statistical Analysis for PRO

Endpoint/ Analysis	Instrument Scale/Sub-Scale	Analysis Population	Method	Statistics
Summary of PRO Compliance	• FKSI-DRS • EORTC QLQ-C30 • EQ-5D-3L	PRO FAS		
Mean score change from baseline through the primary analysis time point	• FKSI-DRS • EORTC QLQ-C30 Global Health status/QoL • EORTC QLQ-C30 physical functional scale, role functional scale, nausea and vomiting symptom scale, Diarrhea symptom scale • EQ-5D VAS	PRO FAS	cLDA	Difference in Lsmean estimate (95% C.I.) and nominal p-value
Time to deterioration	• FKSI-DRS • EORTC QLQ-C30 Global Health status/QoL • EQ-5D VAS	PRO FAS	Stratified Cox model with Efron's tie handling method	Hazard ratio (95% C.I., p-value); Kaplan-Meier plot
Proportion of overall improvement	• FKSI-DRS • EORTC QLQ-C30 Global Health status/QoL • EQ-5D VAS	PRO FAS	Stratified Miettinen and Nurminen's method	Difference in overall improvement rates (95% C.I.)
Proportion of deterioration/stable/improvement at the primary analysis time point	• FKSI-DRS • EORTC QLQ-C30 Global Health status/QoL • EORTC QLQ-C30 physical functional scale, role functional scale, nausea and vomiting symptom scale, Diarrhea symptom scale	PRO FAS	Difference in proportions with imputation base on MAR	Diffeerence estimate (95% C.I.) by treatment group and visit

Results

Participant flow for KEYNOTE-426



Recruitment

A total of 1062 participants were screened (first participant screened on 06-OCT-2016) and 861 were randomly allocated from 24-OCT-2016 to 24-JAN-2018 across 124 global study sites in 16 countries. First and last participant visits were respectively 06-OCT-2018 and 23-AUG-2018.

Data cut-off for IA1 occurred on 24-AUG-2018. During the evaluation, the MAH provided efficacy data from KN426, with a data cutoff date of 2 January 2019.

Conduct of the study

Protocol amendments

The original protocol is dated 10 June 2016. A total of 6 protocol amendments, including 4 global and 2 country-specific amendments, were implemented during the study. In addition to the original protocol this resulted in a total of 7 protocol versions. Amendment versions 6 and 7 were never finalized for distribution, hence the numbers are not in the table below.

The key changes introduced by the protocol amendments are summarized below:

Protocol Amendment	Most relevant changes
#01 (21 July 2016)	Country specific (Japan)
#2 (3 October 2016)	Country specific (France)
# 3 (13 Mar 2017)	First Global Amendment - Inclusion criteria: changed the allowed time period for starting bone resorptive therapy from 4 weeks to 2 weeks prior to randomization. - Exclusion criteria: clarify that subjects who have had chemotherapy as neoadjuvant or adjuvant therapy for RCC qualify for the study. - Exclusion criteria: revised the timeframe of active autoimmune disease exclusion from 3 months to 2 years. Added language on excluded therapies and allowed replacement therapies. - Exclusion criteria: clarify that subjects with brain metastasis who have been treated with steroid treatment at least 14 days (changed "4 weeks" to "14 days") prior to randomization in order to show stability qualify for the study. - Exclusion criteria: exclude subjects with a known history of hepatitis B. - Exclusion criteria: removal of exclusion for "GI perforation": repaired GI perforation is not excluded.
#4 (21 Mar 2017)	Country specific (Japan) version of global amendment #3
#5 (21 Mar 2017)	Country specific (France) version of global amendment #3
#8 (28 August 2017)	Second Global Amendment To further refine general guidance on evaluation and management of overlapping AEs potentially associated with either pembrolizumab and axitinib or both in the combination arm and include a new subsection detailing evaluation and management of transaminase elevations during axitinib and pembrolizumab combination therapy (Section 5.2.2.3). The rational for this change was to provide detailed guidelines on how to systemically approach treatment–emergent alanine aminotransferase [ALT]/aspartate aminotransferase [AST] elevations in the pembrolizumab + axitinib group as there are no specific markers to differentiate drug-induced liver injury from axitinib versus immune-mediated hepatitis from pembrolizumab versus ALT/AST elevations due to other reasons. The amedment also provided detailed algorithms regarding study drug rechallenge for different scenarios following recovery from an initial ALT/AST elevation event.
#9 (07 September 2017)	Country specific (France) version of global amendment #8

#10 (19 October 2017)	Third Global Amendment The primary reason for the amendment was to revise Table 6 in Section 5.2.2.1 (Dose Modification and Toxicity Management Guidelines for Adverse Events Potentially Associated with Pembrolizumab Treatment), to include: 1) myocarditis as a new immunerelated AE (irAE); and 2) under all the "other immune-related AEs", any Grade 3 AE was separated from intolerable Grade 2 as a standalone category. These updates were required to be consistent with the guidelines provided in the IB and product label that were current at that time.
#11 (26 October 2017)	Country specific (France) version of global amendment #10
#12 (03 May 2018)	Fourth Global Amendment - Statistical Analysis Plan: 1) Revised assumptions on control arm median PFS and OS 2) Revised IA1 trigger from 50% final OS events to once achieving 305 PFS events and 7 months of minimum follow up. 3) Added one interim analysis for PFS to have earlier chance of observing positive efficacy of PFS with relatively mature data. 4) Initial alpha to PFS and OS changed from 0.1% and 2.4% to 0.2% and 2.3% respectively. Slightly higher alpha is reallocated to PFS to ensure adequate power for this important primary endpoint without compromising the power of OS 5) Secondary objectives: landmark analyses on PFS and OS are added to compare and characterize the tail of the curve (PFS rate per RECIST 1.1 as assessed by BICR at 12, 18, and 24 months, and OS rates at 12, 18, and 24 months, based on data adequacy). 6) Updated the censoring rules for primary and sensitivity analyses of PFS.
#13 (11 May 2018)	Country specific (France) version of global amendment #12

Note: There was only 1 country-specific protocol amendment for Japan, which was protocol amendment 426-01. Protocol amendment 426-04 was global amendment 426-03 with changes from 426-01 carried over.
There was only 1 country-specific protocol amendment for France, which was amendment 426-02. Protocol amendments 426-05, -09, -11 and -13 were global amendments 426-03, -08, -10 and -12 with changes from 426-02 carried over.

Protocol deviations

The percentage of participants with important deviations, defined as deviations that could significantly impact the quality (ie, completeness, accuracy, and reliability) or integrity of key study data; or that could significantly affect a participant's rights, safety, or well-being, was similar in the 2 groups (14.2% in the pembrolizumab + axitinib group and 12.9% in the sunitinib group).

Deviations were reported across the following categories:

- Discontinuation criteria (n=0 for pembrolizumab + axitinib; n=1 for sunitinib)
- Inclusion/exclusion criteria (n=14 for pembrolizumab + axitinib; n=12 for sunitinib)
- Informed consent form (n=0 for pembrolizumab + axitinib; n=1 for sunitinib)
- Prohibited medications (n=2 for pembrolizumab + axitinib; n=1 for sunitinib)
- Safety reporting (n=19 for pembrolizumab + axitinib; n=14 for sunitinib)
- Study intervention (n=6 for pembrolizumab + axitinib; n=3 for sunitinib)
- Trial procedures (n=27 for pembrolizumab + axitinib; n=27 for sunitinib)

Of these important protocol deviations, one was deemed to be clinically significant. One participant in the pembrolizumab + axitinib group experienced an SAE (peritonitis) that was reported to the Sponsor more

than 90 days after the SAE occurred. The SAE resolved with no action taken with regard to study treatment, and the participant continued in the study. The participant was not excluded from any analyses.

Of note is that 2 patients in the experimental arm received prohibited medication defined as "*Antineoplastic systemic chemotherapy, biologic therapy, immunotherapy, other investigational agents given while on treatment (unless allowed per protocol)*". The prohibited medication received by the patients in the control arm was instead a drug having pro-arrhythmic potential. The rate of patients with "*2 consecutive Imaging Scans up to week 54 or 1 imaging scan after Week 54, not performed for all anatomical locations required or missed entirely*" was slightly higher in the experimental arm (5.1% vs 4%).

Baseline data

Table: Subject Characteristics (ITT Population)

	Pembrolizumab + Axitinib		Sunitinib		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	432		429		861	
Gender						
Male	308	(71.3)	320	(74.6)	628	(72.9)
Female	124	(28.7)	109	(25.4)	233	(27.1)
Age (Years)						
< 65	260	(60.2)	278	(64.8)	538	(62.5)
≥ 65	172	(39.8)	151	(35.2)	323	(37.5)
Subjects with data	432		429		861	
Mean	61.2		60.8		61.0	
SD	10.0		10.2		10.1	
Median	62.0		61.0		62.0	
Range	30 to 89		26 to 90		26 to 90	
Race						
Asian	66	(15.3)	71	(16.6)	137	(15.9)
Black Or African American	10	(2.3)	8	(1.9)	18	(2.1)
White	343	(79.4)	341	(79.5)	684	(79.4)
Other	4	(0.9)	4	(0.9)	8	(0.9)
Missing	9	(2.1)	5	(1.2)	14	(1.6)
Ethnicity						
Hispanic Or Latino	19	(4.4)	18	(4.2)	37	(4.3)
Not Hispanic Or Latino	377	(87.3)	387	(90.2)	764	(88.7)
Not Reported	14	(3.2)	12	(2.8)	26	(3.0)
Unknown	21	(4.9)	11	(2.6)	32	(3.7)
Missing	1	(0.2)	1	(0.2)	2	(0.2)
Geographic Region of Enrolling Site						
North America	104	(24.1)	103	(24.0)	207	(24.0)
Western Europe	106	(24.5)	104	(24.2)	210	(24.4)
Rest of the World	222	(51.4)	222	(51.7)	444	(51.6)

	Pembrolizumab + Axitinib		Sunitinib		Total	
	n	(%)	n	(%)	n	(%)
Region						
EU	161	(37.3)	156	(36.4)	317	(36.8)
Ex-EU	271	(62.7)	273	(63.6)	544	(63.2)
Karnofsky Performance Scale						
90/100	347	(80.3)	341	(79.5)	688	(79.9)
70/80	84	(19.4)	88	(20.5)	172	(20.0)
Missing	1	(0.2)	0	(0.0)	1	(0.1)
IMDC Risk Category						
Favorable	138	(31.9)	131	(30.5)	269	(31.2)
Intermediate	238	(55.1)	246	(57.3)	484	(56.2)
Poor	56	(13.0)	52	(12.1)	108	(12.5)
IMDC Risk Category 2						
Favorable	138	(31.9)	131	(30.5)	269	(31.2)
Intermediate or Poor	294	(68.1)	298	(69.5)	592	(68.8)
PD-L1 Status						
CPS ≥ 1	243	(56.3)	254	(59.2)	497	(57.7)
CPS < 1	167	(38.7)	158	(36.8)	325	(37.7)
Not Available	4	(0.9)	2	(0.5)	6	(0.7)
Missing	18	(4.2)	15	(3.5)	33	(3.8)
Sites of Metastatic Disease*						
Lung						
Yes	312	(72.2)	309	(72.0)	621	(72.1)
No	120	(27.8)	120	(28.0)	240	(27.9)
Lymph Node						
Yes	199	(46.1)	197	(45.9)	396	(46.0)
No	233	(53.9)	232	(54.1)	465	(54.0)
Bone						
Yes	103	(23.8)	103	(24.0)	206	(23.9)
No	329	(76.2)	326	(76.0)	655	(76.1)
Adrenal Gland						
Yes	67	(15.5)	76	(17.7)	143	(16.6)
No	365	(84.5)	353	(82.3)	718	(83.4)
Liver						
Yes	66	(15.3)	71	(16.6)	137	(15.9)
No	366	(84.7)	358	(83.4)	724	(84.1)

	Pembrolizumab + Axitinib		Sunitinib		Total	
	n	(%)	n	(%)	n	(%)
Number of Organs Involved with Disease at Baseline						
1	114	(26.4)	96	(22.4)	210	(24.4)
≥ 2	315	(72.9)	331	(77.2)	646	(75.0)
Missing	3	(0.7)	2	(0.5)	5	(0.6)
RCC Histology						
Clear Cell	403	(93.3)	401	(93.5)	804	(93.4)
Clear Cell Component	28	(6.5)	27	(6.3)	55	(6.4)
Other	1	(0.2)	1	(0.2)	2	(0.2)
Sarcomatoid Feature						
Yes	51	(11.8)	54	(12.6)	105	(12.2)
No	234	(54.2)	239	(55.7)	473	(54.9)

	Pembrolizumab + Axitinib		Sunitinib		Total	
	n	(%)	n	(%)	n	(%)
Unknown	146	(33.8)	135	(31.5)	281	(32.6)
Missing	1	(0.2)	1	(0.2)	2	(0.2)
RCC Tumor Fuhrman Grade						
Grade 1	23	(5.3)	24	(5.6)	47	(5.5)
Grade 2	138	(31.9)	127	(29.6)	265	(30.8)
Grade 3	120	(27.8)	138	(32.2)	258	(30.0)
Grade 4	104	(24.1)	93	(21.7)	197	(22.9)
Missing	47	(10.9)	47	(11.0)	94	(10.9)
Disease Status at Baseline						
Recurrent	238	(55.1)	231	(53.8)	469	(54.5)
Newly Diagnosed	194	(44.9)	198	(46.2)	392	(45.5)
RCC Stage at Initial Diagnosis						
I	68	(15.7)	62	(14.5)	130	(15.1)
II	55	(12.7)	38	(8.9)	93	(10.8)
III	96	(22.2)	101	(23.5)	197	(22.9)
IV	209	(48.4)	227	(52.9)	436	(50.6)
Missing	4	(0.9)	1	(0.2)	5	(0.6)
Prior Oncologic Radiation						
Yes	41	(9.5)	40	(9.3)	81	(9.4)
No	391	(90.5)	389	(90.7)	780	(90.6)
Prior Nephrectomy						
Yes	357	(82.6)	358	(83.4)	715	(83.0)
No	75	(17.4)	71	(16.6)	146	(17.0)

*The sites are five most common metastatic sites and ordered decreasingly by the frequency in total of the two treatment arms. Database Cutoff Date: 24Aug2018.

Numbers analysed

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

Table: Study Population

	Pembrolizumab + Axitinib	Sunitinib	Total
Number of Subjects Screened			1062
Number of Subjects Randomized (Planned Treatment) (ITT)	432	429	861
Number of Subjects Received Treatment (Actual Treatment) (ASaT)	429	425	854
Number of Subjects Randomized and Did not Receive Treatment	3	4	7
Database Cutoff Date: 24Aug2018.			

Source: [P426V01MK3475: adam-adsl]

PRO analyses were based on the FAS population, which consisted of all randomized participants who received at least 1 dose of study medication and completed at least 1 PRO assessment.

Table: Disposition of Subjects

	Pembrolizumab + Axitinib		Sunitinib		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	432		429		861	
Status for Trial						
Discontinued	64	(14.8)	104	(24.2)	168	(19.5)
Death	59	(13.7)	95	(22.1)	154	(17.9)
Withdrawal By Subject	5	(1.2)	9	(2.1)	14	(1.6)
Trial Ongoing	368	(85.2)	325	(75.8)	693	(80.5)
Status for Study Medication in Trial						
Started	429	(100.0)	425	(100.0)	854	(100.0)
Discontinued	176	(41.0)	242	(56.9)	418	(48.9)
Adverse Event	52	(12.1)	57	(13.4)	109	(12.8)
Clinical Progression	12	(2.8)	16	(3.8)	28	(3.3)
Complete Response	3	(0.7)	0	(0.0)	3	(0.4)
Excluded Medication	1	(0.2)	0	(0.0)	1	(0.1)
Non-Compliance With Study Drug	0	(0.0)	1	(0.2)	1	(0.1)
Physician Decision	3	(0.7)	8	(1.9)	11	(1.3)
Progressive Disease	90	(21.0)	141	(33.2)	231	(27.0)
Withdrawal By Subject	15	(3.5)	19	(4.5)	34	(4.0)
Treatment Ongoing	253	(59.0)	183	(43.1)	436	(51.1)

Each subject is counted once for Trial Status based on the latest Survival Follow-up record.
Each subject is counted once for Study Medication Status based on the latest corresponding disposition record.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adpm]

A breakdown of the disposition of participants by individual component in the pembrolizumab + axitinib group shows that the percentage of participants who discontinued either pembrolizumab or axitinib (with or without discontinuation of the other drug) was similar.

Outcomes and estimation

The MAH provided the results of IA1. As of the data cutoff date (24-AUG-2018) for IA1, the median duration of follow up was 13.2 months (range: 0.1 to 21.5 months) in the pembrolizumab + axitinib group and 12.1 months (range: 0.4 to 22.0 months) in the sunitinib group.

Table: Summary of Follow-up Duration

Follow-up duration (months)[†]	Pembrolizumab + Axitinib (N=432)	Sunitinib (N=429)	Total (N=861)
Median (Range)	13.2 (0.1, 21.5)	12.1 (0.4, 22.0)	12.8 (0.1, 22.0)
Mean (SD)	13.2 (4.5)	12.2 (5.0)	12.7 (4.8)

[†] Follow-up duration is defined as the time from randomization to the date of death or the database cutoff date if the subject is still alive.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl]

Primary endpoints

Overall Survival

Table: Analysis of Overall Survival (ITT population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS [†] (Months) (95% CI)	OS Rate at Months 12 in % [†] (95% CI)
Pembrolizumab + Axitinib	432	59 (13.7)	5670.0	1.0	Not Reached (., .)	89.9 (86.4, 92.4)
Sunitinib	429	97 (22.6)	5183.8	1.9	Not Reached (., .)	78.3 (73.8, 82.1)
Pairwise Comparisons					Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]
Pembrolizumab + Axitinib vs. Sunitinib					0.53 (0.38, 0.74)	0.00005

[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by International Metastatic RCC Database Consortium (IMDC) risk group (favorable vs. intermediate vs. poor) and geographic region (North America vs. Western Europe vs. Rest of the World).
[§] One-sided p-value based on log-rank test stratified by the same strata as above.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adtte]

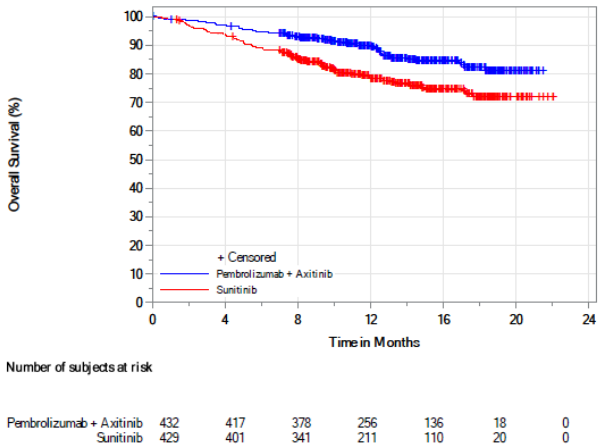
Table: Summary of Overall Survival Rate over time (ITT population)

	Pembrolizumab + Axitinib (N=432)	Sunitinib (N=429)
OS rate at 6 Months in % (95% CI)[†]	94.9 (92.3, 96.6)	89.0 (85.6, 91.6)
OS rate at 12 Months in % (95% CI)[†]	89.9 (86.4, 92.4)	78.3 (73.8, 82.1)
OS rate at 18 Months in % (95% CI)[†]	82.3 (77.2, 86.3)	72.1 (66.3, 77.0)

[†] From the product-limit (Kaplan-Meier) method for censored data.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adtte]

Figure: Kaplan-Meier Estimates of Overall Survival (ITT Population)



Database Cutoff Date: 24Aug2018.
Source: [P426V01MK3475: adam-adsl; adtte]

Progression-Free Survival

Table: Analysis of Progression-Free Survival (Primary Censoring Rule) Based on BICR Assessment per RECIST 1.1 (ITT population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS † (Months) (95% CI)	PFS Rate at Months 12 in % † (95% CI)
Pembrolizumab + Axitinib	432	183 (42.4)	3949.7	4.6	15.1 (12.6, 17.7)	59.6 (54.3, 64.5)
Sunitinib	429	213 (49.7)	3280.7	6.5	11.0 (8.7, 12.5)	46.1 (40.5, 51.5)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value§
Pembrolizumab + Axitinib vs. Sunitinib					0.69 (0.56, 0.84)	0.00012

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by International Metastatic RCC Database Consortium (IMDC) risk group (favorable vs. intermediate vs. poor) and geographic region (North America vs. Western Europe vs. Rest of the World).
§ One-sided p-value based on log-rank test stratified by the same strata as above.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl] [P426V01MK3475: sdtm-_adtte]

Table: Summary of Progression-Free Survival Rate over time (Primary Censoring Rule) Based on BICR Assessment per RECIST 1.1 (ITT population)

	Pembrolizumab + Axitinib (N=432)	Sunitinib (N=429)
PFS rate at 6 Months in % (95% CI)†	74.0 (69.5, 77.9)	65.8 (60.9, 70.2)
PFS rate at 12 Months in % (95% CI)†	59.6 (54.3, 64.5)	46.1 (40.5, 51.5)
PFS rate at 18 Months in % (95% CI)†	41.1 (33.5, 48.5)	32.8 (25.4, 40.4)

† From the product-limit (Kaplan-Meier) method for censored data.
BICR = Blinded independent central review.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adtte]

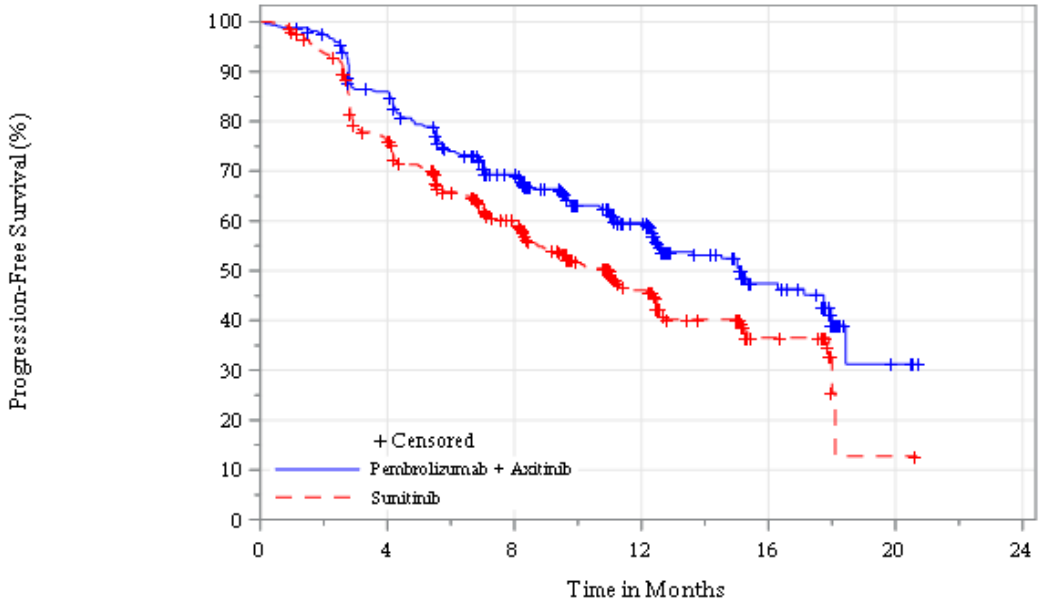
Table: Summary of Event and Censoring Description for Progression-Free Survival (Primary Censoring Rule) Based on BICR Assessment per RECIST 1.1 (ITT Population)

	Pembrolizumab + Axitinib (N=432)	Sunitinib (N=429)
Number of Events (%)	183 (42.4)	213 (49.7)
Death	21 (4.9)	29 (6.8)
Documented Progression	162 (37.5)	184 (42.9)
Number of Censored (%)[†]	249 (57.6)	216 (50.3)
≥ 2 Missing Assessments Immediately Before Death or PD	2 (0.5)	7 (1.6)
Last Radiologic Assessment Showing No Progression	219 (50.7)	155 (36.1)
New Anti-Cancer Therapy	20 (4.6)	41 (9.6)
No Post Baseline Imaging Assessment	8 (1.9)	13 (3.0)

BICR = Blinded independent central review.
[†] Based on primary censoring rule as specified in the protocol.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adtte]

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



Number of subjects at risk

Pembrolizumab + Axitinib	432	357	251	140	42	3	0
Sunitinib	429	302	193	89	29	1	0

Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adtte]

Secondary endpoints

Objective Response Rate

Table: Analysis of Objective Response Rate (Confirmed) Based on BICR Assessment per RECIST 1.1 (ITT population)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Sunitinib	
				Estimate (95% CI)[†]	p-Value[††]
Pembrolizumab + Axitinib	432	256	59.3 (54.5,63.9)	23.6 (17.2,29.9)	<0.0001
Sunitinib	429	153	35.7 (31.1,40.4)		

[†] Based on Miettinen & Nurminen method stratified by International Metastatic RCC Database Consortium (IMDC) risk group (favorable vs. intermediate vs. poor) and geographic region (North America vs. Western Europe vs. Rest of the World).

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

Responses are based on BICR assessment per RECIST 1.1.

BICR = Blinded independent central review.

Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adrs]

Table: Summary of Objective Response Rate (Confirmed) Based on BICR Assessment per RECIST 1.1 (ITT population)

Response Evaluation	Pembrolizumab + Axitinib			Sunitinib		
	n	%	95% CI[†]	n	%	95% CI[†]
Subjects in population	**432**			**429**		
Complete Response (CR)	25	5.8	(3.8, 8.4)	8	1.9	(0.8, 3.6)
Partial Response (PR)	231	53.5	(48.6, 58.3)	145	33.8	(29.3, 38.5)
Objective Response (CR+PR)	**256**	**59.3**	**(54.5, 63.9)**	**153**	**35.7**	**(31.1, 40.4)**
Stable Disease (SD)	106	24.5	(20.5, 28.9)	168	39.2	(34.5, 44.0)
Disease Control (CR+PR+SD ≥ 6 months)	**309**	**71.5**	**(67.0, 75.7)**	**260**	**60.6**	**(55.8, 65.3)**
Progressive Disease (PD)	47	10.9	(8.1, 14.2)	74	17.2	(13.8, 21.2)
Non-evaluable (NE) [‡]	8	1.9	(0.8, 3.6)	6	1.4	(0.5, 3.0)
No Assessment [§]	15	3.5	(2.0, 5.7)	28	6.5	(4.4, 9.3)

[†] Based on binomial exact confidence interval method for binomial data.

[‡] NE: post-baseline assessment(s) available however not being evaluable (i.e., all post-baseline assessment(s) with insufficient data for assessment of response per RECIST 1.1. or CR/PR/SD < 6 weeks from randomization).

[§] No Assessment: no post-baseline assessment available for response evaluation.

For best overall response of CR and PR, only confirmed responses are included.

BICR = Blinded independent central review.

Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adrs; adintdt]

Disease Control Rate

Table: Analysis of Disease Control Rate (Confirmed) Based on BICR Assessment per RECIST 1.1 (ITT population)

Treatment	N	Number of Subjects With Disease Control	Disease Control Rate (%) (95% CI)	Difference in % vs. Sunitinib Estimate (95% CI)[†]
Pembrolizumab + Axitinib	432	309	71.5 (67.0,75.7)	11.0 (4.8,17.0)
Sunitinib	429	260	60.6 (55.8,65.3)	

[†] Based on Miettinen & Nurminen method stratified by International Metastatic RCC Database Consortium (IMDC) risk group (favorable vs. intermediate vs. poor) and geographic region (North America vs. Western Europe vs. Rest of the World).

Responses are based on BICR assessment per RECIST 1.1.

BICR = Blinded independent central review.

Disease control includes confirmed CR, confirmed PR and SD ≥ 6 months.

Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adrs; adintdt]

Duration of Response

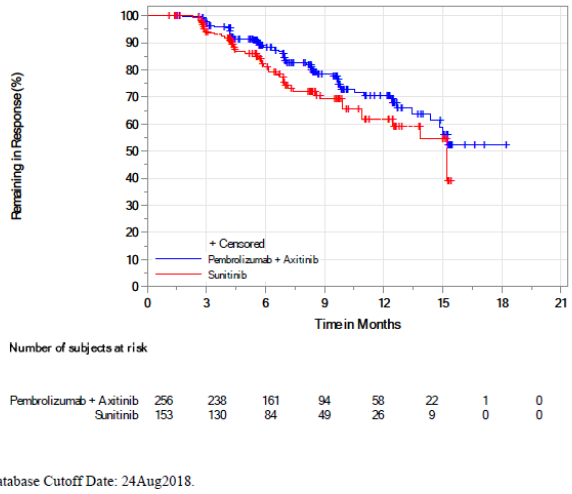
Table: Time to Response and Duration of Response Based on Response in Subjects with Confirmed Response Based on BICR Assessment per RECIST 1.1 (ITT Population)

	Pembrolizumab + Axitinib (N=432)	Sunitinib (N=429)
Number of subjects with response[†]	256	153
Time to Response (months)		
Mean (SD)	3.5 (1.8)	4.0 (2.1)
Median (Range)	2.8 (1.5-16.6)	2.9 (2.1-15.1)
Response Duration[‡] (months)		
Median (Range)	NR (1.4+ - 18.2+)	15.2 (1.1+ - 15.4+)
Number (%[‡]) of Subjects with Extended Response Duration:		
≥6 months	161 (88.4)	84 (81.2)
≥12 months	58 (70.6)	26 (61.6)

[†] Includes subjects with confirmed complete response or partial response.
[‡] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
NR = Not Reached.
BICR = Blinded independent central review.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adtte; adrs]

Figure: Kaplan-Meier Estimates of Duration of Response in Subjects With Confirmed Response Based on BICR Assessment per RECIST 1.1 (ITT Population)



Database Cutoff Date: 24Aug2018.

Patient Reported Outcomes

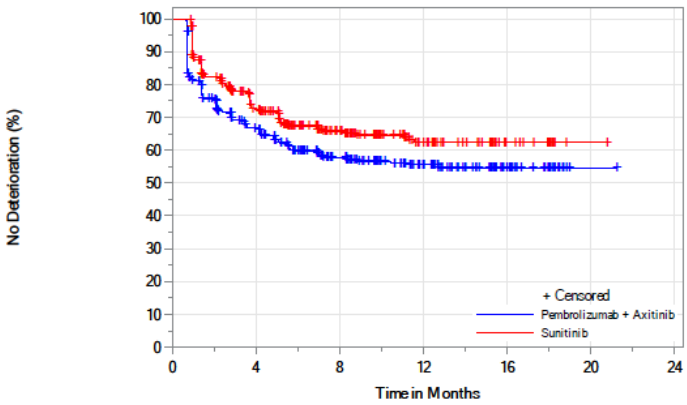
In the pembrolizumab + axitinib group, PROs were assessed on Day 1 of each cycle. In the sunitinib group, PROs were assessed on Days 1 and 29 of each cycle up to Cycle 4, then on Day 1 of each subsequent cycle following the 2-week-off treatment period. Compliance rates for the FKSI-DRS by visit and by treatment at baseline through Week 30 were high (range: 85.9% through 97.1%) in both groups. The compliance rates for EORTC QLQ-C30 [Table 14.2-55] and EQ-5D-3L [Table 14.2-56] were similar to that for the FKSI-DRS. As expected, completion rates generally decreased at each time point as more participants discontinued the study treatment.

Time to True Deterioration from Baseline in the FKSI-DRS

The time to true deterioration (time to first onset of 3 or more decrease from baseline with confirmation under right-censoring rule) in the FKSI-DRS differed between the 2 groups in favor of sunitinib (HR 1.44;

95% CI: 1.14, 1.82; nominal p=0.999). At the time of data cutoff, the median time to true deterioration was not reached in either treatment group.

Figure: Kaplan-Meier Estimates of Time to True Deterioration for FKSI-DRS (Primary Analysis) (FAS Population)



Number of subjects at risk

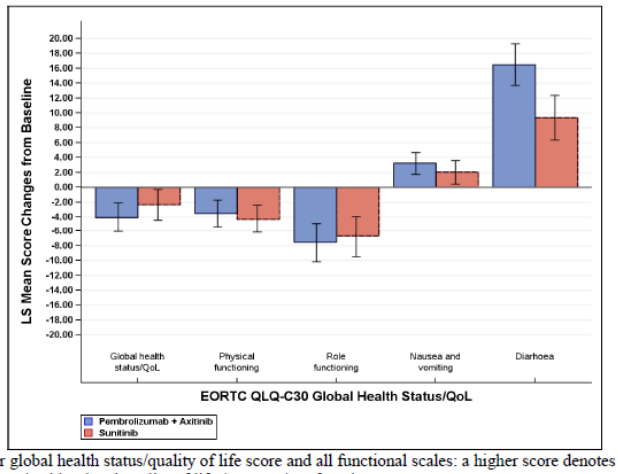
Pembrolizumab + Axitinib	395	227	144	86	32	1	0
Sunitinib	387	226	138	73	26	1	0

Database Cutoff Date: 24Aug2018.
Source: [P426V01MK3475: adam-adpro; adttd]

EORTC QLQ-C30 Global Health Status/Quality of Life Change From Baseline to Week 30

There were no clinically meaningful differences from baseline to Week 30 in the EORTC QLQ-C30 global health status/QoL score for participants in both the pembrolizumab + axitinib group and the sunitinib group. Greater worsening (ie, increase in score) from baseline to Week 30 in the EORTC QLQ-C30 symptom scale for diarrhea was observed for participants in the pembrolizumab + axitinib group compared with those in the sunitinib group. Diarrhea is an AE associated with both pembrolizumab and axitinib.

Figure: Change from Baseline for EORTC QLQ-C30 Global Health Status/QoL and Selected Functional and Symptom Scales at Week 30 LS Mean Change and 95% CI (FAS Population)



For global health status/quality of life score and all functional scales: a higher score denotes better health related quality of life (HRQOL) or function.
For symptoms scales: a higher score denotes worse symptoms.
Database Cutoff Date: 24Aug2018.
Source: [P426V01MK3475: adam-adplda]

Ancillary analyses

PFS Sensitivity Analyses

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

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS [†] (Months) (95% CI)	PFS Rate at Months 12 in % [†] (95% CI)
Pembrolizumab + Axitinib	432	185 (42.8)	3962.6	4.7	15.1 (12.5, 17.7)	59.4 (54.1, 64.3)
Sunitinib	429	223 (52.0)	3346.8	6.7	10.2 (8.5, 12.4)	45.3 (39.8, 50.7)
Pairwise Comparisons					Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]
Pembrolizumab + Axitinib vs. Sunitinib					0.68 (0.56, 0.82)	0.00005

[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by International Metastatic RCC Database Consortium (IMDC) risk group (favorable vs. intermediate vs. poor) and geographic region (North America vs. Western Europe vs. Rest of the World).
[§] One-sided p-value based on log-rank test stratified by the same strata as above.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adtte]

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

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS † (Months) (95% CI)	PFS Rate at Months 12 in % † (95% CI)
Pembrolizumab + Axitinib	432	230 (53.2)	3936.6	5.8	12.4 (10.7, 14.5)	52.4 (47.3, 57.2)
Sunitinib	429	289 (67.4)	3377.1	8.6	8.2 (7.1, 9.2)	35.9 (31.0, 40.8)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value§
Pembrolizumab + Axitinib vs. Sunitinib					0.65 (0.55, 0.78)	0.00000

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by International Metastatic RCC Database Consortium (IMDC) risk group (favorable vs. intermediate vs. poor) and geographic region (North America vs. Western Europe vs. Rest of the World).
§ One-sided p-value based on log-rank test stratified by the same strata as above.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adtte]

PFS Analyses based on Investigator Assessment

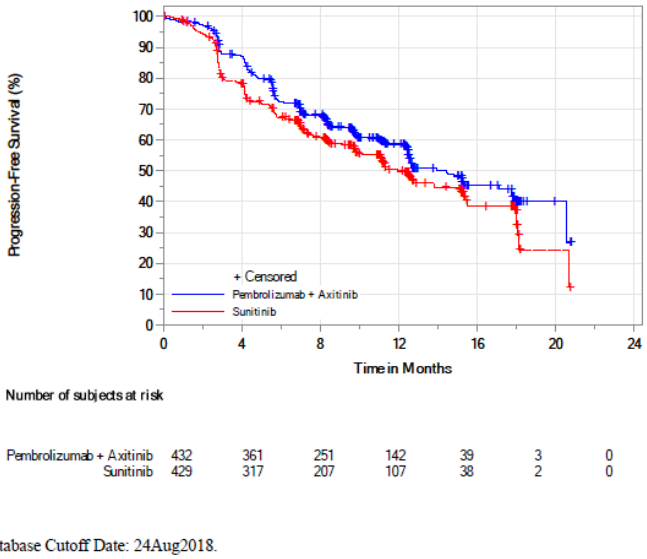
Table: Analysis of Progression-Free Survival (Primary Censoring Rule) Based on Investigator Assessment per RECIST 1.1 (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS † (Months) (95% CI)	PFS Rate at Months 12 in % † (95% CI)
Pembrolizumab + Axitinib	432	190 (44.0)	3925.4	4.8	14.5 (12.5, 17.7)	58.6 (53.4, 63.4)
Sunitinib	429	207 (48.3)	3503.2	5.9	11.9 (10.1, 15.0)	49.9 (44.4, 55.2)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value§
Pembrolizumab + Axitinib vs. Sunitinib					0.82 (0.67, 1.00)	0.02200

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by International Metastatic RCC Database Consortium (IMDC) risk group (favorable vs. intermediate vs. poor) and geographic region (North America vs. Western Europe vs. Rest of the World).
§ One-sided p-value based on log-rank test stratified by the same strata as above.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adtte]

Figure: Kaplan-Meier Estimates of Progression-Free Survival (Primary Censoring Rule) Based on Investigator Assessment per RECIST 1.1 (ITT Population)



Database Cutoff Date: 24Aug2018.

Table: Concordance of Progression Events (Investigator vs. BICR) (ITT Population)

	Pembrolizumab + Axitinib (N=432)	Sunitinib (N=429)	Total (N=861)
Investigator Assessment - PD	169	183	352
BICR Agreed	136(80%)	137(75%)	273(78%)
BICR and Investigator agreed on time	71(42%)	77(42%)	148(42%)
BICR has earlier time	43(25%)	45(25%)	88(25%)
BICR has later time	22(13%)	15(8%)	37(11%)
BICR Disagreed	33(20%)	46(25%)	79(22%)
No BICR Assessment	0(0%)	0(0%)	0(0%)
Investigator Assessment - Non PD	245	215	460
BICR Agreed	219(89%)	168(78%)	387(84%)
BICR Disagreed	26(11%)	47(22%)	73(16%)
No BICR Assessment	0(0%)	0(0%)	0(0%)

PD: Progressive Disease.
BICR: Blinded independent central review.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adrs; adintdt]

Duration of Response based on Investigator Assessment

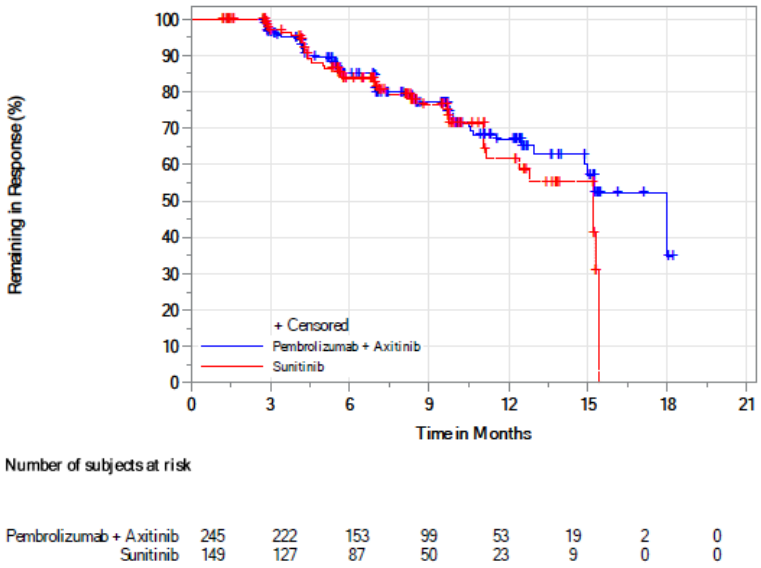
Table: Summary of Time to Response and Duration of Response Based on Response in Subjects with Confirmed Response Based on Investigator Assessment per RECIST 1.1 (ITT Population)

	Pembrolizumab + Axitinib (N=432)	Sunitinib (N=429)
Number of subjects with response[†]	245	149
Time to Response (months)		
Mean (SD)	3.5 (1.4)	4.3 (2.3)
Median (Range)	2.8 (1.5-11.4)	3.0 (2.4-15.1)
Response Duration[‡] (months)		
Median (Range)	18.0 (1.3+ - 18.2+)	15.2 (1.2+ - 15.4)
Number (%[‡]) of Subjects with Extended Response Duration:		
≥6 months	153 (85.2)	87 (83.8)
≥12 months	53 (67.0)	23 (61.7)
≥18 months	2 (34.9)	0 (NR)

[†] Includes subjects with confirmed complete response or partial response.
[‡] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
NR = Not Reached.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adtte; adrs]

Figure: Kaplan-Meier Estimates of Duration of Response in Subjects With Confirmed Response Based on Investigator Assessment per RECIST 1.1 (ITT Population)



Number of subjects at risk

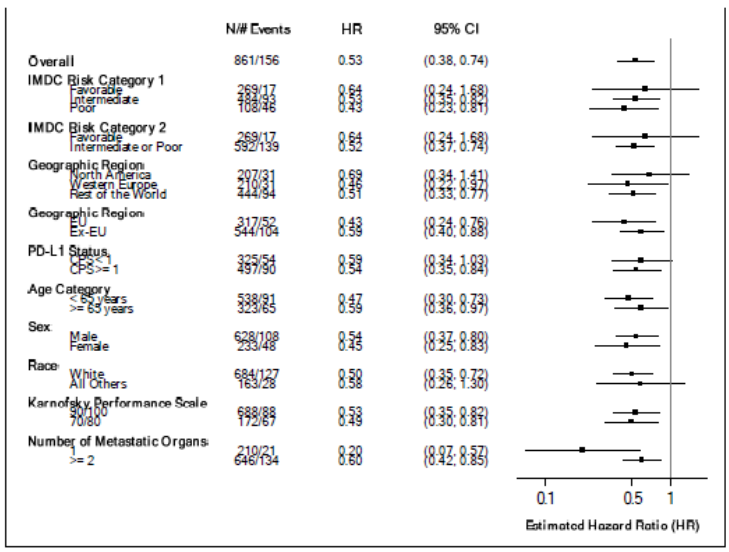
Pembrolizumab + Axitinib	245	222	153	99	53	19	2	0
Sunitinib	149	127	87	50	23	9	0	0

Database Cutoff Date: 24Aug2018.
Source: [P426V01MK3475: adam-adsl; adtte]

Subgroups analyses

OS subgroups analysis

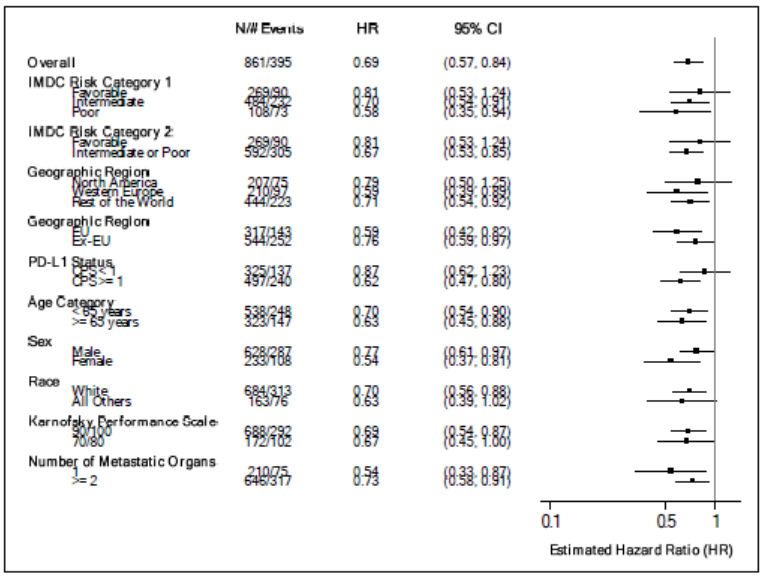
Figure: Forest Plot of OS Hazard Ratio by Subgroup Factors (ITT Population)



Based on Cox regression model treatment as a covariate stratified by International Metastatic RCC Database Consortium (IMDC) risk group (favorable vs. intermediate vs. poor) and Geographic Region (North America vs. Western Europe vs. Rest of the World).
Subjects with PD-L1 not evaluable are not included in the subgroup analysis.
Database Cutoff Date: 24Aug2018.
Source: [P426V01MK3475: adam-adsl; adtte]

PFS subgroups analysis

Figure: Forest Plot of PFS Hazard Ratio by Subgroup Factors (Primary Censoring Rule) Based on BICR Assessment per RECIST 1.1 (ITT Population)



Based on Cox regression model treatment as a covariate stratified by International Metastatic RCC Database Consortium (IMDC) risk group (favorable vs. intermediate vs. poor) and Geographic Region (North America vs. Western Europe vs. Rest of the World).
Subjects with PD-L1 not evaluable are not included in the subgroup analysis.
Database Cutoff Date: 24Aug2018.Source: [P426V01MK3475: adam-adsl; adtte]

IMDC Favourable Risk

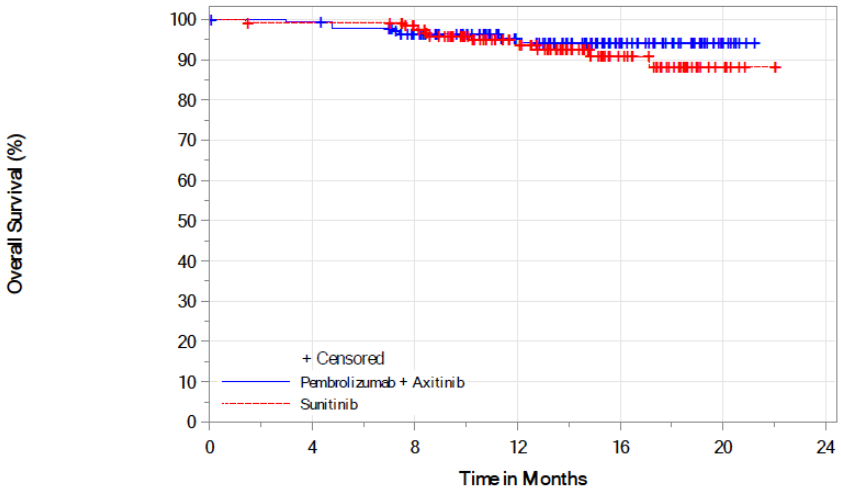
Table 4.4.2.15 : Analysis of Overall Survival Subjects with IMDC Favorable Risk (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS [†] (Months) (95% CI)	OS Rate at Months 12 in % [†] (95% CI)
Pembrolizumab + Axitinib	138	7 (5.1)	1878.6	0.4	Not Reached (., .)	95.2 (89.6, 97.9)
Sunitinib	131	10 (7.6)	1775.9	0.6	Not Reached (., .)	93.8 (87.4, 97.0)
Pairwise Comparisons					Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]
Pembrolizumab + Axitinib vs. Sunitinib					0.64 (0.24, 1.68)	0.18047

[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by International Metastatic RCC Database Consortium (IMDC) risk group (favorable vs. intermediate vs. poor) and geographic region (North America vs. Western Europe vs. Rest of the World).
[§] One-sided p-value based on log-rank test stratified by the same strata as above.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adtte]

Figure 4.4.2.7: Kaplan-Meier Estimates of Overall Survival Subjects with IMDC Favorable Risk (ITT Population)



Number of subjects at risk

Pembrolizumab + Axitinib	138	136	121	85	44	7	0
Sunitinib	131	129	120	82	39	9	0

Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adtte]

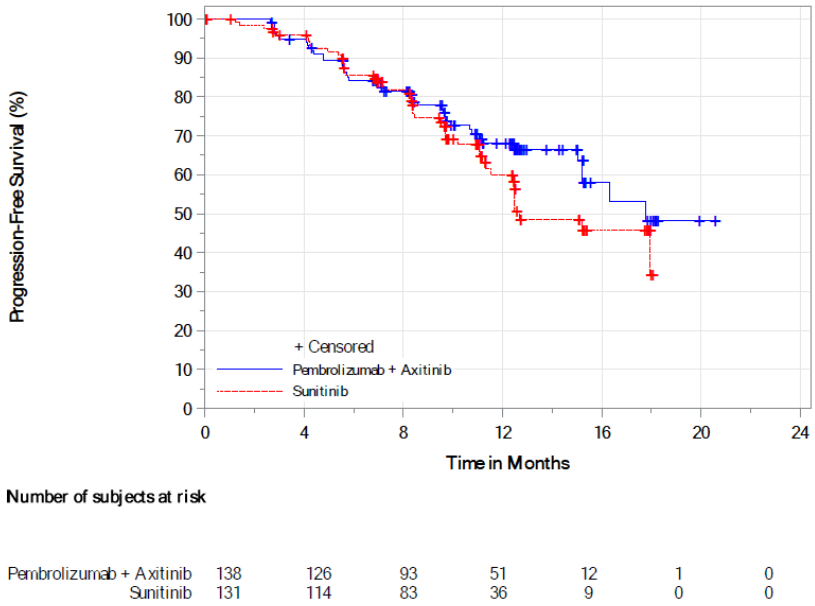
Table 4.4.2.16: Analysis of Progression-Free Survival (Primary Censoring Rule) Based on BICR Assessment per RECIST 1.1 Subjects with IMDC Favorable Risk (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS [†] (Months) (95% CI)	PFS Rate at Months 12 in % [†] (95% CI)
Pembrolizumab + Axitinib	138	43 (31.2)	1380.9	3.1	17.7 (15.2, .)	68.0 (58.4, 75.9)
Sunitinib	131	47 (35.9)	1192.3	3.9	12.7 (11.5, .)	60.0 (48.9, 69.4)
Pairwise Comparisons					Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]
Pembrolizumab + Axitinib vs. Sunitinib					0.81 (0.53, 1.24)	0.16572

[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by International Metastatic RCC Database Consortium (IMDC) risk group (favorable vs. intermediate vs. poor) and geographic region (North America vs. Western Europe vs. Rest of the World).
[§] One-sided p-value based on log-rank test stratified by the same strata as above.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adtte]

Figure 4.4.2.8: Kaplan-Meier Estimates of Progression-Free Survival (Primary Censoring Rule) Based on BICR Assessment per RECIST 1.1 Subjects with IMDC Favorable Risk (ITT Population)



PD-L1 Expression Subgroups

Table 4.4.2.17: Analysis of Overall Survival Subjects with CPS < 1 (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS † (Months) (95% CI)	OS Rate at Months 12 in % † (95% CI)
Pembrolizumab + Axitinib	167	21 (12.6)	2235.9	0.9	Not Reached (., .)	91.5 (85.8, 95.0)
Sunitinib	158	33 (20.9)	1963.8	1.7	Not Reached (., .)	78.3 (70.6, 84.2)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value§
Pembrolizumab + Axitinib vs. Sunitinib					0.59 (0.34, 1.03)	0.03082

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by International Metastatic RCC Database Consortium (IMDC) risk group (favorable vs. intermediate vs. poor) and geographic region (North America vs. Western Europe vs. Rest of the World).
§ One-sided p-value based on log-rank test stratified by the same strata as above.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adtte]

Table 4.4.2.18: Analysis of Overall Survival Subjects with CPS ≥ 1 (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS † (Months) (95% CI)	OS Rate at Months 12 in % † (95% CI)
Pembrolizumab + Axitinib	243	32 (13.2)	3156.5	1.0	Not Reached (., .)	90.1 (85.5, 93.3)
Sunitinib	254	58 (22.8)	3050.3	1.9	Not Reached (., .)	78.4 (72.4, 83.2)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value§
Pembrolizumab + Axitinib vs. Sunitinib					0.54 (0.35, 0.84)	0.00272

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by International Metastatic RCC Database Consortium (IMDC) risk group (favorable vs. intermediate vs. poor) and geographic region (North America vs. Western Europe vs. Rest of the World).
§ One-sided p-value based on log-rank test stratified by the same strata as above.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adtte]

Figure 4.4.2.9: Kaplan-Meier Estimates of Overall Survival Subjects with CPS < 1 (ITT Population)

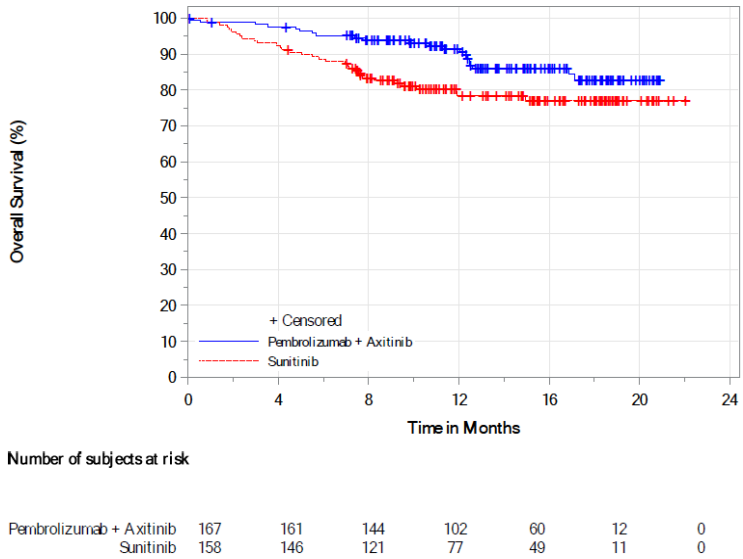
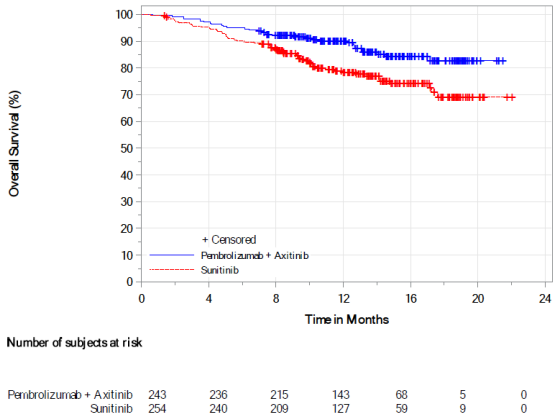


Figure 4.4.2.10: Kaplan-Meier Estimates of Overall Survival Subjects with CPS >= 1 (ITT Population)



Subsequent Anticancer Treatments for RCC

A lower percentage of participants in the pembrolizumab + axitinib group compared with the sunitinib group received any subsequent systemic anti-cancer therapy by type or across lines for advanced RCC. The most common type of subsequent anticancer therapy administered in the pembrolizumab + axitinib group was a VEGF/VEGR inhibitor (most commonly cabozantinib, sunitinib, axitinib, or pazopanib), with a frequency that was similar to that in the sunitinib group. A higher percentage of participants in the sunitinib group received a PD-1 or PD-L1 checkpoint inhibitor (most commonly nivolumab) as subsequent anticancer therapy compared with the pembrolizumab + axitinib group.

Table: Subsequent Systemic Anti-Cancer Treatment (ITT Population)

	Pembrolizumab + Axitinib (N=432)	Sunitinib (N=429)	Total (N=861)
Started Study Treatment	429 (99.3)	425 (99.1)	854 (99.2)
Discontinued Study Treatment	176 (40.7)	242 (56.4)	418 (48.5)
Received Any Subsequent Systemic Anti-cancer Therapy	88 (20.4)	147 (34.3)	235 (27.3)
Subsequent systemic therapy by type			
Any PD1/PD-L1 checkpoint inhibitor	8 (1.9)	91 (21.2)	99 (11.5)
atezolizumab	0 (0.0)	1 (0.2)	1 (0.1)
durvalumab	0 (0.0)	2 (0.5)	2 (0.2)
nivolumab	8 (1.9)	88 (20.5)	96 (11.1)
pembrolizumab	0 (0.0)	1 (0.2)	1 (0.1)
Any VEGF/VEGFR inhibitor	78 (18.1)	86 (20.0)	164 (19.0)
axitinib	7 (1.6)	28 (6.5)	35 (4.1)
bevacizumab	0 (0.0)	1 (0.2)	1 (0.1)
cabozantinib	33 (7.6)	22 (5.1)	55 (6.4)
lenvatinib	9 (2.1)	5 (1.2)	14 (1.6)
pazopanib	13 (3.0)	21 (4.9)	34 (3.9)
sorafenib	0 (0.0)	2 (0.5)	2 (0.2)
sunitinib	29 (6.7)	18 (4.2)	47 (5.5)
Other	21 (4.9)	26 (6.1)	47 (5.5)
everolimus	16 (3.7)	14 (3.3)	30 (3.5)
glutaminase inhibitor (unspecified)	2 (0.5)	2 (0.5)	4 (0.5)
hypoxia inducible factor 2 alpha inhibitor (unspecified)	1 (0.2)	0 (0.0)	1 (0.1)
ibrutinib	0 (0.0)	1 (0.2)	1 (0.1)
interferon (unspecified)	3 (0.7)	2 (0.5)	5 (0.6)
interferon alfa-2a	0 (0.0)	1 (0.2)	1 (0.1)
interferon gamma	1 (0.2)	0 (0.0)	1 (0.1)
investigational drug (unspecified)	0 (0.0)	2 (0.5)	2 (0.2)
ipilimumab	2 (0.5)	6 (1.4)	8 (0.9)
savolitinib	0 (0.0)	1 (0.2)	1 (0.1)
vinblastine	2 (0.5)	0 (0.0)	2 (0.2)
Subsequent systemic therapy by lines			
1 subsequent line	88 (20.4)	141 (32.9)	229 (26.6)
2 subsequent lines	18 (4.2)	46 (10.7)	64 (7.4)
≥3 subsequent lines	4 (0.9)	8 (1.9)	12 (1.4)

Every subject is counted a single time for each applicable specific anti-cancer treatment.
A subject with multiple anti-cancer treatments within a therapy category is counted a single time for that category.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adcm]

UPDATED DATA

As per CHMP request, the MAH provided updated efficacy data from KEYNOTE-426, using a data cutoff of **02-JAN-2019.**

Median follow up duration (ITT population) was 17.4 months (range 0.1, 25.6) in pembrolizumab + axitinib arm, and 15.7 months (0.4, 26.3) in the sunitinib arm.

Overall survival

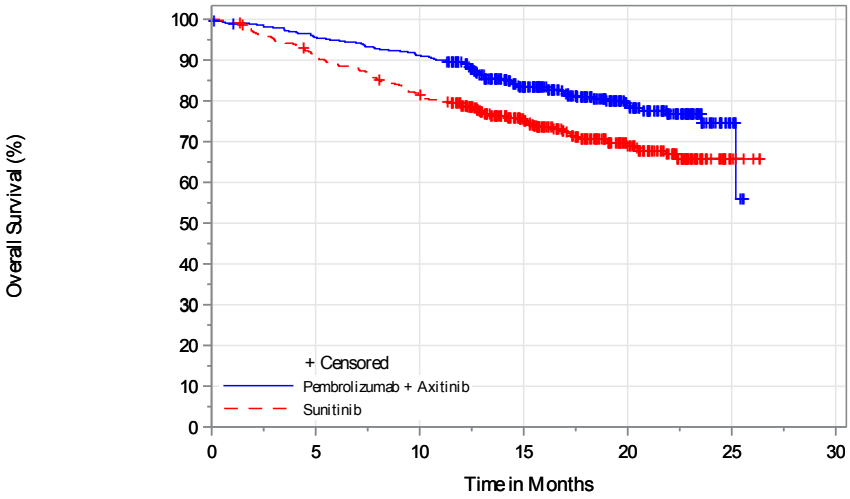
Table: Analysis of Overall Survival and Summary Over Time (ITT Population) – 02-JAN-2019 Cutoff

Endpoint	Pembrolizumab Axitinib n=432	Sunitinib n=429
OS (ITT)		
Number of events (%)	84 (19.4%)	122 (28.4%)
Median in months (95% CI)	Not reached (25. 2, NA)	Not reached (NA, NA)
Hazard ratio* (95% CI)	0.59 (0.45, 0.78)	
p-Value†	0.00010	
OS rate at 6 Months in % (95% CI)†	94.9 (92.3, 96.6)	89.0 (85.6, 91.6)
OS rate at 12 Months in % (95% CI)†	89.5 (86.2, 92.1)	78.8 (74.7, 82.4)
OS rate at 18 Months in % (95% CI)†	81.0 (76.7, 84.6)	70.7 (65.8, 75.1)

Table: Overall Survival in IMDC Risk Category – 02-JAN-2019 Cutoff

Endpoint	Pembrolizumab Axitinib n=432	Sunitinib n=429
OS (IMDC Risk category 1)		
Favorable	n=138	n=131
Number of events (%)	13 (9.4%)	12 (9.2%)
Median in months (95% CI)	Not reached (NA, NA)	Not reached (NA, NA)
Hazard ratio* (95% CI)	0.94 (0.43, 2.07)	
Intermediate	n=238	n=246
Number of events (%)	45 (18.9%)	78 (31.7%)
Median in months (95% CI)	Not reached (NA, NA)	Not reached (NA, NA)
Hazard ratio* (95% CI)	0.52 (0.36, 0.75)	
Poor	n=56	n=52
Number of events (%)	26 (46.4%)	32 (61.5%)
Median in months (95% CI)	21.8 (14.7, 25.2)	10.1 (7.0, 17.6)
Hazard ratio* (95% CI)	0.50 (0.29, 0.87)	

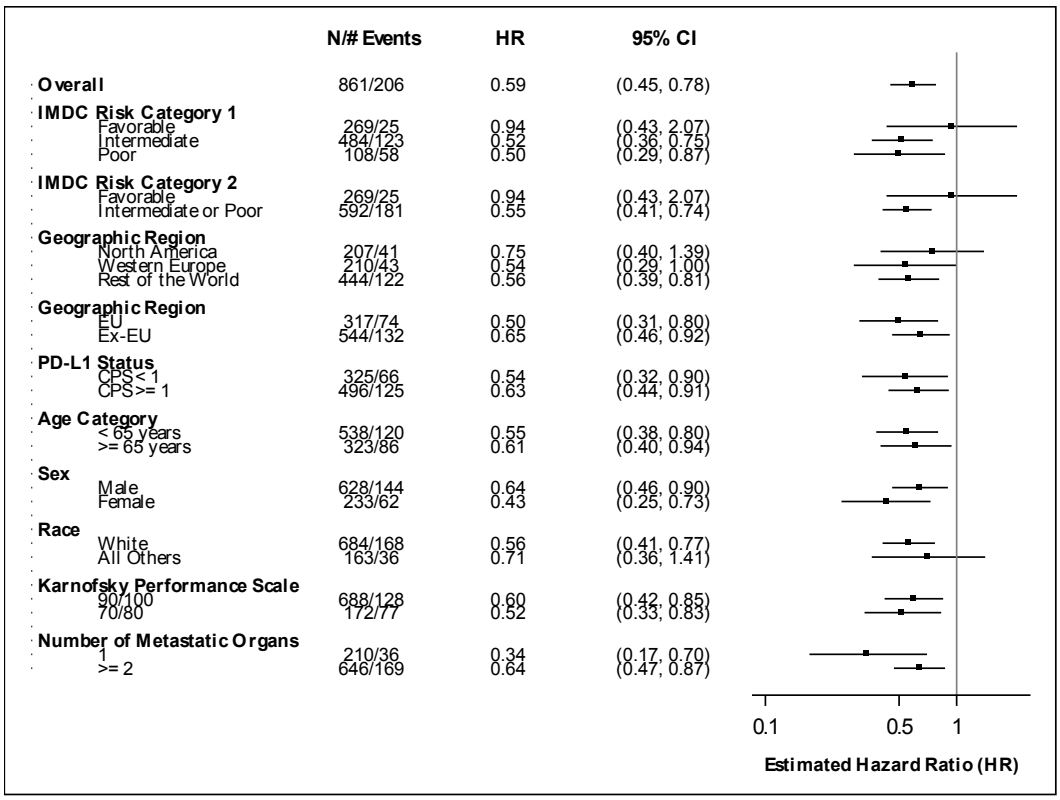
Figure: Kaplan-Meier Estimates of Overall Survival (ITT Population) Database Cutoff Date: 02Jan2019.



Number of subjects at risk

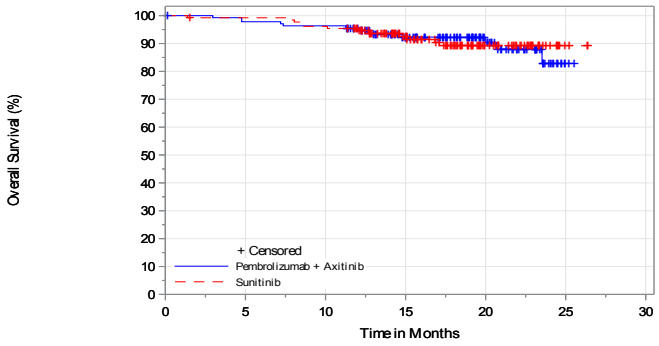
Pembrolizumab + Axitinib	432	411	392	275	133	9	0
Sunitinib	429	389	346	230	111	6	0

Figure: Forest Plot of OS Hazard Ratio by Subgroup Factors (ITT Population) - Database Cutoff Date: 02Jan2019.



Based on Cox regression model treatment as a covariate stratified by International Metastatic RCC Database Consortium (IMDC) risk group (favorable vs. intermediate vs. poor) and Geographic Region (North America vs. Western Europe vs. Rest of the World). Subjects with PD-L1 not evaluable are not included in the subgroup analysis.

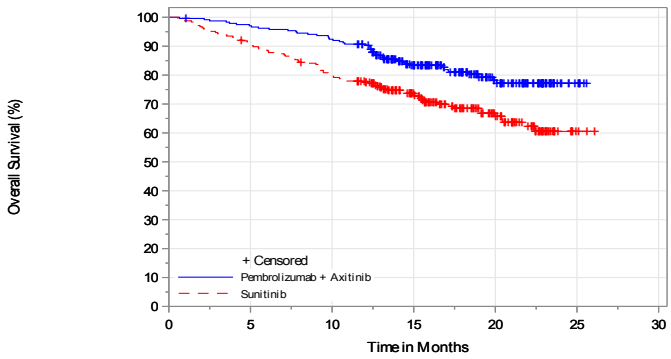
Figure:Kaplan-Meier Estimates of Overall Survival Subjects with IMDC Favorable Risk (ITT Population) Database Cutoff Date: 02Jan2019



Number of subjects at risk

Pembrolizumab + Axitinib	138	134	132	98	46	2	0
Sunitinib	131	129	125	88	39	3	0

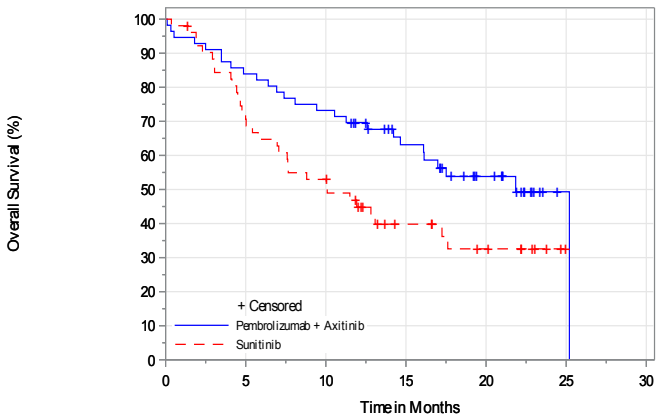
Figure:Kaplan-Meier Estimates of Overall Survival Subjects with IMDC Intermediate Risk (ITT Population) Database Cutoff Date: 02Jan2019.



Number of subjects at risk

Pembrolizumab + Axitinib	238	230	219	149	71	6	0
Sunitinib	246	224	194	129	64	3	0

Figure:Kaplan-Meier Estimates of Overall Survival Subjects with IMDC Poor Risk (ITT Population) Database Cutoff Date: 02Jan2019.



Number of subjects at risk

Pembrolizumab + Axitinib	56	47	41	28	16	1	0
Sunitinib	52	36	27	13	8	0	0

Progression-free Survival

Table: Analysis of Progression-Free Survival (Primary Censoring Rule) Based on BICR Assessment per RECIST 1.1 (ITT Population) Database Cutoff Date: 02Jan2019.

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS [†] (Months) (95% CI)	PFS Rate at Months 12 in % [†] (95% CI)
Pembrolizumab + Axitinib	432	207 (47.9)	4789.2	4.3	17.1 (13.6, 18.9)	60.1 (55.1, 64.7)
Sunitinib	429	232 (54.1)	3775.2	6.1	11.1 (8.7, 12.5)	47.7 (42.5, 52.7)
Pairwise Comparisons					Hazard Ratio[‡] (95% CI)[‡]	p-Value[§]
Pembrolizumab + Axitinib vs. Sunitinib					0.69 (0.57, 0.83)	0.00005

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

[‡] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by International Metastatic RCC Database Consortium (IMDC) risk group (favorable vs. intermediate vs. poor) and geographic region (North America vs. Western Europe vs. Rest of the World).

[§] One-sided p-value based on log-rank test stratified by the same strata as above.

Database Cutoff Date: 02Jan2019.

Figure: Kaplan-Meier Estimates of Progression-Free Survival (Primary Censoring Rule) Based on BICR Assessment per RECIST 1.1 (ITT Population) Database Cutoff Date: 02Jan2019.

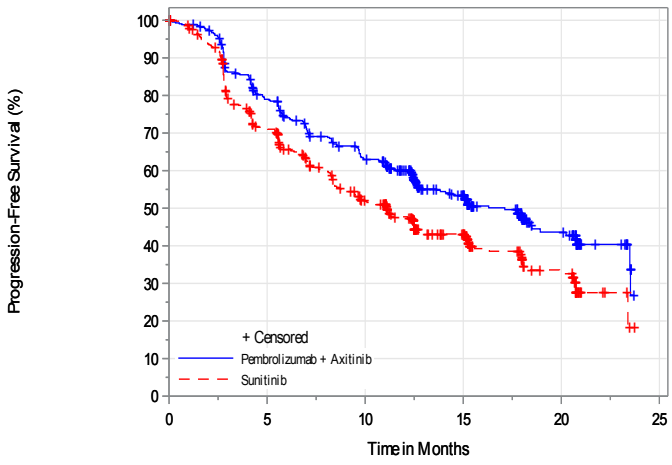
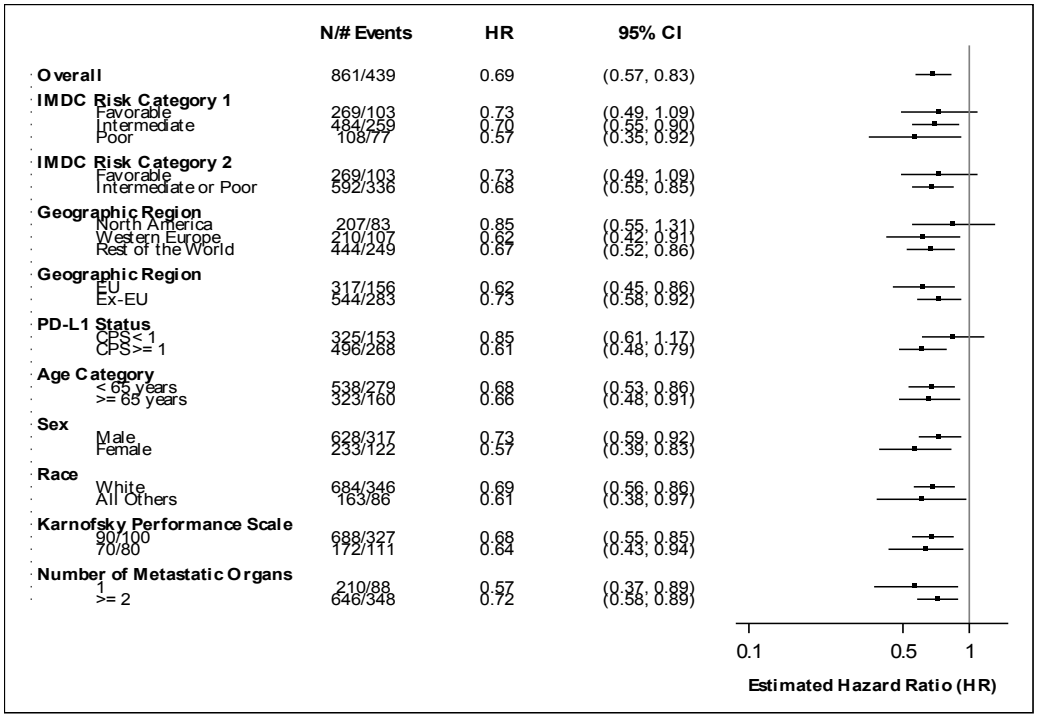


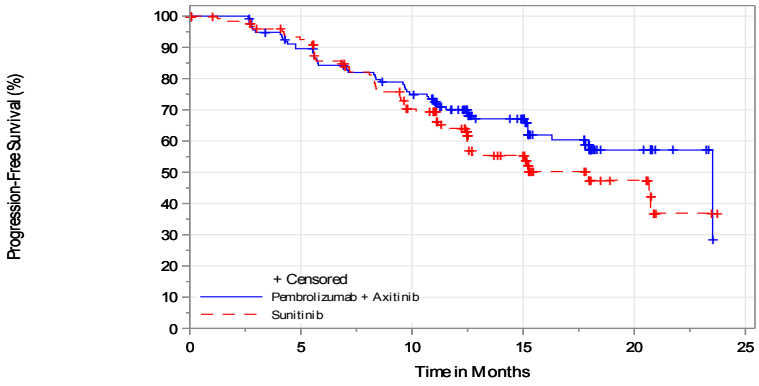
Figure: Forest Plot of PFS Hazard Ratio by Subgroup Factors (Primary Censoring Rule) Based on BICR Assessment per RECIST 1.1 (ITT Population) Database Cutoff Date: 02Jan2019.



Based on Cox regression model treatment as a covariate stratified by International Metastatic RCC Database Consortium (IMDC) risk group (favorable vs. intermediate vs. poor) and Geographic Region (North America vs. Western Europe vs. Rest of the World).

Subjects with PD-L1 not evaluable are not included in the subgroup analysis. Database Cutoff Date: 02Jan2019.

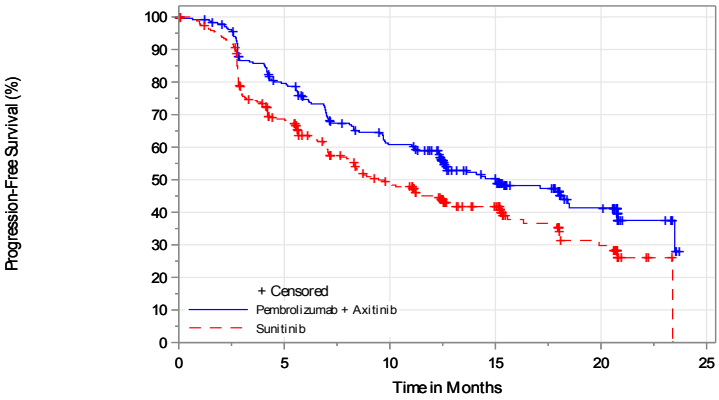
Figure:Kaplan-Meier Estimates of Progression-Free Survival (Primary Censoring Rule) Based on BICR Assessment per RECIST 1.1 Subjects with IMDC Favorable Risk (ITT Population) Database Cutoff Date: 02Jan2019.



Number of subjects at risk

Pembrolizumab + Axitinib	138	119	97	57	13	0
Sunitinib	131	109	74	35	12	0

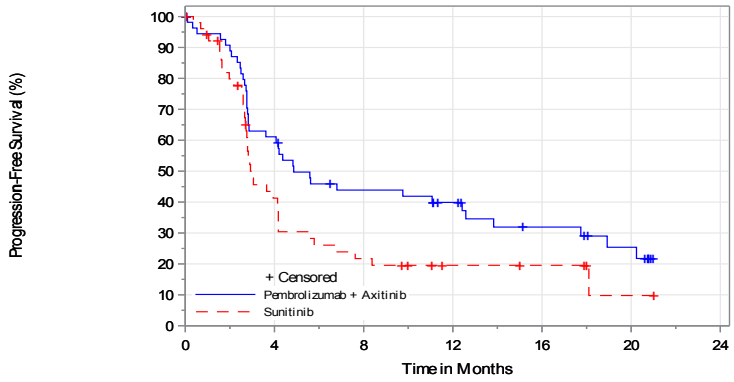
Figure: Kaplan-Meier Estimates of Progression-Free Survival (Primary Censoring Rule) Based on BICR Assessment per RECIST 1.1 Subjects with IMDC Intermediate Risk (ITT Population) Database Cutoff Date: 02Jan2019.



Number of subjects at risk

Pembrolizumab + Axitinib	238	179	129	76	31	0
Sunitinib	246	154	94	51	19	0

Figure: Kaplan-Meier Estimates of Progression-Free Survival (Primary Censoring Rule) Based on BICR Assessment per RECIST 1.1 Subjects with IMDC Poor Risk (ITT Population) Database Cutoff Date: 02Jan2019.



Number of subjects at risk

Pembrolizumab + Axitinib	56	33	22	17	11	7	0
Sunitinib	52	19	10	5	4	1	0

Objective Response Rate

Table: Analysis of Objective Response (Confirmed) Based on BICR Assessment per RECIST 1.1 (ITT Population) Database Cutoff Date: 02Jan2019.

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Sunitinib	
				Estimate (95% CI)[†]	p-Value[††]
Pembrolizumab + Axitinib	432	259	60.0 (55.2,64.6)	21.5 (15.1,27.8)	<0.0001
Sunitinib	429	165	38.5 (33.8,43.2)		

[†] Based on Miettinen & Nurminen method stratified by International Metastatic RCC Database Consortium (IMDC) risk group (favorable vs. intermediate vs. poor) and geographic region (North America vs. Western Europe vs. Rest of the World).

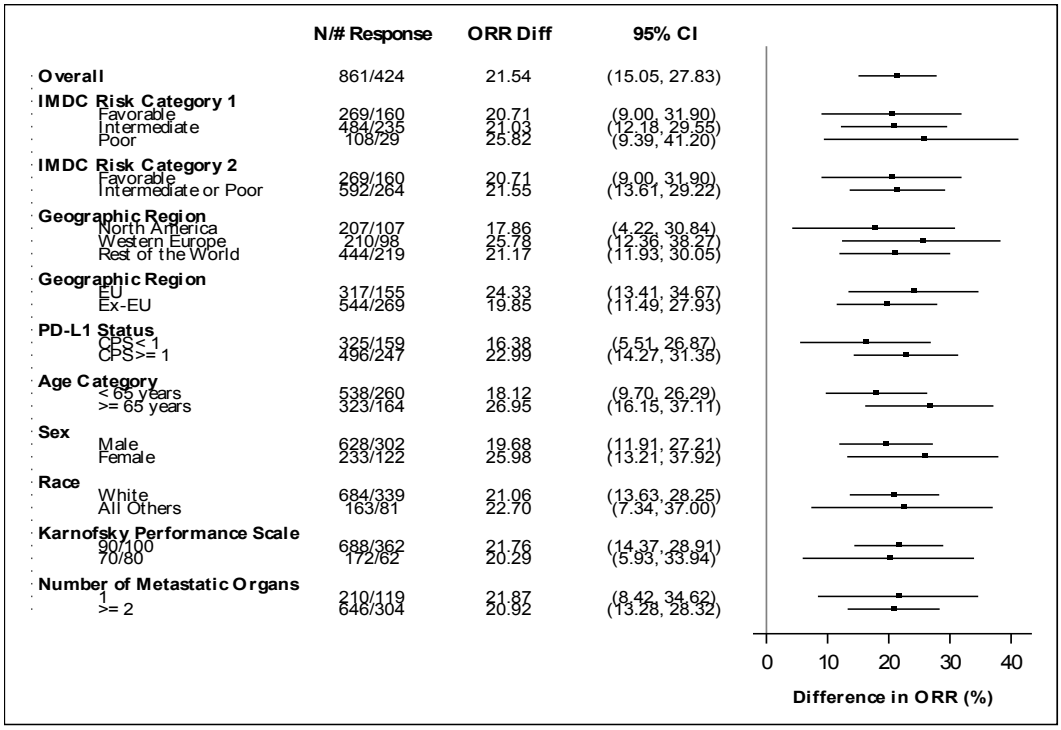
[††] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.

Responses are based on BICR assessment per RECIST 1.1.

BICR = Blinded independent central review.

Database Cutoff Date: 02Jan2019.

Figure: Forest Plot of Objective Response Rate by Subgroup Factors (Confirmed) Based on BICR Assessments per RECIST 1.1 (ITT Population) Database Cutoff Date: 02Jan2019.



Analysis (ORR difference and 95% CI) in the overall population is based on the stratified Miettinen and Nurminen method; analysis in the subgroups is based on the unstratified Miettinen & Nurminen method.

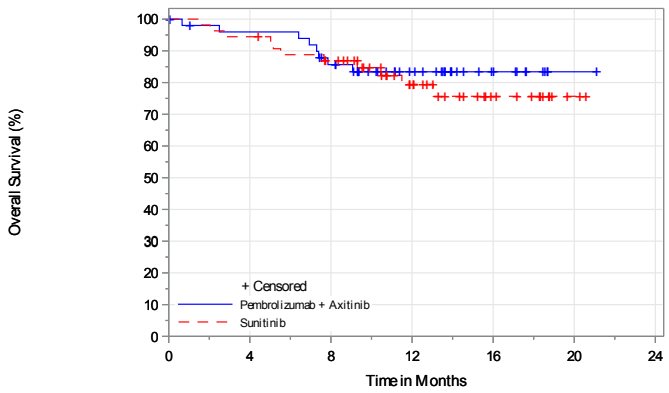
Subjects with PD-L1 not evaluable are not included in the subgroup analysis.

Database Cutoff Date: 02Jan2019.

Additonal subgroup analysis

RCC with sarcomatoid features:

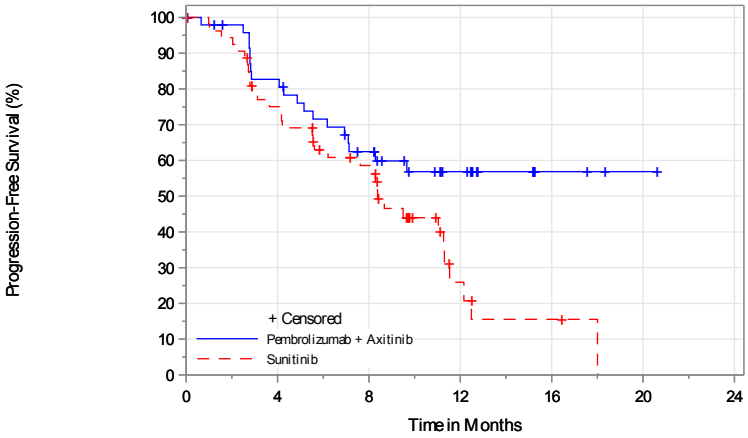
Figure:Kaplan-Meier Estimates of Overall Survival Subjects with Sarcomatoid Feature (ITT Population)



Number of subjects at risk

Pembrolizumab + Axitinib	51	47	40	24	10	1	0
Sunitinib	54	51	44	26	12	2	0

Figure Kaplan-Meier Estimates of Progression-Free Survival (Primary Censoring Rule) Based on BICR Assessment per RECIST 1.1 Subjects with Sarcomatoid Feature (ITT Population)



Number of subjects at risk

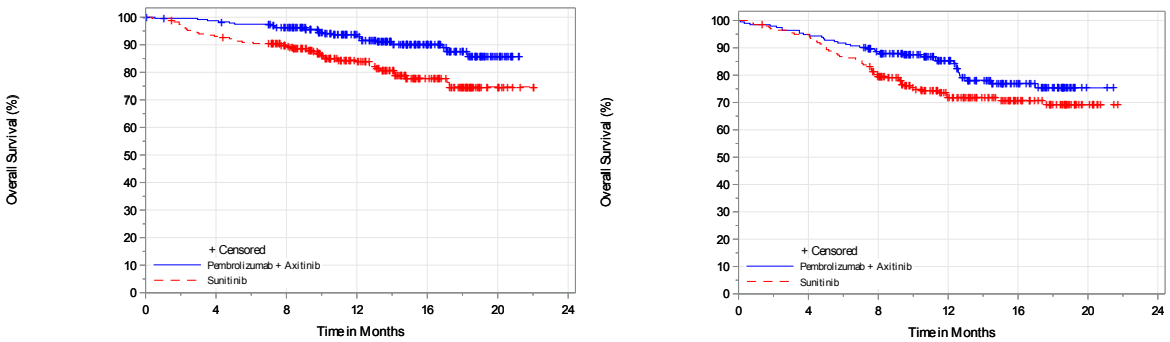
Pembrolizumab + Axitinib	51	38	26	14	3	1	0
Sunitinib	54	38	26	5	2	0	0

Recurrent vs. newly diagnosed RCC

For OS, the HRs (95% CIs) are 0.43 (0.26, 0.73) and 0.65 (0.42, 0.99) for the subgroups with recurrent and newly diagnosed disease, respectively. For PFS, the HRs (95% CIs) are 0.74 (0.55, 0.99) and 0.66 (0.50, 0.87) for these same subgroups. These results indicate a comparable treatment effect in OS and PFS in both subgroups.

Figure: Kaplan-Meier Estimates of Overall Survival Subjects with Recurrent (left) and Newly Diagnosed Stage IV /right RCC

(ITT Population)



Number of subjects at risk

Pembrolizumab + Axitinib	238	233	216	152	84	16	0
Sunitinib	231	214	189	119	59	10	0

Number of subjects at risk

Pembrolizumab + Axitinib	194	184	162	104	52	2	0
Sunitinib	198	187	152	92	51	10	0

Subsequent Anticancer Treatments for RCC in Subjects who Discontinued Treatment due to AEs

As of the data cutoff of 02 JAN 2019, 65 / 429 (15.2%) participants from the pembrolizumab plus axitinib arm and 61 / 425 (14.4%) participants from the sunitinib arm had discontinued study treatment(s) completely due to adverse events (AEs). Subsequent anticancer treatment in these subjects is described in the tables below:

Table 1
Subsequent Systemic Anti-Cancer Treatment
(ITT Population)
(Subjects Who Discontinued Study Treatment Due to AE)

	Pembrolizumab + Axitinib (N=65)	Sunitinib (N=61)	Total (N=126)
Discontinued Study Treatment Due to AEs	65 (100.0)	61 (100.0)	126 (100.0)
Discontinued Study Treatment Due to AEs and Received Any Subsequent Systemic Anti-cancer Therapy	24 (36.9)	30 (49.2)	54 (42.9)
Subsequent systemic therapy by type			
Any PD1/PD-L1 checkpoint inhibitor	3 (4.6)	21 (34.4)	24 (19.0)
nivolumab	3 (4.6)	21 (34.4)	24 (19.0)
pembrolizumab	0 (0.0)	1 (1.6)	1 (0.8)
Any VEGF/VEGFR inhibitor	19 (29.2)	18 (29.5)	37 (29.4)
axitinib	4 (6.2)	5 (8.2)	9 (7.1)
bevacizumab	0 (0.0)	1 (1.6)	1 (0.8)
cabozantinib	5 (7.7)	2 (3.3)	7 (5.6)
lenvatinib	0 (0.0)	1 (1.6)	1 (0.8)
pazopanib	5 (7.7)	5 (8.2)	10 (7.9)
sunitinib	9 (13.8)	6 (9.8)	15 (11.9)
Other	7 (10.8)	2 (3.3)	9 (7.1)
doxorubicin	1 (1.5)	0 (0.0)	1 (0.8)
everolimus	6 (9.2)	2 (3.3)	8 (6.3)
glutaminase inhibitor (unspecified)	1 (1.5)	0 (0.0)	1 (0.8)
interferon (unspecified)	1 (1.5)	0 (0.0)	1 (0.8)
vinblastine	1 (1.5)	0 (0.0)	1 (0.8)
Subsequent systemic therapy by number of lines			
1 subsequent line	24 (36.9)	28 (45.9)	52 (41.3)
2 subsequent lines	7 (10.8)	10 (16.4)	17 (13.5)
≥3 subsequent lines	2 (3.1)	2 (3.3)	4 (3.2)

Every subject is counted a single time for each applicable specific anti-cancer treatment.
A subject with multiple anti-cancer treatments within a therapy category is counted a single time for that category.
Database Cutoff Date: 02Jan2019.

Table 2
Summary of Treatment Duration of the first subsequent anti-cancer therapy
(ASaT Population)
(Subjects Who Discontinued Study Treatment Due to AE)

	Pembrolizumab + Axitinib N =65	Sunitinib N =61
Subjects with first subsequent anti-cancer therapy (2L)	24	28*
Treatment Duration (days)		
Mean	183.3	137.7
SD	145.58	138.83
Median	102.5	74.0
Range	13 to 535	2 to 551

*Two participants who had subsequent sunitinib after having discontinued sunitinib as study treatment could not be included due to data entry didn't indicate this as 2L therapy.
Database Cutoff Date: 02Jan2019.
Treatment duration = last dose date (or data cutoff date if still ongoing)-first dose date+1.

Table 3
Reason for Discontinuation of the first Subsequent Anti-cancer Therapy (2L)
(Subjects Who Discontinued Study Treatment Due to AE)

	Pembrolizumab + Axitinib N =65	Sunitinib N =61
Subjects with first subsequent anti-cancer therapy (2L)	24	28
Discontinued		
Death	0	1
Progression Of Disease	5	6
Toxicity	4	10
Unknown	1	0
Treatment Ongoing	14	11

Database Cutoff Date: 02Jan2019.

Of the 41 participants in the pembrolizumab + axitinib group who discontinued study treatment(s) due to an AE and received no further anti-cancer treatments, 24 participants were still alive and 17 participants had died; of the 31 participants from the sunitinib group who discontinued study treatment(s) due to an AE and received no further anti-cancer treatments, 13 participants were still alive and 18 participants had died.

Summary of main study(ies)

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

Table 1. Summary of Efficacy for trial KEYNOTE-426

Title: A Phase III Randomized, Open-label Study to Evaluate Efficacy and Safety of Pembrolizumab (MK-3475) in Combination with Axitinib versus Sunitinib Monotherapy as a First-line Treatment for Locally Advanced or Metastatic Renal Cell Carcinoma (mRCC)		
Study identifier	KEYNOTE-426 EudraCT NUMBER: 2016-000588-17	
Design	Phase III randomized (1:1), open-label, multicenter, global trial of pembrolizumab in combination with axitinib versus sunitinib monotherapy as a first-line treatment for advanced/metastatic renal cell carcinoma (mRCC).	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Enrolment started on 24-OCT-2016; study ongoing not applicable not applicable
Hypothesis	Superiority	
Treatments groups	Pembrolizumab + Axitinib	Pembrolizumab 200 mg every 3 weeks (Q3W) up to 35 doses or until PD in combination with Axitinib 5 mg twice daily (BID) until PD. 432 subjects randomized
	Sunitinib	Sunitinib 50 mg QD 4 weeks on, 2 weeks off until PD 429 subjects randomized

Endpoints and definitions	Co-Primary endpoint	Overall Survival (OS)	Time from randomization to death due to any cause
	Co-Primary endpoint	Progression-Free Survival (PFS)	Time from randomization to first PD (per RECIST 1.1 based on BICR) or death due to any cause, whichever occur first.
	Secondary endpoint	Objective Response rate (ORR)	Proportion of subjects in the analysis population with a CR or PR, based on blinded independent radiologists' assessment per RECIST 1.1.
	Secondary endpoint	Duration of Response (DoR)	Time from first documented evidence of CR or PR until disease progression or death, whichever occur first.
	Secondary endpoint	Disease Control Rate (DCR)	Percentage of subjects who have achieved CR, PR or SD of ≥ 6 months based on blinded independent radiologists' assessment per RECIST 1.1..
Database lock	24 August 2018		

Results and Analysis

Analysis description	**Primary Analysis (Interim Analysis 1)**		
Analysis population and time point description	Intent to treat Median follow-up 12.8 months		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab + Axitinib	Sunitinib
	Number of subject	432	429
	OS N. with events n (%)	59 (13.7)	97 (22.6)
	Median OS months (95% CI)	NR (.., ..)	NR (.., ..)
	PFS N. with events n (%)	183 (42.4)	213 (50)
	Median PFS months (95% CI)	15.1 (12.6,17.7)	11.0 (8.7, 12.5)

Effect estimate per comparison	OS	Comparison groups	Pembrolizumab + axitinib vs. sunitinib
		HR	0.53
		95% CI	(0.38, 0.74)
		P-value	0.00005
	PFS	Comparison groups	Pembrolizumab + axitinib vs. sunitinib
		HR	0.69
		95% CI	(0.56, 0.84)
		P-value	0.00012
	ORR	Comparison groups	Pembrolizumab + axitinib vs. sunitinib
		Difference in ORR	23.6
		95% CI	(17.2, 29.9)
		P-value	<0.0001
Notes	The analysis indicates a statistical significant superiority of pembrolizumab + axitinib vs sunitinib with regard to OS and PFS.		

Analysis description	**Secondary analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab +Axitinib (n = 432)	Sunitinib (n = 429)
	ORR, %	59.3 %	35.7 %
	95%-CI, %	(54.5, 63.9)	(31.1, 40.4)

	DCR	71.5 %	60.6 %	
	95%-CI, %	(67.9, 75.7)	(55.8, 65.3)	
	DOR (Median (months))	Not reached	15.2	
	95%-CI	(1.4+, 18.2+)	(1.1+, 15.4+)	
Effect estimate per comparison	ORR	Comparison groups	Pembrolizumab + Axitinib vs. Sunitinib	
		Difference	23.6 %	
		95%-CI, %	(17.2, 29.9)	
		P-value	<0.0001	
	DCR	Difference	11.0%	
		95%-CI, %	(4.8, 17.0)	
		P-value		
	DOR	HR	NA	
		95%-CI	NA	
		P-value	NA	
Notes	HR was not applicable for DOR at the time point of data cutoff date. Updated results (data cut-off 2 Jan 2019) have been provided during the procedure.			

Clinical studies in special populations

The Applicant provided data (PFS, OS, ORR, DOR) using the following age subgroups: <65 years and ≥ 65 years

Table: Subgroup Analysis of Overall Survival and Progression-free Survival (ITT Population)

	Pembrolizumab + Axitinib (N=432)			Sunitinib (N=429)			Pembrolizumab + Axitinib vs. Sunitinib
Overall Survival							
	N	Number of Events	(%)	N	Number of Events	(%)	Hazard Ratio (95% CI)†
Overall	432	59	(13.7)	429	97	(22.6)	0.53 (0.38, 0.74)
< 65 years	260	31	(11.9)	278	60	(21.6)	0.47 (0.30, 0.73)
≥ 65 years	172	28	(16.3)	151	37	(24.5)	0.59 (0.36, 0.97)
Progression-free Survival							
Overall	432	183	(42.4)	429	212	(49.4)	0.69 (0.57, 0.84)
< 65 years	260	108	(41.5)	278	140	(50.4)	0.70 (0.54, 0.90)
≥ 65 years	172	75	(43.6)	151	72	(47.7)	0.63 (0.45, 0.88)

† Based on Cox regression model with treatment as a covariate stratified by International Metastatic RCC Database Consortium (IMDC) risk group (favorable vs. intermediate vs. poor) and Geographic Region (North America vs. Western Europe vs. Rest of the World).

Subjects with PD-L1 not evaluable are not included in the subgroup analysis.

Database Cutoff Date: 24Aug2018.

Table Subgroup Analysis of Objective Response (Confirmed) Based on BICR Assessment per RECIST 1.1 (ITT Population)

	Pembrolizumab + Axitinib (N=432)				Sunitinib (N=429)				Difference†	
	N	n	(%)	95% CI (%)	N	n	(%)	95% CI (%)	(%)	95% CI (%)
Overall	432	256	(59.3)	(54.5, 63.9)	429	153	(35.7)	(31.1, 40.4)	(23.6)	(17.2, 29.9)
< 65 years	260	146	(56.2)	(49.9, 62.3)	278	104	(37.4)	(31.7, 43.4)	(18.7)	(10.3, 26.9)
≥ 65 years	172	110	(64.0)	(56.3, 71.1)	151	49	(32.5)	(25.1, 40.5)	(31.5)	(20.8, 41.4)

Overall response is based on best overall response using BICR assessment per RECIST 1.1 with confirmation.
† Analysis (ORR difference and 95% CI) in the overall population is based on the stratified Miettinen & Nurminen method; analysis in the subgroups is based on the unstratified Miettinen & Nurminen method.
Subjects with PD-L1 not evaluable are not included in the subgroup analysis.
Database Cutoff Date: 24Aug2018.

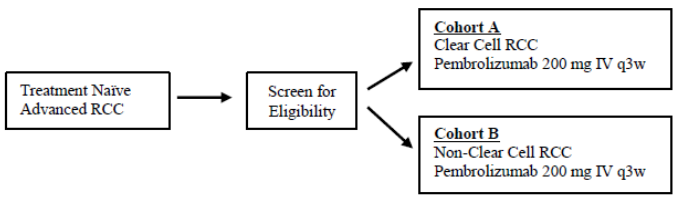
Source: [P426V01MK3475: adam-adsl; adrs]

The benefit of pembrolizumab + axitinib over sunitinib was seen across the above specified age subgroups, supporting the benefit of pembrolizumab + axitinib in the proposed indication.

Supportive study(ies)

Study KEYNOTE-427

KEYNOTE-427 is an ongoing, Phase 2, nonrandomized, open-label, 2-cohort, multicenter, global study of pembrolizumab monotherapy to evaluate the efficacy and safety of pembrolizumab as 1L treatment for locally advanced/metatsatic ccRCC (Cohort A) and nccRCC (Cohort B) in adult participants who had not previously received systemic therapy for metastatic disease. Patients were required to have measurable disease per RECIST 1.1. as assessed by BICR. Key exclusion criteria were prior treatment with any anti-PD-1, or PD-L1, or PD-L2 agent or an antibody targeting any other immune-regulatory receptors or mechanisms, diagnosis of immunodeficiency, treatment with systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to allocation (except in the case of central nervous system metastases), active autoimmune disease requiring systemic treatment within the past 2 years OR a documented history of clinically severe autoimmune disease, and known active central nervous system metastases and/or carcinomatous meningitis.

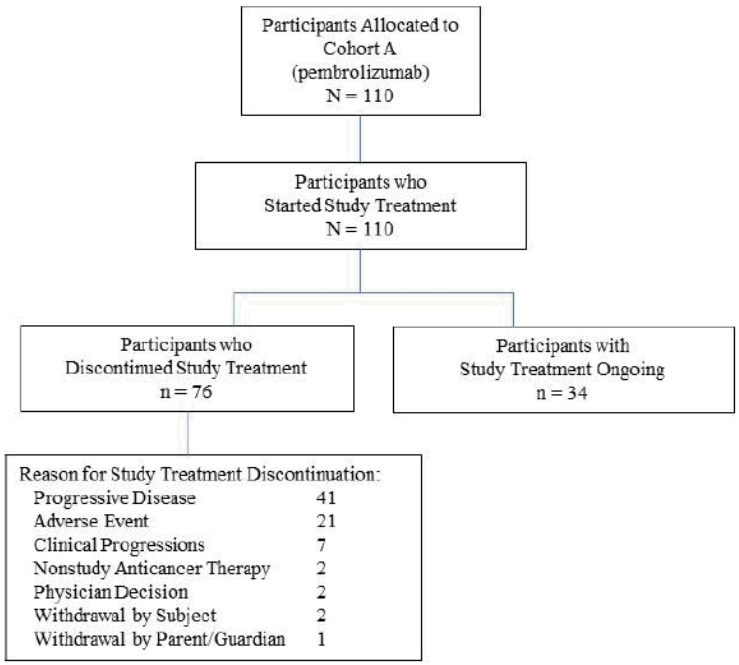


Eligible participants in Cohort A (N=110) were treated with pembrolizumab 200 mg Q3W until a total of 35 doses had been administered or until documented PD, unacceptable AEs, or any of the other discontinuation criteria were met, as outlined in the protocol. Participants were evaluated with radiographic imaging to assess response to treatment at baseline, after randomization at Week 12, then Q6W until Week 54, and Q12W thereafter. All participants are being followed for survival (by phone contact or clinic visit) until death, withdrawal of consent, being lost to follow-up, or until the study is concluded or terminated early, whichever occurs first.

The primary endpoint is ORR per RECIST 1.1 by BICR. Key secondary endpoints include DOR, DCR and PFS per RECIST 1.1 by BICR, and OS. There will be no formal hypothesis testing in this study. The overall sample size selection is based on the confidence interval (CI) width that will provide the appropriate level

of precision needed for estimation. The planned sample size is approximately 105 subjects in ccRCC cohort. With a sample size of 105 subjects with clear cell renal cell carcinoma, the half-width of 95% confidence interval varies between 8% and 10% when the observed response rates vary from 20% to 60%. No power calculation is provided. Efficacy analyses were based on the ASaT population, which consisted of 110 allocated participants in Cohort A who received at least 1 dose of study treatment. The analysis population for DOR consisted of responders.

Figure: Disposition of participants in Cohort A



BICR confirmed ORR of 36.4% was achieved; 3 (2.7%) participants had a CR and 37 (33.6%) participants had PR.

Table: Summary of Best Overall Response (Confirmed) Based on BICR per RECIST 1.1 Cohort A: ccRCC (ASaT Population)

Response Evaluation	Cohort A		
	n	%	95% CI[†]
Subjects in population	**110**		
Complete Response (CR)	3	2.7	(0.6, 7.8)
Partial Response (PR)	37	33.6	(24.9, 43.3)
Objective Response (CR+PR)	**40**	**36.4**	**(27.4, 46.1)**
Stable Disease (SD)	35	31.8	(23.3, 41.4)
Disease Control (CR+PR+SD ≥ 6 months)	**63**	**57.3**	**(47.5, 66.7)**
Progressive Disease (PD)	33	30.0	(21.6, 39.5)
No Assessment[‡]	2	1.8	(0.2, 6.4)

[†] Based on binomial exact confidence interval method for binomial data.
[‡] 'No Assessment' includes subjects discontinuing or death before the first post-baseline scan.
For best overall response of CR and PR, only confirmed responses are included.
Database Cutoff Date: 07Sep2018

Source: [P427V01MK3475: adam-adsl; adrs; adintdr]

Overall, the ORR was consistent across demographic and other predetermined subgroups with the exception of the analyses by gender and PD-L1 status. ORR is lower in females (16.7%) compared with males (41.9%); however, the small sample size precludes a meaningful analysis.

As the cutpoint for PD-L1 status (positive vs negative) was chosen in an attempt to discriminate response by CPS score based on results from an earlier database lock, the ORR was higher for participants with CPS ≥1 (44.2%) compared with CPS <1 (29.3%) with overlapping 95% CIs.

Analysis results, based on investigator assessment, were consistent with the primary analysis results, based on BICR.

As of the data cutoff date, the median DOR was not reached; 63.6% (18 of the 40 responders) of participants had an extended response duration of ≥12 months. Disease control was achieved by 57.3% (63 of 110) of participants. The median PFS for participants was 7.1 months; the PFS rate at 12 months was 37.6%. As of the data cutoff date, the median OS was not reached; the OS rate at 12 months was 88.2%.

Figure 4.4.2.13: Forest Plot of Objective Response Rate (Confirmed) Based on BICR per RECIST 1.1 Cohort A: ccRCC (ASaTPopulation)

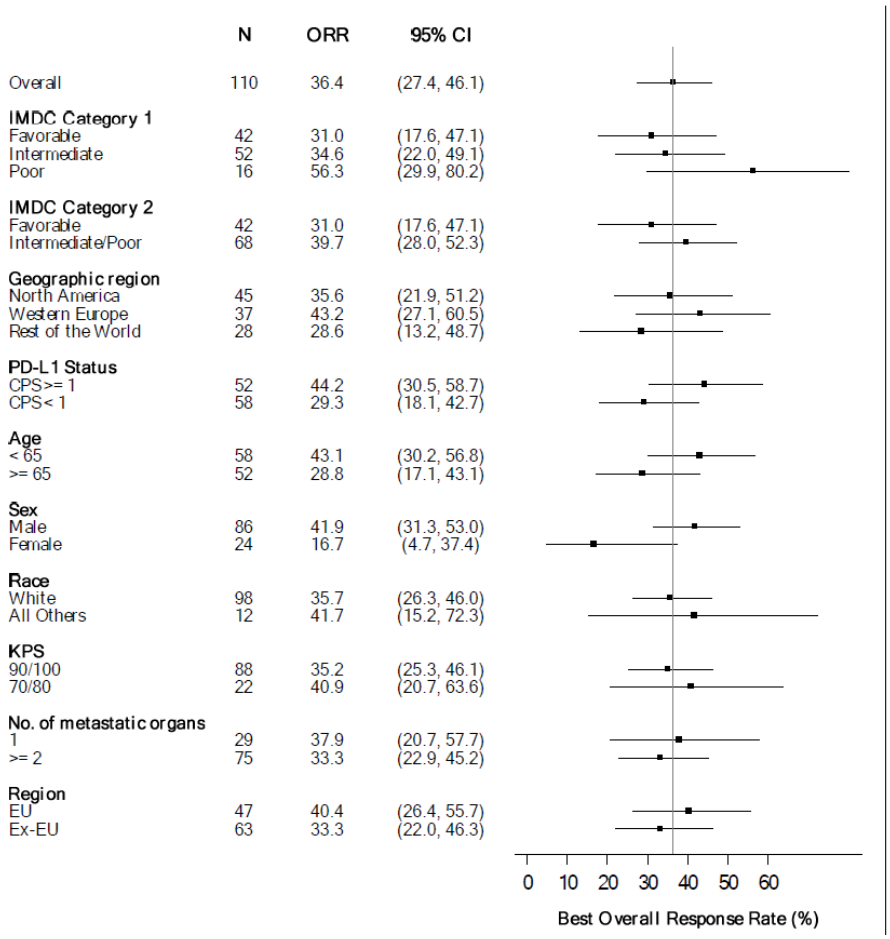


Table Comparison of Efficacy Results from Participants with PD-L1 Positive and Negative Tumors in KEYNOTE-426 and KEYNOTE-427

PD-L1 Status	PD-L1 CPS ≥1		PD-L1 CPS <1	
Study	KEYNOTE-426	KEYNOTE-427	KEYNOTE-426	KEYNOTE-427

Parameter	Pembrolizumab + Axitinib (N=243)	Pembrolizumab (N=52)	Pembrolizumab + Axitinib (N=167)	Pembrolizumab (N=58)
Confirmed Response				
ORR (CR + PR), % (95% CI)	60.5 (54.0, 66.7)	44.2 (30.5, 58.7)	56.3 (48.4, 63.9)	29.3 (18.1, 42.7)
CR, n (%)	15 (6.2)	2 (3.8)	8 (4.8)	1 (1.7)
PR, n (%)	132 (54.3)	21 (40.4)	86 (51.5)	16 (27.6)
PFS				
Median (95% CI), months	15.3 (12.6, –)	9.7 (6.7 to 16.4)	15.0 (12.4, –)	6.9 (3.3, 10.9)
12-month PFS rate, % (95% CI)	58.7 (51.7, 65.1)	40.3 (26.4, 53.7)	60.4 (51.6, 68.0)	35.3 (22.9, 47.9)
OS				
Median (95% CI), months	Not reached	Not reached	Not reached	Not reached
12-month OS rate, % (95% CI)	90.1 (85.5, 93.3)	92.3 (80.79, 97.04)	91.5 (85.8, 95.0)	84.5 (72.30, 91.61)

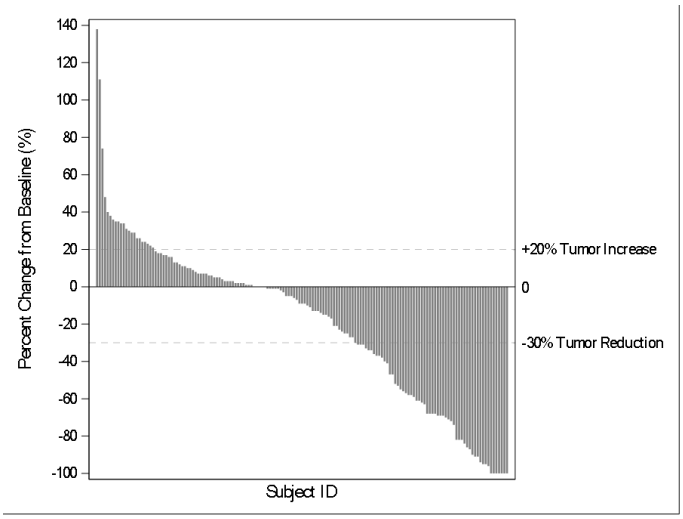
Abbreviations: CI = confidence interval; CPS = combined positive score; CR = complete response; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response.
Database Cutoff Date for KEYNOTE-426: 24Aug2018; Database Cutoff Date for KEYNOTE-427: 07Sep2018

Table: Overall Summary of Efficacy Outcome with Confirmed Responses Cohort B: nccRCC (ASaT Population)

	Cohort B
Number of Subjects	165
ORR Analysis (Central Radiology Assessment per RECIST v1.1, Confirmed Responses)	
ORR, % (95% CI[†])	24.8 (18.5, 32.2)
DCR, % (95% CI[†])	40.6 (33.0, 48.5)
Overall response, n (%)	
CR	8 (4.8)
PR	33 (20.0)
SD	53 (32.1)
PD	61 (37.0)
Non-evaluable (NE)	2 (1.2)
No Assessment	8 (4.8)
Response Duration (Central Radiology Assessment per RECIST v1.1, Confirmed Responses)	
Subjects with a Response (n)	41
Median duration of response in months (range)[‡]	NR (2.8 - 15.2+)
Median time to response (range), months	2.8 (0.1-8.3)
PFS (Central Radiology Assessment per RECIST v1.1)	
Median in months (95% CI)[‡]	4.1 (2.8,5.6)
PFS rate at Month 6 (%)[‡]	41.6 (33.9, 49.1)
OS	
Median in months (95% CI)[‡]	NR NR
OS rate at Month 3 (%)[‡]	91.5 (86.09,94.89)
OS rate at Month 6 (%)[‡]	86.6 (80.41,90.99)

CR=complete response; DCR=disease control rate; ORR=overall response rate; OS=overall survival; PD=progressive disease; PFS= progression-free survival; PR=partial response; SD=stable disease;
† Based on binomial exact confidence interval method for binomial data.
‡ From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there was no progressive disease by the time of last disease assessment.
NR = Not reached
Database Cutoff Date: 07Sep2018

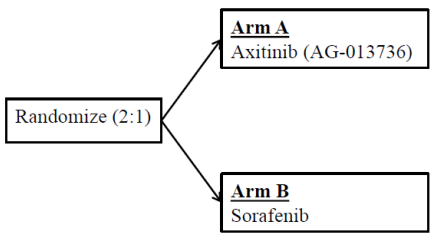
Waterfall Plot of Subjects with Maximum Target Lesion Change from Baseline
Based on BICR
Cohort B: nccRCC
(ASaT Population)



Study A4061051 *(Pfizer Sponsored):*

Study A4064051 was a Phase 3, randomized, open-label, multicenter study sponsored by Pfizer to evaluate the efficacy and safety of axitinib versus sorafenib as a 1L treatment for metastatic RCC. Key eligibiity criteria were

Eligible participants were required to meet eligibility criteria, i.e. histologically or cytologically confirmed ccRCC with metastasis, with no prior systemic first-line therapy (prior adjuvant therapy with interferon (IFN) and/or interleukin allowed if recurrence occurred >6 months after the last dose), ECOG PS 0-1, no evidence of pre-existing uncontrolled hypertension, no active seizure disorder or evidence of brain metastases, spinal cord compression, or carcinomatous meningitis.



Patients were enrolled beginning on 15-JUN-2010 and stratified by ECOG status (0 versus 1), then randomly assigned in a 2:1 ratio to either axitinib (5 mg BID; N=192) or sorafenib (400 mg BID; N=96).

Participants continued to receive study treatment until documented PD, unacceptable AEs, or any of the other discontinuation criteria were met, as outlined in the protocol. Participants with PD who were experiencing a clinical benefit with either axitinib or sorafenib were eligible for continued treatment provided that the treating physician had assessed the risk/benefit of taking such an approach and provided that the sum of longest diameters of measurable lesions remained less than or equal to the baseline sum of longest diameters and no alternative treatment was available.

Participants were evaluated with radiographic imaging to assess response to treatment at baseline, after randomization at Week 6 and Week 12, then Q8W thereafter. All participants were followed for survival.

The primary endpoint was PFS per RECIST 1.0 by central radiology assessment. Key secondary endpoints included OS, ORR, and DOR.

A total of 148 patients with progressive disease or death were required for a log-rank test with an overall 1-sided significance level of 0.025 to have power of 0.90. This assumed a 78% improvement in median PFS from 5.5 months to 9.8 months in treatment-naïve mRCC patients randomized to receive axitinib. Applying a 2:1 randomization and a planned accrual period of 16 months, a follow-up period of approximately 6 months, and assuming 20% of patients dropped out at 24 months in each arm, it was estimated that approximately 247 patients needed to be enrolled in order to observe 148 patients with progressive disease or death by the end of the follow-up period. The nominal significance level for the interim and final efficacy analyses was determined using the Lan-DeMets procedure with an O'Brien-Fleming stopping rule. The final analysis was to take place when the 148th patient had documented progressive disease or death. The overall Type I error rate was preserved at the nominal 0.025 level.

The sample size described above also allowed the assessment of differences in the secondary endpoint of OS with a high level of significance. Median OS in treatment-naïve mRCC patients treated with sorafenib was estimated to be 17.3 months. A total of 178 deaths were required for a log-rank test with an overall 1-sided significance level of 0.025 to have power of 0.80. This assumed an approximately 59% improvement in median OS from 17 months to 27 months in mRCC patients who had received no prior systemic therapy randomized to receive axitinib and a follow-up period of approximately 37 months, assuming a 0% drop out rate. The estimated sample size of 247 patients for PFS was also sufficient to observe the 178 deaths needed for comparing median OS.

Table: Overall Summary of Patient Disposition by Treatment

	Axitinib N=192 n (%)	Sorafenib N=96 n (%)
Page 1 of 2		
Full analysis set (N)[a]	192 (100.0)	96 (100.0)
Safety analysis set (N)[b]	189 (98.4)	96 (100.0)
Maximum cycles started[c]		
1	6 (3.1)	4 (4.2)
2	12 (6.3)	6 (6.3)
3	7 (3.6)	3 (3.1)
4	9 (4.7)	4 (4.2)
5	11 (5.7)	6 (6.3)
6	3 (1.6)	7 (7.3)
7	7 (3.6)	5 (5.2)
8	6 (3.1)	1 (1.0)
9	5 (2.6)	6 (6.3)
10	7 (3.6)	6 (6.3)
11	7 (3.6)	3 (3.1)
12	7 (3.6)	1 (1.0)
13	6 (3.1)	5 (5.2)
14	10 (5.2)	1 (1.0)
≥15	86 (44.8)	38 (39.6)
Primary reason for discontinuation from study treatment		
Adverse event	10 (5.2)	4 (4.2)
Patient died	19 (9.9)	7 (7.3)
Protocol violation	0	1 (1.0)
Lost to follow-up	1 (0.5)	0
Other	3 (1.6)	2 (2.1)
Objective progression or relapse	73 (38.0)	47 (49.0)
Global deterioration of health status	6 (3.1)	5 (5.2)
Patient refused continued treatment for reason other than adverse event	13 (6.8)	3 (3.1)
Primary reason for discontinuation from study		
Adverse event	1 (0.5)	0
Patient died	77 (40.1)	36 (37.5)
Protocol violation	0	0
Lost to follow-up	1 (0.5)	2 (2.1)
Other	0	0
Objective progression or relapse	0	0
Global deterioration of health status	0	0
Patient refused continued treatment for reason other than adverse event	7 (3.6)	2 (2.1)

Source: Table 14.1.1.1
%=(n/N) × 100.
Data cutoff date: 27 July 2012.
Abbreviations: N=number of patients; n=number of patients meeting prespecified criteria

In the first line portion of this study in treatment naïve patients with mRCC, the study did not achieve its primary objective, although there was a 23.3% reduction in the risk of disease progression or death (HR=0.767; 95% CI [0.559, 1.053]; p-value=0.0377) for axitinib vs sorafenib.

OS, a secondary efficacy endpoint, was immature at the time of the final PFS analysis, with only approximately 40% of patients having died. The currently estimated survival probability at 12 months was 72.0% (95% CI [65.0%, 77.9%]) for axitinib and 73.5% (95% CI [63.4%, 81.2%]) for sorafenib. The observed HR was 1.136 (95% CI [0.765, 1.687]) with a 1-sided p-value of 0.7370.

ORR, a secondary endpoint was superior for axitinib compared to sorafenib (ORR of 32.3% and 14.6%, respectively, the risk ratio (axitinib:sorafenib) was 2.214 (95% CI [1.306, 3.753]) with a 1-sided p-value of 0.0006. DoR, a secondary efficacy endpoint, was similar between treatments; the median DoR was 14.7 and 14.3 months for axitinib and sorafenib, respectively.

"Summary table of the contribution of each component in the combination regimen":

	KN426 (Ph3 vs. Sunitinib) Pembrolizumab + axitinib	KN427 Ph2 Cohort A Pembrolizumab monotherapy	Study A4061051 (Ph3 vs. sorafenib) Axitinib monotherapy
Study population	1L advanced RCC Clear cell	1L advanced RCC Clear cell	1L advanced RCC Clear cell
Samples size (ITT)	432	110	192
PFS, median, mos (95% CI)	15.1 (12.6, 17.7)	7.1 (5.6, 11.0)	10.1 (7.2, 12.1)
PFS rate at 12 months (95% CI)	59.6 % (54.3, 64.5)	37.6 % (28.2, 46.9)	NA
OS, median, mos (95% CI)	NR (NR,NR)	NR (NR,NR)	21.7 (18.0, 31.7)
OS rate at 12 months (95% CI)	89.9 % (86.4, 92.4)	88.2 % (80.5, 93.0)	83.8% (75.3, 89.6)
Confirmed ORR, % (95% CI)	59.3% (54.5, 63.9),	36.4% (27.4, 46.1),	32.3% (25.7, 39.4),

Comparison and analyses of results across studies

A comparison of the results from KEYNOTE-427 and Study A4061051 with KEYNOTE-426 has been presented by the MAH to provide the contribution of each component of the combination regimen to the overall efficacy of pembrolizumab + axitinib for the 1L treatment of advanced RCC.

Study design

The separate studies, KEYNOTE-426, KEYNOTE-427 Cohort A (ccRCC), and Study A4061051, were similar in terms of criteria defining the eligible participant population. The following differences were also notable:

- KEYNOTE-426 and KEYNOTE-427 enrolled participants with KPS ≥70%, which is similar to an ECOG performance status of 0 to 2. Study A4061051 enrolled participants with an ECOG performance status of 0 or 1.
- Stratification to study intervention was based on IMDC risk category and geographical region in KEYNOTE-426 and ECOG performance status in Study A4061051. Because KEYNOTE-427 is a single arm study, no stratification was applicable, although outcomes were analyzed by IMDC risk category.

- Randomization to study intervention was 1:1 in KEYNOTE-426 and 2:1 in Study A4061051. Eligible participants with ccRCC were allocated to Cohort A of KEYNOTE-427.
- KEYNOTE-427 was single-arm study and used ORR per RECIST 1.1 by BICR as the primary endpoint.
- In KEYNOTE-426 and KEYNOTE-427, participants were evaluated with radiographic imaging at baseline, after randomization at Week 12, then Q6W until Week 54, and Q12W thereafter. In Study A4061051, participants were evaluated with radiographic imaging at baseline, after randomization at Week 6 and Week 12, then Q8W thereafter.

Participant Characteristics

Table: Key Baseline Demographics from KEYNOTE-426, KEYNOTE-427, and Study A4061051

Study	KEYNOTE-426		KEYNOTE-427	Study A4061051	
	Pembrolizumab + Axitinib	Sunitinib	Pembrolizumab	Axitinib	Sorafenib
Participants in Population	432	429	110	192	96
Gender, n (%)					
Male	308 (71.3)	320 (74.6)	86 (78.2)	134 (69.8)	74 (77.1)
Female	124 (28.7)	109 (25.4)	24 (21.8)	58 (30.2)	22 (22.9)
Age, n (%)					
<65	260 (60.2)	278 (64.8)	58 (52.7)	142 (74.0)	77 (80.2)
≥65	172 (39.8)	151 (35.2)	52 (47.3)	50 (26.0)	19 (19.8)
Median (range)	62.0 (30 to 89)	61.0 (26 to 90)	64.0 (29 to 87)	58 (23 to 83)	58 (20 to 77)
KPS, n (%)					
90/100	347 (80.3)	341 (79.5)	88 (80.0)	-	-
70/80	84 (19.4)	88 (20.5)	22 (20.0)	-	-
Missing	1 (0.2)	0	-	-	-
ECOG, n (%)					
0	-	-	-	114 (59.4)	53 (55.2)
1	-	-	-	78 (40.6)	43 (44.8)
>1	-	-	-	0	0
IMDC Risk Category, n (%)					
Favorable	138 (31.9)	131 (30.5)	42 (38.2)	-	-
Intermediate	238 (55.1)	246 (57.3)	52 (47.3)	-	-
Poor	56 (13.0)	52 (12.1)	16 (14.5)	-	-
MSKCC Risk Group, n (%)					
Favorable	-	-	-	94 (49.0)	53 (55.2)
Intermediate	-	-	-	84 (43.8)	40 (41.7)
Poor	-	-	-	7 (3.6)	2 (2.1)
Missing	-	-	-	7 (3.6)	1 (1.0)
Site of Metastatic Disease, n (%)					
Lung	312 (72.2)	309 (72.0)	73 (66.4)	137 (71.4)	72 (75.0)
Lymph Node	199 (46.1)	197 (45.9)	46 (41.8)	99 (51.6)	55 (57.3)
Bone	103 (23.8)	103 (24.0)	23 (20.9)	56 (29.2)	24 (25.0)
Liver	66 (15.3)	71 (16.6)	14 (12.7)	52 (27.1)	25 (26.0)
RCC Histology, n (%)					
Clear cell	403 (93.3)	401 (93.5)	100 (30.9)	192 (100)	96 (100)

Study	KEYNOTE-426		KEYNOTE-427	Study A4061051	
	Pembrolizumab + Axitinib	Sunitinib	Pembrolizumab	Axitinib	Sorafenib
Clear cell component	28 (6.5)	27 (6.3)	4 (3.6)	-	-
Unknown			6 (5.5)	-	-
Other	1 (0.2)	1 (0.2)	-	19 (9.9)	13 (13.5)

Efficacy summary of all studies

KEYNOTE-427 and Study A4061051 demonstrate the individual contributions of pembrolizumab and axitinib relative to that of the combination. Cohort A (ccRCC) of KEYNOTE-427 was specifically designed to evaluate the efficacy and safety of pembrolizumab monotherapy to support the development of pembrolizumab + axitinib in KEYNOTE-426. Study A4061051 was a multicenter, randomized Phase 3 study of axitinib monotherapy versus sorafenib monotherapy conducted in a similar patient population as that of KEYNOTE-426.

Pembrolizumab and axitinib both demonstrated clinical activity in advanced RCC in KEYNOTE-427 and Study A4061051, respectively. The ORR and PFS results of pembrolizumab + axitinib in KEYNOTE-426 were markedly greater (in some cases doubled) relative to what was observed in either KEYNOTE-427 or Study A4061051 [Table 2.7.3-rcc1: 12]. Even acknowledging that these are cross-study comparisons, the MAH claims that the results from the combination of pembrolizumab and axitinib in KEYNOTE-426 represent substantial improvements in ORR and PFS relative to either component administered as monotherapy as shown by non-overlapping 95% CIs. These data demonstrate the contribution of each of the components to the efficacy of the pembrolizumab and axitinib combination regimen.

Table: Comparison of Efficacy Results from KEYNOTE-426, KEYNOTE-427, and Study A4061051

Study	KEYNOTE-426		KEYNOTE-427	Study A4061051	
Treatment / Parameter	Pembrolizumab + Axitinib	Sunitinib	Pembrolizumab	Axitinib	Sorafenib
ORR, % (95% CI)					
CR + PR	59.3 (54.5, 63.9)	35.7 (31.1, 40.4)	36.4 (27.4, 46.1)	32.3 (25.7, 39.4)	14.6 (8.2, 23.3)
p-value	<0.0001		N/A	0.0006	
CR, n (%)	25 (5.8)	8 (1.9)	3 (2.7)	0	0
PR, n (%)	231 (53.5)	145 (33.8)	37 (33.6)	62 (32.3)	14 (14.6)
PFS					
Median (95% CI), months	15.1 (12.6, 17.7)	11.0 (8.7, 12.5)	7.1 (5.6 to 11.0)	10.1 (7.2 to 12.1)	6.5 (4.7 to 8.3)
HR (95% CI), p-value	0.69 (0.56, 0.84) 0.00012		N/A	0.768 (0.566, 1.042) 0.0441	
OS					
Median (95% CI), months	Not reached	Not reached	Not reached	21.7 (18.0 to 31.7)	23.3 (18.1 to 33.2)
HR (95% CI), p-value	0.53 (0.38, 0.74) 0.00005		N/A	1.136 (0.765, 1.687) 0.7370	
OS rate, 6 Months % (95% CI)	94.9 (92.3, 96.6)	89.0 (85.6, 91.6)	92.7 (85.98, 96.29)	N/A	
OS rate, 12 Months % (95% CI)	89.9 (86.4, 92.4)	78.3 (73.8, 82.1)	88.2 (80.52, 92.96)	72.0 (65.0, 77.9)	73.3 (63.1, 81.0)
OS rate, 18 Months % (95% CI)	82.3 (77.2, 86.3)	72.1 (66.3, 77.0)	N/A	N/A	

2.4.3. Discussion on clinical efficacy

A type II Variation for the extension of Keytruda therapeutic indication for the first-line treatment of advanced renal cell carcinoma (RCC) in adults in combination with axitinib has been submitted by the MAH based on the IA1 results of the pivotal phase III trial KEYNOTE-426. Updated data with cut-off date of 2 Jan 2019 have been further submitted upon CHMP request.

Data from KEYNOTE-427 (Phase 2 study of pembrolizumab monotherapy in participants with RCC) for participants with clear cell RCC (Cohort A), and the Pfizer-sponsored Study A4061051 (Phase 3 study of axitinib versus sorafenib) have been submitted as supportive with the aim to provide the contribution of each of the components to the efficacy of the pembrolizumab + axitinib regimen.

The results of the Pfizer sponsored study KEYNOTE-035/A4061079 (Phase 1b of pembrolizumab + axitinib in RCC), which provided the rationale for evaluating pembrolizumab in combination with axitinib in participants with advanced RCC, have been also submitted.

Design and conduct of clinical studies

Study KEYNOTE-426

KEYNOTE-426 is an ongoing, Phase 3, randomized, multicenter, active-controlled, 2 arms, open-label clinical study in first line adult patients with advanced renal cell carcinoma (RCC), comparing the combination of pembrolizumab 200mg Q3W + axitinib 5 mg BID with sunitinib 50 mg QD 4 weeks n 2 weeks off.

Adult patients with newly diagnosed stage IV per AJCC (locally advanced/metastatic disease) or recurrent histologically confirmed RCC with clear cell component (with or without sarcomatoid features) were eligible provided they had not received prior systemic therapy for advanced renal cancer (prior neoadjuvant/adjuvant therapy for RCC was acceptable if completed >12 months prior to randomization).

Due to the small sample size in both treatment groups and the limited number of events at the time of the data cutoff, a meaningful analysis of OS and PFS in participants with sarcomatoid features cannot be performed at this time. Nevertheless results seem to be consistent with the ITT population.

Patients with non-clear cell RCC were not included in the trial, even though they are not excluded by the sought indication. This is not rejected in principle. To support the activity of pembrolizumab and axitinib in non-clear cell RCC, the MAH provided data from KN-427 cohort B for pembrolizumab, and shortly discussed the results of a multicenter phase II trial of axitinib in patients with recurrent or metastatic nccRCC who had failed prior treatment with temsirolimus (Park, 2018) arguing that these data support the activity of axitinib in nccRCC. Overall, it is considered that there is some evidence supporting the potential activity of both pembrolizumab and axitinib as single agents in nccRCC. No combination data are available. In the SmPC it has been added that patients enrolled in KN-426 trial have clear cell component.

Patients were enrolled regardless of PD-L1 expression. This is not questioned, taking into account that responses had been observed in both PD-L1 positive and PD-L1 negative patients in the phase Ib study KN-035 with the combination of pembrolizumab and axitinib, and also in the phase II study KN-427 with pembrolizumab monotherapy (although more pronounced in PD-L1 CPS $\geq$1). Subgroup analyses according to PD-L1 expression have been included in the protocol.

There was no restriction based on IMDC risk category: this is acceptable, although the heterogeneity of the patient population in terms of prognosis is noted. This was considered as a stratification factor.

Patients should have KPS ≥70% and disease was to be measurable. Other key eligibility criteria to account for the known safety profile of pembrolizumab, axitinib and sunitinib.

Sunitinib is considered an acceptable comparator in the target population of this study, and is administered at the recommended dose for RCC (Sutent SmPC).

With regard to the experimental arm, the main issue is related to the assessment of the contribution of each component of the combination treatment. According the *Guideline on the evaluation of anticancer medicinal products in man* (EMA/CHMP/205/95 Rev.5), when a new combination is tested against a reference regimen, clinical phase I/II data should support the need for both components in the experimental regimen. The documented activity of the individual components of the combination regimen should be taken into account, and if one of the components is regarded as an acceptable treatment regimen in monotherapy, a randomised phase II study comparing the monotherapy regimen with the combination should be considered. This is deemed important since the combination regimen is expected to be more toxic compared to monotherapy with each of the components. The study design of KEYNOTE-426 (with different TKIs in the control and comparator arm) does not allow to evaluate the contribution of the TKI axitinib to the superiority of the combination therapy compared to sunitib. Axitinib could be regarded as comparable to sunitinib with regard to efficacy, but a recent real-world analysis showed that compared with sunitinib, axitinib significantly prolonged OS (Konishi et al. Med Oncol 2018). In other words, the efficacy benefit for the combination could be attributed in part to a higher level of activity with axitinib than with sunitinib, this should be considered.

It is acknowledged that efficacy results from Study KN-035 showed high activity of the combination, with confirmed ORR of 73.1% (95% CI [59.0, 84.4]) that compares favourably with observed ORR with axitinib (32.3%; 95% CI 25.7, 39.4) and pembrolizumab (36.4; 95% CI 27.4, 46.1%) in separate studies (Study A4061061 and Study KN-427). However, no direct comparison has been performed. This is particularly relevant for pembrolizumab, since for immunotherapies there is no evidence of a clear correlation between ORR and long term benefit, and conventional response evaluation criteria may underestimate the long-term benefit from immunotherapies (Anagnostou V et al. Clin Cancer Res 2017, Hodi F et al. J Clin Oncol 2016, Kaufman H et al. J Clin Oncol 2017). Furthermore, it cannot be excluded that pembrolizumab monotherapy could represent a valid treatment option for at least a subgroup of patients (e.g. high PD-L1 expression). In this regard, the MAH was asked to justify the lack of a pembrolizumab monotherapy arm based on all available nonclinical and clinical data. The MAH has provided comparative efficacy data of pembrolizumab in combination with axitinib vs pembrolizumab monotherapy, according to PD-L1 status, from Study KEYNOTE-426 and Study KEYNOTE-427 Cohort A, respectively. Besides the intrinsic limitations of such cross-study comparison, it is acknowledged that data suggests that the combination is more efficacious than pembrolizumab as monotherapy in subjects with PD-L1 CPS<1, with a trend (95%CI overlapping) suggesting a higher benefit even in the CPS≥1 subgroup in terms of ORR and PFS. Indeed, in the CPS≥1 subgroup ORR was 60.5% (95% CI 54.0, 66.7) and 44.2% 95%CI 30.5, 58.7) in the combination and monotherapy, respectively. Median PFS was 15.3 (95% CI 12.6,-) and 9.7 (95%CI 6.7, 16.4). OS data are too immature. No definitive conclusion can be drawn due to the lack of a direct comparison between the combination and pembrolizumab monotherapy in subjects with high PD-L1 expression. However, it is acknowledged that the combination of these two agents with distinct mechanisms of action tend to provide a higher benefit in terms of ORR and PFS.

The rationale for the proposed doses and schedule of the combination is adequately justified based on PK and clinical results of phase Ib Study KN-035 that demonstrated the safety and tolerability feasibility of pembrolizumab 2 mg/Kg Q3W plus axitinib 5 mg BID, and the integrated body of evidence suggesting that 200 mg Q3w is expected to provide similar response and exposures to that expected with the 2 mg/Kg Q3W.

The open-label design is justified on the basis of the different route and schedule of administration of drugs in the two arms. In view of the risk of bias due to the open label-design, the assessment of response has been performed based on blinded independent central review (BICR).

Participants were stratified according to International Metastatic RCC Database Consortium (IMDC) risk group (favourable versus intermediate versus poor), and Geographic region (North America versus Western Europe versus "Rest of the World"). Stratification factors appear appropriate.

The primary objectives of the study were to compare the OS and PFS per RECIST 1.1 by BICR in participants treated with pembrolizumab + axitinib vs sunitinib. ORR, DCR, DoR, safety and tolerability profile of pembrolizumab, PFS and OS rate at 12, 24 and 18 months, and PROs were secondary objectives. The choice of OS and PFS as primary objectives can be considered appropriate.

The expected median PFS time in the control group was 13 months. Based on 487 PFS events, the study had ~99% power to detect a hazard ratio of 0.60 for PFS at alpha=0.2% (1-sided). The expected median OS time in the control group was 33 months. Based on 404 death events, the study had 80% power to detect a hazard ratio of 0.75 for OS at alpha=2.3% (1-sided). The sample size calculations result congruent with the assumptions made.

Efficacy analyses were conducted using the intention-to-treat (ITT) population. The statistical methods used for time to events and binary endpoints are considered adequate. Two interim analyses were planned for OS and one for PFS. A group sequential approach was used to allocate alpha between the interim and final analyses. The IA1 (first interim analysis for PFS and OS) was planned after enrollment completion, when a minimum of 305 PFS events had accrued and all participants were followed for at least 7 months after randomization, and it was expected to be 22 months after the first subject randomized. Approximately 48% of the final required OS events (or 195 deaths) were expected at that time. The study met its primary endpoints at IA1. The approaches, to control Type I error is appropriate.

A total of 1062 participants were screened (first participant screened on 06-OCT-2016) and 861 were randomly allocated from 24-OCT-2016 to 24-JAN-2018 across 124 global study sites in 16 countries. Screen failure was mostly due to not meeting specific eligibility criteria. No new concern arises regarding the conduction of the study.

Important protocol deviations were reported in a similar rate in the 2 groups (14.2% in the pembrolizumab + axitinib group and 12.9% in the sunitinib group), and it is considered unlikely that they impacted on the results.

Overall, there were no meaningful imbalances in patients' baseline characteristics among treatment arms, and the enrolled population is overall representative of real life EU patients. In the experimental arm there were few more women (28.7% vs 25.4%) and subjects aged ≥ 65 years (39.8% vs 35.2%) and less subjects with ≥ 2 organs involved with disease at baseline (72.9% vs 77.2%) than in the control arm. The percentage of participants in the IMDC risk categories of favorable, intermediate, and poor risk was 31.2%, 56.2% and 12.5%, respectively. A total of 57.7% of participants had a tumor tissue PD-L1 expression score of CPS ≥1.

The supportive trial Keynote 427 is a phase 2, open-label trial of pembrolizumab monotherapy to evaluate the efficacy and safety of pembrolizumab as 1L treatment for advanced ccRCC (Cohort A) and nccRCC (Cohort B). Data from Cohort A which included 110 patients are supportive of the present submission. Data up to the DBL of 07-Sep-2018 including a medium follow-up of 18 months are presented. No mature OS data was available and an update should be provided (OC). In Keynote 427, the PD-L1 positive subgroup was constituted by 52 (53.7%) out of the 110 randomised subjects. The OS rates at 3 months, 6 months, and 12 months were 97.3%, 92.7%, and 88.2%, respectively.

Efficacy data and additional analyses

The results submitted by the MAH are based on the pre-planned IA1 for PFS and OS (0.75 information fraction to PFS and 0.48 information fraction to OS) with a data cut-off date 24-AUG-2018. The median duration of follow up was 13.2 months (range: 0.1 to 21.5 months) in the pembrolizumab + axitinib group and 12.1 months (range: 0.4 to 22.0 months) in the sunitinib group. As per CHMP request, updated efficacy data with cut-off date 2 Jan 2019 have been submitted, with an additional 4.3 months of follow-up compared to the IA1. The median follow up is now 17.4 months and 15.7 months in the experimental arm and in the control arm, respectively.

The ITT population included 432 patients randomized to pembro combo and 429 to sunitinib.

Primary endpoints

A statistically significant benefit in OS has been observed for pembrolizumab + axitinib over sunitinib (HR of 0.53, 95% CI 0.38, 0.74; p=0.00005) with 59 (13.7%) and 97 (22.6%) events in the experimental and the control arm, respectively. The median OS for both arms was not reached. The estimated percentage of patients who were alive at 12 months was 89.9% (95% CI, 86.4 to 92.4) in the pembrolizumab–axitinib group and 78.3% (95% CI, 73.8 to 82.1) in the sunitinib group. The corresponding estimates for 18 months were 82.3% (95% CI, 77.2 to 86.3) and 72.1% (95% CI, 66.3 to 77.0). Data are considered rather immature, with an OS event rate of 13.7% and 22.6% for the combination and sunitinib arm. The amount of censoring was high in the tail of the K-M curves, starting at month 7. In order to have estimations regarding OS more precise, updated OS data were requested. Since a statistically significant improvement had been demonstrated at IA1, only descriptive OS and PFS data, not formally tested for statistical significance, were provided. Overall, 50 additional OS events (25 in each arm) were observed. A clear benefit is still observed in the overall population as well as in the IMDC poor (HR= 0.50, 95%CI 0.29, 0.87) and intermediate (HR= 0.52, 95%CI 0.36,0.75) risk categories. With a total of 25 OS events (13 and 12 in the experimental and control arm, respectively), it is not possible to draw any sound conclusion with regard to the IMDC favourable risk group (HR 0.94, 95%CI 0.43, 2.07). The OS KM curves in this subgroup are, as expected, superimposable at this stage.

Overall, OS subgroup analyses show results consistent with the primary analysis, although very few events are observed in specific subgroups such as in the favourable IMDC risk group.

A statistically significant benefit in PFS has been also observed for pembrolizumab + axitinib over sunitinib (HR of 0.69, 95% CI 0.56, 0.84; p=0.00014) with 183 (42.4%) and 213 (49.7%) events in the experimental and the control arm, respectively. The median PFS is 15.1 (95% CI 12.6, 17.7) and 11.0 (95% CI 8.7, 12.5) in the experimental and the control arm, respectively. The KM curves tend to separate quite early and tend to remain parallel over time. The censoring due to≥ 2 missing assessment/New Anticancer Therapy/No Post-Baseline Assessment are much more frequent in the control arm (14.8%) than in the experimental arm (7%). PFS sensitivity analysis based on different censoring rules show a consistent effect. In the updated PFS data, a total of 43 additional PFS events (24 in the experimental arm and 19 in the control arm) were reported. As observed for OS, a clear benefit in terms of PFS is also observed in the ITT population (HR 0.69, 95%CI 0.57, 0.83), as well as in the IMDC poor (HR= 0.57, 95%CI 0.35, 0.92) and intermediate (HR= 0.70, 95%CI 0.55,0.90) risk categories. With 13 additional PFS events observed in the IMDC favourable risk group (now occurred in 103/269 patients, i.e. 38.2% of the subjects with baseline favourable IMDC risk) the HR is 0.73 (95% CI 0.49, 1.09) slightly improved compared to the previous report (HR 0.81, 95%CI 0.53, 1.24). The PFS KM curves in this subgroup tend to separate after 7 months.

Overall, PFS subgroup analyses show results consistent with the primary analysis, although a lower effect is observed in the favourable IMDC risk group and in subjects with CPS<1%.

Interestingly, PFS based on investigator assessment is not statistically significant with an HR of 0.82 (95% CI 0.67, 1.00) and a median PFS of 14.5 (95% CI 12.5, 17.7) and 11.9 (95% CI 10.1, 15.0) in the experimental and the control arm, respectively. The concordance between Investigator and BICR, show an overall agreement around 80%. Compared to Investigator BICR assigned PD at a later time in 13% and 8% for the experimental arm and the control arm, but disagreed in 20% and 25%. Among subjects with no PD based on Investigators' Assessment, BICR detected much more frequently in the control arm (22%) than in the experimental arm (11%). This substantial discrepancy is somewhat unexpected and raises concern with regard to the robustness of the results.

Objective response rate based on BICR assessment were observed in 59.3% (95% CI 54.5,63.9) of the patients treated with the combination compared to 35.7% (95% CI 31.1,40.4) in the control arm. The median time to response is similar in the two arms, while the duration of response tend to be longer in the experimental arm with 70.6% of patients still in response at 12 months in the control arm vs 61.6% in the control arm. At the updated analysis, with only 15 more objective responses reported (3 in the experimental arm and 12 in the control arm), results are very similar to those reported at the IA1. The ORR difference of 20.71% (95% CI 9.00, 31.90) in the IMDC favourable risk group, quite consistent with other IMDC risk subgroups, is noted.

With regard to PROs, Time to true deterioration in the Functional Assessment of Cancer Therapy - Kidney Symptom Index - Disease related Symptoms (FKSI-DRS) differed between the two arms with a worse outcome for the experimental arm (HR 1.44; 95% CI 1.14, 1.82; nominal p:0.999). A worsening from baseline to Week 30 was observed for diarrhea in the EORTC QLQ-C30 symptom scale.

Contribution of each component in the combination regimen.

The absence of a well designed clinical trial testing the combination and monotherapies (pembrolizumab and axitinib) leads to uncertainties when it comes to reaching a benefit risk conclusion. Beneficial result of the comparison of pembrolizumab + axitinib versus sunitinib can be reasoned by each of the two components. It could be possible that the whole treatment effect might be reasoned by axitinib without an additional effect of pembrolizumab or vice versa. Pembrolizumab and axitinib are two different drugs with different action and independent activities. The applicant provides the supportive phase 3 study A4061051, where 288 patients were randomly assigned in a 2:1 ratio to either axitinib or sorafenib. The confirmed ORR for pembrolizumab + axitinib in KEYNOTE-426 (60.0% [55.2, 64.6]) from the 02-JAN-2019 cutoff was higher relative to what was observed for axitinib in Study A4061051 (32.3% [95% CI: 25.7, 39.4]) (Table 24). This was also the case for the median PFS (17.1 months [13.6, 18.9] vs. 10.1 months [95% CI: 7.2, 12.1], respectively). The median OS was still not reached with the updated data for KEYNOTE-426 in comparison to 21.7 months (95% CI: 18.0, 31.7) for axitinib in Study A4061051. The observed OS rate at 12 months in the pembrolizumab + axitinib group continued to be higher relative to what was observed for axitinib in Study A4061051 (89.5% versus 72.0%).

In addition, the applicant provides the supportive phase 2 Keynote-427, where 110 patients with ccRCC were included in a pembrolizumab monotherapy cohort A. The results for the pembrolizumab monotherapy arm of this study showed an ORR of 36.4 % (95%CI: (27.4, 46.1)), a median PFS of 7.1 months (95%CI: (5.6, 11.0)) and an OS rate at 12 month of 88.2%.

Considering the ORR and PFS data described in the supportive studies, these results support the hypothesis that each component is contributing to the treatment effect in the combination regimen, ORR and PFS results of both monotherapies were lower compared to the results of the combination therapy. However, no meaningful differences could be observed between the preliminary OS data for pembrolizumab monotherapy, axitinib monotherapy and the combination of pembrolizumab and axitinib. Even if acknowledging the differences in comparing OS data across different trials, there remains an uncertainty whether both components would be needed in the 1L treatment of RCC.

Analyses of efficacy endpoints according to PD-L1 expression:

Results in terms of OS for patients with PD-L1 CPS≥1% showed a median not reached at the time of the analysis (HR: 0.54 (95%CI: 0.35, 0.84). For patients with PD-L1<1 no medians were reached in either study arm, too (HR: 0.59 (95%CI: 0.34, 1.03). Superior efficacy of pembrolizumab+ axitinib combination over sunitinib therapy has been observed regardless PD-L1 expression.

Favourable risk patients

Efficacy regarding OS benefit is demonstrated for the overall study population based on the first IA with a median follow-up of 13.2 months. OS data are too immature to support efficacy in the favourable risk group which comprises 1/3 of the ITT population (with only 7 events in the pembrolizumab+ axitinib vs. 10 events in the sunitinib group, observed so far).

The MAH was requested to provide updated efficacy data to justify the use this combination in the proposed patient population. Updated OS data do not provide any additional information. Differently, updated PFS data show a trend to an improved effect in the IDMC favourable risk subgroup compared to data initially submitted. Overall, based on the updated data it can be agreed that a benefit in terms of PFS and ORR is observed across all IMDC risk group, including the favourable. There is no apparent detrimental effect in terms of OS in the IMDC favourable risk subgroup, although also updated data are quite immature. It is reassuring that most of the patients (11/15, 73%) who discontinued treatment with pembrolizumab and axitinib due to hepatic AEs received subsequent anti-cancer treatment, which is even higher than the rate of patients (88/176, 50%) who received a subsequent anti-cancer treatment therapy after discontinuing pembrolizumab + axitinib for any reason. Unfortunately, PFS2 data does not seem to have been captured. Taking into account the clearly worse safety profile of the combination, in order to provide further reassurance, the MAH was asked to provide comparative data on the ability to receive subsequent anticancer therapy in all subjects who discontinued treatment due to any AEs in the two arms. While the rate in the two arms appears to be similar (65/429 [15.2%] and 61/425 [14.4%] in the pembrolizumab plus axitinib arm and the sunitinib arm, respectively), less subjects in the experimental arm received subsequent systemic treatments (24/65 [36.9%] and 30/61 [49.2%] in the pembrolizumab plus axitinib arm and the sunitinib arm, respectively). Looking at those patients who received subsequent systemic treatments, it seems that treatment with pembrolizumab and axitinib does not negatively affect the outcome or the ability to tolerate subsequent treatment: indeed, treatment duration of the first subsequent anti-cancer therapy tended to be longer for patients in the experimental arm compared to the control arm, and no relevant differences were observed between the two arms in terms of reason for discontinuation of the first subsequent anti-cancer therapy with the exception of discontinuation for toxicity that were less frequently observed in the experimental arm (4/24) than in the control arm (10/28). Looking at those patients who discontinued study treatment(s) due to an AE and received no further anti-cancer treatments, the rate of patients still alive at the data cutoff of the submitted analysis (02 JAN 2019) was higher in the experimental arm (24/41, corresponding to 58.5%) compared to the sunitinib arm (13/31 corresponding to 41.9%).

Special populations

The benefit of pembrolizumab + axitinib over sunitinib was seen across the age subgroups: <65 years and ≥65 years.

2.4.4. Conclusions on the clinical efficacy

The combination of pembrolizumab and axitinib demonstrated superiority vs sunitinib in terms of PFS and OS in patients with advanced RCC, supported by an advantage in terms of ORR. The lack of monotherapy experimental arms in study KN-426 hampers the assessment of the contribution of each component of the combination treatment. Even though exploratory data show higher ORR with the combination

compared to both pembrolizumab and axitinib, only indirect comparisons are available. This is particularly relevant for pembrolizumab, since conventional response evaluation criteria may underestimate the long-term benefit and it cannot be excluded that pembrolizumab monotherapy could represent a valid treatment option for at least a subgroup of patients (e.g. high PD-L1 expression). Overall, based on the updated data, a benefit in terms of PFS and ORR is observed across all IMDC risk group, including the favourable. Additionally, there is no apparent detrimental effect in terms of OS in the IMDC favourable risk subgroup, although data are quite immature.

The following measures are considered necessary to address issues related to clinical efficacy: the final CSR of the pivotal Keynote-426 study is to be provided post-approval as Annex II condition, in particular to further characterize the benefit of the combination treatment in the favourable IDMC risk group based on data with longer follow-up.

2.5. Clinical safety

Introduction

The safety evaluation provided to support the claimed indication of pembrolizumab in combination with axitinib (Inlyta®, AG-013736) for 1L treatment of subjects with advanced RCC is based on the first interim analysis (IA1) of the KEYNOTE-426 study. This is an ongoing, Phase 3, randomized, open-label, multicenter, global study to evaluate the efficacy and safety of Pembrolizumab+Axitinib versus Sunitinib for the 1L treatment for advanced RCC with clear cell component. Participants were stratified by IMDC risk category and geographic region and then randomized in a 1:1 ratio between treatment arms. IA1 was a combined event- and time-driven analysis with data cut-off date 24-AUG-2018 and a median duration of follow-up of 12.8 months [range: 0.1, 22.0].

Provided safety summary tables including all subjects as treated (ASaT) population show side-by-side safety results of the following four datasets:

- *KEYNOTE-426 Pembrolizumab plus Axitinib Safety Dataset* (N = 429)
- *KEYNOTE-426 Sunitinib Safety Dataset* (N = 425)
- *Pembrolizumab Monotherapy Reference Safety Dataset* (N = 4439): to enable a comparison of safety data from KEYNOTE 426 with the established safety profile for pembrolizumab monotherapy. It included all subjects who received at least one dose of pembrolizumab in KEYNOTE-001 Part B1, B2, B3, D, C, F1, F2, F3, KEYNOTE-002 (original phase), KEYNOTE-006, KEYNOTE-010, KEYNOTE-012 Cohorts B and B2, KEYNOTE-013 Cohort 3, KEYNOTE-024, KEYNOTE-040, KEYNOTE-045, KEYNOTE-052, KEYNOTE-055 and KEYNOTE-087.
- *Cumulative Running Safety Dataset for Pembrolizumab Monotherapy* (N = 6436): to evaluate the consistency of the pembrolizumab safety profile across indications. It included safety data collected as of the data cut-off (07-SEP-2018) for KEYNOTE-427 Cohort A (RCC monotherapy) and participants treated with pembrolizumab from the pembrolizumab monotherapy RSD and studies previously submitted for review in the following indications: KEYNOTE-001 Part B1, B2, B3, D, C, F1, F2, F3; KEYNOTE-002 (original phase); KEYNOTE-006; KEYNOTE-010; KEYNOTE-012 Cohort B and B2 (head and neck cancer), Cohort C (urothelial tract cancer cancer), and Cohort D (gastric cancer); KEYNOTE-013 Cohort 3 (classical Hodgkin lymphoma) and Cohort 4a (primary mediastinal large B-cell lymphoma); KEYNOTE-017; KEYNOTE-024, KEYNOTE-028 Cohort B4; KEYNOTE-040; KEYNOTE-042; KEYNOTE-045 and KEYNOTE-052 (urothelial cancer); KEYNOTE-054; KEYNOTE-055,

KEYNOTE-059 Cohort 1 (gastric cancer); KEYNOTE-087; KEYNOTE-158; KEYNOTE-164 Cohort A (colorectal cancer); KEYNOTE-170; KEYNOTE-224.

Additional supportive safety data is provided to understand the contribution of each drug to the safety profile of the combination in the claimed indication:

- *Axitinib monotherapy* arm: data from the Pfizer-Sponsored, Phase 3, randomized, open-label, multicenter Study A4061051 (Axitinib vs Sorafenib study) for the 1L treatment of metastatic RCC (data cut-off date 27 July 2012; N = 189)

- *Pembrolizumab monotherapy Cohort A* of the ongoing, Phase 2, nonrandomized, open-label, 2-cohort, multicenter, global KEYNOTE-427 study for the 1L treatment of advanced ccRCC (data cut-off date 07 Sept 2018; N =110)

The safety data from the 52 participants enrolled in the Phase 1b study (Study A4061079) of pembrolizumab+axitinib were not pooled with KEYNOTE-426 for this summary and are presented separately in the dossier.

Demographic and other baseline characteristics

Table 2.7.4-rcc1: 4
Subject Characteristics
(ASaT Population)

	KN426 Data for Pembrolizumab + Axitinib‖		KN426 Sunitinib††		Reference Safety Dataset for Pembrolizumab Monotherapy¶		Cumulative Running Safety Dataset for Pembrolizumab Monotherapy#	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	429		425		4,439		6,436	
Gender								
Male	306	(71.3)	318	(74.8)	2,869	(64.6)	4,159	(64.6)
Female	123	(28.7)	107	(25.2)	1,570	(35.4)	2,277	(35.4)
Age (Years)								
<65	257	(59.9)	277	(65.2)	2,453	(55.3)	3,709	(57.6)
>=65	172	(40.1)	148	(34.8)	1,986	(44.7)	2,727	(42.4)
Mean	61.2		60.7		61.1		60.2	
SD	10.0		10.1		13.5		13.6	
Median	62.0		61.0		63.0		62.0	
Range	30 to 89		26 to 88		15 to 94		15 to 94	
Race								
American Indian Or Alaska Native	2	(0.5)	2	(0.5)	14	(0.3)	27	(0.4)
Asian	66	(15.4)	70	(16.5)	411	(9.3)	721	(11.2)
Black Or African American	9	(2.1)	8	(1.9)	94	(2.1)	117	(1.8)
Missing	8	(1.9)	5	(1.2)	63	(1.4)	600	(9.3)
Multiracial	1	(0.2)	2	(0.5)	24	(0.5)	58	(0.9)
Native Hawaiian Or Other Pacific Islander	1	(0.2)	0	(0.0)	4	(0.1)	6	(0.1)
White	342	(79.7)	338	(79.5)	3,829	(86.3)	4,907	(76.2)
Ethnicity								
Hispanic Or Latino	18	(4.2)	18	(4.2)	222	(5.0)	377	(5.9)
Not Hispanic Or Latino	375	(87.4)	383	(90.1)	3,952	(89.0)	5,206	(80.9)
Not Reported	14	(3.3)	12	(2.8)	151	(3.4)	197	(3.1)
Unknown	21	(4.9)	11	(2.6)	109	(2.5)	135	(2.1)
Missing	1	(0.2)	1	(0.2)	5	(0.1)	521	(8.1)
Geographic Region								
US	80	(18.6)	80	(18.8)	1,911	(43.1)	2,242	(34.8)
Ex-US	349	(81.4)	345	(81.2)	2,528	(56.9)	4,194	(65.2)
Geographic Region								
EU	161	(37.5)	154	(36.2)	1,537	(34.6)	2,298	(35.7)
Ex-EU	268	(62.5)	271	(63.8)	2,902	(65.4)	4,138	(64.3)
Geographic Region								
East Asia	62	(14.5)	67	(15.8)	303	(6.8)	601	(9.3)
Non-East Asia	367	(85.5)	358	(84.2)	4,136	(93.2)	5,835	(90.7)

‖ Includes all subjects who received at least one dose of Pembrolizumab and/or Axitinib in KN426.

†† Includes all subjects who received at least one dose of Sunitinib in KN426.

¶ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN045, KN052, KN055 and KN087.

Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma) and Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort B4, KN040, KN042, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158, KN164 Cohort A, KN170, KN224 and KN427 Cohort A.

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

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)

Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)

Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)

Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)

Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)

Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)

Database cutoff date for HCC (KN224: 15MAY2018)

Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)

Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl]

With regards to disease characteristics (KPS, IMDC Risk Category, PD-L1 Status, Sites of Metastatic Disease, Number of Organs Involved, Recurrent/Newly Diagnosed, RCC Stage), treatment arms of the KEYNOTE-426 study were well balanced. Liver metastases were found in approximately 15% of subjects of both treatment arms. In both treatment arms, most subjects (approximately 83%) had undergone prior nephrectomy and only a small proportion (approximately 9%) had received prior radiation therapy.

Patient exposure

Table 2.7.4-rcc1: 2
Summary of Drug Exposure
(ASaT Population)

	KN426 Data for Pembrolizumab + Axitinib‖ (N=429)	KN426 Sunitinib†† (N=425)	Reference Safety Dataset for Pembrolizumab Monotherapy¶ (N=4439)	Cumulative Running Safety Dataset for Pembrolizumab Monotherapy§ (N=6436)
Duration On Therapy (month)				
Mean	10.5	8.4	6.4	6.8
Median	10.42	7.82	4.17	4.83
SD	5.36	5.44	6.08	6.22
Range	0.03 to 21.22	0.07 to 20.47	0.03 to 30.39	0.03 to 30.39
Number of Pembrolizumab Administration				
Mean	13.8	0.0	10.7	11.0
Median	14.00	0.00	7.00	8.00
SD	8.04	0.00	9.56	9.52
Range	1.00 to 31.00	0.00 to 0.00	1.00 to 59.00	1.00 to 59.00

Each subject is counted once on each applicable duration category row.
Duration of Exposure is calculated as (last dose date - first dose date +1)/30.4367 (months).
‖ Includes all subjects who received at least one dose of Pembrolizumab and/or Axitinib in KN426.
†† Includes all subjects who received at least one dose of Sunitinib in KN426.
¶ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN045, KN052, KN055 and KN087.
§ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma) and Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort B4, KN040, KN042, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158, KN164 Cohort A, KN170, KN224 and KN427 Cohort A.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)
Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)
Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)
Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)
Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)
Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)
Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)
Database cutoff date for HCC (KN224: 15MAY2018)
Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)
Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl; adexsum]

Table 2.7.4-rcc1: 3
Drug Exposure by Duration
(ASaT Population)

	KN426 Data for Pembrolizumab + Axitinib‖ (N=429)			KN426 Sunitinib†† (N=425)			Reference Safety Dataset for Pembrolizumab Monotherapy¶ (N=4439)			Cumulative Running Safety Dataset for Pembrolizumab Monotherapy§ (N=6436)		
	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years
Duration of Exposure												
>0 m	429	(100.0)	(376.6)	425	(100.0)	(297.5)	4,439	(100.0)	(2,385.6)	6,436	(100.0)	(3,638.4)
>=1 m	418	(97.4)	(376.0)	387	(91.1)	(295.3)	3,747	(84.4)	(2,362.6)	5,466	(84.9)	(3,606.1)
>=3 m	382	(89.0)	(370.1)	333	(78.4)	(285.4)	2,608	(58.8)	(2,173.2)	3,900	(60.6)	(3,346.5)
>=6m	334	(77.9)	(352.1)	270	(63.5)	(262.5)	1,816	(40.9)	(1,885.9)	2,794	(43.4)	(2,945.5)
>=12m	173	(40.3)	(230.3)	108	(25.4)	(142.9)	851	(19.2)	(1,189.9)	1,253	(19.5)	(1,773.6)
>=18m	41	(9.6)	(64.9)	18	(4.2)	(28.9)	256	(5.8)	(468.2)	430	(6.7)	(783.4)

Each subject is counted once on each applicable duration category row.
Duration of Exposure is calculated as (last dose date - first dose date +1)/30.4367 (months).
‖ Includes all subjects who received at least one dose of Pembrolizumab and/or Axitinib in KN426.
†† Includes all subjects who received at least one dose of Sunitinib in KN426.
¶ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN045, KN052, KN055 and KN087.
§ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma) and Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort B4, KN040, KN042, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158, KN164 Cohort A, KN170, KN224 and KN427 Cohort A.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)
Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)
Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)
Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)
Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)
Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)
Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)
Database cutoff date for HCC (KN224: 15MAY2018)
Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)
Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl; adexsum]

Extent of Exposure - Summary of Days on Drug or Doses (ASaT Population)

	Pembrolizumab + Axitinib		Sunitinib
	Pembrolizumab	Axitinib	Sunitinib
Subjects in population	429	429	425
Number of Days on Drug[†]			
N	-	429	425
Mean (SD)	-	275.6 (164.1)	168.9 (107.8)
Median	-	274.0	162.0
Range	-	1.0 to 618.0	2.0 to 421.0
Total Dose Administered (mg)[†]			
N	-	429	425
Mean (SD)	-	2,535.0 (1,835.2)	7,494.1 (5,012.9)
Median	-	2,245.0	6,650.0
Range	-	10.0 to 9,948.0	100.0 to 21,000.0
Average Daily Dose Administered (mg)[†]			
N	-	429	425
Mean (SD)	-	9.1 (2.4)	45.1 (6.5)
Median	-	9.8	50.0
Range	-	4.2 to 18.7	25.6 to 50.0
Number of Doses Received[§]			
N	429	-	-
Mean (SD)	13.8 (8.0)	-	-
Median	14.0	-	-
Range	1.0 to 31.0	-	-

'Number of Days on Drug' for a subject is the total number of days when the subject took non-zero doses.
'Total Dose Administered' for a subject is the total doses that the subject took.
'Average Daily Dose Administered' for a subject is calculated by (Total Dose Administered) / (Number of Days on Drug).
[†] Only apply for Axitinib and Sunitinib.
[§] Only apply for Pembrolizumab.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adexsum]

Adverse events

The primary safety analyses of IA1 were based on data from the ASaT population. In all tables, individuals are counted only once for a specific AE term by the worst severity recorded.

MedDRA Version 21.0 was used in the generation of AE tables.

Overall and exposure-adjusted Adverse Events

Table 5.3.5.3.3-rcc1: 4

Adverse Event Summary
(ASaT Population)

	KN426 Data for Pembrolizumab + Axitinib‖		KN426 Sunitinib††		Reference Safety Dataset for Pembrolizumab Monotherapy¶		Cumulative Running Safety Dataset for Pembrolizumab Monotherapy§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	429		425		4,439		6,436	
with one or more adverse events	422	(98.4)	423	(99.5)	4,313	(97.2)	6,225	(96.7)
with no adverse event	7	(1.6)	2	(0.5)	126	(2.8)	211	(3.3)
with drug-related† adverse events	413	(96.3)	415	(97.6)	3,140	(70.7)	4,512	(70.1)
with toxicity grade 3-5 adverse events	325	(75.8)	300	(70.6)	2,153	(48.5)	3,107	(48.3)
with toxicity grade 3-5 drug-related adverse events	270	(62.9)	247	(58.1)	660	(14.9)	1,018	(15.8)
with serious adverse events	173	(40.3)	133	(31.3)	1,729	(39.0)	2,472	(38.4)
with serious drug-related adverse events	102	(23.8)	60	(14.1)	464	(10.5)	720	(11.2)
who died	11	(2.6)	15	(3.5)	211	(4.8)	329	(5.1)
who died due to a drug-related adverse event	4	(0.9)	7	(1.6)	22	(0.5)	41	(0.6)
discontinued any drug due to an adverse event	131	(30.5)	59	(13.9)	538	(12.1)	828	(12.9)
discontinued Pembrolizumab	89	(20.7)	0	(0.0)	538	(12.1)	828	(12.9)
discontinued all regimen components	33	(7.7)	59	(13.9)	538	(12.1)	828	(12.9)
discontinued any drug due to a drug-related adverse event	111	(25.9)	43	(10.1)	259	(5.8)	423	(6.6)
discontinued Pembrolizumab	80	(18.6)	0	(0.0)	259	(5.8)	423	(6.6)
discontinued all regimen components	27	(6.3)	43	(10.1)	259	(5.8)	423	(6.6)
discontinued any drug due to a serious adverse event	73	(17.0)	42	(9.9)	407	(9.2)	608	(9.4)
discontinued Pembrolizumab	50	(11.7)	0	(0.0)	407	(9.2)	608	(9.4)
discontinued all regimen components	25	(5.8)	42	(9.9)	407	(9.2)	608	(9.4)
discontinued any drug due to a serious drug-related adverse event	53	(12.4)	28	(6.6)	172	(3.9)	261	(4.1)
discontinued Pembrolizumab	42	(9.8)	0	(0.0)	172	(3.9)	261	(4.1)
discontinued all regimen components	19	(4.4)	28	(6.6)	172	(3.9)	261	(4.1)

† Determined by the investigator to be related to the drug.
Non-serious adverse events up to 30 days following the last dose and serious adverse events up to 90 days following the last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
‖ Includes all subjects who received at least one dose of Pembrolizumab and/or Axitinib in KN426.
†† Includes all subjects who received at least one dose of Sunitinib in KN426.
¶ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN045, KN052, KN055 and KN087.
§ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma) and Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort B4, KN040, KN042, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158, KN164 Cohort A, KN170, KN224 and KN427 Cohort A.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)
Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)
Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)
Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)
Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)
Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)
Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)
Database cutoff date for HCC (KN224: 15MAY2018)
Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)
Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl; adae]

Table 12-2
Exposure-Adjusted Adverse Event Summary
(Including Multiple Occurrences of Events)
(ASaT Population)

	Event Count and Rate (Events/100 person-months)[†]			
	Pembrolizumab + Axitinib		Sunitinib	
Number of Subjects exposed	429		425	
Total exposure[‡] in person-months	4766.94		3924.64	
Total events (rate)				
adverse events	7,017	(147.20)	7,052	(179.69)
drug-related[§] adverse events	3,992	(83.74)	4,955	(126.25)
toxicity grade 3-5 adverse events	846	(17.75)	823	(20.97)
toxicity grade 3-5 drug-related adverse events	551	(11.56)	565	(14.40)
serious adverse events	284	(5.96)	201	(5.12)
serious drug-related adverse events	137	(2.87)	78	(1.99)
adverse events leading to death	11	(0.23)	16	(0.41)
drug-related adverse events leading to death	4	(0.08)	7	(0.18)
adverse events resulting in drug discontinuation	180	(3.78)	65	(1.66)
drug-related adverse events resulting in drug discontinuation	152	(3.19)	47	(1.20)
serious adverse events resulting in drug discontinuation	80	(1.68)	43	(1.10)
serious drug-related adverse events resulting in drug discontinuation	59	(1.24)	28	(0.71)

[†] Event rate per 100 person-months of exposure = event count *100/person-months of exposure.
[‡] Drug exposure is defined as the between the first dose date + 1 day and the earlier of the last dose date + 30 or the database cutoff date.
[§] Determined by the investigator to be related to the drug.
Grades are based on NCI CTCAE version 4.0.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adae]

Adverse Events (AEs)

All AEs

Subjects With Adverse Events
(Incidence ≥ 10% in One or More Treatment Groups)
By Decreasing Frequency of Preferred Term
(ASaT Population)

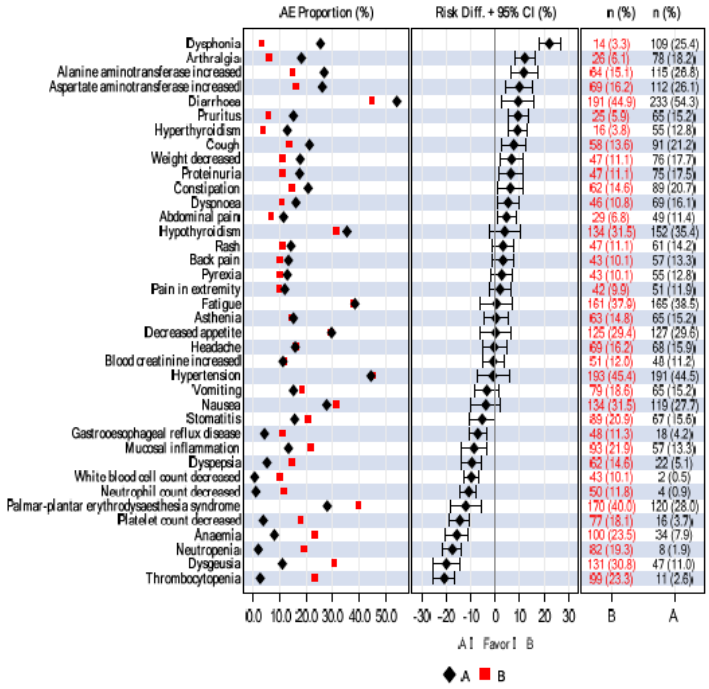
	KN426 Data for Pembrolizumab + Axitinib[‖]		KN426 Sunitinib[††]		Reference Safety Dataset for Pembrolizumab Monotherapy[¶]		Cumulative Running Safety Dataset for Pembrolizumab Monotherapy[#]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	429		425		4,439		6,436	
with one or more adverse events	422	(98.4)	423	(99.5)	4,313	(97.2)	6,225	(96.7)
with no adverse events	7	(1.6)	2	(0.5)	126	(2.8)	211	(3.3)
Diarrhoea	233	(54.3)	191	(44.9)	925	(20.8)	1,311	(20.4)
Hypertension	191	(44.5)	193	(45.4)	165	(3.7)	311	(4.8)
Fatigue	165	(38.5)	161	(37.9)	1,518	(34.2)	2,058	(32.0)
Hypothyroidism	152	(35.4)	134	(31.5)	439	(9.9)	666	(10.3)
Decreased appetite	127	(29.6)	125	(29.4)	927	(20.9)	1,254	(19.5)
Palmar-plantar erythrodysaesthesia syndrome	120	(28.0)	170	(40.0)	12	(0.3)	21	(0.3)
Nausea	119	(27.7)	134	(31.5)	987	(22.2)	1,332	(20.7)
Alanine aminotransferase increased	115	(26.8)	64	(15.1)	268	(6.0)	444	(6.9)
Aspartate aminotransferase increased	112	(26.1)	69	(16.2)	273	(6.2)	469	(7.3)
Dysphonia	109	(25.4)	14	(3.3)	104	(2.3)	140	(2.2)
Cough	91	(21.2)	58	(13.6)	908	(20.5)	1,228	(19.1)
Constipation	89	(20.7)	62	(14.6)	814	(18.3)	1,085	(16.9)
Arthralgia	78	(18.2)	26	(6.1)	692	(15.6)	929	(14.4)
Weight decreased	76	(17.7)	47	(11.1)	392	(8.8)	585	(9.1)
Proteinuria	75	(17.5)	47	(11.1)	38	(0.9)	58	(0.9)
Dyspnoea	69	(16.1)	46	(10.8)	785	(17.7)	1,054	(16.4)
Headache	68	(15.9)	69	(16.2)	527	(11.9)	737	(11.5)
Stomatitis	67	(15.6)	89	(20.9)	111	(2.5)	155	(2.4)
Asthenia	65	(15.2)	63	(14.8)	518	(11.7)	745	(11.6)
Pruritus	65	(15.2)	25	(5.9)	819	(18.5)	1,113	(17.3)
Vomiting	65	(15.2)	79	(18.6)	596	(13.4)	807	(12.5)
Rash	61	(14.2)	47	(11.1)	712	(16.0)	933	(14.5)
Back pain	57	(13.3)	43	(10.1)	530	(11.9)	711	(11.0)
Mucosal inflammation	57	(13.3)	93	(21.9)	77	(1.7)	90	(1.4)
Hyperthyroidism	55	(12.8)	16	(3.8)	145	(3.3)	272	(4.2)
Pyrexia	55	(12.8)	43	(10.1)	602	(13.6)	816	(12.7)
Pain in extremity	51	(11.9)	42	(9.9)	323	(7.3)	416	(6.5)
Abdominal pain	49	(11.4)	29	(6.8)	411	(9.3)	616	(9.6)
Blood creatinine increased	48	(11.2)	51	(12.0)	207	(4.7)	303	(4.7)
Dysgeusia	47	(11.0)	131	(30.8)	117	(2.6)	156	(2.4)
Anaemia	34	(7.9)	100	(23.5)	649	(14.6)	923	(14.3)
Dyspepsia	22	(5.1)	62	(14.6)	101	(2.3)	165	(2.6)
Gastrooesophageal reflux disease	18	(4.2)	48	(11.3)	98	(2.2)	135	(2.1)
Platelet count decreased	16	(3.7)	77	(18.1)	59	(1.3)	83	(1.3)
Thrombocytopenia	11	(2.6)	99	(23.3)	73	(1.6)	105	(1.6)

Neutropenia	8	(1.9)	82	(19.3)	35	(0.8)	67	(1.0)
Neutrophil count decreased	4	(0.9)	50	(11.8)	29	(0.7)	43	(0.7)
White blood cell count decreased	2	(0.5)	43	(10.1)	45	(1.0)	62	(1.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days following the last dose and serious adverse events up to 90 days following the last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
‖ Includes all subjects who received at least one dose of Pembrolizumab and/or Axitinib in KN426.
†† Includes all subjects who received at least one dose of Sunitinib in KN426.
¶ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN045, KN052, KN055 and KN087.
§ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma) and Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort B4, KN040, KN042, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158, KN164 Cohort A, KN170, KN224 and KN427 Cohort A.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)
Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)
Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)
Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)
Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)
Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)
Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)
Database cutoff date for HCC (KN224: 15MAY2018)
Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)
Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl; adae]

Figure 12-1
Between-Treatment Comparisons in Adverse Events
Selected Adverse Events (>= 10% Incidence) and Sorted by Risk Difference
(ASaT Population)
A (N=429) vs. B (N=425)



A stands for Pembrolizumab + Axitinib and B stands for Sunitinib.
Database Cutoff Date: 24Aug2018.
Source: [P426V01MK3475: adam-adsl; adae]

Table 14.3-18
Exposure-Adjusted Adverse Events
(Including Multiple Occurrences of Events)
(Incidence ≥ 10% in One or More Treatment Groups)
(ASaT Population)

	Event Count and Rate (Events/100 person-months)[†]	
	Pembrolizumab + Axitinib	Sunitinib
Number of subjects exposed	429	425
Total exposure[‡] in person-months	4766.9	3924.6
Total events (rate)	7,017 (147.2)	7,052 (179.7)
Blood and lymphatic system disorders	**91 (1.9)**	**577 (14.7)**
Anaemia	36 (0.8)	155 (3.9)
Neutropenia	11 (0.2)	152 (3.9)
Thrombocytopenia	13 (0.3)	168 (4.3)
Cardiac disorders	**64 (1.3)**	**45 (1.1)**
Endocrine disorders	**278 (5.8)**	**196 (5.0)**
Hyperthyroidism	60 (1.3)	18 (0.5)
Hypothyroidism	178 (3.7)	174 (4.4)
Eye disorders	**69 (1.4)**	**87 (2.2)**
Gastrointestinal disorders	**1,402 (29.4)**	**1,407 (35.9)**
Abdominal pain	66 (1.4)	33 (0.8)
Constipation	107 (2.2)	70 (1.8)
Diarrhoea	508 (10.7)	384 (9.8)
Dyspepsia	26 (0.5)	73 (1.9)
Gastrooesophageal reflux disease	18 (0.4)	61 (1.6)
Nausea	176 (3.7)	205 (5.2)
Stomatitis	86 (1.8)	111 (2.8)
Vomiting	99 (2.1)	127 (3.2)
General disorders and administration site conditions	**622 (13.0)**	**711 (18.1)**
Asthenia	88 (1.8)	81 (2.1)
Fatigue	208 (4.4)	214 (5.5)
Mucosal inflammation	78 (1.6)	145 (3.7)
Pyrexia	68 (1.4)	47 (1.2)
Hepatobiliary disorders	**60 (1.3)**	**61 (1.6)**
Infections and infestations	**364 (7.6)**	**266 (6.8)**
Injury, poisoning and procedural complications	**61 (1.3)**	**49 (1.2)**
Investigations	**866 (18.2)**	**944 (24.1)**
Alanine aminotransferase increased	164 (3.4)	81 (2.1)
Investigations	**866 (18.2)**	**944 (24.1)**
Aspartate aminotransferase increased	168 (3.5)	95 (2.4)
Blood creatinine increased	79 (1.7)	72 (1.8)
Neutrophil count decreased	6 (0.1)	109 (2.8)
Platelet count decreased	21 (0.4)	151 (3.8)
Weight decreased	86 (1.8)	54 (1.4)
White blood cell count decreased	2 (0.0)	97 (2.5)
Metabolism and nutrition disorders	**539 (11.3)**	**436 (11.1)**
Decreased appetite	174 (3.7)	156 (4.0)
Musculoskeletal and connective tissue disorders	**453 (9.5)**	**281 (7.2)**
Arthralgia	96 (2.0)	34 (0.9)
Back pain	66 (1.4)	46 (1.2)
Pain in extremity	69 (1.4)	48 (1.2)
Nervous system disorders	**322 (6.8)**	**419 (10.7)**
Dysgeusia	52 (1.1)	185 (4.7)
Headache	95 (2.0)	88 (2.2)
Psychiatric disorders	**110 (2.3)**	**85 (2.2)**
Renal and urinary disorders	**215 (4.5)**	**156 (4.0)**
Proteinuria	105 (2.2)	77 (2.0)
Respiratory, thoracic and mediastinal disorders	**500 (10.5)**	**315 (8.0)**
Cough	108 (2.3)	66 (1.7)
Dysphonia	126 (2.6)	18 (0.5)
Dyspnoea	83 (1.7)	51 (1.3)
Skin and subcutaneous tissue disorders	**555 (11.6)**	**638 (16.3)**
Palmar-plantar erythrodysaesthesia syndrome	142 (3.0)	236 (6.0)
Pruritus	78 (1.6)	33 (0.8)
Rash	84 (1.8)	60 (1.5)
Vascular disorders	**366 (7.7)**	**317 (8.1)**
Vascular disorders	**366 (7.7)**	**317 (8.1)**
Hypertension	319 (6.7)	280 (7.1)

[†] Event rate per 100 person-months of exposure = event count *100/person-months of exposure.
[‡] Drug exposure is defined as the interval between the first dose date + 1 day and the earlier of the last dose date + 30 or the database cutoff date.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms 'Neoplasm progression', 'Malignant neoplasm progression' and 'Disease progression' not related to the drug are excluded.
Including adverse events that occurred in ≥ 10% of subjects in ASaT population in one or more treatment groups.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adae]

Table 14.3-20
Exposure-Adjusted Adverse Events by Observation Period
(Including Multiple Occurrences of Events)
(Incidence ≥ 10% in One or More Treatment Groups)
(ASaT Population)

	Event Count and Rate (Events/100 person-months) [†]							
	Pembrolizumab + Axitinib				Sunitinib			
Observation period of drug exposure	0-3 months	3-6 months	6-12 months	Beyond 12 months	0-3 months	3-6 months	6-12 months	Beyond 12 months
Number of subjects exposed[‡]	429	400	349	187	425	375	295	126
Total exposure[§] in person-months	1261.3	1121.4	1624.1	760.1	1219.6	966.2	1237.1	501.8
Total events (rate)	3096 (245.5)	1561 (139.2)	1660 (102.2)	700 (92.1)	4148 (340.1)	1395 (144.4)	1102 (89.1)	407 (81.1)
Blood and lymphatic system disorders	**28(2.2)**	**23(2.1)**	**28(1.7)**	**12(1.6)**	**285(23.4)**	**137(14.2)**	**117(9.5)**	**38(7.6)**
Anaemia	11(0.9)	11(1.0)	9(0.6)	5(0.7)	71(5.8)	44(4.6)	26(2.1)	14(2.8)
Neutropenia	2(0.2)	3(0.3)	5(0.3)	1(0.1)	67(5.5)	31(3.2)	43(3.5)	11(2.2)
Thrombocytopenia	6(0.5)	2(0.2)	3(0.2)	2(0.3)	98(8.0)	45(4.7)	24(1.9)	1(0.2)
Cardiac disorders	**36(2.9)**	**8(0.7)**	**11(0.7)**	**9(1.2)**	**24(2.0)**	**11(1.1)**	**7(0.6)**	**3(0.6)**
Endocrine disorders	**140(11.1)**	**71(6.3)**	**43(2.6)**	**24(3.2)**	**97(8.0)**	**46(4.8)**	**37(3.0)**	**16(3.2)**
Hyperthyroidism	47(3.7)	3(0.3)	5(0.3)	5(0.7)	6(0.5)	4(0.4)	6(0.5)	2(0.4)
Hypothyroidism	77(6.1)	58(5.2)	27(1.7)	16(2.1)	89(7.3)	41(4.2)	30(2.4)	14(2.8)
Eye disorders	**25(2.0)**	**13(1.2)**	**19(1.2)**	**12(1.6)**	**54(4.4)**	**21(2.2)**	**7(0.6)**	**5(1.0)**
Gastrointestinal disorders	**516(40.9)**	**349(31.1)**	**378(23.3)**	**159(20.9)**	**847(69.4)**	**266(27.5)**	**223(18.0)**	**71(14.1)**
Abdominal pain	18(1.4)	13(1.2)	27(1.7)	8(1.1)	16(1.3)	5(0.5)	10(0.8)	2(0.4)
Constipation	52(4.1)	30(2.7)	20(1.2)	5(0.7)	49(4.0)	12(1.2)	7(0.6)	2(0.4)
Diarrhoea	144(11.4)	123(11.0)	158(9.7)	83(10.9)	188(15.4)	92(9.5)	80(6.5)	24(4.8)
Dyspepsia	13(1.0)	6(0.5)	5(0.3)	2(0.3)	54(4.4)	12(1.2)	6(0.5)	1(0.2)
Gastrooesophageal reflux disease	6(0.5)	4(0.4)	4(0.2)	4(0.5)	35(2.9)	11(1.1)	10(0.8)	5(1.0)
Nausea	82(6.5)	44(3.9)	39(2.4)	11(1.4)	124(10.2)	41(4.2)	27(2.2)	13(2.6)
Stomatitis	49(3.9)	18(1.6)	12(0.7)	7(0.9)	89(7.3)	7(0.7)	12(1.0)	3(0.6)
Vomiting	31(2.5)	24(2.1)	33(2.0)	11(1.4)	69(5.7)	27(2.8)	25(2.0)	6(1.2)
General disorders and administration site conditions	**317(25.1)**	**120(10.7)**	**140(8.6)**	**45(5.9)**	**466(38.2)**	**114(11.8)**	**105(8.5)**	**26(5.2)**
Asthenia	43(3.4)	18(1.6)	22(1.4)	5(0.7)	57(4.7)	9(0.9)	11(0.9)	4(0.8)
Fatigue	122(9.7)	42(3.7)	32(2.0)	12(1.6)	147(12.1)	35(3.6)	25(2.0)	7(1.4)
Mucosal inflammation	47(3.7)	14(1.2)	14(0.9)	3(0.4)	101(8.3)	26(2.7)	16(1.3)	2(0.4)
Pyrexia	29(2.3)	14(1.2)	19(1.2)	6(0.8)	36(3.0)	0(0.0)	10(0.8)	1(0.2)
Hepatobiliary disorders	**34(2.7)**	**14(1.2)**	**9(0.6)**	**3(0.4)**	**38(3.1)**	**15(1.6)**	**7(0.6)**	**1(0.2)**
Infections and infestations	**111(8.8)**	**98(8.7)**	**109(6.7)**	**46(6.1)**	**137(11.2)**	**60(6.2)**	**54(4.4)**	**15(3.0)**
Injury, poisoning and procedural complications	**26(2.1)**	**11(1.0)**	**16(1.0)**	**8(1.1)**	**22(1.8)**	**15(1.6)**	**9(0.7)**	**3(0.6)**
Investigations	**337(26.7)**	**225(20.1)**	**208(12.8)**	**96(12.6)**	**522(42.8)**	**199(20.6)**	**141(11.4)**	**82(16.3)**
Alanine aminotransferase increased	66(5.2)	53(4.7)	33(2.0)	12(1.6)	54(4.4)	13(1.3)	11(0.9)	3(0.6)
Aspartate aminotransferase increased	66(5.2)	54(4.8)	35(2.2)	13(1.7)	56(4.6)	19(2.0)	14(1.1)	6(1.2)
Blood creatinine increased	21(1.7)	15(1.3)	23(1.4)	20(2.6)	35(2.9)	20(2.1)	8(0.6)	9(1.8)
Neutrophil count decreased	1(0.1)	1(0.1)	2(0.1)	2(0.3)	44(3.6)	29(3.0)	22(1.8)	14(2.8)
Platelet count decreased	6(0.5)	6(0.5)	7(0.4)	2(0.3)	90(7.4)	26(2.7)	25(2.0)	10(2.0)
Weight decreased	32(2.5)	23(2.1)	22(1.4)	9(1.2)	27(2.2)	20(2.1)	4(0.3)	3(0.6)
White blood cell count decreased	0(0.0)	2(0.2)	0(0.0)	0(0.0)	46(3.8)	22(2.3)	18(1.5)	11(2.2)
Metabolism and nutrition disorders	**193(15.3)**	**123(11.0)**	**144(8.9)**	**79(10.4)**	**247(20.3)**	**81(8.4)**	**78(6.3)**	**30(6.0)**
Decreased appetite	65(5.2)	43(3.8)	49(3.0)	17(2.2)	101(8.3)	34(3.5)	17(1.4)	4(0.8)
Musculoskeletal and connective tissue disorders	**210(16.6)**	**94(8.4)**	**107(6.6)**	**42(5.5)**	**159(13.0)**	**54(5.6)**	**51(4.1)**	**17(3.4)**
Musculoskeletal and connective tissue disorders	**210(16.6)**	**94(8.4)**	**107(6.6)**	**42(5.5)**	**159(13.0)**	**54(5.6)**	**51(4.1)**	**17(3.4)**
Arthralgia	49(3.9)	20(1.8)	15(0.9)	12(1.6)	19(1.6)	4(0.4)	8(0.6)	3(0.6)
Back pain	29(2.3)	15(1.3)	18(1.1)	4(0.5)	30(2.5)	7(0.7)	5(0.4)	4(0.8)
Pain in extremity	27(2.1)	14(1.2)	22(1.4)	6(0.8)	22(1.8)	15(1.6)	8(0.6)	3(0.6)
Nervous system disorders	**154(12.2)**	**72(6.4)**	**64(3.9)**	**32(4.2)**	**277(22.7)**	**77(8.0)**	**47(3.8)**	**18(3.6)**
Dysgeusia	26(2.1)	14(1.2)	10(0.6)	2(0.3)	136(11.2)	27(2.8)	15(1.2)	7(1.4)
Headache	56(4.4)	21(1.9)	11(0.7)	7(0.9)	60(4.9)	16(1.7)	9(0.7)	3(0.6)
Psychiatric disorders	**52(4.1)**	**23(2.1)**	**26(1.6)**	**9(1.2)**	**51(4.2)**	**18(1.9)**	**9(0.7)**	**7(1.4)**
Renal and urinary disorders	**103(8.2)**	**43(3.8)**	**49(3.0)**	**20(2.6)**	**95(7.8)**	**29(3.0)**	**16(1.3)**	**16(3.2)**
Proteinuria	55(4.4)	16(1.4)	23(1.4)	11(1.4)	44(3.6)	15(1.6)	7(0.6)	11(2.2)
Respiratory, thoracic and mediastinal disorders	**274(21.7)**	**89(7.9)**	**86(5.3)**	**51(6.7)**	**188(15.4)**	**61(6.3)**	**41(3.3)**	**25(5.0)**
Cough	55(4.4)	22(2.0)	22(1.4)	9(1.2)	39(3.2)	15(1.6)	9(0.7)	3(0.6)
Dysphonia	95(7.5)	18(1.6)	9(0.6)	4(0.5)	12(1.0)	2(0.2)	4(0.3)	0(0.0)
Dyspnoea	39(3.1)	13(1.2)	17(1.0)	14(1.8)	30(2.5)	9(0.9)	8(0.6)	4(0.8)
Skin and subcutaneous tissue disorders	**273(21.6)**	**110(9.8)**	**131(8.1)**	**41(5.4)**	**378(31.0)**	**143(14.8)**	**88(7.1)**	**29(5.8)**
Palmar-plantar erythrodysaesthesia syndrome	84(6.7)	26(2.3)	24(1.5)	8(1.1)	127(10.4)	65(6.7)	34(2.7)	10(2.0)
Pruritus	40(3.2)	16(1.4)	18(1.1)	4(0.5)	23(1.9)	5(0.5)	4(0.3)	1(0.2)
Rash	36(2.9)	19(1.7)	21(1.3)	8(1.1)	41(3.4)	9(0.9)	8(0.6)	2(0.4)
Vascular disorders	**229(18.2)**	**58(5.2)**	**69(4.2)**	**10(1.3)**	**227(18.6)**	**38(3.9)**	**47(3.8)**	**5(1.0)**
Vascular disorders	**229(18.2)**	**58(5.2)**	**69(4.2)**	**10(1.3)**	**227(18.6)**	**38(3.9)**	**47(3.8)**	**5(1.0)**
Hypertension	211(16.7)	47(4.2)	56(3.4)	5(0.7)	204(16.7)	31(3.2)	42(3.4)	3(0.6)

[†] Event rate per 100 person-months of exposure = event count *100/person-months of exposure.
[‡] Number of subjects exposed to drug at the start of indicated time interval.
[§] Drug exposure is defined as the interval between the first dose date + 1 day and the earlier of the last dose date + 30 or the database cutoff date.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms 'Neoplasm progression', 'Malignant neoplasm progression' and 'Disease progression' not related to the drug are excluded.
Including adverse events that occurred in ≥ 10% of subjects in ASaT population in one or more treatment groups.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adae]

In the next tables safety data of monotherapy with either pembrolizumab (KN427 Cohort A) or with axitinib (Study A4061051) are provided:

KN427 Cohort A (Pembrolizumab monotherapy)

Table 14.3-5
Subjects With Adverse Events By Decreasing Incidence
(Incidence ≥ 5%)
Cohort A: ccRCC
(ASaT Population)

	Cohort A	
	n	(%)
Subjects in population	110	
with one or more adverse events	108	(98.2)
with no adverse events	2	(1.8)
Fatigue	42	(38.2)
Pruritus	39	(35.5)
Diarrhoea	36	(32.7)
Arthralgia	25	(22.7)
Cough	25	(22.7)
Constipation	22	(20.0)
Nausea	21	(19.1)
Decreased appetite	20	(18.2)
Blood creatinine increased	17	(15.5)
Dyspnoea	16	(14.5)
Asthenia	15	(13.6)
Anaemia	13	(11.8)
Dry mouth	13	(11.8)
Hypothyroidism	13	(11.8)
Rash	13	(11.8)
Alanine aminotransferase increased	12	(10.9)
Headache	12	(10.9)
Musculoskeletal pain	12	(10.9)
Aspartate aminotransferase increased	11	(10.0)
Myalgia	11	(10.0)
Abdominal pain	10	(9.1)
Back pain	10	(9.1)
Pyrexia	10	(9.1)
Hyperglycaemia	9	(8.2)
Hypertension	9	(8.2)
Influenza like illness	9	(8.2)
Insomnia	9	(8.2)
Dizziness	8	(7.3)
Dyspepsia	8	(7.3)
Hyperkalaemia	8	(7.3)
Rash maculo-papular	8	(7.3)
Vomiting	8	(7.3)
Blood alkaline phosphatase increased	7	(6.4)
Depression	7	(6.4)
Hypercalcaemia	7	(6.4)
Nasopharyngitis	7	(6.4)
Oedema peripheral	7	(6.4)
Pneumonia	7	(6.4)
Upper respiratory tract infection	7	(6.4)
Chest pain	6	(5.5)
Dehydration	6	(5.5)
Dry skin	6	(5.5)
Haematuria	6	(5.5)
Hyperthyroidism	6	(5.5)
Hyponatraemia	6	(5.5)
Lymphocyte count decreased	6	(5.5)
Pain in extremity	6	(5.5)
Sinusitis	6	(5.5)

Every subject is counted a single time for each applicable specific adverse event.
A specific adverse event appears on this report only if its incidence meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
MedDRA version used is 21.0.
Database Cutoff Date: 07Sep2018

Source: [P427V01MK3475: adam-adsl; adae]

Study A4061051 (Axitinib monotherapy)

Table 32. Summary of Treatment-Emergent Adverse Events Experienced by ≥5% of Patients by Preferred Term (All Causalities); Safety Analysis Set

Preferred Term	Axitinib N=189		Sorafenib N=96	
	n (%)	No. of Events	n (%)	No. of Events
Page 1 of 2				
Any AE	178 (94.2)	2226	92 (95.8)	746
Diarrhea	94 (49.7)	297	38 (39.6)	81
Hypertension	92 (48.7)	210	28 (29.2)	41
Weight decreased	69 (36.5)	140	23 (24.0)	43
Fatigue	62 (32.8)	113	25 (26.0)	32
Decreased appetite	54 (28.6)	85	18 (18.8)	22
Palmar-plantar erythrodysesthesia syndrome	50 (26.5)	128	37 (38.5)	87
Dysphonia	44 (23.3)	58	10 (10.4)	10
Asthenia	39 (20.6)	63	15 (15.6)	20
Hypothyroidism	39 (20.6)	46	7 (7.3)	7
Nausea	37 (19.6)	84	14 (14.6)	19
Vomiting	35 (18.5)	90	10 (10.4)	12
Abdominal pain upper	31 (16.4)	44	6 (6.3)	8
Cough	31 (16.4)	38	16 (16.7)	24
Stomatitis	30 (15.9)	76	6 (6.3)	8
Back pain	28 (14.8)	43	12 (12.5)	15
Headache	25 (13.2)	35	6 (6.3)	6
Dyspnea	22 (11.6)	30	8 (8.3)	11
Proteinuria	22 (11.6)	64	12 (12.5)	14
Disease progression	21 (11.1)	23	7 (7.3)	7
Mucosal inflammation	21 (11.1)	36	8 (8.3)	10
Pain in extremity	21 (11.1)	32	6 (6.3)	8
Alanine aminotransferase increased	20 (10.6)	28	7 (7.3)	12
Constipation	20 (10.6)	29	13 (13.5)	17
Arthralgia	19 (10.1)	27	9 (9.4)	17
Rash	18 (9.5)	23	19 (19.8)	28
Upper respiratory tract infection	17 (9.0)	21	1 (1.0)	1
Blood thyroid stimulating hormone increased	16 (8.5)	22	2 (2.1)	2
Aspartate aminotransferase increased	15 (7.9)	18	7 (7.3)	11
Abdominal pain	14 (7.4)	24	11 (11.5)	15
Oropharyngeal pain	14 (7.4)	22	5 (5.2)	5
Dizziness	13 (6.9)	18	2 (2.1)	3
Blood creatinine increased	12 (6.3)	27	5 (5.2)	6
Dyspepsia	12 (6.3)	15	2 (2.1)	2
Hypotension	12 (6.3)	14	3 (3.1)	4
Dry mouth	11 (5.8)	14	1 (1.0)	1
Musculoskeletal pain	11 (5.8)	17	3 (3.1)	3
Urinary tract infection	11 (5.8)	14	2 (2.1)	2
Abdominal distension	10 (5.3)	13	2 (2.1)	2
Amylase increased	10 (5.3)	22	1 (1.0)	2
Anxiety	10 (5.3)	14	0	0
Alopecia	8 (4.2)	10	18 (18.8)	21
Erythema	5 (2.6)	6	18 (18.8)	20
Insomnia	9 (4.8)	10	5 (5.2)	5
Pyrexia	8 (4.2)	9	5 (5.2)	5
Epistaxis	5 (2.6)	6	5 (5.2)	5
Hyperglycemia	4 (2.1)	7	5 (5.2)	9
Chest pain	9 (4.8)	14	6 (6.3)	6
Edema peripheral	9 (4.8)	13	6 (6.3)	8
Blood alkaline phosphatase increased	5 (2.6)	5	6 (6.3)	7
Skin exfoliation	3 (1.6)	3	6 (6.3)	8
Anemia	9 (4.8)	13	7 (7.3)	14
Pruritus	7 (3.7)	7	8 (8.3)	11
Pleural effusion	6 (3.2)	6	9 (9.4)	9

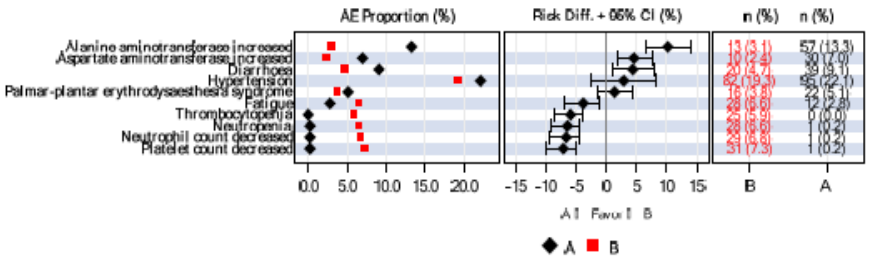
Source: Table 14.3.1.2.3a
%=(n/N) × 100.
MedDRA (v15.0) coding dictionary applied.
Data cutoff date: 27 July 2012.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; v=version; N=number of patients; n=number of patients meeting prespecified criteria; No.=number

Grade 3-5 AEs

Table 5.3.5.3.3-rcc1: 10
Subjects With Grade 3-5 Adverse Events
(Incidence ≥ 5% in the Preferred Term)
By Decreasing Frequency of Preferred Term
(ASaT Population) *(modified by the Assessor)*

	KN426 Data for Pembrolizumab + Axitinib[‡]		KN426 Sunitinib[††]		Reference Safety Dataset for Pembrolizumab Monotherapy[¶]		Cumulative Running Safety Dataset for Pembrolizumab Monotherapy[‡]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	429		425		4,439		6,436	
with one or more adverse events	325	(75.8)	300	(70.6)	2,153	(48.5)	3,107	(48.3)
with no adverse events	104	(24.2)	125	(29.4)	2,286	(51.5)	3,329	(51.7)
Hypertension	95	(22.1)	82	(19.3)	55	(1.2)	103	(1.6)
Alanine aminotransferase increased	57	(13.3)	13	(3.1)	41	(0.9)	79	(1.2)
Diarrhoea	39	(9.1)	20	(4.7)	65	(1.5)	88	(1.4)
Aspartate aminotransferase increased	30	(7.0)	10	(2.4)	52	(1.2)	103	(1.6)
Palmar-plantar erythrodysaesthesia syndrome	22	(5.1)	16	(3.8)	1	(0.0)	1	(0.0)
Fatigue	12	(2.8)	28	(6.6)	118	(2.7)	166	(2.6)
Thrombocytopenia	0	(0.0)	25	(5.9)	15	(0.3)	18	(0.3)
Neutropenia	1	(0.2)	28	(6.6)	13	(0.3)	27	(0.4)
Neutrophil count decreased	1	(0.2)	29	(6.8)	6	(0.1)	11	(0.2)
Platelet count decreased	1	(0.2)	31	(7.3)	6	(0.1)	8	(0.1)

Figure 14.3-3
Between-Treatment Comparisons in Grade 3-5 Adverse Events
Selected Adverse Events (>= 5% Incidence) and Sorted by Risk Difference
(ASaT Population)
A (N=429) vs. B (N=425)



A stands for Pembrolizumab + Axitinib and B stands for Sunitinib.
Database Cutoff Date: 24Aug2018.
Source: [P426V01MK3475: adam-adsl; adae]

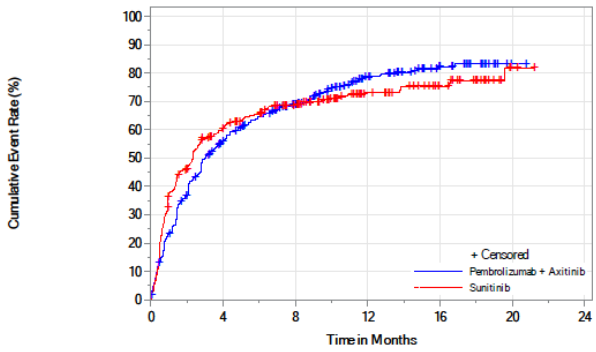
Table 14.3-28
Analysis of Time to First Grade 3, 4 or 5 Adverse Events
(ASaT Population)

Treatment	N	Number of Events (%)	Person-Weeks	Event Rate/ 100 Person-Weeks	Median Time † (Weeks) (95% CI)	Event Free Rate at Weeks 12 in % † (95% CI)
Pembrolizumab + Axitinib	429	325 (75.8)	9411.9	3.5	13.1 (12.0, 16.1)	52.7 (47.9, 57.4)
Sunitinib	425	300 (70.6)	8313.3	3.6	10.1 (7.0, 11.6)	43.7 (38.9, 48.3)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value§
Pembrolizumab + Axitinib vs. Sunitinib					0.96 (0.82, 1.13)	0.3184

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by International Metastatic RCC Database Consortium (IMDC) risk group (favorable vs. intermediate vs. poor) and geographic region (North America vs. Western Europe vs. Rest of the World).
§ One-sided p-value based on log-rank test stratified by the same strata as above.
Time to first Grade 3-5 AE is defined as the time from the first day of study drug to the first Grade 3-5 adverse event. For subjects without a Grade 3-5 AE, the time to first Grade 3-5 AE is censored at 30 days of last dose.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adttae]

Figure 14.3-4
Kaplan-Meier Estimates of Time to First Grade 3, 4 or 5 Adverse Events
(ASaT Population)



Number of subjects at risk

Pembrolizumab + Axitinib	429	177	109	52	21	1	0
Sunitinib	425	152	97	47	26	2	0

Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adttae]

Drug-related AEs

Table 5.3.5.3.3-rcc1: 8

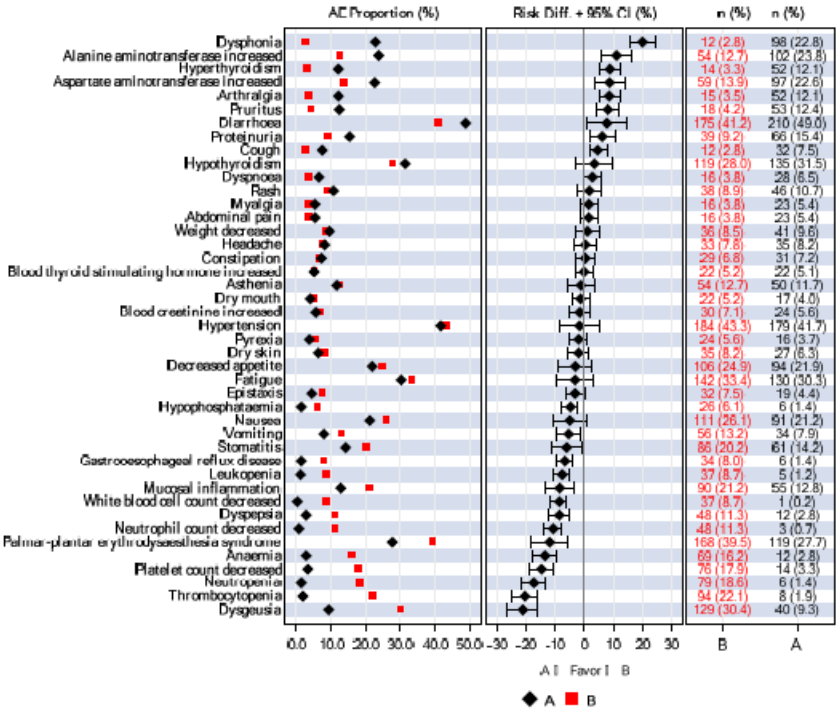
Subjects With Drug-Related Adverse Events
(Incidence ≥ 5% in One or More Treatment Groups)
By Decreasing Frequency of Preferred Term
(ASaT Population)

	KN426 Data for Pembrolizumab + Axitinib‖		KN426 Sunitinib††		Reference Safety Dataset for Pembrolizumab Monotherapy¶		Cumulative Running Safety Dataset for Pembrolizumab Monotherapy§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	429		425		4,439		6,436	
with one or more adverse events	413	(96.3)	415	(97.6)	3,140	(70.7)	4,512	(70.1)
with no adverse events	16	(3.7)	10	(2.4)	1,299	(29.3)	1,924	(29.9)
Diarrhoea	210	(49.0)	175	(41.2)	480	(10.8)	690	(10.7)
Hypertension	179	(41.7)	184	(43.3)	19	(0.4)	36	(0.6)
Hypothyroidism	135	(31.5)	119	(28.0)	378	(8.5)	584	(9.1)
Fatigue	130	(30.3)	142	(33.4)	929	(20.9)	1,285	(20.0)
Palmar-plantar erythrodysaesthesia syndrome	119	(27.7)	168	(39.5)	10	(0.2)	17	(0.3)
Alanine aminotransferase increased	102	(23.8)	54	(12.7)	149	(3.4)	262	(4.1)
Dysphonia	98	(22.8)	12	(2.8)	14	(0.3)	19	(0.3)
Aspartate aminotransferase increased	97	(22.6)	59	(13.9)	147	(3.3)	261	(4.1)
Decreased appetite	94	(21.9)	106	(24.9)	377	(8.5)	499	(7.8)
Nausea	91	(21.2)	111	(26.1)	430	(9.7)	579	(9.0)
Proteinuria	66	(15.4)	39	(9.2)	7	(0.2)	15	(0.2)
Stomatitis	61	(14.2)	86	(20.2)	58	(1.3)	78	(1.2)
Mucosal inflammation	55	(12.8)	90	(21.2)	39	(0.9)	49	(0.8)
Pruritus	53	(12.4)	18	(4.2)	644	(14.5)	871	(13.5)
Arthralgia	52	(12.1)	15	(3.5)	349	(7.9)	489	(7.6)
Hyperthyroidism	52	(12.1)	14	(3.3)	125	(2.8)	243	(3.8)
Asthenia	50	(11.7)	54	(12.7)	279	(6.3)	396	(6.2)
Rash	46	(10.7)	38	(8.9)	531	(12.0)	688	(10.7)
Weight decreased	41	(9.6)	36	(8.5)	100	(2.3)	142	(2.2)
Dysgeusia	40	(9.3)	129	(30.4)	66	(1.5)	91	(1.4)
Headache	35	(8.2)	33	(7.8)	141	(3.2)	201	(3.1)
Vomiting	34	(7.9)	56	(13.2)	157	(3.5)	220	(3.4)
Cough	32	(7.5)	12	(2.8)	159	(3.6)	204	(3.2)
Constipation	31	(7.2)	29	(6.8)	127	(2.9)	172	(2.7)
Dyspnoea	28	(6.5)	16	(3.8)	148	(3.3)	216	(3.4)
Dry skin	27	(6.3)	35	(8.2)	134	(3.0)	189	(2.9)
Blood creatinine increased	24	(5.6)	30	(7.1)	53	(1.2)	75	(1.2)
Abdominal pain	23	(5.4)	16	(3.8)	91	(2.1)	134	(2.1)
Myalgia	23	(5.4)	16	(3.8)	183	(4.1)	262	(4.1)
Blood thyroid stimulating hormone increased	22	(5.1)	22	(5.2)	47	(1.1)	72	(1.1)
Epistaxis	19	(4.4)	32	(7.5)	5	(0.1)	7	(0.1)
Dry mouth	17	(4.0)	22	(5.2)	104	(2.3)	153	(2.4)
Pyrexia	16	(3.7)	24	(5.6)	216	(4.9)	280	(4.4)
Platelet count decreased	14	(3.3)	76	(17.9)	27	(0.6)	34	(0.5)
Anaemia	12	(2.8)	69	(16.2)	152	(3.4)	223	(3.5)
Dyspepsia	12	(2.8)	48	(11.3)	18	(0.4)	36	(0.6)
Thrombocytopenia	8	(1.9)	94	(22.1)	29	(0.7)	43	(0.7)
Gastrooesophageal reflux disease	6	(1.4)	34	(8.0)	12	(0.3)	20	(0.3)
Hypophosphataemia	6	(1.4)	26	(6.1)	31	(0.7)	45	(0.7)
Neutropenia	6	(1.4)	79	(18.6)	20	(0.5)	45	(0.7)
Leukopenia	5	(1.2)	37	(8.7)	18	(0.4)	34	(0.5)
Neutrophil count decreased	3	(0.7)	48	(11.3)	21	(0.5)	27	(0.4)
White blood cell count decreased	1	(0.2)	37	(8.7)	23	(0.5)	30	(0.5)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days following the last dose and serious adverse events up to 90 days following the last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
‖ Includes all subjects who received at least one dose of Pembrolizumab and/or Axitinib in KN426.
†† Includes all subjects who received at least one dose of Sunitinib in KN426.
¶ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN045, KN052, KN055 and KN087.
§ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma) and Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort B4, KN040, KN042, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158, KN164 Cohort A, KN170, KN224 and KN427 Cohort A.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)
Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)
Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)
Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)
Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)
Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)
Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)
Database cutoff date for HCC (KN224: 15MAY2018)
Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)
Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl; adae]

Figure 14.3-2
Between-Treatment Comparisons in Drug-Related Adverse Events
Selected Adverse Events (>= 5% Incidence) and Sorted by Risk Difference
(ASaT Population)
A (N=429) vs. B (N=425)



A stands for Pembrolizumab + Axitinib and B stands for Sunitinib.
Database Cutoff Date: 24Aug2018.
Source: [P426V01MK3475: adam-adsl; adae]

KN427 Cohort A (Pembrolizumab monotherapy)

Table 14.3-8
Subjects With Drug-Related Adverse Events By Decreasing Incidence
(Incidence ≥ 5%)
Cohort A: ccRCC
(ASaT Population)

	Cohort A	
	n	(%)
Subjects in population	110	
with one or more drug-related adverse events	89	(80.9)
with no drug-related adverse events	21	(19.1)
Fatigue	31	(28.2)
Pruritus	31	(28.2)
Diarrhoea	25	(22.7)
Arthralgia	15	(13.6)
Hypothyroidism	12	(10.9)
Rash	9	(8.2)
Alanine aminotransferase increased	8	(7.3)
Aspartate aminotransferase increased	8	(7.3)
Asthenia	8	(7.3)
Decreased appetite	8	(7.3)
Dry mouth	7	(6.4)
Influenza like illness	7	(6.4)
Rash maculo-papular	7	(6.4)
Dyspnoea	6	(5.5)
Hyperthyroidism	6	(5.5)
Nausea	6	(5.5)

Every subject is counted a single time for each applicable specific adverse event.
A specific adverse event appears on this report only if its incidence meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA version used is 21.0.
Database Cutoff Date: 07Sep2018

Source: [P427V01MK3475: adam-adsl; adae]

Study A4061051 (Axitinib monotherapy)

Table 35. Summary of Treatment-Related Adverse Events Experienced by ≥5% of Patients by Treatment and Preferred Term; Safety Analysis Set

Preferred Term	Axitinib N=189		Sorafenib N=96	
	n (%)	No. of Events	n (%)	No. of Events
Any AE	163 (86.2)	1527	84 (87.5)	490
Hypertension	87 (46.0)	201	27 (28.1)	40
Diarrhea	85 (45.0)	260	32 (33.3)	56
Weight decreased	52 (27.5)	95	17 (17.7)	33
Fatigue	51 (27.0)	95	20 (20.8)	23
Palmar-plantar erythrodysesthesia syndrome	50 (26.5)	128	37 (38.5)	87
Dysphonia	44 (23.3)	57	9 (9.4)	9
Decreased appetite	42 (22.2)	69	15 (15.6)	19
Hypothyroidism	39 (20.6)	46	7 (7.3)	7
Nausea	32 (16.9)	69	11 (11.5)	13
Stomatitis	29 (15.3)	74	6 (6.3)	8
Vomiting	25 (13.2)	54	3 (3.1)	5
Asthenia	23 (12.2)	34	7 (7.3)	9
Mucosal inflammation	21 (11.1)	36	8 (8.3)	10
Proteinuria	19 (10.1)	52	9 (9.4)	11
Headache	18 (19.5)	20	4 (4.2)	4
Abdominal pain upper	17 (9.0)	19	4 (4.2)	6
Rash	17 (9.0)	22	19 (19.8)	26
Alanine aminotransferase increased	16 (8.5)	23	7 (7.3)	12
Blood thyroid stimulating hormone increased	16 (8.5)	22	2 (2.1)	2
Aspartate aminotransferase increased	12 (6.3)	15	7 (7.3)	11
Arthralgia	11 (5.8)	15	3 (3.1)	3
Dry mouth	11 (5.8)	13	1 (1.0)	1
Oropharyngeal pain	11 (5.8)	17	4 (4.2)	4
Pain in extremity	11 (5.8)	21	3 (3.1)	3
Constipation	10 (5.3)	12	9 (9.4)	13
Dyspepsia	10 (5.3)	13	2 (2.1)	2
Cough	9 (4.8)	10	7 (7.3)	7
Alopecia	8 (4.2)	10	18 (18.8)	21
Abdominal pain	7 (3.7)	14	5 (5.2)	6
Pruritus	5 (2.6)	5	8 (8.3)	11
Erythema	3 (1.6)	3	18 (18.8)	20
Skin exfoliation	3 (1.6)	3	6 (6.3)	8

Source: Table 14.3.1.3.3a
%=(n/N) × 100
MedDRA (v15.0) coding dictionary applied.
Data cutoff date: 27 July 2012.
Abbreviations: AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; v=version; N=number of patients; n=number of patients meeting prespecified criteria; No.=number

Drug-related Grade 3 to 5 Adverse Events

Table 14.3-24
Subjects With Drug-Related Adverse Events by System Organ Class and Preferred Term by Maximum Toxicity Grade
(Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab + Axitinib								Sunitinib	
	Related to Pembrolizumab and/or Axitinib		Related to both Pembrolizumab and Axitinib		Related to Pembrolizumab		Related to Axitinib			
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	429		429		429		429		425	
with one or more adverse events	413	(96.3)	305	(71.1)	365	(85.1)	409	(95.3)	415	(97.6)
Grade 1	38	(8.9)	73	(17.0)	70	(16.3)	47	(11.0)	49	(11.5)
Grade 2	105	(24.5)	120	(28.0)	136	(31.7)	118	(27.5)	119	(28.0)
Grade 3	242	(56.4)	102	(23.8)	141	(32.9)	224	(52.2)	220	(51.8)
Grade 4	24	(5.6)	10	(2.3)	14	(3.3)	20	(4.7)	20	(4.7)
Grade 5	4	(0.9)	0	(0.0)	4	(0.9)	0	(0.0)	7	(1.6)
with no adverse events	16	(3.7)	124	(28.9)	64	(14.9)	20	(4.7)	10	(2.4)

Table 2.7.4-rcc1: 9
Subjects With Grade 3-5 Drug-related Adverse Events
(Incidence ≥ 1% in One or More Treatment Groups)
By Decreasing Frequency of Preferred Term
(ASaT Population)

	KN426 Data for Pembrolizumab + Axitinib‖		KN426 Sunitinib††		Reference Safety Dataset for Pembrolizumab Monotherapy¶		Cumulative Running Safety Dataset for Pembrolizumab Monotherapy§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	429		425		4,439		6,436	
with one or more adverse events	270	(62.9)	247	(58.1)	660	(14.9)	1,018	(15.8)
with no adverse events	159	(37.1)	178	(41.9)	3,779	(85.1)	5,418	(84.2)
Hypertension	91	(21.2)	78	(18.4)	8	(0.2)	11	(0.2)
Alanine aminotransferase increased	52	(12.1)	11	(2.6)	23	(0.5)	47	(0.7)
Diarrhoea	31	(7.2)	19	(4.5)	45	(1.0)	62	(1.0)
Aspartate aminotransferase increased	29	(6.8)	7	(1.6)	29	(0.7)	53	(0.8)
Palmar-plantar erythrodysaesthesia syndrome	22	(5.1)	15	(3.5)	1	(0.0)	1	(0.0)
Proteinuria	11	(2.6)	6	(1.4)	0	(0.0)	1	(0.0)
Fatigue	10	(2.3)	21	(4.9)	52	(1.2)	77	(1.2)
Decreased appetite	9	(2.1)	2	(0.5)	14	(0.3)	21	(0.3)
Asthenia	6	(1.4)	12	(2.8)	18	(0.4)	27	(0.4)
Blood pressure increased	6	(1.4)	1	(0.2)	0	(0.0)	0	(0.0)
Hepatic function abnormal	6	(1.4)	0	(0.0)	1	(0.0)	5	(0.1)
Hepatitis	6	(1.4)	0	(0.0)	8	(0.2)	14	(0.2)
Hyperglycaemia	6	(1.4)	0	(0.0)	10	(0.2)	16	(0.2)
Weight decreased	6	(1.4)	0	(0.0)	4	(0.1)	7	(0.1)
Blood alkaline phosphatase increased	5	(1.2)	3	(0.7)	12	(0.3)	15	(0.2)
Colitis	5	(1.2)	0	(0.0)	43	(1.0)	61	(0.9)
Hyponatraemia	5	(1.2)	8	(1.9)	19	(0.4)	28	(0.4)
Dehydration	4	(0.9)	5	(1.2)	7	(0.2)	13	(0.2)
Mucosal inflammation	4	(0.9)	7	(1.6)	3	(0.1)	5	(0.1)
Stomatitis	3	(0.7)	9	(2.1)	5	(0.1)	5	(0.1)
Hypophosphataemia	2	(0.5)	11	(2.6)	9	(0.2)	14	(0.2)
Anaemia	1	(0.2)	13	(3.1)	23	(0.5)	36	(0.6)
Neutropenia	1	(0.2)	28	(6.6)	8	(0.2)	20	(0.3)
Neutrophil count decreased	1	(0.2)	29	(6.8)	4	(0.1)	5	(0.1)
Platelet count decreased	1	(0.2)	31	(7.3)	2	(0.0)	2	(0.0)
Pneumonitis	1	(0.2)	0	(0.0)	51	(1.1)	79	(1.2)
Leukopenia	0	(0.0)	6	(1.4)	3	(0.1)	3	(0.0)
Thrombocytopenia	0	(0.0)	22	(5.2)	4	(0.1)	6	(0.1)
White blood cell count decreased	0	(0.0)	11	(2.6)	1	(0.0)	1	(0.0)

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

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

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

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

‖ Includes all subjects who received at least one dose of Pembrolizumab and/or Axitinib in KN426.

†† Includes all subjects who received at least one dose of Sunitinib in KN426.

¶ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN045, KN052, KN055 and KN087.

§ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma) and Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort B4, KN040, KN042, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158, KN164 Cohort A, KN170, KN224 and KN427 Cohort A.

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

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)

Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)

Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)

Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)

Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)

Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)

Database cutoff date for HCC (KN224: 15MAY2018)

Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)

Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl; adae]

Serious Adverse Events

All SAEs

Table 5.3.5.3.3-rcc1: 16

Subjects With Serious Adverse Events Up to 90 Days of Last Dose
(Incidence ≥ 1% in One or More Treatment Groups)
By Decreasing Frequency of Preferred Term
(ASaT Population)

	KN426 Data for Pembrolizumab + Axitinib[‡]		KN426 Sunitinib[††]		Reference Safety Dataset for Pembrolizumab Monotherapy[¶]		Cumulative Running Safety Dataset for Pembrolizumab Monotherapy[§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	429		425		4,439		6,436	
with one or more adverse events	173	(40.3)	133	(31.3)	1,729	(39.0)	2,472	(38.4)
with no adverse events	256	(59.7)	292	(68.7)	2,710	(61.0)	3,964	(61.6)
Diarrhoea	12	(2.8)	4	(0.9)	46	(1.0)	66	(1.0)
Acute kidney injury	7	(1.6)	3	(0.7)	42	(0.9)	58	(0.9)
Alanine aminotransferase increased	6	(1.4)	0	(0.0)	9	(0.2)	20	(0.3)
Dehydration	6	(1.4)	5	(1.2)	39	(0.9)	54	(0.8)
Aspartate aminotransferase increased	5	(1.2)	0	(0.0)	11	(0.2)	27	(0.4)
Hepatic function abnormal	5	(1.2)	0	(0.0)	1	(0.0)	5	(0.1)
Pneumonitis	5	(1.2)	0	(0.0)	80	(1.8)	120	(1.9)
Pneumonia	4	(0.9)	10	(2.4)	153	(3.4)	211	(3.3)
Pulmonary embolism	4	(0.9)	7	(1.6)	54	(1.2)	82	(1.3)
Colitis	3	(0.7)	0	(0.0)	46	(1.0)	67	(1.0)
Dyspnoea	3	(0.7)	2	(0.5)	69	(1.6)	86	(1.3)
Pyrexia	3	(0.7)	1	(0.2)	56	(1.3)	78	(1.2)
Urinary tract infection	3	(0.7)	3	(0.7)	57	(1.3)	68	(1.1)
Anaemia	2	(0.5)	3	(0.7)	55	(1.2)	76	(1.2)
Hyponatraemia	2	(0.5)	5	(1.2)	34	(0.8)	42	(0.7)
Pleural effusion	2	(0.5)	1	(0.2)	66	(1.5)	98	(1.5)

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

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

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

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

[‡] Includes all subjects who received at least one dose of Pembrolizumab and/or Axitinib in KN426.

[††] Includes all subjects who received at least one dose of Sunitinib in KN426.

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

[§] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma) and Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort B4, KN040, KN042, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158, KN164 Cohort A, KN170, KN224 and KN427 Cohort A.

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

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)

Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)

Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)

Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)

Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)

Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)

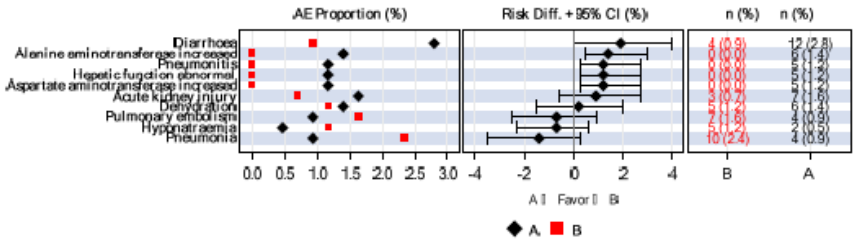
Database cutoff date for HCC (KN224: 15MAY2018)

Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)

Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl; adae]

Figure 14.3-5
Between-Treatment Comparisons in Serious Adverse Events up to 90 Days of Last Dose
Selected Adverse Events (>= 1% Incidence) and Sorted by Risk Difference
(ASaT Population)
A (N=429) vs. B (N=425)



A stands for Pembrolizumab + Axitinib and B stands for Sunitinib.
Database Cutoff Date: 24Aug2018.
Source: [P426V01MK3475: adam-adsl; adae]

When adjusted for exposure, the overall event rate of SAEs was similar for pembrolizumab+axitinib (6.0 events/100 person-months) compared with sunitinib (5.1 events/100 person-months); however differences with higher rates for pembrolizumab+axitinib vs. sunitinib remained for diarrhoea (0.3 vs. 0.1), hepatobiliary disorders (0.4 vs. 0.2), investigations (0.4 vs. 0.1 mainly due to increase of ALT, AST, blood bilirubin, hepatic enzyme, liver function test and transaminases increased), musculoskeletal disorders (0.3 vs. 0.1), nervous system disorders (0.4. vs. 0.2), and renal and urinary disorders (0.4 vs. 0.2 events/100 person-months).

Rates of exposure-adjusted SAEs were highest in the first three months (10 events/100 person-months in both treatment arms) and then decreased subsequently (with higher rates in the pembrolizumab+axitinib arm from 3 months onwards).

Table 4.5.10: Exposure-Adjusted SAEs Up to 90 Days of Last Dose by Observation Period; (Including Multiple Occurrences of Events); (Incidence > 0% in One or More Treatment Groups) Excerpt

	Event Count and Rate (Events/100 person-months) †							
	Pembrolizumab + Axitinib				Sunitinib			
Observation period of drug exposure	0-3 months	3-6 months	6-12 months	Beyond 12 months	0-3 months	3-6 months	6-12 months	Beyond 12 months
Number of subjects exposed‡	429	400	349	187	425	375	295	126
Total exposure§ in person-months	1261.3	1121.4	1624.1	760.1	1219.6	966.2	1237.1	501.8
Total events (rate)	129 (10.2)	59 (5.3)	73 (4.5)	23 (3.0)	123 (10.1)	38 (3.9)	32 (2.6)	8 (1.6)

KN427 Cohort A (Pembrolizumab monotherapy)

Table 14.3-20
Subjects With Serious Drug-Related Adverse Events Up to 90 Days of Last Dose
(Incidence > 0%)
By Body System or Organ Class and Preferred Term
Cohort A: ccRCC
(ASaT Population)

	Cohort A	
	n	(%)
Subjects in population	110	
with one or more serious drug-related adverse events	20	(18.2)
with no serious drug-related adverse events	90	(81.8)
Blood and lymphatic system disorders	**1**	**(0.9)**
Lymphadenopathy	1	(0.9)
Endocrine disorders	**2**	**(1.8)**
Adrenal insufficiency	1	(0.9)
Secondary adrenocortical insufficiency	1	(0.9)
Gastrointestinal disorders	**6**	**(5.5)**
Colitis	3	(2.7)
Diarrhoea	3	(2.7)
General disorders and administration site conditions	**2**	**(1.8)**
Asthenia	1	(0.9)
Pyrexia	1	(0.9)
Hepatobiliary disorders	**2**	**(1.8)**
Hepatitis	2	(1.8)
Immune system disorders	**1**	**(0.9)**
Contrast media allergy	1	(0.9)
Metabolism and nutrition disorders	**4**	**(3.6)**
Hyperglycaemia	1	(0.9)
Hyponatraemia	1	(0.9)
Hypophosphataemia	1	(0.9)
Type 1 diabetes mellitus	1	(0.9)
Musculoskeletal and connective tissue disorders	**1**	**(0.9)**
Muscular weakness	1	(0.9)
Nervous system disorders	**1**	**(0.9)**
Nervous system disorders	**1**	**(0.9)**
Myelopathy	1	(0.9)
Neuropathy peripheral	1	(0.9)
Respiratory, thoracic and mediastinal disorders	**4**	**(3.6)**
Pneumonitis	2	(1.8)
Atelectasis	1	(0.9)
Pulmonary embolism	1	(0.9)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence meets the incidence criterion in the report title, after rounding.
MedDRA version used is 21.0.
Database Cutoff Date: 07Sep2018

Source: [P427V01MK3475: adam-adsl; adae]

Study A4061051 (Axitinib monotherapy)

Table 51. Summary of Serious Adverse Events by Treatm Organ Class, and Preferred Term Experienced Causalities); Safety Analysis Set

System Organ Class Preferred Term	Axitinib N=189	
	n (%)	No. of Events
Any serious AE	64 (33.9)	104
Cardiac disorders		
Acute myocardial infarction	0	0
Cardiac arrest	3 (1.6)	4
Cardio-respiratory arrest	2 (1.1)	2
Gastrointestinal disorders		
Abdominal pain	1 (0.5)	1
Diarrhea	5 (2.6)	5
Nausea	1 (0.5)	1
Rectal hemorrhage	2 (1.1)	2
General disorders and administration site conditions		
Asthenia	2 (1.1)	2
Chest pain	2 (1.1)	2
Disease progression	20 (10.6)	20
Infections and infestations		
Pneumonia	2 (1.1)	2
Urinary tract infection	2 (1.1)	2
Metabolism and nutrition disorders		
Dehydration	1 (0.5)	2
Musculoskeletal and connective tissue disorder		
Pathological fracture	1 (0.5)	1
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Renal cancer metastatic	2 (1.1)	2
Nervous system disorders		
Cerebral ischemia	2 (1.1)	2
Respiratory, thoracic and mediastinal disorders		
Hemoptysis	1 (0.5)	1
Pleural effusion	3 (1.6)	3

Source: Table 14.3.2.2a

Drug-related SAEs

Table 5.3.5.3.3-rcc1: 18

Subjects With Drug-related Serious Adverse Events Up to 90 Days of Last Dose
(Incidence ≥ 1% in One or More Treatment Groups)
By Decreasing Frequency of Preferred Term
(ASaT Population)

	KN426 Data for Pembrolizumab + Axitinib‖		KN426 Sunitinib††		Reference Safety Dataset for Pembrolizumab Monotherapy¶		Cumulative Running Safety Dataset for Pembrolizumab Monotherapy§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	429		425		4,439		6,436	
with one or more adverse events	102	(23.8)	60	(14.1)	464	(10.5)	720	(11.2)
with no adverse events	327	(76.2)	365	(85.9)	3,975	(89.5)	5,716	(88.8)
Diarrhoea	8	(1.9)	3	(0.7)	30	(0.7)	43	(0.7)
Alanine aminotransferase increased	6	(1.4)	0	(0.0)	8	(0.2)	15	(0.2)
Aspartate aminotransferase increased	5	(1.2)	0	(0.0)	8	(0.2)	20	(0.3)
Pneumonitis	5	(1.2)	0	(0.0)	74	(1.7)	113	(1.8)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days following the last dose and serious adverse events up to 90 days following the last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
‖ Includes all subjects who received at least one dose of Pembrolizumab and/or Axitinib in KN426.
†† Includes all subjects who received at least one dose of Sunitinib in KN426.
¶ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN045, KN052, KN055 and KN087.
§ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma) and Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort B4, KN040, KN042, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158, KN164 Cohort A, KN170, KN224 and KN427 Cohort A.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)
Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)
Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)
Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)
Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)
Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)
Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)
Database cutoff date for HCC (KN224: 15MAY2018)
Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)
Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl; adae]

In the pembrolizumab+axitinib arm, aside from *Diarrhoea*, *ALT increased, AST increased,* and *Pneumonitis* (see table above), also *Colitis* (3 subjects), *Hepatic function abnormal* (4 subjects), *Hepatitis* (3 subjects), *Hepatocellular injury* (3 subjects), *Cerebrovascular accident* (3 subjects), *Myasthenia gravis* (4 subjects), *Acute kidney injury* (4 subjects), *Pulmonary embolism* (3 subjects), *Dehydration* (3 subjects) were recorded.

Overall, drug-related SAEs with PTs related to *Hepatobiliar disorders* were reported in a total of 31 subjects (7.2%)*: ALT increased* (6 subjects)*, AST increased* (5 subjects)*, Hepatic function abnormal* (4 subjects), *Hepatitis* (3 subjects), *Hepatocellular injury* (3 subjects), *Hepatic enzyme increased* (2 subjects), *Liver function test increased* (2 subjects), *Transaminases increased* (2 subjects), *Autoimmune hepatitis* (1 subject), *Blood bilirubin increased* (1 subject), *Hepatotoxicity* (1 subject), *Immune mediated hepatitis* (1 subject)

Deaths Due to AEs

Table 4.5.12: Subjects With AEs Resulting in Death Up to 90 Days of Last Dose (Excerpt Incidence >0 in Pembrolizumab + Axitinib Group)

	KN426 Data for Pembrolizumab + Axitinib‖		KN426 Sunitinib††		Reference Safety Dataset for Pembrolizumab Monotherapy¶		Cumulative Running Safety Dataset for Pembrolizumab Monotherapy§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	429		425		4,439		6,436	
with one or more adverse events	11	(2.6)	15	(3.5)	211	(4.8)	329	(5.1)
with no adverse events	418	(97.4)	410	(96.5)	4,228	(95.2)	6,107	(94.9)
Cardiac arrest	1	(0.2)	1	(0.2)	7	(0.2)	11	(0.2)
Death	1	(0.2)	1	(0.2)	30	(0.7)	46	(0.7)
Myasthenia gravis	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Myocarditis	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Necrotising fasciitis	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Plasma cell myeloma	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonitis	1	(0.2)	0	(0.0)	6	(0.1)	8	(0.1)
Pulmonary embolism	1	(0.2)	0	(0.0)	4	(0.1)	12	(0.2)
Pulmonary thrombosis	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Respiratory failure	1	(0.2)	0	(0.0)	14	(0.3)	18	(0.3)
Sudden cardiac death	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)

Table 14.3-32
Subjects With Adverse Events Resulting in Death By Decreasing Incidence
(Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab + Axitinib		Sunitinib	
	n	(%)	n	(%)
Subjects in population	429		425	
with one or more adverse events	11	(2.6)	15	(3.5)
with no adverse events	418	(97.4)	410	(96.5)
Cardiac arrest	1	(0.2)	1	(0.2)
Death	1	(0.2)	1	(0.2)
Myasthenia gravis	1	(0.2)	0	(0.0)
Myocarditis	1	(0.2)	0	(0.0)
Necrotising fasciitis	1	(0.2)	0	(0.0)
Plasma cell myeloma	1	(0.2)	0	(0.0)
Pneumonitis	1	(0.2)	0	(0.0)
Pulmonary embolism	1	(0.2)	0	(0.0)
Pulmonary thrombosis	1	(0.2)	0	(0.0)
Respiratory failure	1	(0.2)	0	(0.0)
Sudden cardiac death	1	(0.2)	0	(0.0)
Acute myocardial infarction	0	(0.0)	1	(0.2)
Cardiac amyloidosis	0	(0.0)	1	(0.2)
Cardiac failure chronic	0	(0.0)	1	(0.2)
Gastric haemorrhage	0	(0.0)	1	(0.2)
Gastrointestinal haemorrhage	0	(0.0)	1	(0.2)
Haemorrhage intracranial	0	(0.0)	1	(0.2)
Hepatitis fulminant	0	(0.0)	1	(0.2)
Malignant neoplasm progression	0	(0.0)	1	(0.2)
Pneumonia	0	(0.0)	3	(0.7)
Sepsis	0	(0.0)	1	(0.2)
Sudden death	0	(0.0)	1	(0.2)

Urinary tract infection	0	(0.0)	1	(0.2)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
The adverse events are ordered decreasingly by the incidence in the first column.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adae]

Table 14.3-34
Subjects With Drug-Related Adverse Events Resulting in Death By Decreasing Incidence
(Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab + Axitinib		Sunitinib	
	n	(%)	n	(%)
Subjects in population	429		425	
with one or more adverse events	4	(0.9)	7	(1.6)
with no adverse events	425	(99.1)	418	(98.4)
Myasthenia gravis	1	(0.2)	0	(0.0)
Myocarditis	1	(0.2)	0	(0.0)
Necrotising fasciitis	1	(0.2)	0	(0.0)
Pneumonitis	1	(0.2)	0	(0.0)
Acute myocardial infarction	0	(0.0)	1	(0.2)
Cardiac arrest	0	(0.0)	1	(0.2)
Gastrointestinal haemorrhage	0	(0.0)	1	(0.2)
Haemorrhage intracranial	0	(0.0)	1	(0.2)
Hepatitis fulminant	0	(0.0)	1	(0.2)
Malignant neoplasm progression	0	(0.0)	1	(0.2)
Pneumonia	0	(0.0)	1	(0.2)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
The adverse events are ordered decreasingly by the incidence in the first column.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adae]

Narratives were provided for all the 11 subjects with AEs leading to death up to 90 days after last dose that occurred in the pembrolizumab-axitinib arm of KN426. Based on the information provided (data not shown), in 6 out of 11 patients experienced also Hepatic AE or Hepatic injury during treatment exposure (Grade 4 in 1 case, Grade 3 in 4 cases and Grade 1 in the remaining case).

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-related events considered by the Sponsor to be causally related to pembrolizumab. Each AEOSI represents a single medical concept (e.g., immune-related hypothyroidism) and is comprised of multiple PTs (hypothyroidism, hypothyroidism, myxoedema, myxoedema coma, primary hypothyroidism). When pembrolizumab is combined with other drugs, the other drug(s) in the combination may have an AE profile whose ADRs overlap with particular PTs contained in 1 or more AEOSI categories (e.g., axitinib is causally associated with hypothyroidism).

Under these circumstances, those AEs reported using these overlapping PTs may not always be immune-mediated. Furthermore, an active control (eg, sunitinib) may have an AE profile that includes ADRs whose PTs overlap with PTs contained in 1 or more AEOSI categories. Unless the control drug(s) are immunomodulatory agents, these ADRs, although reported using PTs that overlap with some PTs contained in the AEOSI categories, are not immune-related.

Table 5.3.5.3.3-rcc1: 36

Adverse Event Summary
for AEOSI
(ASaT Population)

	KN426 Data for Pembrolizumab + Axitinib‖		KN426 Sunitinib††		Reference Safety Dataset for Pembrolizumab Monotherapy¶		Cumulative Running Safety Dataset for Pembrolizumab Monotherapy§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	429		425		4,439		6,436	
with one or more adverse events	220	(51.3)	154	(36.2)	1,007	(22.7)	1,535	(23.9)
with no adverse event	209	(48.7)	271	(63.8)	3,432	(77.3)	4,901	(76.1)
with drug-related† adverse events	202	(47.1)	137	(32.2)	860	(19.4)	1,341	(20.8)
with toxicity grade 3-5 adverse events	46	(10.7)	8	(1.9)	255	(5.7)	395	(6.1)
with toxicity grade 3-5 drug-related adverse events	38	(8.9)	5	(1.2)	217	(4.9)	346	(5.4)
with non-serious adverse events	200	(46.6)	150	(35.3)	827	(18.6)	1,279	(19.9)
with serious adverse events	42	(9.8)	6	(1.4)	256	(5.8)	393	(6.1)
with serious drug-related adverse events	34	(7.9)	5	(1.2)	223	(5.0)	349	(5.4)
with any dose modification‡ due to an adverse event	73	(17.0)	13	(3.1)	346	(7.8)	546	(8.5)
Pembrolizumab dose modification	63	(14.7)	0	(0.0)	346	(7.8)	546	(8.5)
all regimen components dose modification	46	(10.7)	13	(3.1)	346	(7.8)	546	(8.5)
who died	3	(0.7)	1	(0.2)	9	(0.2)	11	(0.2)
who died due to a drug-related adverse event	3	(0.7)	1	(0.2)	9	(0.2)	11	(0.2)
discontinued any drug due to an adverse event	26	(6.1)	4	(0.9)	142	(3.2)	230	(3.6)
discontinued Pembrolizumab	23	(5.4)	0	(0.0)	142	(3.2)	230	(3.6)
discontinued all regimen components	9	(2.1)	4	(0.9)	142	(3.2)	230	(3.6)
discontinued any drug due to a drug-related adverse event	23	(5.4)	4	(0.9)	140	(3.2)	228	(3.5)
discontinued Pembrolizumab	21	(4.9)	0	(0.0)	140	(3.2)	228	(3.5)
discontinued all regimen components	8	(1.9)	4	(0.9)	140	(3.2)	228	(3.5)
discontinued any drug due to a serious adverse event	22	(5.1)	3	(0.7)	109	(2.5)	159	(2.5)
discontinued Pembrolizumab	19	(4.4)	0	(0.0)	109	(2.5)	159	(2.5)
discontinued all regimen components	8	(1.9)	3	(0.7)	109	(2.5)	159	(2.5)
discontinued any drug due to a serious drug-related adverse event	19	(4.4)	3	(0.7)	107	(2.4)	157	(2.4)
discontinued Pembrolizumab	17	(4.0)	0	(0.0)	107	(2.4)	157	(2.4)
discontinued all regimen components	7	(1.6)	3	(0.7)	107	(2.4)	157	(2.4)

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

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

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

‖ Includes all subjects who received at least one dose of Pembrolizumab and/or Axitinib in KN426.

†† Includes all subjects who received at least one dose of Sunitinib in KN426.

¶ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN045, KN052, KN055 and KN087.

§ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma) and Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort B4, KN040, KN042, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158, KN164 Cohort A, KN170, KN224 and KN427 Cohort A.

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

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)

Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)

Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)

Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)

Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)

Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)

Database cutoff date for HCC (KN224: 15MAY2018)

Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)

Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl; adae]

Table 5.3.5.3.3-rcc1: 37

Subjects With Adverse Events of Special Interest (AEOSI)
(Incidence > 0% in One or More Treatment Groups)
By AEOSI Category and Preferred Term
(ASaT Population)

	KN426 Data for Pembrolizumab + Axitinib‖		KN426 Sunitinib††		Reference Safety Dataset for Pembrolizumab Monotherapy¶		Cumulative Running Safety Dataset for Pembrolizumab Monotherapy‖	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	429		425		4,439		6,436	
with one or more adverse events	220	(51.3)	154	(36.2)	1,007	(22.7)	1,535	(23.9)
with no adverse events	209	(48.7)	271	(63.8)	3,432	(77.3)	4,901	(76.1)
Adrenal Insufficiency	**13**	**(3.0)**	**1**	**(0.2)**	**34**	**(0.8)**	**51**	**(0.8)**
Adrenal insufficiency	12	(2.8)	1	(0.2)	32	(0.7)	47	(0.7)
Secondary adrenocortical insufficiency	1	(0.2)	0	(0.0)	1	(0.0)	2	(0.0)
Adrenocortical insufficiency acute	0	(0.0)	0	(0.0)	1	(0.0)	2	(0.0)
Colitis	**11**	**(2.6)**	**3**	**(0.7)**	**79**	**(1.8)**	**125**	**(1.9)**
Colitis	8	(1.9)	1	(0.2)	73	(1.6)	109	(1.7)
Enterocolitis	2	(0.5)	2	(0.5)	5	(0.1)	8	(0.1)
Enterocolitis haemorrhagic	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Autoimmune colitis	0	(0.0)	0	(0.0)	1	(0.0)	7	(0.1)
Colitis microscopic	0	(0.0)	0	(0.0)	2	(0.0)	4	(0.1)
Encephalitis	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.0)**	**2**	**(0.0)**
Encephalitis	0	(0.0)	0	(0.0)	1	(0.0)	2	(0.0)
Guillain-Barre Syndrome	**0**	**(0.0)**	**0**	**(0.0)**	**4**	**(0.1)**	**5**	**(0.1)**
Axonal neuropathy	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Demyelinating polyneuropathy	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Guillain-Barre syndrome	0	(0.0)	0	(0.0)	2	(0.0)	3	(0.0)
Hepatitis	**12**	**(2.8)**	**2**	**(0.5)**	**30**	**(0.7)**	**52**	**(0.8)**
Hepatitis	7	(1.6)	1	(0.2)	13	(0.3)	25	(0.4)
Autoimmune hepatitis	3	(0.7)	0	(0.0)	14	(0.3)	21	(0.3)
Drug-induced liver injury	1	(0.2)	0	(0.0)	4	(0.1)	5	(0.1)
Immune-mediated hepatitis	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)
Hepatitis acute	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Hepatitis fulminant	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
Hyperthyroidism	**55**	**(12.8)**	**16**	**(3.8)**	**145**	**(3.3)**	**272**	**(4.2)**
Hyperthyroidism	55	(12.8)	16	(3.8)	145	(3.3)	272	(4.2)
Hypophysitis	**5**	**(1.2)**	**0**	**(0.0)**	**21**	**(0.5)**	**36**	**(0.6)**
Hypophysitis	5	(1.2)	0	(0.0)	12	(0.3)	22	(0.3)
Hypopituitarism	0	(0.0)	0	(0.0)	9	(0.2)	14	(0.2)
Hypothyroidism	**152**	**(35.4)**	**134**	**(31.5)**	**440**	**(9.9)**	**667**	**(10.4)**
Hypothyroidism	152	(35.4)	134	(31.5)	439	(9.9)	666	(10.3)
Myxoedema	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Primary hypothyroidism	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Infusion Reactions	**7**	**(1.6)**	**4**	**(0.9)**	**113**	**(2.5)**	**142**	**(2.2)**
Hypersensitivity	3	(0.7)	2	(0.5)	37	(0.8)	43	(0.7)
Infusion related reaction	2	(0.5)	0	(0.0)	48	(1.1)	63	(1.0)
Anaphylactic reaction	1	(0.2)	2	(0.5)	5	(0.1)	9	(0.1)
Drug hypersensitivity	1	(0.2)	0	(0.0)	16	(0.4)	20	(0.3)
Anaphylactoid reaction	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Cytokine release syndrome	0	(0.0)	0	(0.0)	8	(0.2)	8	(0.1)
Myasthenic Syndrome	**4**	**(0.9)**	**0**	**(0.0)**	**2**	**(0.0)**	**4**	**(0.1)**
Myasthenia gravis	4	(0.9)	0	(0.0)	0	(0.0)	1	(0.0)
Myasthenic syndrome	0	(0.0)	0	(0.0)	2	(0.0)	3	(0.0)
Myocarditis	**2**	**(0.5)**	**0**	**(0.0)**	**3**	**(0.1)**	**6**	**(0.1)**
Myocarditis	2	(0.5)	0	(0.0)	3	(0.1)	6	(0.1)
Myositis	**4**	**(0.9)**	**0**	**(0.0)**	**18**	**(0.4)**	**26**	**(0.4)**
Myositis	4	(0.9)	0	(0.0)	13	(0.3)	20	(0.3)
Myopathy	0	(0.0)	0	(0.0)	4	(0.1)	4	(0.1)
Rhabdomyolysis	0	(0.0)	0	(0.0)	1	(0.0)	3	(0.0)
Nephritis	**6**	**(1.4)**	**1**	**(0.2)**	**15**	**(0.3)**	**21**	**(0.3)**
Nephritis	4	(0.9)	0	(0.0)	1	(0.0)	4	(0.1)
Autoimmune nephritis	1	(0.2)	0	(0.0)	2	(0.0)	3	(0.0)
Tubulointerstitial nephritis	1	(0.2)	0	(0.0)	7	(0.2)	8	(0.1)
Acute kidney injury	0	(0.0)	0	(0.0)	2	(0.0)	2	(0.0)
Glomerulonephritis membranous	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Nephrotic syndrome	0	(0.0)	1	(0.2)	1	(0.0)	1	(0.0)
Renal failure	0	(0.0)	0	(0.0)	2	(0.0)	2	(0.0)
Pancreatitis	**2**	**(0.5)**	**2**	**(0.5)**	**11**	**(0.2)**	**21**	**(0.3)**
Pancreatitis	2	(0.5)	2	(0.5)	9	(0.2)	18	(0.3)
Autoimmune pancreatitis	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Pancreatitis acute	0	(0.0)	0	(0.0)	1	(0.0)	3	(0.0)

Pneumonitis	**12**	**(2.8)**	**1**	**(0.2)**	**166**	**(3.7)**	**254**	**(3.9)**
Pneumonitis	11	(2.6)	1	(0.2)	154	(3.5)	233	(3.6)
Interstitial lung disease	1	(0.2)	0	(0.0)	13	(0.3)	22	(0.3)
Organising pneumonia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Sarcoidosis	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.1)**	**11**	**(0.2)**
Sarcoidosis	0	(0.0)	0	(0.0)	3	(0.1)	11	(0.2)
Severe Skin Reactions	**8**	**(1.9)**	**6**	**(1.4)**	**63**	**(1.4)**	**96**	**(1.5)**
Exfoliative rash	2	(0.5)	1	(0.2)	2	(0.0)	2	(0.0)
Rash maculo-papular	2	(0.5)	0	(0.0)	10	(0.2)	21	(0.3)
Dermatitis bullous	1	(0.2)	4	(0.9)	5	(0.1)	6	(0.1)
Pruritus	1	(0.2)	0	(0.0)	6	(0.1)	9	(0.1)
Rash	1	(0.2)	2	(0.5)	18	(0.4)	27	(0.4)
Rash generalised	1	(0.2)	0	(0.0)	3	(0.1)	5	(0.1)
Dermatitis exfoliative	0	(0.0)	0	(0.0)	3	(0.1)	5	(0.1)
Dermatitis exfoliative generalised	0	(0.0)	0	(0.0)	2	(0.0)	2	(0.0)
Erythema multiforme	0	(0.0)	0	(0.0)	3	(0.1)	6	(0.1)
Pemphigoid	0	(0.0)	0	(0.0)	3	(0.1)	5	(0.1)
Pemphigus	0	(0.0)	0	(0.0)	1	(0.0)	2	(0.0)
Pruritus generalised	0	(0.0)	0	(0.0)	1	(0.0)	2	(0.0)
Pruritus genital	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Rash erythematous	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Rash pruritic	0	(0.0)	0	(0.0)	1	(0.0)	2	(0.0)
Rash pustular	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Skin necrosis	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Stevens-Johnson syndrome	0	(0.0)	0	(0.0)	3	(0.1)	3	(0.0)
Toxic skin eruption	0	(0.0)	0	(0.0)	2	(0.0)	2	(0.0)
Thyroiditis	**12**	**(2.8)**	**2**	**(0.5)**	**30**	**(0.7)**	**65**	**(1.0)**
Thyroiditis	11	(2.6)	1	(0.2)	22	(0.5)	48	(0.7)
Autoimmune thyroiditis	1	(0.2)	0	(0.0)	7	(0.2)	14	(0.2)
Thyroid disorder	0	(0.0)	1	(0.2)	1	(0.0)	5	(0.1)
Type 1 Diabetes Mellitus	**1**	**(0.2)**	**0**	**(0.0)**	**15**	**(0.3)**	**22**	**(0.3)**
Diabetic ketoacidosis	1	(0.2)	0	(0.0)	7	(0.2)	9	(0.1)
Type 1 diabetes mellitus	0	(0.0)	0	(0.0)	11	(0.2)	18	(0.3)
Uveitis	**2**	**(0.5)**	**0**	**(0.0)**	**17**	**(0.4)**	**22**	**(0.3)**

Uveitis	**2**	**(0.5)**	**0**	**(0.0)**	**17**	**(0.4)**	**22**	**(0.3)**
Uveitis	2	(0.5)	0	(0.0)	11	(0.2)	15	(0.2)
Iridocyclitis	0	(0.0)	0	(0.0)	3	(0.1)	4	(0.1)
Iritis	0	(0.0)	0	(0.0)	3	(0.1)	3	(0.0)

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

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

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

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

‡ Includes all subjects who received at least one dose of Pembrolizumab and/or Axitinib in KN426.

†† Includes all subjects who received at least one dose of Sunitinib in KN426.

¶ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN045, KN052, KN055 and KN087.

§ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma) and Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort B4, KN040, KN042, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158, KN164 Cohort A, KN170, KN224 and KN427 Cohort A.

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

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)

Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)

Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)

Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)

Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)

Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)

Database cutoff date for HCC (KN224: 15MAY2018)

Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)

Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl; adae]

Table 5.3.5.3.3-rcc1: 118

Subjects With Adverse Events of Special Interest (AEOSI) by Maximum Toxicity Grade
(Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	KN426 Data for Pembrolizumab + Axitinib‖		KN426 Sunitinib††		Reference Safety Dataset for Pembrolizumab Monotherapy‡		Cumulative Running Safety Dataset for Pembrolizumab Monotherapy§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	429		425		4,439		6,436	
with one or more adverse events	220	(51.3)	154	(36.2)	1,007	(22.7)	1,535	(23.9)
Grade 1	58	(13.5)	64	(15.1)	259	(5.8)	372	(5.8)
Grade 2	116	(27.0)	82	(19.3)	493	(11.1)	768	(11.9)
Grade 3	36	(8.4)	7	(1.6)	217	(4.9)	341	(5.3)
Grade 4	7	(1.6)	0	(0.0)	29	(0.7)	43	(0.7)
Grade 5	3	(0.7)	1	(0.2)	9	(0.2)	11	(0.2)
with no adverse events	209	(48.7)	271	(63.8)	3,432	(77.3)	4,901	(76.1)

Table 14.3-60
Summary of Outcome for Subjects With AEOSI
(Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

		Pembrolizumab + Axitinib		Sunitinib	
	Outcome	n	(%)	n	(%)
Subjects in population		429		425	
With one or more AEOSI	**Overall**	**220**	**(51.3)**	**154**	**(36.2)**
	Fatal	3	(1.4)	1	(0.6)
	Not Resolved	118	(53.6)	80	(51.9)
	Resolving	27	(12.3)	25	(16.2)
	Unknown	0	(0.0)	0	(0.0)
	Sequelae	7	(3.2)	1	(0.6)
	Resolved	65	(29.5)	47	(30.5)
Hypothyroidism	**Overall**	**152**	**(35.4)**	**134**	**(31.5)**
	Fatal	0	(0.0)	0	(0.0)
	Not Resolved	95	(62.5)	72	(53.7)
	Resolving	19	(12.5)	21	(15.7)
	Unknown	0	(0.0)	0	(0.0)
	Sequelae	0	(0.0)	0	(0.0)
	Resolved	38	(25.0)	41	(30.6)
Hyperthyroidism	**Overall**	**55**	**(12.8)**	**16**	**(3.8)**
	Fatal	0	(0.0)	0	(0.0)
	Not Resolved	7	(12.7)	4	(25.0)
	Resolving	1	(1.8)	4	(25.0)
	Unknown	0	(0.0)	0	(0.0)
	Sequelae	0	(0.0)	0	(0.0)
	Resolved	47	(85.5)	8	(50.0)
Adrenal Insufficiency	**Overall**	**13**	**(3.0)**	**1**	**(0.2)**
	Fatal	0	(0.0)	0	(0.0)
	Not Resolved	4	(30.8)	1	(100.0)
	Resolving	2	(15.4)	0	(0.0)
	Unknown	0	(0.0)	0	(0.0)
	Sequelae	5	(38.5)	0	(0.0)

Adrenal Insufficiency	Resolved	2	(15.4)	0	(0.0)
Colitis	**Overall**	**11**	**(2.6)**	**3**	**(0.7)**
	Fatal	0	(0.0)	0	(0.0)
	Not Resolved	1	(9.1)	2	(66.7)
	Resolving	1	(9.1)	0	(0.0)
	Unknown	0	(0.0)	0	(0.0)
	Sequelae	1	(9.1)	0	(0.0)
	Resolved	8	(72.7)	1	(33.3)
Hepatitis	**Overall**	**12**	**(2.8)**	**2**	**(0.5)**
	Fatal	0	(0.0)	1	(50.0)
	Not Resolved	0	(0.0)	0	(0.0)
	Resolving	2	(16.7)	0	(0.0)
	Unknown	0	(0.0)	0	(0.0)
	Sequelae	1	(8.3)	0	(0.0)
	Resolved	9	(75.0)	1	(50.0)
Severe Skin Reactions	**Overall**	**8**	**(1.9)**	**6**	**(1.4)**
	Fatal	0	(0.0)	0	(0.0)
	Not Resolved	1	(12.5)	2	(33.3)
	Resolving	1	(12.5)	0	(0.0)
	Unknown	0	(0.0)	0	(0.0)
	Sequelae	0	(0.0)	1	(16.7)
	Resolved	6	(75.0)	3	(50.0)
Thyroiditis	**Overall**	**12**	**(2.8)**	**2**	**(0.5)**
	Fatal	0	(0.0)	0	(0.0)
	Not Resolved	7	(58.3)	0	(0.0)
	Resolving	1	(8.3)	0	(0.0)
	Unknown	0	(0.0)	0	(0.0)
	Sequelae	0	(0.0)	0	(0.0)
Thyroiditis	Resolved	4	(33.3)	2	(100.0)
Pneumonitis	**Overall**	**12**	**(2.8)**	**1**	**(0.2)**
	Fatal	1	(8.3)	0	(0.0)
	Not Resolved	2	(16.7)	1	(100.0)
	Resolving	2	(16.7)	0	(0.0)
	Unknown	0	(0.0)	0	(0.0)
	Sequelae	0	(0.0)	0	(0.0)
	Resolved	7	(58.3)	0	(0.0)
Infusion Reactions	**Overall**	**7**	**(1.6)**	**4**	**(0.9)**
	Fatal	0	(0.0)	0	(0.0)
	Not Resolved	1	(14.3)	0	(0.0)
	Resolving	0	(0.0)	0	(0.0)
	Unknown	0	(0.0)	0	(0.0)
	Sequelae	0	(0.0)	0	(0.0)
	Resolved	6	(85.7)	4	(100.0)
Nephritis	**Overall**	**6**	**(1.4)**	**1**	**(0.2)**
	Fatal	0	(0.0)	0	(0.0)
	Not Resolved	2	(33.3)	1	(100.0)
	Resolving	0	(0.0)	0	(0.0)
	Unknown	0	(0.0)	0	(0.0)
	Sequelae	0	(0.0)	0	(0.0)
	Resolved	4	(66.7)	0	(0.0)
Hypophysitis	**Overall**	**5**	**(1.2)**	**0**	**(0.0)**
	Fatal	0	(0.0)	0	(0.0)
	Not Resolved	2	(40.0)	0	(0.0)
	Resolving	1	(20.0)	0	(0.0)
	Unknown	0	(0.0)	0	(0.0)
	Sequelae	0	(0.0)	0	(0.0)

Hypophysitis	Resolved	2	(40.0)	0	(0.0)
Myasthenic Syndrome	**Overall**	**4**	**(0.9)**	**0**	**(0.0)**
	Fatal	1	(25.0)	0	(0.0)
	Not Resolved	1	(25.0)	0	(0.0)
	Resolving	0	(0.0)	0	(0.0)
	Unknown	0	(0.0)	0	(0.0)
	Sequelae	2	(50.0)	0	(0.0)
	Resolved	0	(0.0)	0	(0.0)
Myositis	**Overall**	**4**	**(0.9)**	**0**	**(0.0)**
	Fatal	0	(0.0)	0	(0.0)
	Not Resolved	1	(25.0)	0	(0.0)
	Resolving	0	(0.0)	0	(0.0)
	Unknown	0	(0.0)	0	(0.0)
	Sequelae	1	(25.0)	0	(0.0)
	Resolved	2	(50.0)	0	(0.0)
Pancreatitis	**Overall**	**2**	**(0.5)**	**2**	**(0.5)**
	Fatal	0	(0.0)	0	(0.0)
	Not Resolved	1	(50.0)	0	(0.0)
	Resolving	0	(0.0)	0	(0.0)
	Unknown	0	(0.0)	0	(0.0)
	Sequelae	1	(50.0)	0	(0.0)
	Resolved	0	(0.0)	2	(100.0)
Myocarditis	**Overall**	**2**	**(0.5)**	**0**	**(0.0)**
	Fatal	1	(50.0)	0	(0.0)
	Not Resolved	1	(50.0)	0	(0.0)
	Resolving	0	(0.0)	0	(0.0)
	Unknown	0	(0.0)	0	(0.0)
	Sequelae	0	(0.0)	0	(0.0)
Myocarditis	Resolved	0	(0.0)	0	(0.0)
Uveitis	**Overall**	**2**	**(0.5)**	**0**	**(0.0)**
	Fatal	0	(0.0)	0	(0.0)
	Not Resolved	1	(50.0)	0	(0.0)
	Resolving	0	(0.0)	0	(0.0)
	Unknown	0	(0.0)	0	(0.0)
	Sequelae	0	(0.0)	0	(0.0)
	Resolved	1	(50.0)	0	(0.0)
Type 1 Diabetes Mellitus	**Overall**	**1**	**(0.2)**	**0**	**(0.0)**
	Fatal	0	(0.0)	0	(0.0)
	Not Resolved	0	(0.0)	0	(0.0)
	Resolving	0	(0.0)	0	(0.0)
	Unknown	0	(0.0)	0	(0.0)
	Sequelae	1	(100.0)	0	(0.0)
	Resolved	0	(0.0)	0	(0.0)

Every subject is counted once for each specific AEOSI according to the worst outcome; the ordering of the outcomes is as follows: Fatal>Not Resolved>Resolving>Unknown>Sequelae>Resolved.

"Subjects in population" is used for percentage calculation for the Overall row in each section. Within each section, the overall total is used for percentage calculation for each outcome.

Outcome: Resolved = RECOVERED/RESOLVED, Resolving = RECOVERING/RESOLVING, Sequelae = RECOVERED/RESOLVED WITH SEQUELAE, Not resolved = NOT RECOVERED/NOT RESOLVED.

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

Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adae]

There were 3 deaths (0.7%) due to AEOSIs in the pembrolizumab + axitinib (myasthenia gravis, myocarditis, and pneumonitis) that were considered by the investigator to be related to pembrolizumab; 1 participant in the sunitinib died due to hepatitis fulminant (0.2%).

Adrenal Insufficiency

Table 5.3.5.3.3-rec1: 38

Adverse Event Summary
AEOSI - Adrenal Insufficiency
(ASaT Population)

	KN426 Data for Pembrolizumab + Axitinib[‖]		KN426 Sunitinib[††]		Reference Safety Dataset for Pembrolizumab Monotherapy[¶]		Cumulative Running Safety Dataset for Pembrolizumab Monotherapy[#]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	429		425		4,439		6,436	
with one or more adverse events	13	(3.0)	1	(0.2)	34	(0.8)	51	(0.8)
with no adverse event	416	(97.0)	424	(99.8)	4,405	(99.2)	6,385	(99.2)
with drug-related[†] adverse events	10	(2.3)	1	(0.2)	24	(0.5)	39	(0.6)
with toxicity grade 3-5 adverse events	3	(0.7)	0	(0.0)	17	(0.4)	25	(0.4)
with toxicity grade 3-5 drug-related adverse events	1	(0.2)	0	(0.0)	11	(0.2)	19	(0.3)
with non-serious adverse events	8	(1.9)	1	(0.2)	21	(0.5)	30	(0.5)
with serious adverse events	5	(1.2)	0	(0.0)	17	(0.4)	25	(0.4)
with serious drug-related adverse events	3	(0.7)	0	(0.0)	12	(0.3)	20	(0.3)
with any dose modification[‡] due to an adverse event	4	(0.9)	0	(0.0)	16	(0.4)	25	(0.4)
Pembrolizumab dose modification	3	(0.7)	0	(0.0)	16	(0.4)	25	(0.4)
all regimen components dose modification	2	(0.5)	0	(0.0)	16	(0.4)	25	(0.4)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to an adverse event	0	(0.0)	0	(0.0)	1	(0.0)	5	(0.1)
discontinued Pembrolizumab	0	(0.0)	0	(0.0)	1	(0.0)	5	(0.1)
discontinued all regimen components	0	(0.0)	0	(0.0)	1	(0.0)	5	(0.1)
discontinued any drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	1	(0.0)	5	(0.1)
discontinued Pembrolizumab	0	(0.0)	0	(0.0)	1	(0.0)	5	(0.1)
discontinued all regimen components	0	(0.0)	0	(0.0)	1	(0.0)	5	(0.1)
discontinued any drug due to a serious adverse event	0	(0.0)	0	(0.0)	1	(0.0)	4	(0.1)
discontinued Pembrolizumab	0	(0.0)	0	(0.0)	1	(0.0)	4	(0.1)
discontinued all regimen components	0	(0.0)	0	(0.0)	1	(0.0)	4	(0.1)
discontinued any drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	1	(0.0)	4	(0.1)
discontinued Pembrolizumab	0	(0.0)	0	(0.0)	1	(0.0)	4	(0.1)
discontinued all regimen components	0	(0.0)	0	(0.0)	1	(0.0)	4	(0.1)

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

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

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

[‖] Includes all subjects who received at least one dose of Pembrolizumab and/or Axitinib in KN426.

[††] Includes all subjects who received at least one dose of Sunitinib in KN426.

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

[#] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma) and Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort B4, KN040, KN042, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158, KN164 Cohort A, KN170, KN224 and KN427 Cohort A.

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

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)

Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)

Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)

Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)

Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)

Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)

Database cutoff date for HCC (KN224: 15MAY2018)

Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)

Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl; adae]

Table 5.3.5.3.3-rec1: 39

Time to Onset and Duration of AEOSI - Adrenal Insufficiency
(ASaT Population)

	KN426 Data for Pembrolizumab + Axitinib[I]		KN426 Sunitinib[II]		Reference Safety Dataset for Pembrolizumab Monotherapy[¶]		Cumulative Running Safety Dataset for Pembrolizumab Monotherapy[ǂ]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	429		425		4439		6436	
Subjects with Adrenal Insufficiency	13	(3.0)	1	(0.2)	34	(0.8)	51	(0.8)
Time to Onset of First Adrenal Insufficiency (days)†								
Mean (Std)	215.8 (148.8)		276.0		180.0 (136.8)		189.1 (132.3)	
Median	168.0		276.0		160.0		162.0	
Range	64 to 491		276 to 276		1 to 539		1 to 539	
Total episodes of Adrenal Insufficiency	13		1		36		53	
Average Episodes per patient	1.00		1.00		1.06		1.04	
Episode duration (days)‡								
Median	204.0		Not reached		Not reached		Not reached	
Range	7 to 417+		379+ to 379+		3 to 696+		3 to 797+	

(%) = Number of subjects with Adrenal Insufficiency / Number of subjects in population.

† Time to onset statistics are based on number of subjects with Adrenal Insufficiency.

‡ From product-limit (Kaplan-Meier) method for censored data. If an adverse event is not resolved at the time of analysis or the subject died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.

+ indicates the AE episode is not recovered/resolved by the time of the cutoff date or date of death.

Std = Standard Deviation.

Grades are based on NCI CTCAE 4.0.

[I] Includes all subjects who received at least one dose of Pembrolizumab and/or Axitinib in KN426.

[II] Includes all subjects who received at least one dose of Sunitinib in KN426.

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

[ǂ] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma) and Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort B4, KN040, KN042, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158, KN164 Cohort A, KN170, KN224 and KN427 Cohort A.

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

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)

Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)

Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)

Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)

Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)

Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)

Database cutoff date for HCC (KN224: 15MAY2018)

Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)

Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl; adae]

In the pembrolizumab+axitinib arm, *Adrenal insufficiency* AEOSI presented after a median of 168 days (range, 64-491) of exposure. An average of 1 episode was reported per patient with a median duration of 204 days. Corticosteroid treatment was given to 92.3% of subjects.

Hepatitis

Table 5.3.5.3.3-rcc1: 54

Adverse Event Summary
AEOSI - Hepatitis
(ASaT Population)

	KN426 Data for Pembrolizumab + Axitinib‖		KN426 Sunitinib††		Reference Safety Dataset for Pembrolizumab Monotherapy¶		Cumulative Running Safety Dataset for Pembrolizumab Monotherapy#	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	429		425		4,439		6,436	
with one or more adverse events	12	(2.8)	2	(0.5)	30	(0.7)	52	(0.8)
with no adverse event	417	(97.2)	423	(99.5)	4,409	(99.3)	6,384	(99.2)
with drug-related† adverse events	10	(2.3)	2	(0.5)	25	(0.6)	41	(0.6)
with toxicity grade 3-5 adverse events	10	(2.3)	1	(0.2)	23	(0.5)	40	(0.6)
with toxicity grade 3-5 drug-related adverse events	9	(2.1)	1	(0.2)	19	(0.4)	32	(0.5)
with non-serious adverse events	5	(1.2)	1	(0.2)	13	(0.3)	23	(0.4)
with serious adverse events	7	(1.6)	1	(0.2)	17	(0.4)	31	(0.5)
with serious drug-related adverse events	6	(1.4)	1	(0.2)	17	(0.4)	27	(0.4)
with any dose modification‡ due to an adverse event	10	(2.3)	1	(0.2)	21	(0.5)	34	(0.5)
Pembrolizumab dose modification	9	(2.1)	0	(0.0)	21	(0.5)	34	(0.5)
all regimen components dose modification	8	(1.9)	1	(0.2)	21	(0.5)	34	(0.5)
who died	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
discontinued any drug due to an adverse event	8	(1.9)	1	(0.2)	9	(0.2)	19	(0.3)
discontinued Pembrolizumab	7	(1.6)	0	(0.0)	9	(0.2)	19	(0.3)
discontinued all regimen components	3	(0.7)	1	(0.2)	9	(0.2)	19	(0.3)
discontinued any drug due to a drug-related adverse event	7	(1.6)	1	(0.2)	9	(0.2)	19	(0.3)
discontinued Pembrolizumab	6	(1.4)	0	(0.0)	9	(0.2)	19	(0.3)
discontinued all regimen components	3	(0.7)	1	(0.2)	9	(0.2)	19	(0.3)
discontinued any drug due to a serious adverse event	6	(1.4)	1	(0.2)	8	(0.2)	14	(0.2)
discontinued Pembrolizumab	5	(1.2)	0	(0.0)	8	(0.2)	14	(0.2)
discontinued all regimen components	2	(0.5)	1	(0.2)	8	(0.2)	14	(0.2)
discontinued any drug due to a serious drug-related adverse event	5	(1.2)	1	(0.2)	8	(0.2)	14	(0.2)
discontinued Pembrolizumab	4	(0.9)	0	(0.0)	8	(0.2)	14	(0.2)
discontinued all regimen components	2	(0.5)	1	(0.2)	8	(0.2)	14	(0.2)

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

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

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

‖ Includes all subjects who received at least one dose of Pembrolizumab and/or Axitinib in KN426.

†† Includes all subjects who received at least one dose of Sunitinib in KN426.

¶ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN045, KN052, KN055 and KN087.

Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma) and Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort B4, KN040, KN042, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158, KN164 Cohort A, KN170, KN224 and KN427 Cohort A.

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

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)

Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)

Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)

Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)

Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)

Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)

Database cutoff date for HCC (KN224: 15MAY2018)

Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)

Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl; adae]

Table 5.3.5.3.3-rcc1: 55

Time to Onset and Duration of AEOSI - Hepatitis
(ASaT Population)

	KN426 Data for Pembrolizumab + Axitinib‖		KN426 Sunitinib††		Reference Safety Dataset for Pembrolizumab Monotherapy¶		Cumulative Running Safety Dataset for Pembrolizumab Monotherapy§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	429		425		4439		6436	
Subjects with Hepatitis	12	(2.8)	2	(0.5)	30	(0.7)	52	(0.8)
Time to Onset of First Hepatitis (days)†								
Mean (Std)	79.8 (71.3)		113.0 (72.1)		99.4 (125.9)		144.9 (145.6)	
Median	54.0		113.0		61.0		108.0	
Range	16 to 252		62 to 164		8 to 651		8 to 651	
Total episodes of Hepatitis	12		4		32		69	
Average Episodes per patient	1.00		2.00		1.07		1.33	
Episode duration (days)‡								
Median	47.0		13.0		46.0		33.0	
Range	7 to 457+		4+ to 43		8 to 635+		1 to 635+	

(%) = Number of subjects with Hepatitis / Number of subjects in population.
† Time to onset statistics are based on number of subjects with Hepatitis.
‡ From product-limit (Kaplan-Meier) method for censored data. If an adverse event is not resolved at the time of analysis or the subject died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.
+ indicates the AE episode is not recovered/resolved by the time of the cutoff date or date of death.
Std = Standard Deviation.
Grades are based on NCI CTCAE 4.0.
‖ Includes all subjects who received at least one dose of Pembrolizumab and/or Axitinib in KN426.
†† Includes all subjects who received at least one dose of Sunitinib in KN426.
¶ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN045, KN052, KN055 and KN087.
§ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma) and Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort B4, KN040, KN042, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158, KN164 Cohort A, KN170, KN224 and KN427 Cohort A.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)
Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)
Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)
Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)
Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)
Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)
Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)
Database cutoff date for HCC (KN224: 15MAY2018)
Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)
Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl; adae]

In the pembrolizub+axitinib arm, median time to *Hepatitis* AEOSI was 54 days (range, 16-252). An average of 1.0 episode was reported per patient with a median duration of 47 days. In 66.7% of subjects concomitant corticosteroids were given; all received high starting dose (≥40 mg/day prednisone or equivalent).

Hyperthyroidism

Table 5.3.5.3.3-rcc1: 58

Adverse Event Summary
AEOSI - Hyperthyroidism
(ASaT Population)

	KN426 Data for Pembrolizumab + Axitinib‖		KN426 Sunitinib††		Reference Safety Dataset for Pembrolizumab Monotherapy¶		Cumulative Running Safety Dataset for Pembrolizumab Monotherapy#	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	429		425		4,439		6,436	
with one or more adverse events	55	(12.8)	16	(3.8)	145	(3.3)	272	(4.2)
with no adverse event	374	(87.2)	409	(96.2)	4,294	(96.7)	6,164	(95.8)
with drug-related† adverse events	52	(12.1)	14	(3.3)	125	(2.8)	243	(3.8)
with toxicity grade 3-5 adverse events	5	(1.2)	0	(0.0)	4	(0.1)	6	(0.1)
with toxicity grade 3-5 drug-related adverse events	4	(0.9)	0	(0.0)	4	(0.1)	6	(0.1)
with non-serious adverse events	53	(12.4)	16	(3.8)	138	(3.1)	263	(4.1)
with serious adverse events	2	(0.5)	0	(0.0)	8	(0.2)	10	(0.2)
with serious drug-related adverse events	1	(0.2)	0	(0.0)	8	(0.2)	10	(0.2)
with any dose modification‡ due to an adverse event	11	(2.6)	0	(0.0)	10	(0.2)	18	(0.3)
Pembrolizumab dose modification	10	(2.3)	0	(0.0)	10	(0.2)	18	(0.3)
all regimen components dose modification	6	(1.4)	0	(0.0)	10	(0.2)	18	(0.3)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to an adverse event	0	(0.0)	0	(0.0)	2	(0.0)	3	(0.0)
discontinued Pembrolizumab	0	(0.0)	0	(0.0)	2	(0.0)	3	(0.0)
discontinued all regimen components	0	(0.0)	0	(0.0)	2	(0.0)	3	(0.0)
discontinued any drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	2	(0.0)	3	(0.0)
discontinued Pembrolizumab	0	(0.0)	0	(0.0)	2	(0.0)	3	(0.0)
discontinued all regimen components	0	(0.0)	0	(0.0)	2	(0.0)	3	(0.0)
discontinued any drug due to a serious adverse event	0	(0.0)	0	(0.0)	2	(0.0)	2	(0.0)
discontinued Pembrolizumab	0	(0.0)	0	(0.0)	2	(0.0)	2	(0.0)
discontinued all regimen components	0	(0.0)	0	(0.0)	2	(0.0)	2	(0.0)
discontinued any drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	2	(0.0)	2	(0.0)
discontinued Pembrolizumab	0	(0.0)	0	(0.0)	2	(0.0)	2	(0.0)
discontinued all regimen components	0	(0.0)	0	(0.0)	2	(0.0)	2	(0.0)

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

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

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

‖ Includes all subjects who received at least one dose of Pembrolizumab and/or Axitinib in KN426.

†† Includes all subjects who received at least one dose of Sunitinib in KN426.

¶ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN045, KN052, KN055 and KN087.

Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma) and Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort B4, KN040, KN042, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158, KN164 Cohort A, KN170, KN224 and KN427 Cohort A.

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

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)

Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)

Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)

Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)

Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)

Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)

Database cutoff date for HCC (KN224: 15MAY2018)

Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)

Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl; adae]

Table 5.3.5.3.3-rcc1: 59

Time to Onset and Duration of AEOSI - Hyperthyroidism
(ASaT Population)

	KN426 Data for Pembrolizumab + Axitinib‖		KN426 Sunitinib††		Reference Safety Dataset for Pembrolizumab Monotherapy¶		Cumulative Running Safety Dataset for Pembrolizumab Monotherapy#	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	429		425		4439		6436	
Subjects with Hyperthyroidism	55	(12.8)	16	(3.8)	145	(3.3)	272	(4.2)
Time to Onset of First Hyperthyroidism (days)†								
Mean (Std)	70.3 (91.9)		166.8 (138.5)		70.1 (98.1)		67.4 (81.8)	
Median	43.0		114.0		43.0		43.0	
Range	11 to 440		29 to 483		1 to 707		1 to 707	
Total episodes of Hyperthyroidism	60		18		155		292	
Average Episodes per patient	1.09		1.13		1.07		1.07	
Episode duration (days)‡								
Median	43.0		85.0		62.0		57.0	
Range	3 to 634		4+ to 578+		10 to 471+		4 to 887+	

(%) = Number of subjects with Hyperthyroidism / Number of subjects in population.
† Time to onset statistics are based on number of subjects with Hyperthyroidism.
‡ From product-limit (Kaplan-Meier) method for censored data. If an adverse event is not resolved at the time of analysis or the subject died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.
+ indicates the AE episode is not recovered/resolved by the time of the cutoff date or date of death.
Std = Standard Deviation.
Grades are based on NCI CTCAE 4.0.
‖ Includes all subjects who received at least one dose of Pembrolizumab and/or Axitinib in KN426.
†† Includes all subjects who received at least one dose of Sunitinib in KN426.
¶ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN045, KN052, KN055 and KN087.
# Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma) and Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort B4, KN040, KN042, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158, KN164 Cohort A, KN170, KN224 and KN427 Cohort A.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)
Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)
Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)
Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)
Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)
Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)
Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)
Database cutoff date for HCC (KN224: 15MAY2018)
Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)
Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl; adae]

In the pembrolizub+axitinib arm, median time to *Hyperthyroidism* AEOSI was 142 days (range, 61-245). An average of 1.1 episodes were reported per patient with a median duration of 43 days. Corticosteroids were given at high doses in 1.7% and low doses in 6.7%.

Hypothyroidism

Table 5.3.5.3.3-rcc1: 66

Adverse Event Summary
AEOSI - Hypothyroidism
(ASaT Population)

	KN426 Data for Pembrolizumab + Axitinib‖		KN426 Sunitinib††		Reference Safety Dataset for Pembrolizumab Monotherapy¶		Cumulative Running Safety Dataset for Pembrolizumab Monotherapy§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	429		425		4,439		6,436	
with one or more adverse events	152	(35.4)	134	(31.5)	440	(9.9)	667	(10.4)
with no adverse event	277	(64.6)	291	(68.5)	3,999	(90.1)	5,769	(89.6)
with drug-related† adverse events	135	(31.5)	119	(28.0)	379	(8.5)	585	(9.1)
with toxicity grade 3-5 adverse events	1	(0.2)	1	(0.2)	7	(0.2)	10	(0.2)
with toxicity grade 3-5 drug-related adverse events	1	(0.2)	0	(0.0)	7	(0.2)	10	(0.2)
with non-serious adverse events	152	(35.4)	133	(31.3)	436	(9.8)	661	(10.3)
with serious adverse events	1	(0.2)	2	(0.5)	5	(0.1)	7	(0.1)
with serious drug-related adverse events	1	(0.2)	1	(0.2)	5	(0.1)	7	(0.1)
with any dose modification‡ due to an adverse event	8	(1.9)	5	(1.2)	27	(0.6)	47	(0.7)
Pembrolizumab dose modification	5	(1.2)	0	(0.0)	27	(0.6)	47	(0.7)
all regimen components dose modification	5	(1.2)	5	(1.2)	27	(0.6)	47	(0.7)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to an adverse event	1	(0.2)	0	(0.0)	1	(0.0)	2	(0.0)
discontinued Pembrolizumab	1	(0.2)	0	(0.0)	1	(0.0)	2	(0.0)
discontinued all regimen components	0	(0.0)	0	(0.0)	1	(0.0)	2	(0.0)
discontinued any drug due to a drug-related adverse event	1	(0.2)	0	(0.0)	1	(0.0)	2	(0.0)
discontinued Pembrolizumab	1	(0.2)	0	(0.0)	1	(0.0)	2	(0.0)
discontinued all regimen components	0	(0.0)	0	(0.0)	1	(0.0)	2	(0.0)
discontinued any drug due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued Pembrolizumab	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued all regimen components	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued Pembrolizumab	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued all regimen components	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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

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

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

‖ Includes all subjects who received at least one dose of Pembrolizumab and/or Axitinib in KN426.

†† Includes all subjects who received at least one dose of Sunitinib in KN426.

¶ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN045, KN052, KN055 and KN087.

§ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma) and Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort B4, KN040, KN042, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158, KN164 Cohort A, KN170, KN224 and KN427 Cohort A.

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

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)

Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)

Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)

Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)

Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)

Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)

Database cutoff date for HCC (KN224: 15MAY2018)

Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)

Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl; adae]

Table 5.3.5.3.3-rcc1: 67

Time to Onset and Duration of AEOSI - Hypothyroidism
(ASaT Population)

	KN426 Data for Pembrolizumab + Axitinib‖ n (%)	KN426 Sunitinib†† n (%)	Reference Safety Dataset for Pembrolizumab Monotherapy¶ n (%)	Cumulative Running Safety Dataset for Pembrolizumab Monotherapy§ n (%)
Subjects in population	429	425	4439	6436
Subjects with Hypothyroidism	152 (35.4)	134 (31.5)	440 (9.9)	667 (10.4)
Time to Onset of First Hypothyroidism (days)†				
Mean (Std)	122.0 (99.1)	123.4 (129.7)	116.2 (87.0)	116.8 (87.7)
Median	94.0	71.0	105.0	104.0
Range	2 to 491	15 to 587	1 to 623	1 to 623
Total episodes of Hypothyroidism	178	174	460	730
Average Episodes per patient	1.17	1.30	1.05	1.09
Episode duration (days)‡				
Median	Not reached	295.0	Not reached	Not reached
Range	7 to 592+	7 to 599+	2 to 909+	1+ to 992+

(%) = Number of subjects with Hypothyroidism / Number of subjects in population.
† Time to onset statistics are based on number of subjects with Hypothyroidism.
‡ From product-limit (Kaplan-Meier) method for censored data. If an adverse event is not resolved at the time of analysis or the subject died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.
+ indicates the AE episode is not recovered/resolved by the time of the cutoff date or date of death.
Std = Standard Deviation.
Grades are based on NCI CTCAE 4.0.
‖ Includes all subjects who received at least one dose of Pembrolizumab and/or Axitinib in KN426.
†† Includes all subjects who received at least one dose of Sunitinib in KN426.
¶ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN045, KN052, KN055 and KN087.
§ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma) and Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort B4, KN040, KN042, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158, KN164 Cohort A, KN170, KN224 and KN427 Cohort A.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)
Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)
Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)
Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)
Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)
Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)
Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)
Database cutoff date for HCC (KN224: 15MAY2018)
Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)
Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl; adae]

In the pembrolizub+axitinib arm, median time to *Hypothyroidism* AEOSI was 94 days (range, 2-491). An average of 1.2 episodes were reported per patient with a not reached median duration (range, 7-592+). Overall 5.3% of subjects with one or more *Hypothyroidism* AEOSIs received concomitant corticosteroid treatment (high and low starting dose in 2.2% each).

Myasthenic syndrome

Table 5.3.5.3.3-rcc1: 74

Adverse Event Summary
AEOSI - Myasthenic Syndrome
(ASaT Population)

	KN426 Data for Pembrolizumab + Axitinib‖		KN426 Sunitinib††		Reference Safety Dataset for Pembrolizumab Monotherapy¶		Cumulative Running Safety Dataset for Pembrolizumab Monotherapy§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	429		425		4,439		6,436	
with one or more adverse events	4	(0.9)	0	(0.0)	2	(0.0)	4	(0.1)
with no adverse event	425	(99.1)	425	(100.0)	4,437	(100.0)	6,432	(99.9)
with drug-related† adverse events	4	(0.9)	0	(0.0)	2	(0.0)	4	(0.1)
with toxicity grade 3-5 adverse events	2	(0.5)	0	(0.0)	1	(0.0)	2	(0.0)
with toxicity grade 3-5 drug-related adverse events	2	(0.5)	0	(0.0)	1	(0.0)	2	(0.0)
with non-serious adverse events	0	(0.0)	0	(0.0)	1	(0.0)	3	(0.0)
with serious adverse events	4	(0.9)	0	(0.0)	1	(0.0)	2	(0.0)
with serious drug-related adverse events	4	(0.9)	0	(0.0)	1	(0.0)	2	(0.0)
with any dose modification‡ due to an adverse event	4	(0.9)	0	(0.0)	2	(0.0)	4	(0.1)
Pembrolizumab dose modification	4	(0.9)	0	(0.0)	2	(0.0)	4	(0.1)
all regimen components dose modification	4	(0.9)	0	(0.0)	2	(0.0)	4	(0.1)
who died	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to an adverse event	4	(0.9)	0	(0.0)	0	(0.0)	2	(0.0)
discontinued Pembrolizumab	4	(0.9)	0	(0.0)	0	(0.0)	2	(0.0)
discontinued all regimen components	3	(0.7)	0	(0.0)	0	(0.0)	2	(0.0)
discontinued any drug due to a drug-related adverse event	4	(0.9)	0	(0.0)	0	(0.0)	2	(0.0)
discontinued Pembrolizumab	4	(0.9)	0	(0.0)	0	(0.0)	2	(0.0)
discontinued all regimen components	3	(0.7)	0	(0.0)	0	(0.0)	2	(0.0)
discontinued any drug due to a serious adverse event	4	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued Pembrolizumab	4	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued all regimen components	3	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	4	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued Pembrolizumab	4	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued all regimen components	3	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Non-serious adverse events up to 30 days following the last dose and serious adverse events up to 90 days following the last dose are included.
‖ Includes all subjects who received at least one dose of Pembrolizumab and/or Axitinib in KN426.
†† Includes all subjects who received at least one dose of Sunitinib in KN426.
¶ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN045, KN052, KN055 and KN087.
§ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma) and Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort B4, KN040, KN042, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158, KN164 Cohort A, KN170, KN224 and KN427 Cohort A.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)
Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)
Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)
Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)
Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)
Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)
Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)
Database cutoff date for HCC (KN224: 15MAY2018)
Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)
Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl; adae]

Table 5.3.5.3.3-rcc1: 75

Time to Onset and Duration of AEOSI - Myasthenic Syndrome
(ASaT Population)

	KN426 Data for Pembrolizumab + Axitinib‖ n (%)	KN426 Sunitinib†† n (%)	Reference Safety Dataset for Pembrolizumab Monotherapy¶ n (%)	Cumulative Running Safety Dataset for Pembrolizumab Monotherapy§ n (%)
Subjects in population	429	425	4439	6436
Subjects with Myasthenic Syndrome	4 (0.9)	0	2 (0.0)	4 (0.1)
Time to Onset of First Myasthenic Syndrome (days)†				
Mean (Std)	40.5 (13.6)	0	57.5 (23.3)	68.8 (40.5)
Median	40.5	0.0	57.5	57.5
Range	24 to 57	0 to 0	41 to 74	36 to 124
Total episodes of Myasthenic Syndrome	4	0	2	6
Average Episodes per patient	1.00	0	1.00	1.50
Episode duration (days)‡				
Median	343.0	0	330.0	330.0
Range	28+ to 384	0 to 0	255+ to 330	8 to 376+

(%) = Number of subjects with Myasthenic Syndrome / Number of subjects in population.
† Time to onset statistics are based on number of subjects with Myasthenic Syndrome.
‡ From product-limit (Kaplan-Meier) method for censored data. If an adverse event is not resolved at the time of analysis or the subject died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.
+ indicates the AE episode is not recovered/resolved by the time of the cutoff date or date of death.
Std = Standard Deviation.
Grades are based on NCI CTCAE 4.0.
‖ Includes all subjects who received at least one dose of Pembrolizumab and/or Axitinib in KN426.
†† Includes all subjects who received at least one dose of Sunitinib in KN426.
¶ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN045, KN052, KN055 and KN087.
§ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma) and Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort B4, KN040, KN042, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158, KN164 Cohort A, KN170, KN224 and KN427 Cohort A.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)
Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)
Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)
Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)
Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)
Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)
Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)
Database cutoff date for HCC (KN224: 15MAY2018)
Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)
Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl; adae]

In the pembrolizub+axitinib arm, median time to *Myasthenic syndrome* AEOSI was 40.5 days (range, 24-57). An average of 1 episode was reported per patient with a median duration of 343 days. All subjects developing myasthenic syndrome were treated with concomitant corticosteroids (high doses 75%; low doses 25%).

Nephritis

Table 5.3.5.3.3-rcc1: 86

Adverse Event Summary
AEOSI - Nephritis
(ASaT Population)

	KN426 Data for Pembrolizumab + Axitinib‖		KN426 Sunitinib††		Reference Safety Dataset for Pembrolizumab Monotherapy¶		Cumulative Running Safety Dataset for Pembrolizumab Monotherapy§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	429		425		4,439		6,436	
with one or more adverse events	6	(1.4)	1	(0.2)	15	(0.3)	21	(0.3)
with no adverse event	423	(98.6)	424	(99.8)	4,424	(99.7)	6,415	(99.7)
with drug-related† adverse events	3	(0.7)	1	(0.2)	14	(0.3)	20	(0.3)
with toxicity grade 3-5 adverse events	1	(0.2)	0	(0.0)	11	(0.2)	14	(0.2)
with toxicity grade 3-5 drug-related adverse events	1	(0.2)	0	(0.0)	11	(0.2)	14	(0.2)
with non-serious adverse events	4	(0.9)	1	(0.2)	2	(0.0)	4	(0.1)
with serious adverse events	2	(0.5)	0	(0.0)	13	(0.3)	17	(0.3)
with serious drug-related adverse events	1	(0.2)	0	(0.0)	13	(0.3)	17	(0.3)
with any dose modification‡ due to an adverse event	4	(0.9)	1	(0.2)	12	(0.3)	16	(0.2)
Pembrolizumab dose modification	2	(0.5)	0	(0.0)	12	(0.3)	16	(0.2)
all regimen components dose modification	2	(0.5)	1	(0.2)	12	(0.3)	16	(0.2)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to an adverse event	2	(0.5)	1	(0.2)	7	(0.2)	9	(0.1)
discontinued Pembrolizumab	1	(0.2)	0	(0.0)	7	(0.2)	9	(0.1)
discontinued all regimen components	1	(0.2)	1	(0.2)	7	(0.2)	9	(0.1)
discontinued any drug due to a drug-related adverse event	1	(0.2)	1	(0.2)	7	(0.2)	9	(0.1)
discontinued Pembrolizumab	0	(0.0)	0	(0.0)	7	(0.2)	9	(0.1)
discontinued all regimen components	0	(0.0)	1	(0.2)	7	(0.2)	9	(0.1)
discontinued any drug due to a serious adverse event	2	(0.5)	0	(0.0)	6	(0.1)	8	(0.1)
discontinued Pembrolizumab	1	(0.2)	0	(0.0)	6	(0.1)	8	(0.1)
discontinued all regimen components	1	(0.2)	0	(0.0)	6	(0.1)	8	(0.1)
discontinued any drug due to a serious drug-related adverse event	1	(0.2)	0	(0.0)	6	(0.1)	8	(0.1)
discontinued Pembrolizumab	0	(0.0)	0	(0.0)	6	(0.1)	8	(0.1)
discontinued all regimen components	0	(0.0)	0	(0.0)	6	(0.1)	8	(0.1)

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

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

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

‖ Includes all subjects who received at least one dose of Pembrolizumab and/or Axitinib in KN426.

†† Includes all subjects who received at least one dose of Sunitinib in KN426.

¶ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN045, KN052, KN055 and KN087.

§ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma) and Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort B4, KN040, KN042, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158, KN164 Cohort A, KN170, KN224 and KN427 Cohort A.

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

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)

Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)

Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)

Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)

Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)

Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)

Database cutoff date for HCC (KN224: 15MAY2018)

Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)

Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl; adae]

Table 5.3.5.3.3-rcc1: 87

Time to Onset and Duration of AEOSI - Nephritis
(ASaT Population)

	KN426 Data for Pembrolizumab + Axitinib‖ n (%)	KN426 Sunitinib†† n (%)	Reference Safety Dataset for Pembrolizumab Monotherapy¶ n (%)	Cumulative Running Safety Dataset for Pembrolizumab Monotherapy# n (%)
Subjects in population	429	425	4439	6436
Subjects with Nephritis	6 (1.4)	1 (0.2)	15 (0.3)	21 (0.3)
Time to Onset of First Nephritis (days)†				
Mean (Std)	227.2 (177.6)	238.0	146.1 (129.6)	172.1 (141.7)
Median	206.0	238.0	150.0	150.0
Range	42 to 505	238 to 238	12 to 388	12 to 424
Total episodes of Nephritis	6	1	15	21
Average Episodes per patient	1.00	1.00	1.00	1.00
Episode duration (days)‡				
Median	46.0	Not reached	57.0	57.0
Range	6 to 248+	215+ to 215+	10 to 319+	6 to 366

(%) = Number of subjects with Nephritis / Number of subjects in population.
† Time to onset statistics are based on number of subjects with Nephritis.
‡ From product-limit (Kaplan-Meier) method for censored data. If an adverse event is not resolved at the time of analysis or the subject died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.
+ indicates the AE episode is not recovered/resolved by the time of the cutoff date or date of death.
Std = Standard Deviation.
Grades are based on NCI CTCAE 4.0.
‖ Includes all subjects who received at least one dose of Pembrolizumab and/or Axitinib in KN426.
†† Includes all subjects who received at least one dose of Sunitinib in KN426.
¶ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN045, KN052, KN055 and KN087.
# Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma) and Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort B4, KN040, KN042, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158, KN164 Cohort A, KN170, KN224 and KN427 Cohort A.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)
Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)
Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)
Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)
Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)
Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)
Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)
Database cutoff date for HCC (KN224: 15MAY2018)
Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)
Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl; adae]

In the pembrolizub+axitinib arm, median time to *Nephritis* AEOSI was 206 days (range, 42-505). An average of 1 episode was reported per patient with a median duration of 46 days. Corticosteroids were given at high doses in 66.7%.

Pneumonitis

Table 5.3.5.3.3-rcc1: 94

Adverse Event Summary
AEOSI - Pneumonitis
(ASaT Population)

	KN426 Data for Pembrolizumab + Axitinib‖		KN426 Sunitinib††		Reference Safety Dataset for Pembrolizumab Monotherapy¶		Cumulative Running Safety Dataset for Pembrolizumab Monotherapy§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	429		425		4,439		6,436	
with one or more adverse events	12	(2.8)	1	(0.2)	166	(3.7)	254	(3.9)
with no adverse event	417	(97.2)	424	(99.8)	4,273	(96.3)	6,182	(96.1)
with drug-related† adverse events	12	(2.8)	1	(0.2)	152	(3.4)	231	(3.6)
with toxicity grade 3-5 adverse events	2	(0.5)	0	(0.0)	60	(1.4)	92	(1.4)
with toxicity grade 3-5 drug-related adverse events	2	(0.5)	0	(0.0)	55	(1.2)	85	(1.3)
with non-serious adverse events	6	(1.4)	1	(0.2)	89	(2.0)	136	(2.1)
with serious adverse events	6	(1.4)	0	(0.0)	87	(2.0)	133	(2.1)
with serious drug-related adverse events	6	(1.4)	0	(0.0)	81	(1.8)	125	(1.9)
with any dose modification‡ due to an adverse event	8	(1.9)	0	(0.0)	111	(2.5)	176	(2.7)
Pembrolizumab dose modification	7	(1.6)	0	(0.0)	111	(2.5)	176	(2.7)
all regimen components dose modification	4	(0.9)	0	(0.0)	111	(2.5)	176	(2.7)
who died	1	(0.2)	0	(0.0)	7	(0.2)	9	(0.1)
who died due to a drug-related adverse event	1	(0.2)	0	(0.0)	7	(0.2)	9	(0.1)
discontinued any drug due to an adverse event	3	(0.7)	0	(0.0)	67	(1.5)	101	(1.6)
discontinued Pembrolizumab	3	(0.7)	0	(0.0)	67	(1.5)	101	(1.6)
discontinued all regimen components	0	(0.0)	0	(0.0)	67	(1.5)	101	(1.6)
discontinued any drug due to a drug-related adverse event	3	(0.7)	0	(0.0)	66	(1.5)	100	(1.6)
discontinued Pembrolizumab	3	(0.7)	0	(0.0)	66	(1.5)	100	(1.6)
discontinued all regimen components	0	(0.0)	0	(0.0)	66	(1.5)	100	(1.6)
discontinued any drug due to a serious adverse event	3	(0.7)	0	(0.0)	54	(1.2)	78	(1.2)
discontinued Pembrolizumab	3	(0.7)	0	(0.0)	54	(1.2)	78	(1.2)
discontinued all regimen components	0	(0.0)	0	(0.0)	54	(1.2)	78	(1.2)
discontinued any drug due to a serious drug-related adverse event	3	(0.7)	0	(0.0)	53	(1.2)	77	(1.2)
discontinued Pembrolizumab	3	(0.7)	0	(0.0)	53	(1.2)	77	(1.2)
discontinued all regimen components	0	(0.0)	0	(0.0)	53	(1.2)	77	(1.2)

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

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

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

‖ Includes all subjects who received at least one dose of Pembrolizumab and/or Axitinib in KN426.

†† Includes all subjects who received at least one dose of Sunitinib in KN426.

¶ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN045, KN052, KN055 and KN087.

§ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma) and Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort B4, KN040, KN042, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158, KN164 Cohort A, KN170, KN224 and KN427 Cohort A.

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

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)

Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)

Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)

Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)

Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)

Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)

Database cutoff date for HCC (KN224: 15MAY2018)

Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)

Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl; adae]

Table 5.3.5.3.3-rcc1: 95

Time to Onset and Duration of AEOSI - Pneumonitis
(ASaT Population)

	KN426 Data for Pembrolizumab + Axitinib‖		KN426 Sunitinib††		Reference Safety Dataset for Pembrolizumab Monotherapy¶		Cumulative Running Safety Dataset for Pembrolizumab Monotherapy§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	429		425		4439		6436	
Subjects with Pneumonitis	12	(2.8)	1	(0.2)	166	(3.7)	254	(3.9)
Time to Onset of First Pneumonitis (days)†								
Mean (Std)	261.3 (133.2)		169.0		157.7 (150.9)		154.4 (152.6)	
Median	199.0		169.0		111.5		102.0	
Range	126 to 527		169 to 169		2 to 647		2 to 816	
Total episodes of Pneumonitis	12		1		183		295	
Average Episodes per patient	1.00		1.00		1.10		1.16	
Episode duration (days)‡								
Median	91.0		Not reached		64.0		61.0	
Range	16+ to 260		46+ to 46+		1 to 771+		1 to 771+	

(%) = Number of subjects with Pneumonitis / Number of subjects in population.
† Time to onset statistics are based on number of subjects with Pneumonitis.
‡ From product-limit (Kaplan-Meier) method for censored data. If an adverse event is not resolved at the time of analysis or the subject died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.
+ indicates the AE episode is not recovered/resolved by the time of the cutoff date or date of death.
Std = Standard Deviation.
Grades are based on NCI CTCAE 4.0.
‖ Includes all subjects who received at least one dose of Pembrolizumab and/or Axitinib in KN426.
†† Includes all subjects who received at least one dose of Sunitinib in KN426.
¶ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN045, KN052, KN055 and KN087.
§ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma) and Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort B4, KN040, KN042, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158, KN164 Cohort A, KN170, KN224 and KN427 Cohort A.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)
Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)
Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)
Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)
Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)
Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)
Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)
Database cutoff date for HCC (KN224: 15MAY2018)
Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)
Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl; adae]

In the pembrolizub+axitinib arm, median time to *Pneumonitis* AEOSI was 199 days (range, 126-527). An average of 1 episode was reported per patient with a median duration of 91 days. Corticosteroids were given at high doses in 58.3% and low doses in 16.7%.

Thyroiditis

Table 5.3.5.3.3-rcc1: 110

Adverse Event Summary
AEOSI - Thyroiditis
(ASaT Population)

	KN426 Data for Pembrolizumab + Axitinib‖		KN426 Sunitinib††		Reference Safety Dataset for Pembrolizumab Monotherapy¶		Cumulative Running Safety Dataset for Pembrolizumab Monotherapy§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	429		425		4,439		6,436	
with one or more adverse events	12	(2.8)	2	(0.5)	30	(0.7)	65	(1.0)
with no adverse event	417	(97.2)	423	(99.5)	4,409	(99.3)	6,371	(99.0)
with drug-related† adverse events	11	(2.6)	1	(0.2)	30	(0.7)	64	(1.0)
with toxicity grade 3-5 adverse events	1	(0.2)	0	(0.0)	1	(0.0)	2	(0.0)
with toxicity grade 3-5 drug-related adverse events	1	(0.2)	0	(0.0)	1	(0.0)	2	(0.0)
with non-serious adverse events	12	(2.8)	2	(0.5)	28	(0.6)	61	(0.9)
with serious adverse events	0	(0.0)	0	(0.0)	2	(0.0)	5	(0.1)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	2	(0.0)	5	(0.1)
with any dose modification‡ due to an adverse event	4	(0.9)	0	(0.0)	2	(0.0)	7	(0.1)
Pembrolizumab dose modification	3	(0.7)	0	(0.0)	2	(0.0)	7	(0.1)
all regimen components dose modification	2	(0.5)	0	(0.0)	2	(0.0)	7	(0.1)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued Pembrolizumab	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued all regimen components	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued Pembrolizumab	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued all regimen components	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued Pembrolizumab	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued all regimen components	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued Pembrolizumab	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued all regimen components	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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

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

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

‖ Includes all subjects who received at least one dose of Pembrolizumab and/or Axitinib in KN426.

†† Includes all subjects who received at least one dose of Sunitinib in KN426.

¶ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN045, KN052, KN055 and KN087.

§ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma) and Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort B4, KN040, KN042, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158, KN164 Cohort A, KN170, KN224 and KN427 Cohort A.

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

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)

Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)

Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)

Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)

Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)

Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)

Database cutoff date for HCC (KN224: 15MAY2018)

Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)

Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl; adae]

Table 5.3.5.3.3-rcc1: 111

Time to Onset and Duration of AEOSI - Thyroiditis
(ASaT Population)

	KN426 Data for Pembrolizumab + Axitinib‖ n (%)	KN426 Sunitinib†† n (%)	Reference Safety Dataset for Pembrolizumab Monotherapy¶ n (%)	Cumulative Running Safety Dataset for Pembrolizumab Monotherapy# n (%)
Subjects in population	429	425	4439	6436
Subjects with Thyroiditis	12 (2.8)	2 (0.5)	30 (0.7)	65 (1.0)
Time to Onset of First Thyroiditis (days)†				
Mean (Std)	71.7 (57.0)	71.0 (0.0)	69.2 (56.4)	67.6 (51.1)
Median	61.0	71.0	63.5	63.0
Range	22 to 224	71 to 71	15 to 260	7 to 260
Total episodes of Thyroiditis	12	2	30	69
Average Episodes per patient	1.00	1.00	1.00	1.06
Episode duration (days)‡				
Median	Not reached	23.0	462.0	188.0
Range	22 to 508+	15 to 31	15 to 785+	2 to 785+

(%) = Number of subjects with Thyroiditis / Number of subjects in population.
† Time to onset statistics are based on number of subjects with Thyroiditis.
‡ From product-limit (Kaplan-Meier) method for censored data. If an adverse event is not resolved at the time of analysis or the subject died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.
+ indicates the AE episode is not recovered/resolved by the time of the cutoff date or date of death.
Std = Standard Deviation.
Grades are based on NCI CTCAE 4.0.
‖ Includes all subjects who received at least one dose of Pembrolizumab and/or Axitinib in KN426.
†† Includes all subjects who received at least one dose of Sunitinib in KN426.
¶ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN045, KN052, KN055 and KN087.
# Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma) and Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort B4, KN040, KN042, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158, KN164 Cohort A, KN170, KN224 and KN427 Cohort A.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)
Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)
Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)
Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)
Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)
Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)
Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)
Database cutoff date for HCC (KN224: 15MAY2018)
Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)
Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl; adae]

In the pembrolizub+axitinib arm, median time to *Thyroiditis* AEOSI was 61 days (range, 22-224). An average of 1 episode was reported per patient with a not reached median duration (range, 22-508+). None of the subjects presenting with thyroiditis in either treatment arms received corticosteroids.

Hepatic Adverse Events

A higher than expected incidence of Grade 3 or 4 hepatic AEs was observed during the conduct of this study via medical monitoring and was confirmed at IA1. In order to better understand treatment-emergent hepatic events, a formal analysis plan was developed to accurately quantify and characterize these events. A combined list of preferred AE terms from 3 MedDRA hepatic SMQs and the hepatitis AEOSI were predefined as hepatic AEs in the Hepatic Events Analysis Plan in the sSAP. A Hepatic Events Analysis Set (HEAS) was identified to include any participant who had received at least 1 dose of study treatment and experienced any treatment-emergent AE matching a hepatic AE PT from the pre-selected list.

Demography and Baseline Disease Characteristics of the HEAS

A total of 287 participants (174 in the pembrolizumab+axitinib group, 113 in the sunitinib arm) were included in the HEAS. Participant demographics were generally similar to those reported for the ITT population. Comparison between study arms shows comparable characteristics, except for proportion of subjects aged >65 years (pembrolizumab+axitinib 44.3%, sunitinib 31.9%). Also, disease characteristics were comparable in the two treatment arms. Liver metastases were described in 15.5% and 14.2% of subjects treated with pembrolizumab+axitinib and sunitinib, respectively. Subject characteristics in the pembrolizumab+axitinib arm were generally similar for the HEAS population (n=174) compared to those reported for the non-HEAS population (n=255); however a slightly higher proportion of Asian population was reported for the HEAS (19.5%) compared to the non-HEAS population (12.5%); the proportion of

patient with liver metastasis was 15% in both groups.

Overall hepatic AEs and most common PTs

Table 12-14
Overall Hepatic Adverse Event Summary
(ASaT Population)

	Pembrolizumab + Axitinib		Sunitinib	
	n	(%)	n	(%)
Subjects in population	429		425	
with one or more hepatic adverse events[§]	174	(40.6)	113	(26.6)
with no hepatic adverse event	255	(59.4)	312	(73.4)
with drug-related[†] hepatic adverse events	147	(34.3)	88	(20.7)
with toxicity grade 3-5 hepatic adverse events	91	(21.2)	26	(6.1)
with toxicity grade 3-5 drug-related hepatic adverse events	81	(18.9)	17	(4.0)
with serious hepatic adverse events	30	(7.0)	4	(0.9)
with serious drug-related hepatic adverse events	27	(6.3)	2	(0.5)
who died due to a hepatic adverse event	0	(0.0)	1	(0.2)
who died due to a drug-related hepatic adverse event	0	(0.0)	1	(0.2)
discontinued any drug due to a hepatic adverse event	57	(13.3)	2	(0.5)
discontinued Pembrolizumab	43	(10.0)	0	(0.0)
discontinued Axitinib	29	(6.8)	0	(0.0)
discontinued Both Pembrolizumab and Axitinib	13	(3.0)	0	(0.0)
discontinued any drug due to a drug-related hepatic adverse event	56	(13.1)	2	(0.5)
discontinued Pembrolizumab	42	(9.8)	0	(0.0)
discontinued Axitinib	29	(6.8)	0	(0.0)
discontinued Both Pembrolizumab and Axitinib	13	(3.0)	0	(0.0)
discontinued any drug due to a serious hepatic adverse event	21	(4.9)	1	(0.2)
discontinued Pembrolizumab	18	(4.2)	0	(0.0)
discontinued Axitinib	11	(2.6)	0	(0.0)
discontinued Both Pembrolizumab and Axitinib	8	(1.9)	0	(0.0)
discontinued any drug due to a serious drug-related hepatic adverse event	20	(4.7)	1	(0.2)
discontinued Pembrolizumab	17	(4.0)	0	(0.0)
discontinued Axitinib	11	(2.6)	0	(0.0)
discontinued Both Pembrolizumab and Axitinib	8	(1.9)	0	(0.0)

[†] Determined by the investigator to be related to the drug.
[§] Refer to Hepatic Events Analysis Plan in KEYNOTE 426 sSAP regarding hepatic events PT terms search strategy and full listing of hepatic PT terms included for this analysis.
Grades are based on NCI CTCAE version 4.0.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adae]

Table 12-15
Subjects With Hepatic Adverse Events by Decreasing Incidence
(Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab + Axitinib		Sunitinib	
	n	(%)	n	(%)
Subjects in population	429		425	
with one or more hepatic adverse events	174	(40.6)	113	(26.6)
with no hepatic adverse events	255	(59.4)	312	(73.4)
Alanine aminotransferase increased	115	(26.8)	64	(15.1)
Aspartate aminotransferase increased	112	(26.1)	69	(16.2)
Blood bilirubin increased	28	(6.5)	24	(5.6)
Hepatic function abnormal	15	(3.5)	7	(1.6)
Gamma-glutamyltransferase increased	8	(1.9)	4	(0.9)
Hepatitis	7	(1.6)	1	(0.2)
Hyperbilirubinaemia	7	(1.6)	8	(1.9)
Liver function test increased	5	(1.2)	1	(0.2)
Hepatocellular injury	4	(0.9)	4	(0.9)
Hepatotoxicity	4	(0.9)	0	(0.0)
Autoimmune hepatitis	3	(0.7)	0	(0.0)
Bilirubin conjugated increased	3	(0.7)	4	(0.9)
Hepatic steatosis	3	(0.7)	0	(0.0)
Ascites	2	(0.5)	3	(0.7)
Hepatic enzyme increased	2	(0.5)	2	(0.5)
Liver disorder	2	(0.5)	0	(0.0)
Transaminases increased	2	(0.5)	2	(0.5)
Blood bilirubin unconjugated increased	1	(0.2)	1	(0.2)
Drug-induced liver injury	1	(0.2)	0	(0.0)
Hepatic cirrhosis	1	(0.2)	0	(0.0)
Hepatic pain	1	(0.2)	2	(0.5)
Immune-mediated hepatitis	1	(0.2)	0	(0.0)
Liver injury	1	(0.2)	0	(0.0)
Hepatitis fulminant	0	(0.0)	1	(0.2)

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A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
The adverse events are ordered decreasingly by the incidence in the first column.
Database Cutoff Date: 24Aug2018.

ource: [P426V01MK3475: adam-adsl; adae]

Grade 3 to 5 hepatic AEs

Table 12-16
Subjects With Grade 3-5 Hepatic Adverse Events by Decreasing Incidence
(Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab + Axitinib		Sunitinib	
	n	(%)	n	(%)
Subjects in population	429		425	
with one or more hepatic adverse events	91	(21.2)	26	(6.1)
with no hepatic adverse events	338	(78.8)	399	(93.9)
Alanine aminotransferase increased	57	(13.3)	13	(3.1)
Aspartate aminotransferase increased	30	(7.0)	10	(2.4)
Hepatic function abnormal	7	(1.6)	0	(0.0)
Hepatitis	6	(1.4)	0	(0.0)
Blood bilirubin increased	4	(0.9)	3	(0.7)
Gamma-glutamyltransferase increased	4	(0.9)	2	(0.5)
Hepatotoxicity	4	(0.9)	0	(0.0)
Hepatocellular injury	3	(0.7)	3	(0.7)
Liver function test increased	3	(0.7)	0	(0.0)
Autoimmune hepatitis	2	(0.5)	0	(0.0)
Hepatic enzyme increased	2	(0.5)	0	(0.0)
Transaminases increased	2	(0.5)	0	(0.0)
Ascites	1	(0.2)	2	(0.5)
Drug-induced liver injury	1	(0.2)	0	(0.0)
Hepatic cirrhosis	1	(0.2)	0	(0.0)
Hepatic pain	1	(0.2)	1	(0.2)
Immune-mediated hepatitis	1	(0.2)	0	(0.0)
Bilirubin conjugated increased	0	(0.0)	2	(0.5)
Hepatitis fulminant	0	(0.0)	1	(0.2)
Hyperbilirubinaemia	0	(0.0)	1	(0.2)

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Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
The adverse events are ordered decreasingly by the incidence in the first column.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adae]

Drug-related hepatic AEs

Table 12-17
Subjects With Drug-Related Hepatic Adverse Events by Decreasing Incidence
(Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab + Axitinib		Sunitinib	
	n	(%)	n	(%)
Subjects in population	429		425	
with one or more hepatic adverse events	147	(34.3)	88	(20.7)
with no hepatic adverse events	282	(65.7)	337	(79.3)
Alanine aminotransferase increased	102	(23.8)	54	(12.7)
Aspartate aminotransferase increased	97	(22.6)	59	(13.9)
Blood bilirubin increased	19	(4.4)	20	(4.7)
Hepatic function abnormal	13	(3.0)	6	(1.4)
Hepatitis	6	(1.4)	1	(0.2)
Hyperbilirubinaemia	5	(1.2)	6	(1.4)
Hepatocellular injury	4	(0.9)	3	(0.7)
Hepatotoxicity	4	(0.9)	0	(0.0)
Bilirubin conjugated increased	3	(0.7)	2	(0.5)
Gamma-glutamyltransferase increased	3	(0.7)	4	(0.9)
Liver function test increased	3	(0.7)	1	(0.2)
Autoimmune hepatitis	2	(0.5)	0	(0.0)
Hepatic enzyme increased	2	(0.5)	1	(0.2)
Liver disorder	2	(0.5)	0	(0.0)
Transaminases increased	2	(0.5)	1	(0.2)
Blood bilirubin unconjugated increased	1	(0.2)	1	(0.2)
Drug-induced liver injury	1	(0.2)	0	(0.0)
Hepatic steatosis	1	(0.2)	0	(0.0)
Immune-mediated hepatitis	1	(0.2)	0	(0.0)
Liver injury	1	(0.2)	0	(0.0)
Hepatitis fulminant	0	(0.0)	1	(0.2)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
The adverse events are ordered decreasingly by the incidence in the first column.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adae]

Grade 3 to 5 drug-related hepatic AEs

Table 12-18
Subjects With Drug-Related Grade 3-5 Hepatic Adverse Events by Decreasing Incidence
(Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab + Axitinib		Sunitinib	
	n	(%)	n	(%)
Subjects in population	429		425	
with one or more hepatic adverse events	81	(18.9)	17	(4.0)
with no hepatic adverse events	348	(81.1)	408	(96.0)
Alanine aminotransferase increased	52	(12.1)	11	(2.6)
Aspartate aminotransferase increased	29	(6.8)	7	(1.6)
Hepatic function abnormal	6	(1.4)	0	(0.0)
Hepatitis	6	(1.4)	0	(0.0)
Hepatotoxicity	4	(0.9)	0	(0.0)
Hepatocellular injury	3	(0.7)	2	(0.5)
Liver function test increased	3	(0.7)	0	(0.0)
Blood bilirubin increased	2	(0.5)	1	(0.2)
Hepatic enzyme increased	2	(0.5)	0	(0.0)
Transaminases increased	2	(0.5)	0	(0.0)
Autoimmune hepatitis	1	(0.2)	0	(0.0)
Drug-induced liver injury	1	(0.2)	0	(0.0)
Gamma-glutamyltransferase increased	1	(0.2)	2	(0.5)
Immune-mediated hepatitis	1	(0.2)	0	(0.0)
Hepatitis fulminant	0	(0.0)	1	(0.2)
Hyperbilirubinaemia	0	(0.0)	1	(0.2)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
The adverse events are ordered decreasingly by the incidence in the first column.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adae]

Table Subjects in the HEAS Population With Serious Hepatic Adverse Events by Decreasing Incidence
(Incidence > 0% in One or More Treatment Groups)
(ASaT Population)

	Pembrolizumab + Axitinib		Sunitinib	
	n	(%)	n	(%)
Subjects in population	429		425	
with one or more hepatic adverse events	30	(7.0)	4	(0.9)
with no hepatic adverse events	399	(93.0)	421	(99.1)
Alanine aminotransferase increased	6	(1.4)	0	(0.0)
Aspartate aminotransferase increased	5	(1.2)	0	(0.0)
Hepatic function abnormal	5	(1.2)	0	(0.0)
Hepatitis	3	(0.7)	0	(0.0)
Hepatocellular injury	3	(0.7)	1	(0.2)
Autoimmune hepatitis	2	(0.5)	0	(0.0)
Hepatic enzyme increased	2	(0.5)	0	(0.0)
Liver function test increased	2	(0.5)	0	(0.0)
Transaminases increased	2	(0.5)	0	(0.0)
Blood bilirubin increased	1	(0.2)	0	(0.0)
Drug-induced liver injury	1	(0.2)	0	(0.0)
Hepatic cirrhosis	1	(0.2)	0	(0.0)
Hepatotoxicity	1	(0.2)	0	(0.0)
Immune-mediated hepatitis	1	(0.2)	0	(0.0)
Ascites	0	(0.0)	1	(0.2)
Hepatic pain	0	(0.0)	1	(0.2)
Hepatitis fulminant	0	(0.0)	1	(0.2)

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

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

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

The adverse events are ordered decreasingly by the incidence in the first column.

Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adae]

Table Subjects in the HEAS Population With Hepatic Adverse Events Resulting in Treatment Discontinuation By Decreasing Incidence (Incidence > 0% in One or More Treatment Groups) (ASaT Population)

	Pembrolizumab + Axitinib		Sunitinib	
	n	(%)	n	(%)
Subjects in population	429		425	
with one or more hepatic adverse events	57	(13.3)	2	(0.5)
with no hepatic adverse events	372	(86.7)	423	(99.5)
Alanine aminotransferase increased	31	(7.2)	1	(0.2)
Aspartate aminotransferase increased	20	(4.7)	1	(0.2)
Hepatic function abnormal	6	(1.4)	0	(0.0)
Hepatitis	4	(0.9)	0	(0.0)
Hepatotoxicity	4	(0.9)	0	(0.0)
Hepatocellular injury	3	(0.7)	0	(0.0)
Autoimmune hepatitis	2	(0.5)	0	(0.0)
Liver function test increased	2	(0.5)	0	(0.0)
Blood bilirubin unconjugated increased	1	(0.2)	0	(0.0)
Drug-induced liver injury	1	(0.2)	0	(0.0)
Hepatic enzyme increased	1	(0.2)	0	(0.0)
Immune-mediated hepatitis	1	(0.2)	0	(0.0)
Transaminases increased	1	(0.2)	0	(0.0)
Hepatitis fulminant	0	(0.0)	1	(0.2)
Hyperbilirubinaemia	0	(0.0)	1	(0.2)

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

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

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

The adverse events are ordered decreasingly by the incidence in the first column.

Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adae]

Overall, 15 participants discontinued both pembrolizumab + axitinib due to hepatic AEs; 11 (73.3%) of these participants received subsequent anti-cancer treatment, with a median interval from last dose of study treatment to first dose of subsequent treatment of 44 days (range 29 days to 252 days); 9 of these participants were alive at the time of data cutoff (02-JAN-2019). In context, 88 of 176 (50%) of participants who discontinued pembrolizumab + axitinib for any reason received a subsequent anti-cancer treatment therapy. Four participants who discontinued pembrolizumab + axitinib due to hepatic AEs did not receive subsequent anti-cancer treatments. Of those, 3 participants were alive at the time of data cutoff.

Table Recovery from the First ALT or AST ≥3 × ULN Events and Steroid Use during the First Events (HEAS Population from Pembrolizumab + Axitinib Arm)

	First ALT or AST ≥3 × ULN events categories (N = 120)	
	Group1[†]	Group2[‡]
Subjects with events	76	44
Recovered, n (%)	71 (93.4)	41 (93.2)
Received steroid during the 1st event, n (%)	42 (59.2)	34 (82.9)
Received high dose*, n	28	28
Time to recovery (days), median (range)	10.0 (5 to 176)	17.5 (3 to 43)
Received low dose, n	12	6
Time to recovery (days), median (range)	11.5 (5 to 73)	22.5 (16 to 64)
Received no steroid during the 1st event, n (%)	29	7
Time to recovery (days), median (range)	8.0 (4 to 71)	22.0 13 to 44)
Not recovered, n (%)	5 (6.6)	3 (6.8)
Received steroid during the 1st event, n (%)	1 (20.0)	3 (100.0)
Received high dose, n	1	3
Received low dose, n	0	0
Received no steroid during the 1st event, n (%)	4 (80.0)	0

[†] Subjects with ALT or AST ≥ 3xULN - < 10xULN but no concurrent T-bili ≥ 2xULN.

[‡] Subjects with ALT or AST ≥ 10xULN, or ALT or AST ≥ 3xULN with concurrent T-bili ≥ 2xULN.

* High dose steroid is defined as any prednisone dose of ≥40 mg daily or equivalent.

Time to recovery is calculated from onset of ALT or AST ≥ 3xULN event date to both ALT and AST returned to < 3xULN.

Laboratory records up to 90 days of last dose are included.

Database Cutoff Date: 24Aug2018.

Laboratory findings

In pembrolizumab+axitinib arm the following were the most common laboratory abnormalities: *Glucose increased* (61.9%), *ALT increased* (59.6%), *AST increased* (56.7%), *Creatinine increased* (43.0%), *Sodium decreased* (35.0%), *Potassium increased* (34.1%), *Lymphocyte decreased* (33.3%), and *Albumin decreased* (31.9%).

In comparison of the sunitinib arm, the proportion of subjects with abnormal laboratory findings was higher in the pembrolizumab+axitinib arm for: *ALT increased* (59.6% vs 44.4%; grade 3-4 20.1% vs 5.5%), *AST increased* (56.7% and 55.6%; grade 3-4 13.2% vs 4.5%), *Bilirubin increased* (22.0% vs 21.1%), *Calcium increased* (26.6% vs 15.3%). While similar proportions across study arms were found for and *Creatinine increased* (43% and 40%), sunitinib-treated participants had lower frequency of the following: *Potassium increased* (34.1% vs 22%), *Hemoglobin dec*reased (28.7% vs 65.3%; grade 3-4 8.9% vs 3.2%), *Leukocytes decreased* (13.9% vs 71.8%; grade 3-4 1.4% vs 7.8%), *Neutrophils decreased* (26.6% vs 49%; 1.2% vs 18.8%), *Phosphate decreased* (26.2% vs 77.7%; grade 3-4 6.4% vs 17.5%), *Platelet decreased* (26.6% vs 77.7%; grade 3-4 1.4% vs 14.5%).

Hepatic Laboratory Analysis

Table 12-19
Subjects With Liver Function Laboratory Findings That Met Predetermined Criteria
(ASaT Population)

Criteria	Pembrolizumab + Axitinib		Sunitinib	
	n/m	(%)	n/m	(%)
Subjects in population	429		425	
Alanine Aminotransferase				
≥3 x ULN	119/425	(28.0)	42/419	(10.0)
≥5 x ULN	85/425	(20.0)	23/419	(5.5)
≥10 x ULN	37/425	(8.7)	6/419	(1.4)
≥20 x ULN	13/425	(3.1)	2/419	(0.5)
Aspartate Aminotransferase				
≥3 x ULN	101/425	(23.8)	36/419	(8.6)
≥5 x ULN	57/425	(13.4)	19/419	(4.5)
≥10 x ULN	28/425	(6.6)	7/419	(1.7)
≥20 x ULN	9/425	(2.1)	2/419	(0.5)
Aminotransferase (ALT or AST)				
≥3 x ULN	123/425	(28.9)	51/418	(12.2)
≥5 x ULN	87/425	(20.5)	26/418	(6.2)
≥10 x ULN	44/425	(10.4)	7/418	(1.7)
≥20 x ULN	13/425	(3.1)	3/418	(0.7)
Bilirubin				
≥2 x ULN	21/425	(4.9)	29/418	(6.9)
Alkaline Phosphatase				
≥1.5 x ULN	75/424	(17.7)	70/416	(16.8)
Aminotransferase (ALT or AST) and Bilirubin				
AT ≥3 x ULN and BILI ≥1.5 x ULN	23/425	(5.4)	10/417	(2.4)
AT ≥3 x ULN and BILI ≥2 x ULN	15/425	(3.5)	7/417	(1.7)
Aminotransferase (ALT or AST) and Bilirubin and Alkaline Phosphatase				
Aminotransferase (ALT or AST) and Bilirubin and Alkaline Phosphatase				
AT ≥3 x ULN and BILI ≥2 x ULN and ALP <2 x ULN	9/425	(2.1)	0/417	(0.0)

n = Number of Subjects with postbaseline test results (or combination of test results from the same day) that met predetermined criteria.
m = Number of Subjects with at least one postbaseline test result or combination of test results from the same day.
ALP = Alkaline phosphatase; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; AT = Aminotransferase (ALT or AST); BILI = Bilirubin; ULN = Upper limit of normal range.
Laboratory records up to 90 days of last dose are included.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; addili]

Table 12-20
HEAS Subjects With Liver Function Laboratory Findings That Met Predetermined Criteria (ASaT Population)

Criteria	Pembrolizumab + Axitinib n/m	(%)	Sunitinib n/m	(%)
Subjects in population	429		425	
Alanine Aminotransferase				
≥3 x ULN	116/425	(27.3)	35/419	(8.4)
≥5 x ULN	83/425	(19.5)	18/419	(4.3)
≥10 x ULN	37/425	(8.7)	4/419	(1.0)
≥20 x ULN	13/425	(3.1)	2/419	(0.5)
Aspartate Aminotransferase				
≥3 x ULN	100/425	(23.5)	27/419	(6.4)
≥5 x ULN	56/425	(13.2)	13/419	(3.1)
≥10 x ULN	28/425	(6.6)	5/419	(1.2)
≥20 x ULN	9/425	(2.1)	1/419	(0.2)
Aminotransferase (ALT or AST)				
≥3 x ULN	120/425	(28.2)	41/418	(9.8)
≥5 x ULN	85/425	(20.0)	20/418	(4.8)
≥10 x ULN	44/425	(10.4)	5/418	(1.2)
≥20 x ULN	13/425	(3.1)	2/418	(0.5)
Bilirubin				
≥2 x ULN	20/425	(4.7)	20/418	(4.8)
Alkaline Phosphatase				
≥1.5 x ULN	41/424	(9.7)	31/416	(7.5)
Aminotransferase (ALT or AST) and Bilirubin				
AT ≥3 x ULN and BILI ≥1.5 x ULN	22/425	(5.2)	7/417	(1.7)
AT ≥3 x ULN and BILI ≥2 x ULN	14/425	(3.3)	4/417	(1.0)
Aminotransferase (ALT or AST) and Bilirubin and Alkaline Phosphatase				
Aminotransferase (ALT or AST) and Bilirubin and Alkaline Phosphatase				
AT ≥3 x ULN and BILI ≥2 x ULN and ALP <2 x ULN	9/425	(2.1)	0/417	(0.0)

n = Number of HEAS Subjects with postbaseline test results (or combination of test results from the same day) that met predetermined criteria.
m = Number of Subjects with at least one postbaseline test result or combination of test results from the same day.
ALP = Alkaline phosphatase; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; AT = Aminotransferase (ALT or AST); BILI = Bilirubin; ULN = Upper limit of normal range.
Laboratory records up to 90 days of last dose are included.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; addili]

Figure 12-6
Overall Peak ALT/ULN Ratio Over the Whole Study Duration vs.
Overall Peak Total Bilirubin/ULN Ratio Over the Whole Study Duration
(ASaT Population)
Pembrolizumab + Axitinib Arm (N=429)

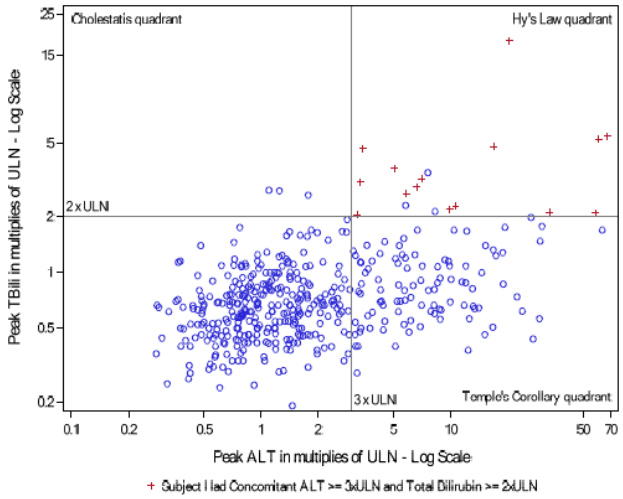
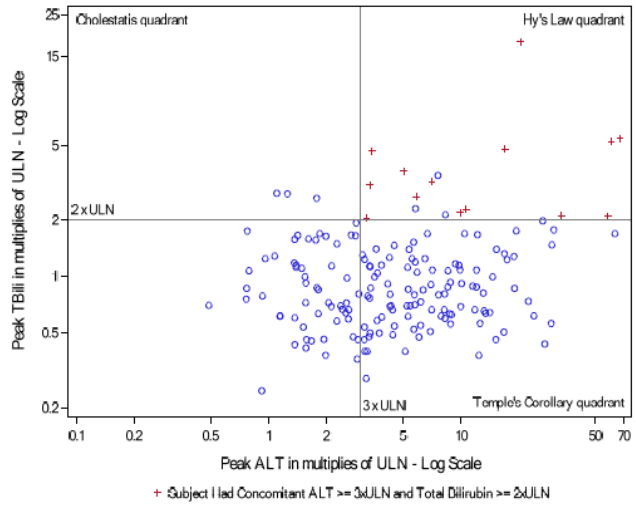


Figure 12-7
Overall Peak ALT/ULN Ratio Over the Whole Study Duration vs.
Overall Peak Total Bilirubin/ULN Ratio Over the Whole Study Duration
(HEAS Population)
Pembrolizumab + Axitinib Arm (N=174)



Characterization of ALT ≥3 x ULN Events in the HEAS

Table 12-21
Time to Onset of the First ALT ≥ 3xULN Events
(HEAS Population)

	Pembrolizumab + Axitinib N =429 (ASaT)
Subjects in HEAS population	174
Subjects in HEAS population with treatment-emergent ALT ≥ 3xULN events	116
Time to onset of the first ALT ≥ 3xULN events since the first study treatment (days)[†]	
Mean	103.3
SD	93.59
Median	70.5
Range	7 to 603

[†] Analysis of time to onset of the first ALT ≥ 3xULN events is based on all HEAS subjects with ALT ≥ 3xULN events.
SD: standard deviation.
Laboratory records up to 90 days of last dose are included.

Source: [P426V01MK3475: adam-adsl; adheas]

Recovery from the First ALT ≥ 3xULN Events and Study Treatment Status after the First Events
(HEAS Population from Pembrolizumab + Axitinib Arm)

	First ALT ≥ 3xULN events[†] categories				
	ALT ≥ 3xULN	ALT ≥ 5xULN	ALT ≥ 10xULN	ALT ≥ 20xULN	ALT ≥ 3xULN with concurrent T-bili ≥ 2xULN
Subjects with any events	116	74	34	11	12
With ALT recovered to < 3xULN from the first event, n (%)[‡]	109 (94.0)	72 (97.3)	32 (94.1)	9 (81.8)	10 (83.3)
Immunosuppressive use during the first event					
Received systemic steroid, n (%)[§]	**65 (59.6)**	**53 (73.6)**	**25 (78.1)**	**7 (77.8)**	**8 (80.0)**
Received other systemic immunosuppressive, n (%)[§]	0	0	0	0	0
Study treatment status after recovery from the first event					
Received no more study treatment after recovery, n (%)[§ ¶]	17 (15.6)	14 (19.4)	10 (31.3)	6 (66.7)	4 (40.0)
Received any study treatment on/after recovery, n (%)[§]	92 (84.4)	58 (80.6)	22 (68.8)	3 (33.3)	6 (60.0)
Received axitinib monotherapy on/after recovery, n (%)[§]	34 (31.2)	31 (43.1)	15 (46.9)	1 (11.1)	4 (40.0)
Duration of treatment after recovery in days[#]					
Median	155.0	152.0	152.0	342.0	80.5
Range	15 to 543	15 to 543	22 to 416	342 to 342	49 to 404
Received pembro monotherapy on/after recovery, n (%)[§]	3 (2.8)	2 (2.8)	1 (3.1)	1 (11.1)	1 (10.0)
Duration of treatment after recovery in days					
Median	28.0	15.0	28.0	28.0	28.0
Range	2 to 57	2 to 28	28 to 28	28 to 28	28 to 28
Received pembro and axitinib on/after recovery, n (%)[§]	55 (50.5)	25 (34.7)	6 (18.8)	1 (11.1)	1 (10.0)
Duration of treatment after recovery in days					
Median	263.0	257.0	408.5	499.0	85.0
Range	8 to 525	22 to 525	154 to 525	499 to 499	85 to 85
With ALT not recovered to < 3xULN from the first event, n (%)	7 (6.0)	2 (2.7)	2 (5.9)	2 (18.2)	2 (16.7)
Steroid use during the first event					
Received systemic steroid, n (%)[‖]	3 (42.9)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)
Received other systemic immunosuppressive, n (%)[‖]	0	0	0	0	0

[†] First ALT ≥ 3xULN event is defined as when the first time a post-baseline ALT ≥ 3xULN occurs until ALT recovered to < 3xULN or with no recovery.
[‡] Proportion of recovery is calculated using subjects with any events in each ALT ≥ 3xULN category as denominators.
[§] Proportion of steroid treatment, study treatment received after recovery is calculated using subjects with ALT recovered in each ALT elevation category as denominator.
[‖] Proportion of steroid treatment in subjects not recovered is calculated using subjects with ALT not recovered in each ALT elevation category as denominator.
[¶] Received no more study treatment after recovery means last dose dates are before recovery from the first event to <3xULN. Reason that study treatment discontinued prior to recovery from the first ALT = 3xULN events can be any.
[#] Duration is calculated from date of recovery to last recorded dose date prior to data cutoff.
Laboratory records up to 90 days of last dose are included.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adheas]

Table 14.4-8
Outcome of Rechallenge after Recovery from the First ALT ≥ 3xULN Events
(HEAS Population from Pembrolizumab + Axitinib Arm)

	Received any study treatment after recovery[†]	Received axitinib only after recovery[†]	Received pembrolizumab only after recovery[†]	Received both axitinib and pembrolizumab after recovery[†]
Subjects in population	92	34	3	55
With no ALT ≥ 3xULN recurred	51 (55.4)	18 (52.9)	2 (66.7)	31 (56.4)
With ALT ≥ 3xULN recurred[‡] and recovered[§]	41 (44.6)	16 (47.1)	1 (33.3)	24 (43.6)
With ALT ≥ 3xULN recurred[‡] and no recovery[§]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[†] Recovery here means from the first ALT ≥ 3xULN events.
[‡] Any recurrence after received study treatment since recovery from the first ALT ≥ 3xULN event.
[§] Recovery status is based on last ALT value showing < 3xULN prior to clinical data cutoff for this analysis.
Laboratory records up to 90 days of last dose are included.
Database Cutoff Date: 24Aug2018.

Source: [P426V01MK3475: adam-adsl; adheas]

Table: Summary of Steroid Use in Subjects with Recurrence of ALT ≥3 × ULN following Rechallenge in the Combination Arm (HEAS Population from Pembrolizumab + Axitinib Arm)

	Received any study treatment after recovery	Received axitinib only after recovery	Received pembrolizumab only after recovery	Received both axitinib and pembrolizumab after recovery
Subjects with ALT ALT ⩾ 3xULN recurred after rechallenge[†]	41	16	1	24
With steroid use[‡]	23	10	1	12

[†] Subjects were rechallenged after recovery from the first ALT ⩾ 3xULN events.
[‡] Steroid use from the second ALT ⩾ 3xULN events to the second recovery.
Laboratory records up to 90 days of last dose are included.
Database Cutoff Date: 24Aug2018.

Table: Outcome of Rechallenge after Recovery from the First ALT ≥ 3xULN Events for Subjects with ALT≥5xULN during the First Event (HEAS Population from Pembrolizumab + Axitinib Arm)

	Received any study treatment after recovery[†]	Received axitinib only after recovery[†]	Received pembrolizumab only after recovery[†]	Received both axitinib and pembrolizumab after recovery[†]
Subjects in population	58	31	2	25
With no ALT ≥ 3xULN recurred	32 (55.2)	17 (54.8)	2 (100.0)	13 (52.0)
With ALT ≥ 3xULN recurred[‡] and recovered[§]	26 (44.8)	14 (45.2)	0 (0.0)	12 (48.0)
With ALT ≥ 3xULN recurred[‡] and no recovery[§]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[†] Recovery here means from the first ALT ≥ 3xULN events.
[‡] Any recurrence after received study treatment since recovery from the first ALT ≥ 3xULN event.
[§] Recovery status is based on last ALT value showing < 3xULN prior to clinical data cutoff for this analysis.
Laboratory records up to 90 days of last dose are included.
Database Cutoff Date: 24Aug2018.

Specific Hepatic Events Subgroups in the Pembrolizumab + Axitinib Group

As specified in the in the Hepatic Events Analysis Plan in the supplemental Statistical Analysis Plan, narratives of the following subgroups of hepatic events have been medically reviewed:

- Group A: Summary of Concurrent ALT or AST ≥3 x ULN and Total Bilirubin ≥2 x ULN

15 of the 429 (3.5%) participants in the pembrolizumab + axitinib group were identified with concurrent ALT >3 × ULN and total bilirubin ≥2 × ULN. Of these 15 participants, 5 participants were

identified as having elevated ALT with concurrent hepatic dysfunction. Of the remaining 10 participants, 4 participants lacked sufficient information to determine if hepatic dysfunction was present; 4 participants had laboratory values that were not consistent with hepatic dysfunction (eg, elevated indirect bilirubin); and 2 participants were determined to have elevated ALT related to other causes (ie, acute cholecystitis, multi-organ failure following myocarditis).

All but two participants with hepatic AEs recovered to Grade 1 or Grade 0 (1 participant with concurrent hepatic dysfunction recovered from Grade 4 to Grade 3, but died subsequently due to drug-related necrotizing fasciitis; 1 participant in whom hepatic dysfunction could not be fully established, continued to increase after study treatment discontinuation. This participant died due to disease progression).

•Group B: Summary of ALT ≥20 x ULN

Overall, 13 participants (3.1%) from the pembrolizumab + axitinib group were identified with peak ALT ≥20 × ULN. Five participants had concurrent total bilirubin ≥2 × ULN, and are included in Group A. Of the remaining 8 cases, five had onset ALT ≥20 x ULN (Grade 4) and the remaining 3 participants had onset ALT ≥3 x ULN but <5 x ULN (Grade 2) and of these, 2 participants had ALT increased to ≥20 x ULN after rechallenge. In all 8 participants, ALT elevations recovered to <3 × ULN with corticosteroid use (n=6) or no corticosteroid use (n=2).

- Group C: Participants with Treatment-emergent ALT ≥3 x ULN Without Recovery to ALT <3 x ULN

Seven participants with treatment-emergent ALT elevation ≥3 × ULN did not demonstrate recovery of ALT <3 × ULN at the time of data cutoff [Table 4.5.22].

- 2 participants had concurrent ALT ≥3 x ULN, total bilirubin ≥2 x ULN, and peak ALT ≥20 x ULN.
  - 1 participant had ALT elevation that decreased from Grade 4 to low Grade 3 after discontinuation of both study treatments and initiation of steroid treatment. This participant subsequently died due to drug-related necrotizing fasciitis.
  - 1 participant with elevated ALT, AST, ALP, and total bilirubin continued to increase after study treatment discontinuation and steroid treatment. This participant subsequently died due to disease progression without further follow-up data
- 5 participants had peak ALT ≥3 x ULN but <5 x ULN without concurrent total bilirubin elevation (Grad 2).
  - 3 participants discontinued study treatment due to disease progression with no follow-up data at the 90 day cutoff for this lab data analysis.
  - 1 participant had onset of ALT elevation (Grade 2) 15 days prior to data cutoff and was still in study treatment and at the time of the cutoff was being followed for this event.
  - 1 participant with no follow-up ALT data provided died due to myasthenia gravis that was considered by the investigator to be related to treatment.

Table: Study Treatment Received After Recovery from the Second Episode of ALT ≥3 × ULN Events

Study treatment received following recovery from the second episode of ALT ≥ 3xULN event	ALT based on peak value of the 2nd episode				
	Total	ALT × ULN ≥3 to < 5	ALT × ULN ≥5 to < 10	ALT × ULN ≥10 to < 20	ALT × ULN ≥20
Participants recovered from the second episode, n	44	21	16	5	2
Received any study drug, n	37	20	10	5	2
Received both pembrolizumab and axitinib, n	17	11	3	3	0
Received pembrolizumab only, n	6	2	2	1	1
Received axitinib only, n	14	7	5	1	1
Received neither study drug, n	7	1	6	0	0
Data cutoff: 02Jan2019					

Cardiac Arrythmias/Atrial Fibrillation

During the evaluation the MAH provided in depth analysis of Atrial Fibrillation and more generally Cardiac Arrythmias SMQ AEs within the KN-426 study, as well as out an overall Safety Database Review to identify any reported event from all types of sources.

Table 2 Overall Summary of Cardiac Arrhythmia Adverse Events (ASaT Population)

	Pembrolizumab + Axitinib		Sunitinib	
	n	(%)	n	(%)
Subjects in population	429		425	
with one or more cardiac arrhythmia adverse events[§]	25	(5.8)	10	(2.4)
with no cardiac arrhythmia adverse event	404	(94.2)	415	(97.6)
with drug-related[†] cardiac arrhythmia adverse events	10	(2.3)	1	(0.2)
with toxicity grade 3-5 cardiac arrhythmia adverse events	5	(1.2)	1	(0.2)
with toxicity grade 3-5 drug-related cardiac arrhythmia adverse events	3	(0.7)	0	(0.0)
with serious cardiac arrhythmia adverse events	6	(1.4)	1	(0.2)
with serious drug-related cardiac arrhythmia adverse events	4	(0.9)	0	(0.0)
who died due to a cardiac arrhythmia adverse event	0	(0.0)	0	(0.0)
who died due to a drug-related cardiac arrhythmia adverse event	0	(0.0)	0	(0.0)
discontinued any drug due to a cardiac arrhythmia adverse event	1	(0.2)	0	(0.0)
discontinued Pembrolizumab	0	(0.0)	0	(0.0)
discontinued Axitinib	1	(0.2)	0	(0.0)
discontinued Both Pembrolizumab and Axitinib	0	(0.0)	0	(0.0)
discontinued any drug due to a drug-related cardiac arrhythmia adverse event	1	(0.2)	0	(0.0)
discontinued Pembrolizumab	0	(0.0)	0	(0.0)
discontinued Axitinib	1	(0.2)	0	(0.0)
discontinued Both Pembrolizumab and Axitinib	0	(0.0)	0	(0.0)
discontinued any drug due to a serious cardiac arrhythmia adverse event	1	(0.2)	0	(0.0)
discontinued Pembrolizumab	0	(0.0)	0	(0.0)
discontinued Axitinib	1	(0.2)	0	(0.0)
discontinued Both Pembrolizumab and Axitinib	0	(0.0)	0	(0.0)
discontinued any drug due to a serious drug-related cardiac arrhythmia adverse event	1	(0.2)	0	(0.0)
discontinued Pembrolizumab	0	(0.0)	0	(0.0)
discontinued Axitinib	1	(0.2)	0	(0.0)
discontinued Both Pembrolizumab and Axitinib	0	(0.0)	0	(0.0)

	Pembrolizumab + Axitinib		Sunitinib	
	n	(%)	n	(%)

[†] Determined by the investigator to be related to the drug.
Grades are based on NCI CTCAE version 4.0.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Database Cutoff Date: 24Aug2018.

Table 3 Subjects With Cardiac Arrhythmia Adverse Events by Decreasing Incidence (Incidence > 0% in One or More Treatment Groups) (ASaT Population)

	Pembrolizumab + Axitinib		Sunitinib	
	n	(%)	n	(%)
Subjects in population	429		425	
with one or more cardiac arrhythmia adverse events	25	(5.8)	10	(2.4)
with no cardiac arrhythmia adverse events	404	(94.2)	415	(97.6)
Atrial fibrillation	7	(1.6)	1	(0.2)
Sinus tachycardia	4	(0.9)	3	(0.7)
Sinus bradycardia	3	(0.7)	1	(0.2)
Supraventricular tachycardia	2	(0.5)	0	(0.0)
Ventricular extrasystoles	2	(0.5)	1	(0.2)
Arrhythmia supraventricular	1	(0.2)	0	(0.0)
Atrial flutter	1	(0.2)	1	(0.2)
Atrial tachycardia	1	(0.2)	0	(0.0)
Atrioventricular block	1	(0.2)	1	(0.2)
Bradyarrhythmia	1	(0.2)	0	(0.0)
Bundle branch block right	1	(0.2)	1	(0.2)
Electrocardiogram QT prolonged	1	(0.2)	0	(0.0)
Sinus node dysfunction	1	(0.2)	0	(0.0)
Ventricular arrhythmia	1	(0.2)	0	(0.0)
Arrhythmia	0	(0.0)	1	(0.2)
Rhythm idioventricular	0	(0.0)	1	(0.2)

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

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

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

The adverse events are ordered decreasingly by the incidence in the first column.

Database Cutoff Date: 24Aug2018.

Table 4
Exposure-Adjusted Cardiac Arrhythmias Adverse Events
(Including Multiple Occurrences of Events)
(Incidence > 0% In One or More Treatment Groups)
(By Decreasing Frequency of Preferred Term)
(Asat Population)

	Event Count and Rate (Events/100 person-months)[†]			
	KN426 Data for Pembrolizumab + Axitinib[‖]	KN426 Sunitinib[††]	Reference Safety Dataset for Pembrolizumab Monotherapy[¶]	Cumulative Running Safety Dataset for Pembrolizumab Monotherapy[#]
Number of subjects exposed	429	425	4439	6436
Total exposure[‡] person-months	4766.94	3924.64	32354.30	49189.73
Total events (rate)	28 (0.59)	11 (0.28)	181 (0.56)	244 (0.50)
SMQ Cardiac Arrhythmia	28 (0.6)	11 (0.3)	181 (0.6)	244 (0.5)

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

[‡] Drug exposure is defined as the interval of min (last dose date+30, Cutoff Date) – first dose date+1.

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

Preferred terms 'Neoplasm progression', 'Malignant neoplasm progression' and 'Disease progression' not related to the drug are excluded.

[‖] Includes all subjects who received at least one dose of Pembrolizumab and/or Axitinib in KN426.

[††] Includes all subjects who received at least one dose of Sunitinib in KN426.

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

[#] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma) and Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort B4, KN040, KN042, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158, KN164 Cohort A, KN170, KN224 and KN427 Cohort A.

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

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)

Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)

Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)

Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)

Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)

Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)

Database cutoff date for HCC (KN224: 15MAY2018)

Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)

Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl; adae]

Table 5
Exposure-Adjusted Cardiac Arrhythmias Adverse Events
(Including Multiple Occurrences of Events)
(Incidence > 0% In One or More Treatment Groups)
(By Decreasing Frequency of Preferred Term)
(ASAT POPULATION)

	Event Count and Rate (Events/100 person-months)[†]			
	KN426 Data for Pembrolizumab + Axitinib[‖]	KN426 Sunitinib[††]	Reference Safety Dataset for Pembrolizumab Monotherapy[¶]	Cumulative Running Safety Dataset for Pembrolizumab Monotherapy[#]
Number of subjects exposed	429	425	4439	6436
Total exposure[‡] person-months	4766.94	3924.64	32354.30	49189.73
Total events (rate)	28 (0.59)	11 (0.28)	181 (0.56)	244 (0.50)
Atrial fibrillation	8 (0.2)	1 (0.0)	63 (0.2)	83 (0.2)
Sinus tachycardia	4 (0.1)	3 (0.1)	37 (0.1)	45 (0.1)
Sinus bradycardia	3 (0.1)	1 (0.0)	14 (0.0)	21 (0.0)
Supraventricular tachycardia	2 (0.0)	0 (0.0)	18 (0.1)	26 (0.1)
Ventricular extrasystoles	2 (0.0)	1 (0.0)	3 (0.0)	4 (0.0)
Arrhythmia supraventricular	1 (0.0)	0 (0.0)	1 (0.0)	1 (0.0)
Atrial flutter	1 (0.0)	1 (0.0)	16 (0.0)	18 (0.0)
Atrial tachycardia	1 (0.0)	0 (0.0)	1 (0.0)	1 (0.0)
Atrioventricular block	1 (0.0)	1 (0.0)	1 (0.0)	2 (0.0)
Bradyarrhythmia	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bundle branch block right	1 (0.0)	1 (0.0)	3 (0.0)	3 (0.0)
Electrocardiogram QT prolonged	1 (0.0)	0 (0.0)	9 (0.0)	10 (0.0)
Sinus node dysfunction	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ventricular arrhythmia	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Adams-Stokes syndrome	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Arrhythmia	0 (0.0)	1 (0.0)	4 (0.0)	6 (0.0)
Atrioventricular block complete	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.0)
Atrioventricular block first degree	0 (0.0)	0 (0.0)	4 (0.0)	4 (0.0)
Bundle branch block left	0 (0.0)	0 (0.0)	1 (0.0)	3 (0.0)
Electrocardiogram repolarisation abnormality	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.0)
Heart rate irregular	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.0)
Paroxysmal arrhythmia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Rhythm idioventricular	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Supraventricular extrasystoles	0 (0.0)	0 (0.0)	2 (0.0)	4 (0.0)
Tachyarrhythmia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Ventricular fibrillation	0 (0.0)	0 (0.0)	1 (0.0)	2 (0.0)
Ventricular tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.0)
Wolff-Parkinson-White syndrome	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)

	Event Count and Rate (Events/100 person-months)[†]			
	KN426 Data for Pembrolizumab + Axitinib[‖]	KN426 Sunitinib[††]	Reference Safety Dataset for Pembrolizumab Monotherapy[¶]	Cumulative Running Safety Dataset for Pembrolizumab Monotherapy[#]

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

[‡] Drug exposure is defined as the interval of min (last dose date+30, Cutoff Date) – first dose date+1.

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

Preferred terms 'Neoplasm progression', 'Malignant neoplasm progression' and 'Disease progression' not related to the drug are excluded.

[‖] Includes all subjects who received at least one dose of Pembrolizumab and/or Axitinib in KN426.

[††] Includes all subjects who received at least one dose of Sunitinib in KN426.

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

[#] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma) and Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort B4, KN040, KN042, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158, KN164 Cohort A, KN170, KN224 and KN427 Cohort A.

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

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)

Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)

Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)

Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)

Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)

Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)

Database cutoff date for HCC (KN224: 15MAY2018)

Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)

Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl; adae]

The pembrolizumab OASE is the largest source of unblinded aggregate (i.e. across indications) safety data from pembrolizumab monotherapy including all open-label, unmasked, or completed randomized study for which there has been a database lock on or before 31-Mar--2018 (n=9118). Pooled data from all studies using chemotherapy comparators (all cytotoxic treatments combined, N=1324) is provided in this response for context and comparison.

The OASE database was queried to identify participants with AEs (including AE count and frequency) from the MedDRA sub-SMQ Cardiac arrhythmias (including bradyarrhythmias and tachyarrhythmias).

Table 7
Adverse Event Summary
By Treatment Group in the OASE
Preferred Terms for the SMQ of Cardiac Arrhythmia
(APaT Population)

	All MK-3475 Combined†		Chemotherapy	
	n	(%)	n	(%)
Subjects in population	9,118		1,324	
with one or more adverse events	297	(3.3)	34	(2.6)
with no adverse event	8,821	(96.7)	1,290	(97.4)
with drug-related‡ adverse events	22	(0.2)	6	(0.5)
with toxicity grade 3-5 adverse events	65	(0.7)	12	(0.9)
with toxicity grade 3-5 drug-related adverse events	5	(0.1)	2	(0.2)
with non-serious adverse events	240	(2.6)	27	(2.0)
with serious adverse events	63	(0.7)	10	(0.8)
with serious drug-related adverse events	3	(0.0)	1	(0.1)
who died	4	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	7	(0.1)	1	(0.1)
discontinued drug due to a drug-related adverse event	2	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	7	(0.1)	1	(0.1)
discontinued drug due to a serious drug-related adverse event	2	(0.0)	0	(0.0)

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

MedDRA version 21.0 is applied.

†Includes the following subjects on MK-3475 monotherapy: 1) all subjects in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN012, KN013 HL and PMBCL Cohorts, KN013 non-Hodgkin Lymphoma Cohorts with PD-L1 positive (4B), with relapsed/refractory Follicular Lymphoma (4C) and with relapsed/refractory Diffuse Large B-Cell Lymphoma (4D), KN025, KN028, KN041, KN051, KN052, KN055, KN057, KN086, KN087, KN100, KN151, KN158, KN164, KN170 PMBCL, KN180, KN199 and KN224, 2) all subjects in KN002 treated with pembrolizumab in the original phase, and 3) all subjects treated with pembrolizumab monotherapy in KN006, KN010, KN024, KN040, KN045, KN054, KN059 and KN061.

††From KN054, an adjuvant therapy with Pembrolizumab versus placebo after complete resection of high-risk Stage III melanoma.

(MK-3475 KN001 Database Cutoff Date: 18SEP2015).

(MK-3475 KN002 Database Cutoff Date: 03FEB2017).

(MK-3475 KN006 Database Cutoff Date: 04DEC2017).

(MK-3475 KN010 Database Cutoff Date: 24MAR2017).

(MK-3475 KN012 Database Cutoff Date: 26APR2016).

(MK-3475 KN013 Database Cutoff Date for Hodgkin lymphoma: 27SEP2016).

(MK-3475 KN013 Database Cutoff Date for Primary Mediastinal Large B Cell Lymphoma (Cohort 4A): 04AUG2017).

(MK-3475 KN013 Database Cutoff Date for non-Hodgkin Lymphoma with PD-L1 positive (Cohort 4B), with relapsed/refractory Follicular Lymphoma (Cohort 4C) and with relapsed/refractory Diffuse Large B-Cell Lymphoma (Cohort 4D): 13SEP2017).

(MK-3475 KN024 Database Cutoff Date: 10JUL2017).

(MK-3475 KN025 Database Cutoff Date: 07JUN2017).

(MK-3475 KN028 Database Cutoff Date: 31JAN2018).

(MK-3475 KN040 Database Cutoff Date: 15MAY2017).

(MK-3475 KN041 Database Cutoff Date: 31AUG2017).

(MK-3475 KN045 Database Cutoff Date: 26OCT2017).

(MK-3475 KN051 Database Cutoff Date: 16FEB2018).

(MK-3475 KN052 Database Cutoff Date: 30NOV2017).

(MK-3475 KN054 Database Cutoff Date: 02OCT2017).

(MK-3475 KN055 Database Cutoff Date: 22APR2016).

(MK-3475 KN057 Database Cutoff Date: 12FEB2018).

	All MK-3475 Combined†		Chemotherapy	
	n	(%)	n	(%)
(MK-3475 KN059 Database Cutoff Date: 21APR2017).				
(MK-3475 KN061 Database Cutoff Date: 26OCT2017).				
(MK-3475 KN086 Database Cutoff Date: 10NOV2017).				
(MK-3475 KN087 Database Cutoff Date: 21MAR2017).				
(MK-3475 KN100 Database Cutoff Date: 02JAN2017).				
(MK-3475 KN151 Database Cutoff Date: 27DEC2017).				
(MK-3475 KN158 Database Cutoff Date: 15JAN2018).				
(MK-3475 KN164 Database Cutoff Date for Cohort A and Cohort B: 12SEP2017).				
(MK-3475 KN170 Database Cutoff Date for the PMBCL Cohort: 19JAN2018).				
(MK-3475 KN180 Database Cutoff Date: 18SEP2017).				
(MK-3475 KN199 Database Cutoff Date: 13OCT2017).				
(MK-3475 KN224 Database Cutoff Date: 13FEB2018).				

Source: [1Q2018OASE: adam.iadsl; iadae]

Table 8
Subjects with Adverse Events
(Incidence >0% in One or More Treatment Groups)
By Treatment Group in the OASE
Preferred Terms for the SMQ of Cardiac Arrhythmias Sorted by Decreasing Incidence
(APaT Population)

	All MK-3475 Combined†		Chemotherapy	
	n	(%)	n	(%)
Subjects in population	9,118		1,324	
with one or more adverse events	297	(3.3)	34	(2.6)
with no adverse events	8,821	(96.7)	1,290	(97.4)
Atrial fibrillation	96	(1.1)	13	(1.0)
Sinus tachycardia	85	(0.9)	8	(0.6)
Sinus bradycardia	26	(0.3)	2	(0.2)
Supraventricular tachycardia	24	(0.3)	2	(0.2)
Atrial flutter	21	(0.2)	1	(0.1)
Electrocardiogram QT prolonged	13	(0.1)	0	(0.0)
Arrhythmia	10	(0.1)	4	(0.3)
Ventricular tachycardia	6	(0.1)	0	(0.0)
Bundle branch block right	5	(0.1)	0	(0.0)
Atrioventricular block first degree	4	(0.0)	0	(0.0)
Ventricular extrasystoles	4	(0.0)	1	(0.1)
Atrioventricular block complete	3	(0.0)	0	(0.0)
Heart rate irregular	3	(0.0)	0	(0.0)
Supraventricular extrasystoles	3	(0.0)	0	(0.0)
Ventricular fibrillation	3	(0.0)	1	(0.1)
Atrial tachycardia	2	(0.0)	0	(0.0)
Arrhythmia supraventricular	1	(0.0)	0	(0.0)
Atrioventricular block	1	(0.0)	2	(0.2)
Bundle branch block	1	(0.0)	0	(0.0)
Bundle branch block left	1	(0.0)	1	(0.1)
Electrocardiogram repolarisation abnormality	1	(0.0)	0	(0.0)

	All MK-3475 Combined†		Chemotherapy	
	n	(%)	n	(%)
Extrasystoles	1	(0.0)	0	(0.0)
Pulseless electrical activity	1	(0.0)	0	(0.0)
Sinus arrhythmia	1	(0.0)	0	(0.0)
Tachyarrhythmia	1	(0.0)	1	(0.1)
Ventricular arrhythmia	1	(0.0)	0	(0.0)
Conduction disorder	0	(0.0)	1	(0.1)

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

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

MedDRA version 21.0 is applied.

†Includes the following subjects on MK-3475 monotherapy: 1) all subjects in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN012, KN013 HL and PMBCL Cohorts, KN013 non-Hodgkin Lymphoma Cohorts with PD-L1 positive (4B), with relapsed/refractory Follicular Lymphoma (4C) and with relapsed/refractory Diffuse Large B-Cell Lymphoma (4D), KN025, KN028, KN041, KN051, KN052, KN055, KN057, KN086, KN087, KN100, KN151, KN158, KN164, KN170 PMBCL, KN180, KN199 and KN224, 2) all subjects in KN002 treated with pembrolizumab in the original phase, and 3) all subjects treated with pembrolizumab monotherapy in KN006, KN010, KN024, KN040, KN045, KN054, KN059 and KN061.

(MK-3475 KN001 Database Cutoff Date: 18SEP2015).

(MK-3475 KN002 Database Cutoff Date: 03FEB2017).

(MK-3475 KN006 Database Cutoff Date: 04DEC2017).

(MK-3475 KN010 Database Cutoff Date: 24MAR2017).

(MK-3475 KN012 Database Cutoff Date: 26APR2016).

(MK-3475 KN013 Database Cutoff Date for Hodgkin lymphoma: 27SEP2016).

(MK-3475 KN013 Database Cutoff Date for Primary Mediastinal Large B Cell Lymphoma (Cohort 4A): 04AUG2017).

(MK-3475 KN013 Database Cutoff Date for non-Hodgkin Lymphoma with PD-L1 positive (Cohort 4B), with relapsed/refractory Follicular Lymphoma (Cohort 4C) and with relapsed/refractory Diffuse Large B-Cell Lymphoma (Cohort 4D): 13SEP2017).

(MK-3475 KN024 Database Cutoff Date: 10JUL2017).

(MK-3475 KN025 Database Cutoff Date: 07JUN2017).

(MK-3475 KN028 Database Cutoff Date: 31JAN2018).

(MK-3475 KN040 Database Cutoff Date: 15MAY2017).

(MK-3475 KN041 Database Cutoff Date: 31AUG2017).

(MK-3475 KN045 Database Cutoff Date: 26OCT2017).

(MK-3475 KN051 Database Cutoff Date: 16FEB2018).

(MK-3475 KN052 Database Cutoff Date: 30NOV2017).

(MK-3475 KN054 Database Cutoff Date: 02OCT2017).

(MK-3475 KN055 Database Cutoff Date: 22APR2016).

(MK-3475 KN057 Database Cutoff Date: 12FEB2018).

(MK-3475 KN059 Database Cutoff Date: 21APR2017).

(MK-3475 KN061 Database Cutoff Date: 26OCT2017).

(MK-3475 KN086 Database Cutoff Date: 10NOV2017).

(MK-3475 KN087 Database Cutoff Date: 21MAR2017).

(MK-3475 KN100 Database Cutoff Date: 02JAN2017).

(MK-3475 KN151 Database Cutoff Date: 27DEC2017).

(MK-3475 KN158 Database Cutoff Date: 15JAN2018).

(MK-3475 KN164 Database Cutoff Date for Cohort A and Cohort B: 12SEP2017).

(MK-3475 KN170 Database Cutoff Date for the PMBCL Cohort: 19JAN2018).

(MK-3475 KN180 Database Cutoff Date: 18SEP2017).

(MK-3475 KN199 Database Cutoff Date: 13OCT2017).

(MK-3475 KN224 Database Cutoff Date: 13FEB2018).

Source: [1Q2018OASE: adam:iadsl; iadae]

The risk of all cardiac arrhythmias in the pooled pembrolizumab monotherapy dataset shown by age categories is depicted in the Table below.

Table 10
Subjects With Adverse Events
(Incidence > 0% in One or More Treatment Groups)
By Age Category (years)
Preferred Terms for the SMQ of Cardiac Arrhythmia Sorted by Decreasing Frequency
(APaT Population)

	<50		50 to <60		60 to <70		70 to <80		>=80	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	1,894		2,073		2,862		1,881		408	
with one or more adverse events	41	(2.2)	52	(2.5)	91	(3.2)	87	(4.6)	26	(6.4)
with no adverse events	1,853	(97.8)	2,021	(97.5)	2,771	(96.8)	1,794	(95.4)	382	(93.6)
Sinus tachycardia	27	(1.4)	16	(0.8)	27	(0.9)	13	(0.7)	2	(0.5)
Atrial fibrillation	4	(0.2)	9	(0.4)	31	(1.1)	38	(2.0)	14	(3.4)
Sinus bradycardia	3	(0.2)	5	(0.2)	5	(0.2)	10	(0.5)	3	(0.7)
Supraventricular tachycardia	3	(0.2)	5	(0.2)	7	(0.2)	5	(0.3)	4	(1.0)
Atrial flutter	2	(0.1)	5	(0.2)	10	(0.3)	4	(0.2)	0	(0.0)
Electrocardiogram QT prolonged	1	(0.1)	3	(0.1)	3	(0.1)	5	(0.3)	1	(0.2)
Extrasystoles	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Heart rate irregular	1	(0.1)	1	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)
Tachyarrhythmia	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Ventricular tachycardia	1	(0.1)	2	(0.1)	2	(0.1)	0	(0.0)	1	(0.2)
Arrhythmia	0	(0.0)	1	(0.0)	2	(0.1)	7	(0.4)	0	(0.0)
Arrhythmia supraventricular	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Atrial tachycardia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.2)
Atrioventricular block	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Atrioventricular block complete	0	(0.0)	1	(0.0)	1	(0.0)	1	(0.1)	0	(0.0)
Atrioventricular block first degree	0	(0.0)	1	(0.0)	1	(0.0)	2	(0.1)	0	(0.0)
Bundle branch block	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Bundle branch block left	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Bundle branch block right	0	(0.0)	2	(0.1)	2	(0.1)	0	(0.0)	1	(0.2)
Electrocardiogram repolarisation abnormality	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pulseless electrical activity	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Sinus arrhythmia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)
Supraventricular extrasystoles	0	(0.0)	0	(0.0)	1	(0.0)	2	(0.1)	0	(0.0)
Ventricular arrhythmia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)
Ventricular extrasystoles	0	(0.0)	2	(0.1)	0	(0.0)	2	(0.1)	0	(0.0)
Ventricular fibrillation	0	(0.0)	0	(0.0)	1	(0.0)	2	(0.1)	0	(0.0)

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

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

MedDRA version 21.0 is applied.

Includes the following subjects on MK-3475 monotherapy: 1) all subjects in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN012, KN013 HL and PMBCL Cohorts, KN013 non-Hodgkin Lymphoma Cohorts with PD-L1 positive (4B), with relapsed/refractory Follicular Lymphoma (4C) and with relapsed/refractory Diffuse Large B-Cell Lymphoma (4D), KN025, KN028, KN041, KN051, KN052, KN055, KN057, KN086, KN087, KN100, KN151, KN158, KN164, KN170 PMBCL, KN180, KN199 and KN224, 2) all subjects in KN002 treated with pembrolizumab in the original phase, and 3) all subjects treated with pembrolizumab monotherapy in KN006, KN010, KN024, KN040, KN045, KN054, KN059 and KN061.

	<50		50 to <60		60 to <70		70 to <80		>=80	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
(MK-3475 KN001 Database Cutoff Date: 18SEP2015).										
(MK-3475 KN002 Database Cutoff Date: 03FEB2017).										
(MK-3475 KN006 Database Cutoff Date: 04DEC2017).										
(MK-3475 KN010 Database Cutoff Date: 24MAR2017).										
(MK-3475 KN012 Database Cutoff Date: 26APR2016).										
(MK-3475 KN013 Database Cutoff Date for Hodgkin lymphoma: 27SEP2016).										
(MK-3475 KN013 Database Cutoff Date for Primary Mediastinal Large B Cell Lymphoma (Cohort 4A): 04AUG2017).										
(MK-3475 KN013 Database Cutoff Date for non-Hodgkin Lymphoma with PD-L1 positive (Cohort 4B), with relapsed/refractory Follicular Lymphoma (Cohort 4C) and with relapsed/refractory Diffuse Large B-Cell Lymphoma (Cohort 4D): 13SEP2017).										
(MK-3475 KN024 Database Cutoff Date: 10JUL2017).										
(MK-3475 KN025 Database Cutoff Date: 07JUN2017).										
(MK-3475 KN028 Database Cutoff Date: 31JAN2018).										
(MK-3475 KN040 Database Cutoff Date: 15MAY2017).										
(MK-3475 KN041 Database Cutoff Date: 31AUG2017).										
(MK-3475 KN045 Database Cutoff Date: 26OCT2017).										
(MK-3475 KN051 Database Cutoff Date: 16FEB2018).										
(MK-3475 KN052 Database Cutoff Date: 30NOV2017).										
(MK-3475 KN054 Database Cutoff Date: 02OCT2017).										
(MK-3475 KN055 Database Cutoff Date: 22APR2016).										
(MK-3475 KN057 Database Cutoff Date: 12FEB2018).										
(MK-3475 KN059 Database Cutoff Date: 21APR2017).										
(MK-3475 KN061 Database Cutoff Date: 26OCT2017).										
(MK-3475 KN086 Database Cutoff Date: 10NOV2017).										
(MK-3475 KN087 Database Cutoff Date: 21MAR2017).										
(MK-3475 KN100 Database Cutoff Date: 02JAN2017).										
(MK-3475 KN151 Database Cutoff Date: 27DEC2017).										
(MK-3475 KN158 Database Cutoff Date: 15JAN2018).										
(MK-3475 KN164 Database Cutoff Date for Cohort A and Cohort B: 12SEP2017).										
(MK-3475 KN170 Database Cutoff Date for the PMBCL Cohort: 19JAN2018).										
(MK-3475 KN180 Database Cutoff Date: 18SEP2017).										
(MK-3475 KN199 Database Cutoff Date: 13OCT2017).										
(MK-3475 KN224 Database Cutoff Date: 13FEB2018).										

Source: [1Q2018OASE: adam-iadsl; iadae]

Immunogenicity

Table 4.5.25: Overview of Impact of ADA on Adverse Events Incidence after Pembrolizumab Combination Therapy, 200 mg Pembrolizumab Q3W + 5 mg Axitinib BID (KN426)

	negative		non-TE nAB Neg		non-TE nAB Pos		TE nAB Neg		TE nAB Pos	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	358		5		2		21		3	
with one or more adverse events	354	(98.9)	5	(100.0)	2	(100.0)	21	(100.0)	3	(100.0)
with no adverse event	4	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
with drug-related† adverse events	349	(97.5)	4	(80.0)	2	(100.0)	21	(100.0)	3	(100.0)
with toxicity grade 3-5 adverse events	269	(75.1)	4	(80.0)	2	(100.0)	17	(81.0)	3	(100.0)
with toxicity grade 3-5 drug-related adverse events	221	(61.7)	3	(60.0)	2	(100.0)	16	(76.2)	2	(66.7)
with serious adverse events	147	(41.1)	3	(60.0)	1	(50.0)	10	(47.6)	2	(66.7)
with serious drug-related adverse events	84	(23.5)	3	(60.0)	1	(50.0)	6	(28.6)	1	(33.3)
who died	13	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	100	(27.9)	3	(60.0)	2	(100.0)	11	(52.4)	1	(33.3)
discontinued drug due to a drug-related adverse event	81	(22.6)	1	(20.0)	2	(100.0)	9	(42.9)	1	(33.3)
discontinued drug due to a serious adverse event	61	(17.0)	2	(40.0)	1	(50.0)	5	(23.8)	1	(33.3)
discontinued drug due to a serious drug-related adverse event	41	(11.5)	1	(20.0)	1	(50.0)	3	(14.3)	1	(33.3)

† Determined by the investigator to be related to the drug.
Grades are based on NCI CTCAE version 4.0.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Database Cutoff Date: 24Aug2018.
Subjects with inconclusive ADA results are excluded

Safety in special populations

Intrinsic Factors

Age

Table 5.3.5.3.3-rcc1: 122

Adverse Event Summary by Age Category (<65, 65-74, 75-84, >= 85)
(ASaT Population)

	KN426 Data for Pembrolizumab + Axitinib‖								KN426 Sunitinib††							
	<65		65-74		75-84		>=85		<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	257		136		34		2		277		111		35		2	
with one or more adverse events	253	(98.4)	133	(97.8)	34	(100.0)	2	(100.0)	275	(99.3)	111	(100.0)	35	(100.0)	2	(100.0)
with no adverse event	4	(1.6)	3	(2.2)	0	(0.0)	0	(0.0)	2	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
with drug-related† adverse events	247	(96.1)	131	(96.3)	34	(100.0)	1	(50.0)	270	(97.5)	108	(97.3)	35	(100.0)	2	(100.0)
with toxicity grade 3-5 adverse events	177	(68.9)	116	(85.3)	30	(88.2)	2	(100.0)	181	(65.3)	89	(80.2)	28	(80.0)	2	(100.0)
with toxicity grade 3-5 drug-related adverse events	144	(56.0)	96	(70.6)	29	(85.3)	1	(50.0)	145	(52.3)	75	(67.6)	25	(71.4)	2	(100.0)
with serious adverse events	95	(37.0)	57	(41.9)	19	(55.9)	2	(100.0)	68	(24.5)	49	(44.1)	15	(42.9)	1	(50.0)
with serious drug-related adverse events	56	(21.8)	35	(25.7)	10	(29.4)	1	(50.0)	26	(9.4)	24	(21.6)	9	(25.7)	1	(50.0)
who died	3	(1.2)	4	(2.9)	3	(8.8)	1	(50.0)	7	(2.5)	6	(5.4)	2	(5.7)	0	(0.0)
who died due to a drug-related adverse event	1	(0.4)	2	(1.5)	1	(2.9)	0	(0.0)	2	(0.7)	4	(3.6)	1	(2.9)	0	(0.0)
discontinued any drug due to an adverse event	70	(27.2)	47	(34.6)	13	(38.2)	1	(50.0)	30	(10.8)	22	(19.8)	7	(20.0)	0	(0.0)
discontinued Pembrolizumab	49	(19.1)	28	(20.6)	11	(32.4)	1	(50.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued all regimen components	16	(6.2)	11	(8.1)	5	(14.7)	1	(50.0)	30	(10.8)	22	(19.8)	7	(20.0)	0	(0.0)
discontinued any drug due to a drug-related adverse event	63	(24.5)	37	(27.2)	11	(32.4)	0	(0.0)	22	(7.9)	15	(13.5)	6	(17.1)	0	(0.0)
discontinued Pembrolizumab	48	(18.7)	23	(16.9)	9	(26.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued all regimen components	16	(6.2)	8	(5.9)	3	(8.8)	0	(0.0)	22	(7.9)	15	(13.5)	6	(17.1)	0	(0.0)
discontinued any drug due to a serious adverse event	35	(13.6)	30	(22.1)	7	(20.6)	1	(50.0)	23	(8.3)	14	(12.6)	5	(14.3)	0	(0.0)
discontinued Pembrolizumab	24	(9.3)	18	(13.2)	7	(20.6)	1	(50.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued all regimen components	12	(4.7)	9	(6.6)	3	(8.8)	1	(50.0)	23	(8.3)	14	(12.6)	5	(14.3)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	29	(11.3)	19	(14.0)	5	(14.7)	0	(0.0)	16	(5.8)	8	(7.2)	4	(11.4)	0	(0.0)
discontinued Pembrolizumab	24	(9.3)	13	(9.6)	5	(14.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

discontinued all regimen components	12	(4.7)	6	(4.4)	1	(2.9)	0	(0.0)	16	(5.8)	8	(7.2)	4	(11.4)	0	(0.0)

† Determined by the investigator to be related to the drug.
Non-serious adverse events up to 30 days following the last dose and serious adverse events up to 90 days following the last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
‡ Includes all subjects who received at least one dose of Pembrolizumab and/or Axitinib in KN426.
†† Includes all subjects who received at least one dose of Sunitinib in KN426.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)
Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)
Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)
Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)
Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)
Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)
Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)
Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)
Database cutoff date for HCC (KN224: 15MAY2018)
Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)
Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl; adae]

Table 5.3.5.3.3-rcc1: 123

Adverse Event Summary by Age Category (<65, 65-74, 75-84, >= 85)
(ASaT Population)

	Reference Safety Dataset for Pembrolizumab Monotherapy†								Cumulative Running Safety Dataset for Pembrolizumab Monotherapy‡							
	<65		65-74		75-84		>=85		<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	2,453		1,333		563		90		3,709		1,897		722		108	
with one or more adverse events	2,381	(97.1)	1,292	(96.9)	551	(97.9)	89	(98.9)	3,579	(96.5)	1,836	(96.8)	703	(97.4)	107	(99.1)
with no adverse event	72	(2.9)	41	(3.1)	12	(2.1)	1	(1.1)	130	(3.5)	61	(3.2)	19	(2.6)	1	(0.9)
with drug-related† adverse events	1,716	(70.0)	951	(71.3)	405	(71.9)	68	(75.6)	2,570	(69.3)	1,351	(71.2)	508	(70.4)	83	(76.9)
with toxicity grade 3-5 adverse events	1,111	(45.3)	681	(51.1)	307	(54.5)	54	(60.0)	1,669	(45.0)	964	(50.8)	410	(56.8)	64	(59.3)
with toxicity grade 3-5 drug-related adverse events	318	(13.0)	227	(17.0)	100	(17.8)	15	(16.7)	509	(13.7)	349	(18.4)	139	(19.3)	21	(19.4)
with serious adverse events	865	(35.3)	561	(42.1)	261	(46.4)	42	(46.7)	1,301	(35.1)	780	(41.1)	339	(47.0)	52	(48.1)
with serious drug-related adverse events	228	(9.3)	156	(11.7)	71	(12.6)	9	(10.0)	370	(10.0)	243	(12.8)	93	(12.9)	14	(13.0)
who died	95	(3.9)	70	(5.3)	38	(6.7)	8	(8.9)	149	(4.0)	111	(5.9)	59	(8.2)	10	(9.3)
who died due to a drug-related adverse event	11	(0.4)	7	(0.5)	3	(0.5)	1	(1.1)	20	(0.5)	14	(0.7)	6	(0.8)	1	(0.9)
discontinued any drug due to an adverse event	255	(10.4)	176	(13.2)	99	(17.6)	8	(8.9)	415	(11.2)	263	(13.9)	137	(19.0)	13	(12.0)
discontinued Pembrolizumab	255	(10.4)	176	(13.2)	99	(17.6)	8	(8.9)	415	(11.2)	263	(13.9)	137	(19.0)	13	(12.0)
discontinued all regimen components	255	(10.4)	176	(13.2)	99	(17.6)	8	(8.9)	415	(11.2)	263	(13.9)	137	(19.0)	13	(12.0)
discontinued any drug due to a drug-related adverse event	114	(4.6)	93	(7.0)	49	(8.7)	3	(3.3)	210	(5.7)	142	(7.5)	64	(8.9)	7	(6.5)
discontinued Pembrolizumab	114	(4.6)	93	(7.0)	49	(8.7)	3	(3.3)	210	(5.7)	142	(7.5)	64	(8.9)	7	(6.5)
discontinued all regimen components	114	(4.6)	93	(7.0)	49	(8.7)	3	(3.3)	210	(5.7)	142	(7.5)	64	(8.9)	7	(6.5)
discontinued any drug due to a serious adverse event	198	(8.1)	127	(9.5)	76	(13.5)	6	(6.7)	303	(8.2)	188	(9.9)	107	(14.8)	10	(9.3)
discontinued Pembrolizumab	198	(8.1)	127	(9.5)	76	(13.5)	6	(6.7)	303	(8.2)	188	(9.9)	107	(14.8)	10	(9.3)
discontinued all regimen components	198	(8.1)	127	(9.5)	76	(13.5)	6	(6.7)	303	(8.2)	188	(9.9)	107	(14.8)	10	(9.3)
discontinued any drug due to a serious drug-related adverse event	79	(3.2)	59	(4.4)	33	(5.9)	1	(1.1)	128	(3.5)	87	(4.6)	42	(5.8)	4	(3.7)
discontinued Pembrolizumab	79	(3.2)	59	(4.4)	33	(5.9)	1	(1.1)	128	(3.5)	87	(4.6)	42	(5.8)	4	(3.7)

Adverse Event Summary by Age Category (<65, 65-74, 75-84, >= 85)
(ASaT Population)

	Reference Safety Dataset for Pembrolizumab Monotherapy[¶]								Cumulative Running Safety Dataset for Pembrolizumab Monotherapy[#]							
	<65		65-74		75-84		>=85		<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
discontinued all regimen components	79	(3.2)	59	(4.4)	33	(5.9)	1	(1.1)	128	(3.5)	87	(4.6)	42	(5.8)	4	(3.7)

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

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

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

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

[#] Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma) and Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort B4, KN040, KN042, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158, KN164 Cohort A, KN170, KN224 and KN427 Cohort A.

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

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)

Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)

Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)

Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)

Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)

Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)

Database cutoff date for HCC (KN224: 15MAY2018)

Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)

Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl; adae]

Table 4.5.28: Adverse Event Summary for Elderly Subjects by Age

	Age (Years)															
	Pembrolizumab + Axitinib								Sunitinib							
	< 65		65-74		75-84		≥ 85		< 65		65-74		75-84		≥ 85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in Population	257		136		34		2		277		111		35		2	
with one or more adverse events	253	(98.4)	133	(97.8)	34	(100.0)	2	(100.0)	275	(99.3)	111	(100.0)	35	(100.0)	2	(100.0)
who died	3	(1.2)	4	(2.9)	3	(8.8)	1	(50.0)	7	(2.5)	6	(5.4)	2	(5.7)	0	(0.0)
with serious adverse events	95	(37.0)	57	(41.9)	19	(55.9)	2	(100.0)	68	(24.5)	49	(44.1)	15	(42.9)	1	(50.0)
discontinued due to an adverse event	70	(27.2)	47	(34.6)	13	(38.2)	1	(50.0)	30	(10.8)	22	(19.8)	7	(20.0)	0	(0.0)
CNS (confusion/extrapyramidal)	72	(28.0)	45	(33.1)	19	(55.9)	1	(50.0)	21	(7.6)	7	(6.3)	3	(8.6)	0	(0.0)
AE related to falling	16	(6.2)	14	(10.3)	7	(20.6)	0	(0.0)	16	(5.8)	10	(9.0)	4	(11.4)	1	(50.0)
CV events	127	(49.4)	79	(58.1)	21	(61.8)	1	(50.0)	142	(51.3)	71	(64.0)	17	(48.6)	0	(0.0)
Cerebrovascular events	8	(3.1)	2	(1.5)	0	(0.0)	0	(0.0)	4	(1.4)	7	(6.3)	1	(2.9)	1	(50.0)
Infections	105	(40.9)	64	(47.1)	21	(61.8)	2	(100.0)	108	(39.0)	48	(43.2)	16	(45.7)	1	(50.0)

AEs were followed 30 after last dose of study treatment; SAEs were followed 90 after last dose of study treatment.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 24Aug2018.

Gender

Table 5.3.5.3.3-rcc1: 124

Adverse Event Summary by Gender
(ASaT Population)

	KN426 Data for Pembrolizumab + Axitinib‖				KN426 Sunitinib††				Reference Safety Dataset for Pembrolizumab Monotherapy¶				Cumulative Running Safety Dataset for Pembrolizumab Monotherapy#			
	M		F		M		F		M		F		M		F	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	306		123		318		107		2,869		1,570		4,159		2,277	
with one or more adverse events	301	(98.4)	121	(98.4)	316	(99.4)	107	(100.0)	2,788	(97.2)	1,525	(97.1)	4,020	(96.7)	2,205	(96.8)
with no adverse event	5	(1.6)	2	(1.6)	2	(0.6)	0	(0.0)	81	(2.8)	45	(2.9)	139	(3.3)	72	(3.2)
with drug-related† adverse events	293	(95.8)	120	(97.6)	309	(97.2)	106	(99.1)	2,030	(70.8)	1,110	(70.7)	2,903	(69.8)	1,609	(70.7)
with toxicity grade 3-5 adverse events	223	(72.9)	102	(82.9)	210	(66.0)	90	(84.1)	1,414	(49.3)	739	(47.1)	2,035	(48.9)	1,072	(47.1)
with toxicity grade 3-5 drug-related adverse events	182	(59.5)	88	(71.5)	166	(52.2)	81	(75.7)	446	(15.5)	214	(13.6)	696	(16.7)	322	(14.1)
with serious adverse events	128	(41.8)	45	(36.6)	103	(32.4)	30	(28.0)	1,152	(40.2)	577	(36.8)	1,635	(39.3)	837	(36.8)
with serious drug-related adverse events	73	(23.9)	29	(23.6)	43	(13.5)	17	(15.9)	316	(11.0)	148	(9.4)	493	(11.9)	227	(10.0)
who died	10	(3.3)	1	(0.8)	13	(4.1)	2	(1.9)	146	(5.1)	65	(4.1)	235	(5.7)	94	(4.1)
who died due to a drug-related adverse event	3	(1.0)	1	(0.8)	6	(1.9)	1	(0.9)	15	(0.5)	7	(0.4)	28	(0.7)	13	(0.6)
discontinued any drug due to an adverse event	92	(30.1)	39	(31.7)	41	(12.9)	18	(16.8)	352	(12.3)	186	(11.8)	551	(13.2)	277	(12.2)
discontinued Pembrolizumab	60	(19.6)	29	(23.6)	0	(0.0)	0	(0.0)	352	(12.3)	186	(11.8)	551	(13.2)	277	(12.2)
discontinued all regimen components	23	(7.5)	10	(8.1)	41	(12.9)	18	(16.8)	352	(12.3)	186	(11.8)	551	(13.2)	277	(12.2)
discontinued any drug due to a drug-related adverse event	78	(25.5)	33	(26.8)	29	(9.1)	14	(13.1)	176	(6.1)	83	(5.3)	286	(6.9)	137	(6.0)
discontinued Pembrolizumab	56	(18.3)	24	(19.5)	0	(0.0)	0	(0.0)	176	(6.1)	83	(5.3)	286	(6.9)	137	(6.0)
discontinued all regimen components	19	(6.2)	8	(6.5)	29	(9.1)	14	(13.1)	176	(6.1)	83	(5.3)	286	(6.9)	137	(6.0)
discontinued any drug due to a serious adverse event	53	(17.3)	20	(16.3)	31	(9.7)	11	(10.3)	271	(9.4)	136	(8.7)	410	(9.9)	198	(8.7)
discontinued Pembrolizumab	37	(12.1)	13	(10.6)	0	(0.0)	0	(0.0)	271	(9.4)	136	(8.7)	410	(9.9)	198	(8.7)
discontinued all regimen components	20	(6.5)	5	(4.1)	31	(9.7)	11	(10.3)	271	(9.4)	136	(8.7)	410	(9.9)	198	(8.7)
discontinued any drug due to a serious drug-related adverse event	39	(12.7)	14	(11.4)	21	(6.6)	7	(6.5)	119	(4.1)	53	(3.4)	181	(4.4)	80	(3.5)
discontinued Pembrolizumab	33	(10.8)	9	(7.3)	0	(0.0)	0	(0.0)	119	(4.1)	53	(3.4)	181	(4.4)	80	(3.5)
discontinued all regimen components	16	(5.2)	3	(2.4)	21	(6.6)	7	(6.5)	119	(4.1)	53	(3.4)	181	(4.4)	80	(3.5)

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

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

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

‖ Includes all subjects who received at least one dose of Pembrolizumab and/or Axitinib in KN426.

†† Includes all subjects who received at least one dose of Sunitinib in KN426.

¶ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN045, KN052, KN055 and KN087.

Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma) and Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort B4, KN040, KN042, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158, KN164 Cohort A, KN170, KN224 and KN427 Cohort A.

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

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)

Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)

Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)

Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)

Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)

Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)

Database cutoff date for HCC (KN224: 15MAY2018)

Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)

Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl; adae]

Table 1 Adverse Event Summary by KPS Range (ASaT Population)

	Pembrolizumab + Axitinib				Sunitinib			
	90/100		70/80		90/100		70/80	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	345		84		339		86	
with one or more adverse events	340	(98.6)	82	(97.6)	337	(99.4)	86	(100.0)
with no adverse event	5	(1.4)	2	(2.4)	2	(0.6)	0	(0.0)
with drug-related[†] adverse events	336	(97.4)	77	(91.7)	332	(97.9)	83	(96.5)
with toxicity grade 3-5 adverse events	263	(76.2)	62	(73.8)	230	(67.8)	70	(81.4)
with toxicity grade 3-5 drug-related adverse events	223	(64.6)	47	(56.0)	192	(56.6)	55	(64.0)
with serious adverse events	136	(39.4)	37	(44.0)	94	(27.7)	39	(45.3)
with serious drug-related adverse events	86	(24.9)	16	(19.0)	42	(12.4)	18	(20.9)
who died	9	(2.6)	2	(2.4)	6	(1.8)	9	(10.5)
who died due to a drug-related adverse event	3	(0.9)	1	(1.2)	2	(0.6)	5	(5.8)
discontinued drug due to an adverse event	106	(30.7)	25	(29.8)	40	(11.8)	19	(22.1)
discontinued drug due to a drug-related adverse event	92	(26.7)	19	(22.6)	29	(8.6)	14	(16.3)
discontinued drug due to a serious adverse event	59	(17.1)	14	(16.7)	26	(7.7)	16	(18.6)
discontinued drug due to a serious drug-related adverse event	44	(12.8)	9	(10.7)	16	(4.7)	12	(14.0)

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

Grades are based on NCI CTCAE version 4.0.

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

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

Database Cutoff Date: 24Aug2018.

Extrinsic Factors

Region

Table 5.3.5.3.3-rcc1: 126

Adverse Event Summary by Region
(ASaT Population)

	KN426 Data for Pembrolizumab + Axitinib‖				KN426 Sunitinib††				Reference Safety Dataset for Pembrolizumab Monotherapy¶				Cumulative Running Safety Dataset for Pembrolizumab Monotherapy#			
	EU		Ex-EU		EU		Ex-EU		EU		Ex-EU		EU		Ex-EU	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	161		268		154		271		1,537		2,902		2,298		4,138	
with one or more adverse events	156	(96.9)	266	(99.3)	154	(100.0)	269	(99.3)	1,480	(96.3)	2,833	(97.6)	2,211	(96.2)	4,014	(97.0)
with no adverse event	5	(3.1)	2	(0.7)	0	(0.0)	2	(0.7)	57	(3.7)	69	(2.4)	87	(3.8)	124	(3.0)
with drug-related† adverse events	152	(94.4)	261	(97.4)	151	(98.1)	264	(97.4)	1,048	(68.2)	2,092	(72.1)	1,583	(68.9)	2,929	(70.8)
with toxicity grade 3-5 adverse events	126	(78.3)	199	(74.3)	115	(74.7)	185	(68.3)	732	(47.6)	1,421	(49.0)	1,077	(46.9)	2,030	(49.1)
with toxicity grade 3-5 drug-related adverse events	104	(64.6)	166	(61.9)	89	(57.8)	158	(58.3)	235	(15.3)	425	(14.6)	364	(15.8)	654	(15.8)
with serious adverse events	77	(47.8)	96	(35.8)	60	(39.0)	73	(26.9)	618	(40.2)	1,111	(38.3)	885	(38.5)	1,587	(38.4)
with serious drug-related adverse events	41	(25.5)	61	(22.8)	31	(20.1)	29	(10.7)	181	(11.8)	283	(9.8)	273	(11.9)	447	(10.8)
who died	7	(4.3)	4	(1.5)	7	(4.5)	8	(3.0)	80	(5.2)	131	(4.5)	114	(5.0)	215	(5.2)
who died due to a drug-related adverse event	1	(0.6)	3	(1.1)	4	(2.6)	3	(1.1)	10	(0.7)	12	(0.4)	14	(0.6)	27	(0.7)
discontinued any drug due to an adverse event	59	(36.6)	72	(26.9)	27	(17.5)	32	(11.8)	178	(11.6)	360	(12.4)	288	(12.5)	540	(13.0)
discontinued Pembrolizumab	43	(26.7)	46	(17.2)	0	(0.0)	0	(0.0)	178	(11.6)	360	(12.4)	288	(12.5)	540	(13.0)
discontinued all regimen components	18	(11.2)	15	(5.6)	27	(17.5)	32	(11.8)	178	(11.6)	360	(12.4)	288	(12.5)	540	(13.0)
discontinued any drug due to a drug-related adverse event	47	(29.2)	64	(23.9)	21	(13.6)	22	(8.1)	94	(6.1)	165	(5.7)	158	(6.9)	265	(6.4)
discontinued Pembrolizumab	35	(21.7)	45	(16.8)	0	(0.0)	0	(0.0)	94	(6.1)	165	(5.7)	158	(6.9)	265	(6.4)
discontinued all regimen components	12	(7.5)	15	(5.6)	21	(13.6)	22	(8.1)	94	(6.1)	165	(5.7)	158	(6.9)	265	(6.4)
discontinued any drug due to a serious adverse event	33	(20.5)	40	(14.9)	19	(12.3)	23	(8.5)	142	(9.2)	265	(9.1)	207	(9.0)	401	(9.7)
discontinued Pembrolizumab	22	(13.7)	28	(10.4)	0	(0.0)	0	(0.0)	142	(9.2)	265	(9.1)	207	(9.0)	401	(9.7)
discontinued all regimen components	13	(8.1)	12	(4.5)	19	(12.3)	23	(8.5)	142	(9.2)	265	(9.1)	207	(9.0)	401	(9.7)
discontinued any drug due to a serious drug-related adverse event	20	(12.4)	33	(12.3)	13	(8.4)	15	(5.5)	67	(4.4)	105	(3.6)	93	(4.0)	168	(4.1)
discontinued Pembrolizumab	15	(9.3)	27	(10.1)	0	(0.0)	0	(0.0)	67	(4.4)	105	(3.6)	93	(4.0)	168	(4.1)
discontinued all regimen components	7	(4.3)	12	(4.5)	13	(8.4)	15	(5.5)	67	(4.4)	105	(3.6)	93	(4.0)	168	(4.1)

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

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

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

‖ Includes all subjects who received at least one dose of Pembrolizumab and/or Axitinib in KN426.

†† Includes all subjects who received at least one dose of Sunitinib in KN426.

¶ Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN045, KN052, KN055 and KN087.

Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KN013 Cohort 3 (Hodgkin Lymphoma) and Cohort 4A (MLBCL), KN017, KN024, KN028 Cohort B4, KN040, KN042, KN045, KN052, KN054, KN055, KN059 Cohort 1, KN087, KN158, KN164 Cohort A, KN170, KN224 and KN427 Cohort A.

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

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 26FEB2018)

Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN055: 22APR2016)

Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1: 21APR2017)

Database cutoff date for cHL (KN013-Cohort 3: 27SEP2016, KN087: 25SEP2016)

Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 09MAR2017)

Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016)

Database cutoff date for MLBCL (KN013-Cohort 4A: 04AUG2017, KN170: 19JAN2018)

Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158: 15JAN2018)

Database cutoff date for HCC (KN224: 15MAY2018)

Database cutoff date for RCC (KN426: 24AUG2018, KN427-Cohort A: 07SEP2018)

Database cutoff date for MCC (KN017: 06FEB2018)

Source: [ISS: adam-adsl; adae]

Adverse Reactions supporting Table 2 in Section 4.8 of the SmPC

Adverse Reactions in Patients Treated with Pembrolizumab in Combination with Axitinib (KEYNOTE-426 version)
(Support for Table 2 of the SmPC)

	Combination with axitinib	Frequency All Grades % (n)	Grade of Severity (Grade 3-5) % (n)
Infections and infestations			
Common	pneumonia	3.5% (15)	0.9% (4)
Blood and lymphatic system disorders			
Common	anaemia	7.9% (34)	0.7% (3)
	neutropaenia	1.9% (8)	0.2% (1)
	leukopaenia	1.4% (6)	0
	thrombocytopaenia	2.6% (11)	0
Uncommon	lymphopaenia	0.9% (4)	0.2% (1)
	eosinophilia	0.7% (3)	0
Immune system disorders			
Common	infusion related reaction[a]	1.2% (5)	0.2% (1)
Endocrine disorders			
Very common	hyperthyroidism	12.8% (55)	1.2% (5)
	hypothyroidism[b]	35.4% (152)	0.2% (1)
Common	hypophysitis[c]	1.2% (5)	0.9% (4)
	thyroiditis[d]	2.8% (12)	0.2% (1)
	adrenal insufficiency	2.8% (12)	0.7% (3)
Metabolism and nutrition disorders			
Very common	decreased appetite	29.6% (127)	2.8% (12)
Common	hypokalaemia hyponatraemia	4.7% (20)	0.9% (4)
	hypocalcaemia	4.9% (21)	2.3% (10)
		1.4% (6)	0
Uncommon	type 1 diabetes mellitus[e]	0.2% (1)	0.2% (1)
Psychiatric disorders			
Common	insomnia	8.4% (36)	0
Nervous system disorders			
Very common	headache	15.9% (68)	0.9% (4)
	dysgeusia	11.0% (47)	0.2% (1)
Common	dizziness	5.1% (22)	0
	lethargy	2.1% (9)	0
	neuropathy peripheral	1.2% (5)	0
Uncommon	myasthenic syndrome[g]	0.9% (4)	0.5% (2)
Eye disorders			
Common	dry eye	1.9% (8)	0
Uncommon	uveitis[h]	0.5% (2)	0
Cardiac disorders			
Common	cardiac arrhythmia[†] (including atrial fibrillation)	5.8% (25)	1.2% (5)
Uncommon	myocarditis	0.5% (2)	0.5% (2)
Vascular disorders			
Very common	hypertension	44.5% (191)	22.1% (95)
Respiratory, thoracic and mediastinal disorders			
Very common	dyspnoea	16.1% (69)	1.6% (7)
	cough	21.2% (91)	0.2% (1)
	dysphonia	25.4% (109)	0.2% (1)
Common	pneumonitis[i]	2.8% (12)	0.5% (2)
Gastrointestinal disorders			

	Combination with axitinib	Frequency All Grades % (n)	Grade of Severity (Grade 3-5) % (n)
Very common	diarrhoea	54.3% (233)	9.1% (39)
	abdominal pain[j]	19.3% (83)	2.1% (9)
	nausea	27.7% (119)	0.9% (4)
	vomiting	15.2% (65)	0.2% (1)
	constipation	20.7% (89)	0
Common	colitis[k]	2.6% (11)	1.9% (8)
	dry mouth	5.8% (25)	0
Uncommon	pancreatitis[l]	0.5% (2)	0.5% (2)
Hepatobiliary disorders			
Common	hepatitis[m]	2.8% (12)	2.3% (10)
Skin and subcutaneous tissue disorders			
Very common	palmar-plantar erythrodysaesthesia syndrome	28.0% (120)	5.1% (22)
	rash[n]	20.5% (88)	0
	pruritus[o]	16.6% (71)	0
Common	severe skin reactions[p]	2.1% (9)	1.4% (6)
	dermatitis acneiform	1.6% (7)	0.2% (1)
	dermatitis	1.9% (8)	0.2% (1)
	dry skin	6.8% (29)	0.2% (1)
	alopecia	3.5% (15)	0
	eczema	1.2% (5)	0
	erythema	3.0% (13)	0
Uncommon	hair colour changes lichenoid	0.5% (2)	0
	keratosis[r] papule	0.2% (1)	0
	psoriasis	0.7% (3)	0
	vitiligo[q]	0.7% (3)	0
		0.2% (1)	0
Musculoskeletal and connective tissue disorders			
Very common	musculoskeletal pain[s]	21.4% (92)	1.9% (8)
	arthralgia	18.2% (78)	0.9% (4)
	pain in extremity	11.9% (51)	0.9% (4)
Common	myositis[t]	9.8% (42)	0.5% (2)
	arthritis[u]	2.1% (9)	0.5% (2)
	tenosynovitis[v]	1.2% (5)	0
Renal and urinary disorders			
Common	nephritis[w]	3.3% (14)	0.5% (2)
	acute kidney injury	4.0% (17)	1.9% (8)
General disorders and administration site conditions			
Very common	fatigue	38.5% (165)	2.8% (12)
	asthenia	15.2% (65)	2.6% (11)
	pyrexia	12.8% (55)	0
Common	oedema[x]	8.2% (35)	0.2% (1)
	influenza like illness	3.3% (14)	0.2% (1)
	chills	4.9% (21)	0
Investigations			
Very common	alanine aminotransferase increased	26.8% (115)	13.3% (57)
	aspartate aminotransferase increased	26.1% (112)	7.0% (30)
	blood creatinine increased	11.2% (48)	0.5% (2)

	Combination with axitinib	Frequency All Grades % (n)	Grade of Severity (Grade 3-5) % (n)
Common	blood alkaline phosphatase increased	6.3% (27)	1.2% (5)
	hypercalcaemia	4.0% (17)	0.5% (2)
	blood bilirubin increased	6.5% (28)	0.9% (4)
Uncommon	amylase increased	0.2% (1)	0

*Adverse reaction frequencies presented in Table 2 may not be fully attributable to pembrolizumab alone but may contain contributions from the underlying disease or from other medicinal products used in a combination.

[†]Based upon a standard query including bradyarrhythmias and tachyarrhythmias.

The following terms represent a group of related events that describe a medical condition rather than a single event.

a. infusion-related reaction (drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, hypersensitivity and cytokine release syndrome)
b. hypothyroidism (myxoedema)
c. hypophysitis (hypopituitarism)
d. thyroiditis (autoimmune thyroiditis and thyroid disorder)
e. type 1 diabetes mellitus (diabetic ketoacidosis)
f. Guillain-Barré syndrome (axonal neuropathy and demyelinating polyneuropathy)
g. myasthenic syndrome (myasthenia gravis, including exacerbation)
h. uveitis (iritis and iridocyclitis)
i. pneumonitis (interstitial lung disease)
j. abdominal pain (abdominal discomfort, abdominal pain upper and abdominal pain lower)
k. colitis (colitis microscopic, enterocolitis, enterocolitis haemorrhagic, and autoimmune colitis)
l. pancreatitis (autoimmune pancreatitis and pancreatitis acute)
m. hepatitis (autoimmune hepatitis, immune-mediated hepatitis and drug induced liver injury)
n. rash (rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular and genital rash)
o. pruritus (urticaria, urticaria papular, pruritus generalised and pruritus genital)
p. severe skin reactions (dermatitis bullous, dermatitis exfoliative, erythema multiforme, exfoliative rash, pemphigus, skin necrosis, toxic skin eruption and Grade ≥ 3 of the following: acute febrile neutropaenic dermatosis, contusion, decubitus ulcer, dermatitis psoriasiform, drug eruption, jaundice, pemphigoid, pruritus, pruritus generalised, rash, rash erythematous, rash generalised, rash maculo-papular, rash pruritic, rash pustular and skin lesion)
q. vitiligo (skin depigmentation, skin hypopigmentation and hypopigmentation of the eyelid)
r. lichenoid keratosis (lichen planus and lichen sclerosus)
s. musculoskeletal pain (musculoskeletal discomfort, back pain, musculoskeletal stiffness, musculoskeletal chest pain and torticollis)
t. myositis (myalgia, myopathy, polymyalgia rheumatica and rhabdomyolysis)
u. arthritis (joint swelling, polyarthritis and joint effusion)
v. tenosynovitis (tendonitis, synovitis and tendon pain)
w. nephritis (nephritis autoimmune, tubulointerstitial nephritis and renal failure, renal failure acute, or acute kidney injury with evidence of nephritis, nephrotic syndrome)
x. oedema (oedema peripheral, generalised oedema, fluid overload, fluid retention, eyelid oedema and lip oedema, face oedema, localised oedema and periorbital oedema)

Safety related to drug-drug interactions and other interactions

As pembrolizumab is an IgG antibody that is administered parenterally and cleared by catabolism, food and DDI are not anticipated to influence exposure. Drugs that affect the cytochrome P450 enzymes, and other metabolizing enzymes, are not expected to interfere with the metabolism of an IgG antibody. The IgG antibodies, in general, do not directly regulate the expression of cytochrome P450 enzymes, other enzymes, or transporters involved in drug elimination. Therefore, no dedicated DDI studies have been performed. In addition, in vitro experiments and studies conducted in preclinical species have been shown to have limited value in predicting DDI potential in humans [Ref. 5.4: 03JJPS]. Therefore, no preclinical pharmacokinetic studies were conducted to assess the propensity of pembrolizumab to be a victim or perpetrator of pharmacokinetic DDIs. Similarly, the potential of a DDI between pembrolizumab and a TKI is expected to be low due to differences in metabolic pathways.

Studies evaluating pharmacodynamics drug interactions with pembrolizumab have not been conducted. However, as systemic corticosteroids may be used in combination with pembrolizumab to ameliorate potential side effects, the potential for a pharmacokinetic DDI with pembrolizumab as a victim was assessed as part of the population pharmacokinetic analysis. No relationship was observed between prolonged use of systemic corticosteroids and pembrolizumab exposure. Systemic corticosteroids, or other immunosuppressants, can be used during pembrolizumab treatment to treat immune-related adverse reactions.

Discontinuation due to adverse events

Discontinuation Due to AEs

Table 5.3.5.3.3-rcc1: 26
Subjects With Drug-Related Adverse Events Resulting in Any Treatment Discontinuation
(Incidence > 1% in Preferred Term)
By Decreasing Frequency of Preferred Term
(ASaT Population) *(modified by the Assessor)*

	KN426 Data for Pembrolizumab + Axitinib[‡]		KN426 Sunitinib[††]		Reference Safety Dataset for Pembrolizumab Monotherapy[†]		Cumulative Running Safety Dataset for Pembrolizumab Monotherapy[‡]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	429		425		4,439		6,436	
with one or more adverse events	111	(25.9)	43	(10.1)	259	(5.8)	423	(6.6)
with no adverse events	318	(74.1)	382	(89.9)	4,180	(94.2)	6,013	(93.4)
Alanine aminotransferase increased	31	(7.2)	1	(0.2)	7	(0.2)	19	(0.3)
Aspartate aminotransferase increased	20	(4.7)	1	(0.2)	10	(0.2)	18	(0.3)
Hepatic function abnormal	6	(1.4)	0	(0.0)	0	(0.0)	2	(0.0)

Aside from ALT and AST increased as well as *Hepatic function abnormal* occurring among AEs leading to treatment discontinuation with frequencies >1%, *Decreased appetite, Diarrhoea, Hepatitis, Hepatotoxicity,* and *Myasthenia gravis* were documented in 4 patients each, and *Acute kidney injury, Cerebrovascular accident, Hepatocellular injury, Palmar-plantar erythrodysaesthesia Syndrome, Proteinuria, Pulmonary embolism* were found in 3 subjects each.

Table 14.3-41
Subjects With Adverse Events Resulting in Treatment Discontinuation By Decreasing Incidence
(Incidence > 1% in One or More Treatment Groups)
(ASaT Population) *(modified by the Assessor)*

	Pembrolizumab + Axitinib								Sunitinib	
	Pembrolizumab and/or Axitinib Discontinuation		Pembrolizumab and Axitinib Discontinuation		Pembrolizumab Discontinuation		Axitinib Discontinuation			
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	429		429		429		429		425	
with one or more adverse events	131	(30.5)	33	(7.7)	89	(20.7)	88	(20.5)	59	(13.9)
with no adverse events	298	(69.5)	396	(92.3)	340	(79.3)	341	(79.5)	366	(86.1)
Alanine aminotransferase increased	31	(7.2)	5	(1.2)	20	(4.7)	16	(3.7)	1	(0.2)
Aspartate aminotransferase increased	20	(4.7)	3	(0.7)	16	(3.7)	7	(1.6)	1	(0.2)
Hepatic function abnormal	6	(1.4)	3	(0.7)	4	(0.9)	5	(1.2)	0	(0.0)

In the combination arm, discontinuation of both drugs due to drug-related AEs was found in 27 subjects with a median time to event of 63.0 days. Discontinuation of pembrolizumab was reported for 80 participants after a similar time on treatment (median 65 days).

Table 14.3-45
Time to Discontinuation of Both Drugs in Pembrolizumab + Axitinib Arm Due to Drug-related Adverse Events
(ASaT Population)

	Pembrolizumab + Axitinib N =429 (ASaT)
Subjects with discontinuation of both drugs due to drug-related adverse events	27
Time to discontinuation of both drugs due to drug-related adverse events (days)[†]	
Median	63.0
[†] Time to discontinuation of both drugs due to drug-related adverse events = last dose date of both drugs - first dose date + 1 day.	
Database Cutoff Date: 24Aug2018.	

Source: [P426V01MK3475: adam-adsl; adae; adpm]

Table 14.3-46
Time to Discontinuation of Pembrolizumab Due to Drug-related Adverse Events
(ASaT Population)

	Pembrolizumab + Axitinib N =429 (ASaT)
Subjects with discontinuation of Pembrolizumab due to drug-related adverse events	80
Time to discontinuation of Pembrolizumab due to drug-related adverse events (days)[†]	
Median	65.0
[†] Time to discontinuation of Pembrolizumab due to drug-related adverse events = last dose date of Pembrolizumab - first dose date + 1 day.	
Database Cutoff Date: 24Aug2018.	

Source: [P426V01MK3475: adam-adsl; adae; adpm]

Interruption Due to Adverse Events

Table 14.3-47
Subjects With Adverse Events Resulting in Treatment Interruption By Decreasing Incidence
(Incidence > 10% in Preferred Term)
(ASaT Population) (*modified by Assessor*)

	Pembrolizumab + Axitinib								Sunitinib	
	Pembrolizumab and/or Axitinib Interruption		Pembrolizumab and Axitinib Interruption		Pembrolizumab Interruption		Axitinib Interruption			
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	429		429		429		429		425	
with one or more adverse events	300	(69.9)	153	(35.7)	216	(50.3)	274	(63.9)	212	(49.9)
with no adverse events	129	(30.1)	276	(64.3)	213	(49.7)	155	(36.1)	213	(50.1)
Diarrhoea	70	(16.3)	31	(7.2)	41	(9.6)	63	(14.7)	21	(4.9)
Alanine aminotransferase increased	60	(14.0)	31	(7.2)	41	(9.6)	52	(12.1)	12	(2.8)
Aspartate aminotransferase increased	57	(13.3)	29	(6.8)	37	(8.6)	50	(11.7)	8	(1.9)
Hypertension	57	(13.3)	3	(0.7)	3	(0.7)	57	(13.3)	34	(8.0)

Dose Reduction Due to Adverse Events

Number of subjects with dose change from initial dose were similar in the two treatment arms (pembrolizumab+axitinib 429 [100%]; sunitinib 425 [1005]). In the combination arm 69 subjects (16.1%) had Dose Escalation from Initial Dose, while 284 (66.2%) had Dose Reduction from Initial Dose. In the axitinib arm, none of the participants had Dose Escalation from Initial Dose, while 207 (48.7%) had Dose Reduction from Initial Dose.

Table 14.3-52
Subjects With Adverse Events Resulting in Dose Reduction By Decreasing Incidence
(Incidence > 1% in Preferred Term)*
(ASaT Population) (*modified by Assessor*)

	Pembrolizumab + Axitinib		Sunitinib	
	n	(%)	n	(%)
Subjects in population	429		425	
with one or more adverse events	87	(20.3)	128	(30.1)
with no adverse events	342	(79.7)	297	(69.9)
Hypertension	17	(4.0)	15	(3.5)
Diarrhoea	14	(3.3)	13	(3.1)
Palmar-plantar erythrodysaesthesia syndrome	9	(2.1)	15	(3.5)
Fatigue	7	(1.6)	17	(4.0)

Table 14.3-54
Subjects With Drug-Related Adverse Events Resulting in Dose Reduction By Decreasing Incidence
(Incidence > 1% in Preferred Term)*
(ASaT Population) (*modified by Assessor*)

	Pembrolizumab + Axitinib		Sunitinib	
	n	(%)	n	(%)
Subjects in population	429		425	
with one or more adverse events	86	(20.0)	121	(28.5)
with no adverse events	343	(80.0)	304	(71.5)
Hypertension	17	(4.0)	14	(3.3)
Diarrhoea	14	(3.3)	13	(3.1)
Palmar-plantar erythrodysaesthesia syndrome	9	(2.1)	15	(3.5)
Fatigue	7	(1.6)	15	(3.5)

Table 14.3-56
Subjects With Grade 3-5 Adverse Events Resulting in Dose Reduction By Decreasing Incidence
(Incidence > 1% in Preferred Term)*
(ASaT Population) (*modified by Assessor*)

	Pembrolizumab + Axitinib		Sunitinib	
	n	(%)	n	(%)
Subjects in population	429		425	
with one or more adverse events	44	(10.3)	61	(14.4)
with no adverse events	385	(89.7)	364	(85.6)
Hypertension	11	(2.6)	7	(1.6)
Diarrhoea	7	(1.6)	5	(1.2)
Fatigue	5	(1.2)	6	(1.4)
Palmar-plantar erythrodysaesthesia syndrome	5	(1.2)	4	(0.9)

*Partial tables with adverse events with an incidence >1% in the combination arm only.

Post marketing experience

The safety profile of pembrolizumab was summarized in the PSUR covering the period 04-MAR-2018 through 03-SEP-2018. No revocation or withdrawal of pembrolizumab registration for safety reasons has occurred in any country.

2.5.1. Discussion on clinical safety

The claimed indication of pembrolizumab in combination with axitinib for 1L treatment of subjects with advanced RCC is based on safety data from the IA1 on the ASaT population of KEYNOTE-426, which is an

ongoing, Phase 3, randomized, open-label, multicenter, global study (data cut-off 24 Aug 2018). Submitted side-by-side safety tables show data from the pembrolizumab+axitinib (N=429) and the sunitinib (N=425) arms. In addition, the pooled Pembrolizumab Monotherapy Reference SD (N=4439) is provided to compare safety data from KN426 with the established safety profile for pembrolizumab monotherapy across indications approved in the EU, and the Cumulative Running Safety Dataset for Pembrolizumab Monotherapy (including all pembrolizumab monotherapy indications globally) is provided to evaluate consistency of the pembrolizumab safety profile across indications. Finally, as supportive safety information data from the *Axitinib monotherapy* arm of Phase 3 Study A4061051 for the 1L treatment of metastatic RCC (data cut-off 27 July 2012; N=189) and the *Pembrolizumab monotherapy Cohort A* of KEYNOTE-427 study for the 1L treatment of advanced ccRCC (data cut-off 07 Sept 2018; N=110) are presented. The safety data from the 52 participants enrolled in the Phase 1b study (Study A4061079) of pembrolizumab+axitinib were presented separately in the dossier. Safety data from KEYNOTE-427 Cohort A (subjects treated with pembrolizumab monotherapy for 1L treatment of advanced ccRCC) has been provided either pooled within the Cumulative Running Safety Dataset for Pembrolizumab Monotherapy (including all pembrolizumab monotherapy indications globally) or separately in the CSR P427V01MK3475.

Demographics of KN426 study population depict mainly White (80%) subjects of male gender (70-75%) with mean age of 61 years. Two thirds of participants were enrolled outside the EU. Regarding previous RCC treatments approximately 83% had undergone prior nephrectomy and 9% previous radiotherapy, with similar proportions in study arms. With the exception of proportion of subjects aged $\geq$65, that was slightly increased in the pembrolizumab+axitinib group if compared to the sunitinib group (40.1% vs 34.8%, respectively), patient demographics and disease characteristics were quite well balanced among the two KN426 treatment arms. In the experimental arm there were few more women (28.7% vs 25.4%) than in the control arm. Liver metastases were found in approximately 15% of subjects of both arms. In respect to the Pembrolizumab Monotherapy RSD and as expected for RCC patients, KN426 participants were more often male gender than in the reference dataset (73% vs 65%, respectively). The other demographics were consistent between the pivotal trial and the pooled dataset.

With regards to **duration of exposure**, median time on therapy was longer in the pembrolizumab+axitinib arm (10.42 months), when compared to the sunitinib arm (7.82 months) and the Pembrolizumab Monotherapy RSD (4.17 months), which is likely associated with the OS benefit as compared to the control arm and the 2L settings for the indications in the pembrolizumab monotherapy RSD. Similarly, proportion of subjects with exposures for $\geq$6 or $\geq$12 months were higher in the pembrolizumab+axitinib arm (77.9% and 40.3%), followed by the sunitinib arm (63.5% and 25.4%) and the Pembrolizumab Monotherapy RSD (40.9% and 19.2%). Mean number of pembrolizumab administrations were higher in the pembrolizumab+axitinib arm (13.8$\pm$8.04) than in the Pembrolizumab Monotherapy RSD (10.7$\pm$9.56). This finding could be related to the disease setting (1L treatment of RCC) where the drug combination has been studied.

Based on the **safety summary** overall AEs were observed in similar proportions in subjects receiving pembrolizumab+axitinib compared to those treated with sunitinib. However, the following AE categories were reported more frequently in the experimental combination arm: Grade 3-5 AEs (75.8% vs 70.6%), Grade 3-5 drug-related AEs (62.9% vs 58.1%), SAEs (40.3% vs 31.3%), drug-related SAEs (23.8% vs 14.1%), and drug discontinuations due to AEs (30.5% vs 13.5%), to drug-related AEs (25.9% vs 10.1%), to SAEs (17.0% vs 9.9%), or to drug-related SAEs (12.4% vs 6.6%). Even adjusting for exposure and including multiple event occurrences, the increased rate of drug-related SAEs (2.87 vs 1.99/100 person-months, respectively) and of drug discontinuations due to AEs (3.78 vs 1.66/100 person-months, respectively), to drug-related AEs (3.19 vs 1.2/100 person-months, respectively), to SAEs (1.68 vs 1.1/100 person-months, respectively), or to drug-related SAEs (1.24 vs 0.71/100 person-months,

respectively) is observed. These data suggest that the tolerability of the combination is poor with a much higher rate of treatment discontinuation due to AEs, drug-related AEs and drug-related AEs compared to sunitinib and to what observed so far with pembrolizumab monotherapy.

In KN426, at least one AE was found in almost all participants (98.4% in pembrolizumab+axitinib and 99.5% in sunitinib) and **PTs most commonly** (incidence ≥30%) reported for the pembrolizumab+axitinib arm, in some cases occurred with similar frequencies as in the sunitinib arm: *Diarrhea* (54.3% and 44.9%, respectively), *Hypertension* (44.5% and 45.4%), *Fatigue* (38.5% and 37.9%), and *Hypothyroidism* (35.4% and 31.5%). Between-treatment comparisons showed increased risk in the pembrolizumab-axitinib arm (risk with 95%CI exceeding 0) for *Dysphonia*, *Arthralgia*, *ALT increased, AST increased, Diarrhea, Pruritus, Hyperthyroidism, Cough, Weight decreased, Proteinuria, Constipation, Dyspnea, Abdominal pain*, while the sunitinib arm was in disadvantage for blood system disorders, *Palmar-plantar erythrodysesthesia syndrome*, *Dysgeusia*, *Mucosal Inflammation* and some gastrointestinal disorders. When looking at exposure-adjusted SOCs incidence, a slightly higher rate of *Respiratory, thoracic and mediastinal disorders* was found for the group treated with pembrolizumab+axitinib in respect to that receiving sunitinib (10.5 vs 8.0/100 p-m), that could be related to higher *Dysphonia* rates. Most of other SOCs were reported either less often for the combination treatment versus controls (*Blood and lymphatic disorders* 1.9 vs 14.7/100 p-m, *Gastrointestinal disorders* 29.4 vs 35.9/100 p-m, *General disorders* 13.0 vs 18.1/100 p-m, *Investigations* 18.1 vs 24.1/100 p-m, *Nervous system disorders* 6.8 vs 10.7/100 p-m, *Skin and subcutaneous tissue disorders* 11.6 vs 16.3/100 p-m), or similarly frequent in the two study arms (*Endocrine disorders* 5.8 and 5.0/100 p-m, *Hepatobiliary disorders* 1.3 and 1.2/100 p-m*, Infections and infestations* 7.6 and 6.8/100 p-m*, Renal and urinary disorders* 4.5 and 4.0/100 p-m). When looking at exposure periods, in both treatment arms most event rates were the highest during the first months. Based on indirect comparison of data from Study KN-426, Study A4061051 (Axitinib monotherapy) and available data for pembrolizumab monotherapy, it is observed that the combination is associated with an increased frequency of some AEs compared to what previously observed with monotherapies, such as *Diarrhoea, Hypothiroidism, ALT increased, AST increased, Fatigue, Nausea, Proteinuria, Hyperthyroidism*. **Grade 3-5 AEs** were reported in 75.8% of subjects treated with pembrolizumab+axitinib and in 70.6% of those receiving sunitinib. PTs with incidence rates ≥5% in the combination treatment were *Hypertension* (22.1%), *ALT increased* (13.3%), *Diarrhea* (9.1%), *AST increased* (7.0%), *Palmar-plantar erythrodysaesthesia syndrome* (5.1%), while in the sunitinib arm the following were reported: *Hypertension* (19.3%), *Platelet count decreased* (7.3%), *Neutrophil count decreased* (6.8%), *Neutropenia* (6.6%), *Fatigue* (6.6%) and *Thrombocytopenia* (5.9%). Between-treatment risk differences with 95%CI exceeding 0 showed advantage of controls over the combination treatment for *ALT increased, AST increased* and *Diarrhea*; while pembrolizumab+axitinib arm was in favor for most Grade 3-5 myelotoxicity AEs and *Fatigue*. Although median time to first Grade 3-5 AE was shorter for the sunitinib arm when compared to pembrolizumab+axitinib arm (10.1 vs 13.1 weeks, respectively), no statistically significant difference was documented.

With regards to **drug-related AEs**, similar overall proportions were reported across study arms (96.3% in pembrolizumab+axitinib and 97.6% in sunitinib). Type and frequency of the most common events (≥30% incidence) in subjects receiving the combination treatment mirrored the expected safety profile of drug components, and, apart from Diarrhoea, were not substantially dissimilar from those reported for sunitinib-treated participants (*Diarrhea* 49.0% and 41.2%; *Hypertension* 41.7% and 43.3%, *Hypothyroidism* 31.5% and 28.0%, and *Fatigue* 30.3% and 33.4%, respectively). Among events with incidence >20%, *ALT increased* (23.8% vs 12.7%), *AST increased* (22.6% vs 13.9%), and *Dysphonia* (22.8% vs 2.8%) were all more often found in the combination arm when compared to sunitinib. Analysis of between-treatment difference was in agreement with the results found for overall AEs by showing increased risks for the pembrolizumab+axitinib arm of *Dysphonia*, *ALT increased, Hyperthyroidism, AST increased, Arthralgia, Pruritus, Diarrhea, Proteinuria,* and *Cough*, and for the sunitinib arm of *Dysgeusia*,

Thrombocytopenia, *Neutropenia*, *Platelet count decreased*, *Anemia*, *Palmar-plantar erythrodysesthesia syndrome*, *Neutrophil count decreased*, *Dyspepsia*, *White blood cell count decreased*, *Mucosal inflammation*, *Leukopenia*, *Gastroesophageal reflux disease*, *Stomatitis*, and *Vomiting* AEs. Based on indirect comparison of data from Study KN-426, Study A4061051 (Axitinib monotherapy) and available data for pembrolizumab monotherapy, it is observed that the combination is associated with an increased frequency of some drug-related AEs compared to what previously observed with monotherapies, such as *Diarrhoea, Hypothiroidism, ALT increased, AST increased, Fatigue, Nausea, Proteinuria, Arthralgia, Hyperthyroidism*. Proportions of overall **grade 3-5 drug-related AEs** were somehow increased in the pembrolizumab+axitinib arm if compared to the sunitinib arm (62.9% vs 58.1%, respectively). Based on investigator's judgments, within the combination arm, the grade 3-5 drug-related AEs were considered related to axitinib (56.9%), to pembrolizumab (37.1%) or to both the compounds (26.1%). Grade 5 drug-related AEs were reported in 4 subjects of the pembrolizumab+axitinib arm (0.9%; all considered related to pembrolizumab by investigators) and 7 subjects (1.6%) of the sunitinib arm. PTs with difference >2% between treatment arms and higher proportions in the pembrolizumab+axitinib than in the sunitinib group were: *Hypertension* (21.2% vs 18.4%, respectively), *ALT increased* (12.1% vs 18.4%), *Diarrhea* (7.2% vs 4.5%), and *AST increased* (6.8% vs 1.6%). Differently, the sunitinib-treated group had enlarged proportions for *Thrombocytopenia* (5.2% vs 0.0%, respectively), *Platelet count decreased* (7.3% vs 0.2%), *Neutropenia* (6.6% vs 0.2%), *Hypophosphatasemia* (2.6% vs 0.5%).

More subjects in the pembrolizumab+axitinib arm compared to the sunitinib arm were found with **SAEs** (40.3% vs 31.3%, respectively). Most often reported events for pembrolizumab+axitinib arm were: *Diarrhea* (2.8%), *Acute kidney injury* (1.6%), *ALT increased* (1.4%), *Dehydration* (1.4%), *AST increased* (1.2%), *Hepatic function abnormal* (1.2%), *Pneumonitis* (1.2%). Between-treatment comparisons of SAEs showed sunitinib being in favor for *Diarrhea*, *ALT increased, Pneumonitis, Hepatic function abnormal, AST increased*, while combination treatment did not result of advantage for any event. Also, **drug-related SAEs** were more often reported for the combination arm than for controls (23.8% vs 14.1%, respectively). Aside from the gastrointestinal (*Diarrhea* 1.9%; *Colitis* 0.8%) and respiratory events (*Pneumonitis* 1.2%; *Pulmonary embolism* 0.8%), drug-related SAEs due to *Hepatobiliar disorders* were the most frequent and were reported in 31 subjects (7.2%): *ALT increased* (6 subjects), *AST increased* (5 subjects), *Hepatic function abnormal* (4 subjects), *Hepatitis* (3 subjects), *Hepatocellular injury* (3 subjects), *Hepatic enzyme increased* (2 subjects), *Liver function test increased* (2 subjects), *Transaminases increased* (2 subjects), *Autoimmune hepatitis* (1 subject), *Blood bilirubin increased* (1 subject), *Hepatotoxicity* (1 subject), *Immune mediated hepatitis* (1 subject). Serious drug-related *Acute kidney injury* and *Myasthenia gravis* were reported in 4 subjects each, while *Cerebrovascular event* in 3. When drug-related SAEs are analyzed by SOCs, *Gastrointestinal disorders* (4.2%), *Hepatobiliary disorders* (3.5%) and *Investigations* (3%, mainly liver tests) were the most frequently reported. *Cardiac disorders,* whilst having rates of 0.4% for pembrolizumab monotherapy, are reported at 1.6% for the pembrolizumab+axitinib arm (most common PTs: *Atrial fibrillation* and *Myocarditis* in 2 cases each; 0.5%) and 1.4% the sunitinib arm.

With regard to cardiac disorders, while myocarditis is a known side effect of pembrolizumab, atrial fibrillation is not reported in Pembrolizumab SmPC, nor in axitinib one. Further, analysis of aggregated Cardiac arrhythmias SMQ confirmed an increased proportion of events in subjects treated with pembrolizumab+axitinib compared to those receiving sunitinib (5.8% vs 2.4%, respectively), and similar differences for drug-related AEs (2.3% vs 0.2%) and SAEs (1.4% vs 0.2%). Based on these findings, the MAH was asked to provide further information and, if applicable, to propose modifications to the SmPC. *Cardiac arrhythmias* SMQ (0.59 vs 0.28/100 person-months, respectively) and *Atrial fibrillation* PT (0.2 vs 0.0/100 person-months, respectively), clearly show higher exposure-adjusted rates in KN-426 pembrolizumab+axitinib-treated subjects when compared to those receiving sunitinib. Exposure-adjusted event rates in RCC patients treated with pembrolizumab combo were similar to those

observed in subjects receiving pembrolizumab monotherapy across indications of the Reference safety Dataset, suggesting no additional safety issues when pembrolizumab is combined with axitinib. The query of the OASE database aimed at comparing safety data of pembrolizumab monotherapy including all open-label, unmasked, or completed randomized study for which there has been a database lock on or before 31-Mar--2018 (n=9118) with that of all cytotoxic treatments from all studies using chemotherapy comparators combined (N=1324) did not find differences in frequency or in exposure-adjusted rates of overall and drug-related MedDRA sub-SMQ *Cardiac arrhythmias,* as well as related PTs. When analyzing *Atrial fibrillation* by age strata, as expected, the risk significantly increases in higher age groups treated with pembrolizumab (0.2-0.4% in subjects <60 y vs 1.1-3.4% in subjects >60 y). Review of the Company's global safety Database (MARRS) identified 725 arrhythmia events (atrial fibrillation in 46.76% of cases) occurring in 665 subjects (approximately 90% SAEs), having characteristics as expected (higher prevalence in males and more aged subjects). While a relatively short elapse of time between treatment start and AE occurrence is noted (median 56 days for atrial fibrillation, 33 days for fatal cases), the high frequency of concurrent morbidity acts as confounder in causality analysis. The MAH stated that there is insufficient evidence to suggest a causal relationship between pembrolizumab and cardiac arrhythmia, however, this is not agreed, and as a drug/class-induced safety issue cannot be ruled out. The MAH was requested to add atrial fibrillation/cardiac arrhythmias to ADRs in Section 4.8 of the SmPC. (See SmPC 4.8)

In addition, a trend toward higher incidences of severe and serious *Acute kidney injury* was notable in the pembrolizumab+axitinib group compared to the sunitinib arm, although the numbers are likely to small to draw definitive conclusion. The incidences of serious AEs were 1.6% [n=7] vs 0.7% [n=3], (risk difference not statistically significant); incidences of drug-related SAEs were 0.9% for pembrolizumab+axitinib and 0.2% for both sunitinib and the RSD; Grade 3 to 5 events were 1.9% for pembrolizumab+axitinib vs 1.2% for sunitinib and 0.9% for the RSD and drug-related Grade 3 to 5 AEs were 0.9% [n=4] vs 0.2% [n=1] for pembrolizumab+axitinib compared to sunitinib. The (higher) rates of Nephritis and Creatinine increased (compared to the RSD) are depicted in the SmPC. Review of the renal toxicity, showed a higher proportion of Renal Adverse Events (40.3% vs. 29.4%, respectively), in particular of drug-related and of more severe renal AEs, for the pembrolizumab+axitinib in respect to the SOC arm. PTs with largest difference between study treatments were the following: *Proteinuria, Acute renal failure, Renal failure* and *Renal impairment*. The well-known association of diarrhea and acute kidney failure occurred only in few participants. No modifications to the SmPC are needed, as Acute Kidney Injury is already included in Table 2 of Section 4.8 and Proteinuria rates appear overall similar to those reported for axitinib monotherapy.

Subjects with AEs leading to **deaths** up to 90 days of last dose were quite comparable among study arms with 11 (2.6%) subjects in the pembrolizumab+axitinib and 15 (3.5%) in the sunitinib arm. In the combination arm reported reasons for death were: *Cardiac arrest, Death, Myasthenia gravis, Myocarditis, Necrotizing fasciitis, Plasma cell myeloma, Pneumonitis, Pulmonary embolism, Pulmonary thrombosis,* and *Respiratory failure* (all registered in one case each). In the combination treatment, 4 fatal events were judged by the investigator to be associated with pembrolizumab: *Myasthenia gravis, Myocarditis, Necrotizing fasciitis,* and *Pneumonitis.* With regard to the AEs leading to death considered pembrolizumab-related by investigator, *Pneumonitis*, *Myastenic syndrome* and *Myocarditis* are already reported in Keytruda SmPC. After additional review of *Necrotizing fasciitis* as possibly immune-related event, based on available information it is agreed with the MAH that data are currently insufficient to support an update of the SmPC and that these AEs will be further monitored through routine pharmacovigilance activities. Though it is noted that in 6 out of the 11 patients who died following AEs, there was an history of hepatic toxicity during treatment exposure (Grade 4 in 1 case, Grade 3 in 4 cases and Grade 1 in the remaining case) and that in two instances (ID numbers redacted) the time between

hepatic AE and death is rather short, based on patient history review, a relationship between the liver toxicity and the fatal outcome is considered unlikely.

In the group treated with pembrolizumab-axitinib, the proportions of overall **AEOSIs** (51.3% vs 36.2%) and of all event categories (except deaths) were increased in respect to the sunitinib group. Dose modifications and treatment discontinuations due to AEOSIs were much more frequent with the combination compared to sunitib and pembrolizumab monotherapy (Reference safety dataset). A difference of ≥2% in frequencies between study arms were found for *Adrenal insufficiency* (3.0% vs 0.2% in pembrolizumab-axitinib and sunitinib groups respectively), *Hepatitis* (2.8% vs 0.5%), *Hyperthyroidism* (12.8% vs 3.8%), *Pneumonitis* (2.8% vs 0.2%), and *Thyroiditis* (2.8% vs 0.5%). Notably, similar proportions across study arms were reported for *Hypothyroidism* and *Nephritis*. AEOSIs with Grade 3-5 in severity were documented in 10.7% of subjects treated with combination treatment and in only 1.9% of those receiving sunitinib. Distribution of outcomes of AEOSIs were similar in KN426 study arms, with approximately one third that resolved without sequelae. Fatal events were *Pneumonitis, Myasthenic Syndrome, Myocarditis* in one case each of the combination arm and *Hepatitis* in the sunitinib arm. With regard to *Myositis*, the MAH adapted Table 2 and classified the AE of myositis in the same frequency category for pembrolizumab monotherapy and the combination with axitinib.

Out of the 12 *Hepatitis* AEOSIs, that presented after a median of 54 days, 10 were judged to be drug-related (9 Grade 3-5) and 9 were classified as SAEs. Overall, 67% of patients were treated with corticosteroids, and, except 1 that developed sequelae, all resolved (9 subjects; 75%) or were resolving at the time of data cut-off (2 subjects; 16.7%).

With regards to thyroid AEOSIs, in the safety profile of pembrolizumab+axitinib an exceeding frequency of *Hypothyroidism* as well as of *Hyperthyroidism* is noted in respect to known pembrolizumab monotherapy safety. Furthermore, a slight increase in *Thyroiditis* is also found (2.8% in pembrolizumab+axitinib vs 0.5% in sunitinib). Although these are expected ADR of both pembrolizumab and axitinib, the frequencies appear relevant, in particular for hyperthyroidism. Median time to onset was approximately similar among combination treatment and pembrolizumab monotherapy. Regarding outcomes, while most of hypothyroidism events did not resolve (62.5%) (and are treated with continued hormone replacement therapy), most of the hyperthyroidism events (85.5%) reassuringly did resolve. It is agreed not to add the information regarding high rate of thyroid disturbances when pembrolizumab is used in combination with axitinib in Section 4.4 of the SmPC, as frequencies [very common] are provided in Table 2 of Section 4.8.

With regards to **laboratory findings,** in the pembrolizumab+axitinib arm the following were the most common abnormalities: *Glucose increased* (61.9%), *ALT increased* (59.6%), *AST increased* (56.7%), *Creatinine increased* (43.0%), *Sodium decreased* (35.0%), *Potassium increased* (34.1%), *Lymphocyte decreased* (33.3%), and *Albumin decreased* (31.9%). When comparing study arms, pembrolizumab+axitinib had higher liver test abnormalities, while the sunitinib arm showed increased myelotoxicity abnormalities.

Analysis of **treatment-emergent Hepatic Adverse Events**, defined by 3 MedDRA SMQs and hepatitis AEOSI and assessed in the overall study population and in the Hepatic Events Analysis Set (HEAS; n=287), showed in the pembrolizumab+axitinib arm when compared to sunitinib controls increased proportions of overall hepatic events (40.6% vs 26.6%), drug-related hepatic AEs (34.3% vs 20.7%), grade 3-5 hepatic AEs (21.2% vs 6.1%), grade 3-5 drug-related hepatic AEs (18.9% vs 4.0%), serious hepatic AEs (7.0% vs 0.9%), serious drug-related hepatic AEs (6.3% vs 0.5%), and of drug discontinuation due to hepatic AEs (13.3% vs 0.5%), to drug-related hepatic AEs (13.1% vs 0.5%), to serious hepatic AEs (4.9% vs 0.2%), and to serious drug-related hepatic AEs (4.7% vs 0.2%). Most

common (>1% incidence) PTs for hepatic AEs were principally *ALT increased* (26.8%; grade 3-5 13.3%; drug-related 23.8%) and *AST increased* (26.1%; grade 3-5 7.0%; drug-related 22.6%), followed by *Blood bilirubin increased* (6.5%; grade 3-5 0.9%; drug-related 4.4%), *Hepatic function abnormal* (3.5%; grade 3-5 1.6%; drug-related 3.0%), *γ-GT increased* (1.9%; grade 3-5 0.9%; drug-related 0.7%), *Hepatitis* (1.6%; grade 3-5 1.4%; drug-related 1.4%), *Hyperbilirubinemia* (1.6%; grade 3-5 0%; drug-related 1.2%), *Liver function test increased* (1.2%; grade 3-5 0.7%; drug-related 0.7%). Subjects treated with pembrolizumab+axitinib in comparison to those receiving sunitinib, showed higher proportions in ALT and AST increased. Additionally, ALT or AST elevation concurrent with total bilirubin elevation (+/- ALP elevation) was more common in the pembrolizumab+axitinib arm.Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plots displayed subjects (n=15) in the Hy's Law quadrant, raising the concern of Drug-Induced Liver Injury with pembrolizumab+axitinib. First treatment-emergent ALT ≥3xULN events, that occurred after a mean of 103 days of exposure and was treated with systemic steroids in 62-100% of cases (growing frequency with increasing severity), resolved in 82-94% of subjects with decreasing frequency based on highest level reached. Based on ALT increase category (≥3 x ULN, ≥5 x ULN, ≥10 x ULN and ≥20 x ULN), re-challenge with combination treatment was carried out in 51-11% of cases, with further ALT elevation (≥3xULN) event in 43.6% with consequent recovery in all (guidance for evaluation and management of patients with AST/ALT elevation, including algorithms regarding study drug rechallenge, were progressively updated during the study conduction). In only 7 patients ALT did not recover to Grade 0-1 after the first hepatic event (ALT ⩾ 3xULN). For most of these patients, non-recovery appeared to be related to limited follow-up (lack of follow-up data, death, event 15 days prior to data cutoff). No correlation could be determined with lack of corticosteroid treatment based on this limited number. 41 patients (45%) had a recurrence of ALT elevation after rechallenge with treatment and all recovered (see Table 4.5.23). In the pembrolizumab + axitinib arm 92 participants received study treatment following recovery of the first ALT ⩾3 x ULN. Of these 41 participants (44.6%) had a second episode of ALT ⩾3xULN, 23 (56%) received steroids, and all recovered to <3xULN prior to the data cutoff. Considering that 44% of patients (18/41) recovered also from the second hepatic event without corticosteroid treatment it is not justified to recommend corticosteroids as mandatory.

Within the HEAS population, ALT≥3xULN occurrence seems not associated with clinically relevant patient or disease characteristics or use of potentially concomitant hepatotoxic medications. Due to first ALT≥3xULN event, median treatment delay was of 37.5 days, and subjects permanently discontinuing pembrolizumab+axitinib due to hepatic toxicity in 73% of cases subsequently received antineoplastic therapy.

With regard to corticosteroid treatment for hepatic AEs, it is notable that the lack of immunosuppressive therapy did not appear to have had a negative impact on the rate of recovery and only 62% received systemic steroids for ALT ⩾3 x ULN, 76% for ALT ⩾5 x ULN and 84.4% for ALT ⩾ 10 x ULN, although systemic corticosteroids had been recommended in the protocol for Grade ⩾ 2 AEs in line with recommendations in the SmPC. The MAH clarified that Management guidelines implemented in the protocol (Amendment 8) recommended to promptly interrupt both study drugs if ALT/AST elevations >3×ULN were observed and initiate steroids only if the elevations did not resolve promptly without corticosteroid treatment (recommendations based on the difference in half-life of axitinib (~6 hours) and pembrolizumab (3 to 4 weeks). Further, the MAH provided data to support that the frequency of corticosteroid use for hepatic AEs in KEYNOTE-426 is generally consistent with the frequency of corticosteroid use for the adverse event of special interest (AEOSI) of hepatitis across the entire pembrolizumab program (that means that despite the recommendations in the SmPC to initiate corticosteroid treatment for hepatic AEs ⩾2, corticosteroids are applied in a lower proportion in clinical practice). Data for re-challenge of patients with more severe ALT elevations (ALT ≥10 × ULN, ALT ≥20 × ULN, and ALT ≥3 × ULN associated with bilirubin ≥2 × ULN) were provided and show, although based on limited patient numbers, that even in these patients subsequent recurrences following re-challenge recovered again. In the SmPC, for subjects with "ALT or AST ⩾ 10 times ULN or > 3 times ULN with

concurrent total bilirubin ⩾ 2 times ULN, both KEYTRUDA and axitinib should be permanently discontinued and corticosteroid therapy may be considered" according to the SmPC which is endorsed.

In section 4.2 of the SmPC, "rechallenge with a single medicine or sequential rechallenge with both medicines after recovery may be considered" if ALT or AST ⩾ 3 times ULN but < 10 times ULN. According to Table 4.5.23 the choice of retreatment after recovery did not appear to influence the probability of a second hepatic AE (nearly 50%). However only 3 patients received pembrolizumab monotherapy after recovery and median duration of treatment after recovery was only 28 days for pembro mono (as opposed to 155 days for axitinib monotherapy in 34 patients and 263 days for pembrolizumab + axitinib in 55 patients). Drug discontinuation was due to PD in 2 out of 3 cases. In view of these limited data the recommendation of a rechallenge with pembrolizumab as monotherapy appears somewhat questionable, but from provided updated data it appears to be no profound rationale to assume that a re-challenge with pembrolizumab mono would not be a reasonable option for patients with axitinib related AEs or that one sequence of re-challenge would be more preferable.
In the same SmPC section, the MAH provided dosing guidelines for liver enzyme elevations when Keytruda is combined with axitinib:

In patients with RCC being treated with KEYTRUDA in combination with axitinib:

- If ALT or AST ≥ 3 times ULN but < 10 times ULN, both KEYTRUDA and axitinib should be withheld until these adverse reactions recover to Grades 0-1. Corticosteroid therapy may be considered. Rechallenge with a single medicine or sequential rechallenge with both medicines after recovery may be considered.
- If ALT or AST ≥ 10 times ULN or > 3 times ULN with concurrent total bilirubin ≥ 2 times ULN, both KEYTRUDA and axitinib should be permanently discontinued and corticosteroid therapy may be considered.

In participants with ALT or AST ⩾3×ULN to <10×ULN, without concurrent total bilirubin elevation a higher proportion of patients without steroids did not recover (14%; 4/29) compared to those that received high or low dose steroids (2%; 1/42). However, most of the patients without steroid treatment recovered (86%; 25/29), time to recovery was similar for all patients and numbers for non-recovered patients after the first AE are too small to draw definitive conclusions and justify steroid treatment for all patients treated with the combination therapy. In participants with ALT or AST ⩾10×ULN, or ALT/AST ⩾ 3×ULN with concurrent total bilirubin ⩾2×ULN most of the patients received steroids (34/44) and 6.8% (3/44) patients did not recover from the first events, but all received steroid treatment. In view of these data, the very general recommendation for patients with liver enzyme elevations "corticosteroid therapy may be considered" can be considered acceptable.
The rewording of the text applicable to RCC patients in Table 1 of Section 4.2 of the SmPC is endorsed (see SmPC), but the different approach used with regards to subjects with ALT >5 times ULN, (permanently discontinue for all indications while could be rechallenged in RCC) might be misleading as in section 4.4 (*Immune-related hepatitis*) it is stated that "Corticosteroid should be administered". Concerning this, the MAH clarified that the provided information is meant to be understood as complementary in view of the different underlying pathophysiologic mechanisms of both drugs. This is acceptable.
In addition, the MAH provided data for 37 patients with a second re-challenge (with pembrolizumab alone, axitinib alone or both pembrolizumab and axitinib). A total of 12 participants had another recurrence of ALT ⩾3×ULN, most of these subsequent ALT elevations (7 out of 12) were ⩾3 to <5×ULN and all these recurrent ALT elevations subsequently resolved. Despite the limited patient numbers, it is agreed that data support the safety of multiple re-challenges. Based on provided updated data including results for a second re-challenge of study drugs, there appears to be no profound rationale to assume that a re-challenge with pembrolizumab mono would not be a reasonable option for patients with axitinib related AEs or that one sequence of re-challenge would be more preferable. The MAH further clarifies that the recommendation to discontinue pembrolizumab permanently for recurrent Grade 3 adverse reactions

applies also for the combination therapy but only for immune-related (hepatic) events. This is further clarified in the SmPC by:
"*KEYTRUDA, as monotherapy or as combination therapy, should be permanently discontinued for Grade 4 or recurrent Grade 3 immune-related adverse reactions, unless otherwise specified in Table 1*".

In section 4.4, the MAH added the following paragraph:

> *Use of pembrolizumab in combination with axitinib for first-line treatment of patients with RCC*
> When pembrolizumab is given with axitinib, higher than expected frequencies of Grades 3 and 4 ALT and AST elevations have been reported in patients with advanced RCC (see section 4.8). Liver enzymes should be monitored before initiation of and periodically throughout treatment. More frequent monitoring of liver enzymes as compared to when the medicines are used in monotherapy may be considered. Medical management guidelines for both medicines should be followed (see section 4.2 and refer to the Summary of Product Characteristics for axitinib).

The inclusion of this paragraph and its wording is supported, as it is agreed that an increased incidence of elevated ALT and AST represents the most frequent observed hepatic AEs, and reflects the hepatic AE profile associated with the combination of pembrolizumab+axitinib most appropriately. Although, "more frequent monitoring" may be considered an unclear indication, as in the SmPCs of pembrolizumab and axitinib there an exact frequency of monitoring is not stated, the MAH argues that the frequency of liver function monitoring depends on the clinical circumstances and that a more definitive recommendation would not be considered helpful to address this variability, and this is agreed.

KN426 safety analyses did show more subjects receiving pembrolizumab+axitinib having **drug discontinuation due to AEs** than those treated with sunitinib (25.9% vs 10.1%, respectively). The observed incidence of AEs leading to the discontinuation of any drug was 30.5% in the pembrolizumab+axitinib group, but simultaneous discontinuation of both drugs in the pembrolizumab+axitinib group (7.7%) was lower compared with AEs leading to discontinuation of sunitinib (13.9%). The most common reason for stopping study drug in the combination arm was *ALT increased* (31 subjects, [7.2 %]) *AST increased* (20 subjects, [4.7%]), and *Hepatic function abnormal* (6 subjects, [1.4%]). When looking at frequency and reasons for specific study drug discontinuation, no relevant differences could be found between pembrolizumab and axitinib. Median time to discontinuation is around 60 days. Overall **interruption of study drugs due to AEs** was reported in 69.9% for pembrolizumab and/or axitinib (pembrolizumab and axitinib 35.7%, pembrolizumab 50.3%, axitinib 63.9%) and in 49.9% for sunitinib. Among reasons, diarrhoea and transaminase elevation were as frequently recorded for pembrolizumab and axitinib, this latter was interrupted more often due to *Hypertension* (13.3% vs 0.7%, respectively) and *Palmar-plantar erythrodysaesthesia syndrome* (6.8% vs 0.5%, respectively). Compared to sunitinib, in the pembrolizumab+axitinib arm an overall lower proportion of subjects with dose reduction due to AEs (20.3% vs 30.1%, respectively), due to drug-related AEs (20% vs 28.5%), or due to grade 3-5 AEs (10.3% vs 14.4%) were found.

AEs summary by subgroups shows an increase in incidences of all AEs categories for elderly across treatments, with a more pronounced difference between younger and older age categories in pembrolizumab+axitinib-treated subjects than in those receiving suntinib. Between-treatment comparisons showed the largest differences in AEs frequencies among the 75-84 age group. With only 36 participants ≥75 years in the pembrolizumab + axitinib group the safety data were insufficient for a thorough characterization in this age group, and this has been reflected in the SmPC.

At gender analyses, female subjects had higher proportions of grade 3-5 AEs (82.9% vs 72.9%) and of drug-related grade 3-5 AEs (71.5% vs 59.5%), while SAE, drug-related SAEs compared to males, while discontinuations were not dissimilar between subgroups. Also, in the sunitinib arm, a higher frequency of grade 3-5 AEs and grade 3-5 drug-related AEs was found in females compared to males. Frequency of AEs

leading to death was slightly higher in males (3.3%) than in females (0.8%), in accordance with that found in the Pembrolizumab Monotherapy RSD (5.1%). AEs summary table by KPS ranges (90/100 vs 70/80) did not show relevant differences in safety profiles among groups With regards to extrinsic factors, the safety profile of pembrolizumab+axitinib was comparable between geographical regions of enrollment.

Immunogenicity assessment in pembrolizumab+axitinib-treated subjects documented treatment emergent ADA in 6.2% (1.4–3.8% for pembrolizumab monotherapy across indications) and incidence of treatment-emergent neutralizing positive status in 0.8% (0.2–1.6% for pembrolizumab monotherapy). Due to limited number of patients with treatment-emergent ADA, it is difficult to draw conclusions on the impact on safety profile or to merit further investigations regarding possible confounding factors.

Comparison of AEs for pembrolizumab+axitinib in KN426 versus axitinib in study A4061051

There is no direct comparison between pembrolizumab+axitinib and axitinib alone. Therefore, the assessment of safety should take into account the limitation of indirect comparison between different studies. Based on the data provided, proportions of subjects with overall AEs (98.4% vs 88.9%, respectively) and of drug-related AEs (96.3% vs 86.2%, respectively) were higher in pembrolizumab combination treatment in respect to axitinib when used for RCC treatment. The pattern of most common PTs found for the combination treatment was similar to that reported for axitinib monotherapy: *Diarrhea* (54.3% and 49.7%, respectively) *Hypertension* (44.5% and 48.7%, respectively), *Fatigue* (38.5% and 32.8%, respectively), *Decreased appetite* (29.6% and 28.6%, respectively), *Palmar-plantar erythrodysaesthesia syndrome* (28% and 26.5%), *Dysphonia* (25.4% and 23.3%, respectively). Compared to axitinib, in pembrolizumab+axitinib-treated subjects, increased proportions of thyroid AEs (*Hypothyroidism* 35.4% vs 20.6%; *Hyperthyroidism* 12.8% vs 3.2%, respectively) as well as of hepatotoxicity (*ALT increased* 26.8% vs 10.6%; *AST increased* 26.1% vs 7.9%, respectively) were reported. Incidences of Grade 3 to 5 hypertension, ALT increased, and AST increased were higher in pembrolizumab+axitinib as expected based on the safety profile for axitinib monotherapy; Hypertension is a known AE for axitinib, but the reason for the higher incidence of Grade 3 to 5 hypertension (22.1%) in the pembrolizumab + axitinib group relative to what was observed for axitinib in Study A4061051 (13.8%) remains unclear; however apart from one Grade 4 event (hypertensive crisis), all events were Grade 3 and only 1 participant discontinued either pembrolizumab or axitinib due to hypertension.

Noteworthy the incidence of drug-related SAEs in the pembrolizumab + axitinib group (23.8%) was four times higher relative to what was observed for axitinib monotherapy in Study A4061051 (5.3%). While the incidence of *Diarrhoea* was similar to what was observed for axitinib in Study A4061051 (2.8% versus 2.6%, respectively), the rates of hepatic SAEs as well as of *ALT increased* and *AST increased*, in particular Grade 3 to 4 elevations, in the pembrolizumab + axitinib group were higher than would be expected from the combination of pembrolizumab and axitinib monotherapies.

Comparison of AEs for pembrolizumab+axitinib in KN426 versus pembrolizumab monotherapy in KN427 study

In the indirect comparison between the KN426 and the KN427, both conducted for treatment of RCC, whilst similar proportions of subjects with overall AEs in the two treatment strategies, drug-related AEs were more often found in pembrolizumab combination treatment compared to monotherapy (96.3% vs 80.9%, respectively). The frequency of almost all most common ($\geq$30% incidence) PTs reported for in pembrolizumab+axitinib resulted higher than that found with pembrolizumab monotherapy: *Diarrhea* (54.3% vs 22.7%, respectively), *Hypertension* (44.5% vs 8.2%, respectively), *Fatigue* (38.5% vs 38.2%, respectively), *Hypothyroidism* (35.4% vs 11.2%, respectively).

Comparison of KN426 study with pooled Pembrolizumab Monotherapy Reference Safety Dataset

In comparison with the pooled reference dataset for pembrolizumab monotherapy across indications, the KN426 AEs summary highlights a clearly worse safety profile for pembrolizumab when associated with axitinib. Indeed, higher incidence of drug-related AEs (96.3% vs 70.7%, respectively), Grade 3-5 AEs (75.8% vs 48.5%), Grade 3-5 drug-related AEs (62.9% vs 14.9%) and drug-related SAEs (23.8% vs 10.5%) were found. Furthermore, while AEs leading to deaths were similar in pembrolizumab+axitinib-treated subjects of KN426 and the pooled monotherapy dataset, a considerably higher proportion of subjects experienced overall and drug-related AEs leading to drug discontinuation, interruption or dose modification with the combination. With regards to AEOSIs, a higher proportion of subjects with at least one event was found in the combination arm compared to pembrolizumab monotherapy for overall and all event categories (overall 51.3% vs 22.7%, drug-related events 47.1% vs 19.4%, grade 3-5 events 10.7% vs 5.7%, grade 3-5 drug-related events 8.9% vs 4.9%, and SAEs (9.8% vs 5.8%). *Adrenal Insufficiency* (3.0% vs 0.8%), *Hepatitis* (2.8% vs 0.7%), *Hyperthyroidism* (12.8% vs 3.3%), *Hypothyroidism* (35.4% vs 9.9%), *Nephritis* (1.4% vs 0.3%), *Thyroiditis* (2.8% vs 0.7%) all had a >1% higher incidence in the combination treatment when compared to pembrolizumab monotherapy. Median time to first AEOSI tended to be shorter in the combination treatment than in the pembrolizumab monotherapy dataset for the following events: *Hepatitis* (54 vs 61 days, respectively), *Hypothyroidism* (94 vs 105 days), and *Myasthenic syndrome* (40.5 vs 57.5 days). Compared to pembrolizumab monotherapy, a higher incidence of adrenal insufficiency is noted in subjects treated with pembrolizumab combined with axitinib, however rates are low and possibly related to longer exposure in RCC setting than in other indications.

2.5.2. Conclusions on clinical safety

Overall, the safety assessment of the combination of pembrolizumab+axitinib is partially hampered by the lack of a direct comparison with axitinib in particular within a single study. For 1L treatment of subjects with advanced RCC, the overall safety profile of pembrolizumab+axitinib compares less favourable to sunitinib, but demonstrated as apparently overall manageable. In KEYNOTE-426, a higher rate of all adverse event categories (particularly grade 3-5 AES, SAEs and drug discontinuations due to AEs) for the combination of pembrolizumab with axitinib. Even adjusting for exposure an increased rate of drug-related SAEs and of drug discontinuations due to AEs is observed.

Based on indirect comparison the combination has a clearly worst safety profile compare to monotherapies. Many of the observed toxicities (i.e. diarrhea, hypertension, dysphonia, fatigue, palmar-plantar erythrodysaestesia syndrome) mirror the known individual safety profiles of axitinib and pembrolizumab, although with a higher incidence for some of them. The high occurrence of hepatic adverse events has been addressed in the SmPC (sections 4.2, 4.4. 4.8). A higher frequency Cardiac Arrythmias SMQ/Atrial Fibrillation is observed in the pembrolizumab/axitinib arm compared to the sunitinib arm in KN-426 trial. As causal relationship with pembrolizumab cannot be ruled out, the MAH has added atrial fibrillation/cardiac arrhythmias to ADRs in Section 4.8 of the SmPC.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The PRAC considered that the risk management plan version 25.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 25.0 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Immune-Related Adverse Reactions (including immune related pneumonitis, colitis,hepatitis, nephritis, and endocrinopathies)
Important potential risks	For hematologic malignancies: increased risk of severe complications of allogeneic stem cell transplantation (SCT) in patients who have previously received pembrolizumab Graft versus host disease (GVHD) after pembrolizumab administration in patients with a history of allogeneic stem cell transplant (SCT)
Missing information	Long term safety

No changes to the list of safety concerns were made as a result of this extension of indication.

Pharmacovigilance plan

Table: On-going and planned additional pharmacovigilance activities

Study Status	**Study/activity Type, title and category**	**Summary of Objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 - Required additional pharmacovigilance activities					
Started	Clinical trial A Randomized, Open Label, Phase III Study of Overall Survival Comparing Pembrolizumab (MK-3475) versus Platinum Based Chemotherapy in Treatment Naïve Subjects with PD-L1 Positive Advanced or Metastatic Non-Small Cell Lung Cancer (KN042)	To evaluate the overall survival (OS) and progression free survival (PFS) and to examine the safety and tolerability profile of pembrolizumab in subjects with PD-L1 positive 1L advanced/metastatic NSCLC, treated with pembrolizumab compared to standard of care (SOC) chemotherapies.	-Important identified risks (Immune-related adverse reactions) -Important potential risks (GVHD after pembrolizumab administration in patients with a history of allogeneic SCT) -Missing information (Long term safety)	Final Study Report	Dec 2019

Table: On-going and planned additional pharmacovigilance activities

Study Status	Study/activity Type, title and category	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Started	Clinical Trial A Phase Ib Multi-Cohort Trial of MK-3475 (pembrolizumab) in Subjects with Hematologic Malignancies (KN013)	To examine the safety and tolerability of pembrolizumab in subjects with hematologic malignancies including, Hodgkin lymphoma, mediastinal large B cell lymphoma (MLBCL), relapsed/refractory non-Hodgkin lymphoma (NHL), myelodysplastic syndrome (MDS) and multiple myeloma.	-Important identified risks (Immune-related adverse reactions) -Important potential risks (For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab ; GVHD after pembrolizumab administration in patients with a history of allogeneic SCT)	Final Study Report	Mar 2019
Started	Clinical Trial A Phase II Clinical Trial of MK-3475 (Pembrolizumab) in Subjects with Relapsed or Refractory (R/R) Classical Hodgkin Lymphoma (cHL) (KN087)	To determine the safety and tolerability of pembrolizumab in subjects with relapsed or refractory classical Hodgkin Lymphoma (cHL) and to evaluate overall response rate (ORR), progression free survival (PFS), duration of response (DOR) and overall survival (OS) of pembrolizumab in study subjects.	-Important identified risks (Immune-related adverse reactions) -Important potential risks (For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab ; GVHD after pembrolizumab administration in patients with a history of allogeneic SCT)	Final Study Report	Aug 2021

Table: On-going and planned additional pharmacovigilance activities

Study Status	Study/activity Type, title and category	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Started	Clinical Trial A Phase III, Randomized, Open-label, Clinical Trial to Compare Pembrolizumab with Brentuximab Vedotin in Subjects with Relapsed or Refractory Classical Hodgkin Lymphoma (KN204)	To compare overall survival (OS), progression free survival (PFS) and overall response rate (ORR) of pembrolizumab when compared to Brentuximab Vedotin in subjects with relapsed or refractory cHL and to examine the safety and tolerability between treatment groups.	-Important identified risks (Immune-related adverse reactions) -Important potential risks (For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab ; GVHD after pembrolizumab administration in patients with a history of allogeneic SCT)	Final Study Report	Apr 2021
Planned	Cumulative review of literature, clinical trial and post-marketing cases for the risks of encephalitis, sarcoidosis and GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	To monitor, identify and evaluate reports of encephalitis, sarcoidosis and GVHD after pembrolizumab administration in patients with a history of allogeneic SCT.	Important potential risk of GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	PSUR	2019
Started	Clinical trial A Phase I/II Study of MK-3475 in Combination with Chemotherapy or Immunotherapy in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Carcinoma (KN021)	To determine the recommended Phase II dose for MK-3475 in combination with chemotherapy or immunotherapy in subjects with unresectable or metastatic NSCLC.	-Important identified risks (Immune-related adverse reactions) -Important potential risks (GVHD after pembrolizumab administration in patients with a history of allogeneic SCT)	Final Study Report	Apr 2020

Table: On-going and planned additional pharmacovigilance activities

Study Status	Study/activity Type, title and category	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Started	Clinical Trial A Randomized, Double-Blind, Phase III Study of Platinum+ Pemetrexed Chemotherapy with or without Pembrolizumab (MK-3475) in First Line Metastatic Non-squamous Non-small Cell Lung Cancer Subjects (KN189)	To evaluate the antitumor activity of pembrolizumab in combination with chemotherapy compared with saline placebo in combination with chemotherapy and to evaluate the antitumor activity of pembrolizumab in combination with chemotherapy compared with saline placebo in combination with chemotherapy using OS.	-Important identified risks (Immune-related adverse reactions) -Important potential risks (GVHD after pembrolizumab administration in patients with a history of allogeneic SCT)	Final Study Report	Jun 2021
Started	Clinical Trial A randomized, active-controlled, multicenter, open-label Phase III clinical trial to examine the efficacy and safety of Pembrolizumab versus the choice of 3 different standard treatment options in subjects with recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) whose disease has progressed on or after prior platinum-containing chemotherapy (KN040)	To compare the overall survival (OS) in subjects with R/M HNSCC treated with pembrolizumab compared to standard treatment.	-Important identified risks (Immune-related adverse reactions) -Important potential risks (GVHD after pembrolizumab administration in patients with a history of allogeneic SCT)	Final Study Report	May 2020
Started	Clinical Trial A Phase III Randomized, Open-label Study to Evaluate Efficacy and Safety of Pembrolizumab (MK-3475) in Combination with Axitinib versus Sunitinib Monotherapy as a First-line Treatment for Locally Advanced or Metastatic Renal Cell Carcinoma (mRCC) (KN426)	To evaluate and compare PFS per RECIST 1.1 as assessed by BICR and OS in subjects treated with pembrolizumab plus axitinib versus sunitinib monotherapy.	-Important identified risks (Immune-related adverse reactions) -Important potential risks (GVHD after pembrolizumab administration in patients with a history of allogeneic SCT)	Final Study Report	March 2021

Study KEYNOTE 426 was added to the pharmacovigilance plan in order to address existing safety concerns in the new indication (first line treatment of advanced or metastatic renal cell carcinoma).

Risk minimisation measures

No changes to the risk minimisation measures were made as a result of this extension of indication.

2.7. Update of the Product information

As a result of this variation, section(s) 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are being updated.

The MAH provided supporting extensive summary tables for section 4.8 of the SmPC. The MAH provided a summary Table of ADRs with related frequencies (all grades and grade 3-5) to support the new column for the use of pembrolizumab in combination with axitinib.

The package leaflet has been updated accordingly in section 1. The base file for the revised Product Information in the current submission is the final Product Information from variations EMEA/H/C/3820/II/058 & II/047 and PSUSA/00010403/201803.

2.7.1. User consultation

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

This extension of indication of Keytruda is for the first line treatment of advanced or metastatic renal cell carcinoma (RCC) in combination with axitinib.

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.

According to the main guidelines (RCC: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, update January 2019; NCCN Clinical Practice Guidelines in Oncology: kidney cancer: version 3.2019) tumor histology and risk stratification is important in treatment selection. A prognostic model

derived from a population of patients with metastatic RCC treated with VEGF-targeted treatment has been more recently developed, known as International Metastatic RCC Database Consortium (IMDC) score: this model take into consideration six clinical parameters to stratify patients into favourable, intermediate and poor prognosis groups: interval from diagnosis to treatment less than 1 year, Karnofski PS<80%, corrected serum calcium>ULN, serum hemoglobin<ULN, absolute neutrophil count>ULN and platelets>ULN. The IMDC model has been derived from a retrospective study of 645 patients treated with VEGF-targeted agents (Heng DY, et al. J Clin Oncol 2009), and validated in an independent dataset (Heng DY, et al.Lancet Oncol 2013). The 2-year OS ranges from 75% in the favourable risk group (none of the 6 factors identified) to 7% in the poor-risk group (3 to 6 factors identified).

3.1.3. Main clinical studies

The application is based upon the interim analysis 1 of KEYNOTE-426 Study, is an ongoing, Phase 3, randomized, multicenter, active-controlled, 2 arms, open-label clinical study in first line adult patients with advanced renal cell carcinoma (RCC), comparing the combination of pembrolizumab 200mg Q3W + axitinib 5 mg BID with sunitinib 50 mg QD 4 weeks on 2 weeks off.

The primary objectives of the study were to compare the OS and PFS per RECIST 1.1 by BICR in participants treated with pembrolizumab + axitinib vs sunitinib. ORR, DCR, DoR, safety and tolerability profile of pembrolizumab, PFS and OS rate at 12, 24 and 18 months, and PROs were secondary objectives.

A total of 861 patients were randomly allocated in one of the 2 arms from 24-OCT-2016 to 24-JAN-2018 across 124 global study sites in 16 countries.

3.2. Favourable effects

- A statistically significant benefit in OS has been observed for pembrolizumab + axitinib over sunitinib (HR of 0.53, 95% CI 0.38, 0.74; p=0.00005);
- A statistically significant benefit in PFS has been also observed for pembrolizumab + axitinib over sunitinib (HR of 0.69, 95% CI 0.57, 0.84; p=0.00014);
- Objective response rate based on BICR assessment were observed in 59.3% (95% CI 54.5,63.9) of the patients treated with the combination compared to 35.7% (95% CI 31.1,40.4) in the control arm. The median time to response is similar in the two arms, while the duration of response tend to be longer in the experimental arm with 70.6% of patients still in response at 12 months in the control arm vs 61.6% in the control arm.
- Updated data confirmed the OS benefit in the overall population, as well as in the IDMC poor (HR= 0.50, 95%CI 0.29,0.87) and intermediate (HR= 0.52, 95%CI 0.36,0.75) risk categories.
- Updated PFS data show a trend to an improved effect in the IDMC favourable risk subgroup compared to data initially submitted.
- Permanent discontinuation treatment due to AEs does not seem to negatively affect neither the outcome of patients on subsequent treatments nor their prognosis if left untreated.

3.3. Uncertainties and limitations about favourable effects

- The immaturity of efficacy data that do not allow to draw any sound conclusion with regard to the IMDC favourable risk group (HR 0.94, 95%CI 0.43, 2.07). The OS KM curves in this subgoup are

superimposable at this stage. The final CSR should be provided post-approval, in particular to further characterize the benefit of the combination treatment.

- The lack of monotherapy experimental arms in study KN-426 hampers the assessment of the contribution of each component of the combination treatment. However, a positive contribution of each component can be assumed on the basis of the plausible mechanism of action of the two agents in the combination, evidence of single-agent activity, high activity of the combination in terms of ORR and PFS compared to monotherapy albeit in indirect comparisons, and the established contribution of these agents in different tumour types.

3.4. Unfavourable effects

Overall, the safety assessment of the combination of pembrolizumab+axitinib is partially hampered by the lack of a direct comparison within a single study. In the pembrolizumab+axitinib arm when compared to the sunitinib arm, the following were found:

- Increased frequencies of all AE categories, except for deaths;
- Confirmed higher risk for drug-related SAE (2.87 vs 1.99/100 p-m, respectively) and for all types of AEs leading to drug discontinuation when exposure-adjusted rates were considered;
- Increased risk of drug-related transaminase elevation and drug-related dysphonia;
- Overall AEOSIs frequency of 51.3% vs 36.2%;
- Overall treatment-emergent Hepatic Adverse Events frequency of 40.6% vs 26.6%;
- Non-fatal Drug-Induced Liver Injury in 15 subjects;
- High frequency of thyroid adverse events: *Hyperthyroidism* 12.8% vs 3.8%, *Hypothyroidism* 35.4% vs 31.5%*, Thyroiditis* 2.8% vs 0.5%;
- The incidences of ALT increased and AST increased, in particular Grade 3 to 4 elevations, were higher than would be expected from the combination of pembrolizumab and axitinib monotherapies; the incidences of the PTs ALT and AST increased were 26.8% and 26.1%, respectively in the pembrolizumab+axitinib group, 6.0% and 6.2% in the RSD, and 10.6% and 7.9% for axitinib in Study A4061051.
- Incidences of Grade 3 to 5 hypertension (22.1%) and hyperthyroidism (12.8%) in the pembrolizumab + axitinib group were higher compared to those for sunitinib, pembrolizumab monotherapy, and axitinib. However both AEs were clinically manageable.
- A trend toward higher incidences of severe and serious acute kidney injury was notable in the pembrolizumab + axitinib group; however absolute numbers were small (Grade 3 to 5 events 1.9%, SAEs 1.6).
- Among-drug related SAEs, it is noted that cardiac disorders, whilst having rates of 0.4% for pembrolizumab monotherapy, are reported at 1.6% for the pembrolizumab+axitinib arm (1.4% the sunitinib arm). Cardiac arrhythmias SMQ showed an increased proportion of events in subjects treated with pembrolizumab+axitinib compared to those receiving sunitinib (5.8% vs 2.4%, respectively), and similar differences for drug-related AEs (2.3% vs 0.2%) and SAEs (1.4% vs 0.2%). Similarly, subjects with Atrial Fibrillation were 1.6% vs 0.2%, respectively. *Cardiac arrhythmias* SMQ also show higher exposure-adjusted rates pembrolizumab+axitinib-treated subjects when compared to those receiving sunitinib (0.6 in

pembro combo vs 0.3/100 person-months in sunitinib). Cardiac arrhythmias (including atrial fibrillation) has been included as ADR in the Keytruda SmPC.

The safety profile of pembrolizumab in combination with axitinib compares unfavourable to sunitinib in 1L RCC treatment.

3.5. Uncertainties and limitations about unfavourable effects

- Safety data in the age group ≥75 years are limited. This is reflected in the SmPC.

3.6. Effects Table

Table 2. Effects Table for KN426 Trial. Data cut-off: 24-AUG-2018 (database lock 24 August 2018)

Effect	Short description	Unit	Pembro+ axitinib	Sunitinib	Uncertainties / Strength of evidence
Favourable Effects					
OS (ITT)	Time from randomization to death due to any cause	Months HR (95% CI)	NR vs NR HR of 0.53, (95% CI 0.38, 0.74; p=0.00005)		Dual Primary Endpoints ITT: statistically significant data from IA1 too immature to assess the B/R in all relevant subgroups Lack of direct comparison with monotherapies hampers the assessment of the contribution of each component. Updated descriptive results (data cut-off date 2 Jan 2019) confirmed OS, PFS and ORR benefit of the combination. Updated PFS in the IDMC favourable risk group showed a trend toward improved effect compared to prior data, with ORR advantage. No apparent detrimental effect is seen in OS, although data are quite immature.
PFS per RECIST 1.1 by BICR (ITT)	Time from randomization to first PD (per RECIST 1.1 based on BICR) or death due to any cause	Months HR (95% CI)	15.1 vs 11.0 HR of 0.69 (95% CI 0.56, 0.84; p=0.00012)		
ORR per RECIST 1.1 by BICR (ITT)	proportion of patients who achieved complete or partial response (secondary endpoint)	%	59.3%	35.7%	
Unfavourable Effects					
	Drug-related G 3-5 AEs	%	62.9	58.1	
	Drug-related SAEs	%	40.3	31.3	
	Discontinuation due to drug-related AEs	%	30.5	13.5	
	Discontinuation due to AEs	%	25.9	10.1	
	Discontinuation due to drug-related SAEs	%	17.0	9.9	
	Cardiac Arrythmias SMQ	%	5.8	2.4	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The combination of pembrolizumab and axitinib demonstrated superiority vs sunitinib in terms of PFS and OS in patients with advanced RCC, supported by an advantage in terms of ORR. Based on updated data, a benefit in PFS and ORR is observed across all IMDC risk group, with no apparent detrimental OS effect in the favourable risk.

For 1L treatment of subjects with advanced RCC, the overall safety profile of pembrolizumab+axitinib compares less favourable to sunitinib, but demonstrated as apparently overall manageable. In KEYNOTE-426, a higher rate of all adverse event categories (particularly grade 3-5 AES, SAEs and drug discontinuations due to AEs) for the combination of pembrolizumab with axitinib. Even adjusting for exposure an increased rate of drug-related SAEs and of drug discontinuations due to AEs is observed.

Concerns were raised regarding high occurrence of hepatic adverse events, which are addressed in the SmPC. Taking into account the worse safety profile of the combination compared to sunitinib, it is reassuring that permanent discontinuation treatment due to AEs does not seem to negatively affect neither the outcome of patients on subsequent treatments nor their prognosis if left untreated.

3.7.2. Balance of benefits and risks

Overall, a benefit in terms of PFS and ORR was observed across all IMDC risk group with pembrolizumab and axitinib compared to sunitinib. Although the safety profile of the combination compares less favourable to sunitinib, it appears overall manageable. The benefits of the combination treatment are considered to outweigh the risks.

3.7.3. Additional considerations on the benefit-risk balance

None.

3.8. Conclusions

The overall B/R of pembrolizumab in the first line treatment of advanced or metastatic renal cell carcinoma, in combination with axitinib, is positive.

The CHMP considers the following measures necessary to address issues related to clinical efficacy:

The final CSR of the pivotal Keynote-426 study should be provided post-approval as Annex II condition, in particular to further characterize the benefit of the combination treatment in the favourable IDMC risk group with longer follow-up.

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, II and IIIB

Extension of Indication to include first line treatment of advanced or metastatic renal cell carcinoma (RCC) as combination therapy of pembrolizumab together with axitinib based on the results of the first Interim Analysis (IA1) from the pivotal study, KN426, an ongoing, Phase 3, randomized, open-label, multicenter, global study, to evaluate the efficacy and safety of pembrolizumab in combination with axitinib versus sunitinib in previously untreated subjects with advanced/metastatic RCC. It also includes supportive data from KEYNOTE-427 Cohort A (pembrolizumab monotherapy) and a Sponsored Study A4061051 (axitinib monotherapy). As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance.

The MAH took the opportunity to update the educational materials in Annex II of the Product Information in relation to the adopted variation procedure EMEA/H/C/003820/II/0068. Furthermore, the due date of the Post-authorisation efficacy study P361 is updated to 2Q 2020.

In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.
The risk management plan (RMP) Version 25 is submitted.

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

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-authorisation efficacy study (PAES): The MAH should submit the final study report for study P426: A Phase III Randomized, Open-label Study to Evaluate Efficacy and Safety of Pembrolizumab (MK-3475) in combination with Axitinib versus Sunitinib Monotherapy as a First-line Treatment for Locally Advanced or Metastatic Renal Cell Carcinoma (mRCC)	1Q 2021

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP P/0043/2018 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

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

Scope

Extension of Indication to include first line treatment of advanced or metastatic renal cell carcinoma (RCC) as combination therapy of pembrolizumab together with axitinib based on the results of the first Interim Analysis (IA1) from the pivotal study, KN426, an ongoing, Phase 3, randomized, open-label, multicenter, global study, to evaluate the efficacy and safety of pembrolizumab in combination with axitinib versus sunitinib in previously untreated subjects with advanced/metastatic RCC. It also includes supportive data from KEYNOTE-427 Cohort A (pembrolizumab monotherapy) and a Sponsored Study A4061051 (axitinib monotherapy). As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance.

The MAH took the opportunity to update the educational materials in Annex II of the Product Information in relation to the adopted variation procedure EMEA/H/C/003820/II/0068. Furthermore, the due date of the Post-authorisation efficacy study P361 is updated to 2Q 2020.

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The risk management plan (RMP) Version 25 is submitted.

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

Summary

Please refer to the Scientific Discussion EMEA/H/C/003820/II/0069.