EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 December 2020
EMA/CHMP/33664/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: **pembrolizumab**

Procedure No. EMEA/H/C/003820/II/0091

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 (participants who have not received prior therapy)
2L	Second-line therapy (participants who have received 1 prior therapy)
2L+	Second-line or later therapy (participants who have received 1 or more prior therapies)
3L	Third-line (participants who have received 2 prior therapies)
3L+	Third-line or later therapy (participants who have received 2 or more prior therapies)
ADA	Antidrug antibodies
AE(s)	Adverse event(s)
AEOSI	Adverse event(s) of special interest
ASaT	All subjects as treated
ASCO	American Society of Clinical Oncology
BCG	Bacillus Calmette-Guerin
cHL	Classic Hodgkin's lymphoma
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIS	Carcinoma in situ
CR	Complete response (per RECIST)
CRC	Colorectal carcinoma
CSR	Clinical Study Report
DCR	Disease control rate (per RECIST)
dMMR	Deficient mismatch repair
DNA	Deoxyribonucleic acid
DOR	Duration of response (per RECIST)
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EMA/SAWP	European Medicines Agency/Scientific Advice Working Party
EMEA	European Medicines Evaluation Agency
EOP1	End of Phase 1
EORTC QLQ	European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire
E-R	Exposure response

Abbreviation	Definition
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
FOLFIRI	Irinotecan (180 mg/m^2); leucovorin (calcium folinate) 400 mg/m^2; 5-fluorouracil 2400 mg/m^2
GCP	Good Clinical Practice
GI	Gastrointestinal
HCC	Hepatocellular carcinoma
HL	Hodgkin lymphoma
HNSCC	Head and neck squamous cell carcinoma
HR	Hazard ratio
HTA	Health Technology Assessment
IA1/IA2	Interim analysis 1/2
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IV	Intravenous
KM	Kaplan-Meier
KRAS	Kirsten rat sarcoma
LSM	Least-squares method
mAb	Monoclonal antibody
M&S	Modeling and Simulation
MCC	Merkel cell carcinoma
mFOLFOX	Oxaliplatin (85 mg/m^2); leucovorin (calcium folinate) 400 mg/m^2; 5-fluorouracil 2400 mg/m^2
MMR	Mismatch repair
MSI	Microsatellite instability
MSI-H	Microsatellite instability-high
NCCN	National Comprehensive Cancer Network
NMIBC	Non-muscle invasive bladder cancer
NRAS	Neuroblastoma RAS
NSCLC	Non-small cell lung cancer
ORR	Objective response rate (per RECIST)
OS	Overall survival

Abbreviation	Definition
PCR	Polymerase chain reaction
PD-1	Programmed cell death-1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival (per RECIST)
PK	Pharmacokinetic
PMBCL	Primary mediastinal large B-cell lymphoma
PMDA	Pharmaceuticals and Medical Devices Agency
PMR	Post-marketing requirement
PR	Partial response (per RECIST)
PRO	Patient-reported outcomes
PS	Performance status
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q6W	Every 6 weeks
QoL	Quality of life
QTc	QT [interval] corrected for heart rate
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumours
RSD	Reference Safety Dataset
SAE(s)	Serious adverse event(s)
SCLC	Small-cell lung cancer
SD	Stable disease (per RECIST)
sJNDA	Supplementary Japan New Drug Application
SOC	Standard of care
TTD	Time to deterioration
TTP	Time to progression
US	United States
VAS	Visual analog scale

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 29 June 2020 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

C.I.6 -Extension of indication to include first-line treatment of unresectable or metastatic microsatellite instability-high (MSI H) or mismatch repair deficient (dMMR) colorectal cancer in adults for Keytruda based on the results from KEYNOTE-177 (an international, randomised, open-label Phase 3 trial of pembrolizumab versus chemotherapy in MSI-H or dMMR Stage IV Colorectal Carcinoma). As a consequence, sections 4.1, 4.2, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, a minor correction has been made in section 4.4, "Immune related endocrinopathies" subsection. Version 29.1 of the RMP has also been submitted.

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 MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific Advice from the CHMP in 2015 on the design elements of the clinical trial KEYNOTE-177, which is the pivotal study for this application (procedure EMEA/H/SA/2437/8/2015/II).

1.2. Steps taken for the assessment of the product

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

Rapporteur: Armando Genazzani Co-Rapporteur: Jan Mueller-Berghaus

Timetable	Actual dates
Submission date	29 June 2020
Start of procedure:	18 July 2020
Co-Rapporteur's preliminary assessment report circulated on:	14 September 2020
Rapporteur's preliminary assessment report circulated on:	14 September 2020
PRAC Rapporteur's preliminary assessment report circulated on:	16 September 2020
PRAC Rapporteur's updated assessment report circulated on:	9 October 2020
PRAC RMP advice and assessment overview adopted by PRAC on:	1 October 2020
Joint Rapporteur's updated assessment report circulated on:	9 October 2020
Request for supplementary information and timetable adopted by the CHMP on:	15 October 2020
MAH's responses submitted to the CHMP on:	20 October 2020
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	19 November 2020
Joint Rapporteur's preliminary assessment report on the MAH's responses circulated on:	26 November 2020
PRAC RMP advice and assessment overview adopted by PRAC on:	26 November 2020
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	4 December 2020
CHMP opinion:	10 December 2020

2. Scientific discussion

2.1. Introduction

The MAH for Keytruda is applying for an extension of indication of pembrolizumab as first line treatment of unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults, based on the results of the open-label international randomized phase 3 trial KEYNOTE-177 of pembrolizumab versus chemotherapy in MSI-H or dMMR Stage IV Colorectal Carcinoma.

2.1.1. Problem statement

Disease or condition

The claimed therapeutic indication at the time of submission was:

"KEYTRUDA as monotherapy is indicated for the first-line treatment of unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults"

During the procedure, the MAH updated the sought indication as follows:

"KEYTRUDA as monotherapy is indicated for the first-line treatment of ~~unresectable or~~ metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults"

Epidemiology and risk factors, screening tools/prevention

Colorectal cancer ranks third in terms of incidence and second in terms of mortality worldwide[1]. Approximately 12-15% of all CRC and 4% of metastatic CRC are characterized as microsatellite instability-high (MSI-H) and/or mismatch repair-deficiency (dMMR).[2]

Biologic features, aetiology and pathogenesis

Mismatch repair proteins (MMR) repair insertions or deletions in microsatellites, which are repetitive DNA units. MLH1, MSH2, MSH6 and PMS2 are known MMR gene products. Dysfunction of this system is known as deficient mismatch repair (dMMR), which leads to the insertion of deletion of the repeating nucleotides microsatellites during DNA replication and accumulation of mutations due to failure to correct errors in nucleotide repeat. This form of genomic instability is called microsatellite instability (MSI).

MSI-H/dMMR has been observed in many types of cancer including CRC, gastric, endometrial, biliary, urinary tract, ovarian and breast tumours. Some tumour types have noticeably higher MSI-H prevalence than others (endometrial and colon cancer in particular), being the overall prevalence in stage IV cancers of approximately 5%.[3]

There are two forms of MSI colorectal cancer: (1) the hereditary type, caused by the deficiency of MMR system resulting from a germline mutation in MMR genes predisposing to Lynch syndrome (LS) or hereditary non-polyposis colorectal cancer, which is the most common hereditary colon cancer syndrome, inherited in an autosomal dominant pattern; (2) the sporadic form, which is related to the somatic inactivation of the same pathway, most commonly through hypermethylation (epigenetic inactivation) of the *MLH1* gene, leading to sporadic MSI/dMMR CRC.

Recent studies highlighted genetic diversity and distinct patterns in CRC with MSI, suggesting substantial heterogeneity, also based on MSI etiology.[4]

Methylation of the MLH1 promoter region in the sporadic form is strongly associated with the BRAF V600E gene mutation. The presence of the BRAF V600E mutation in CRC essentially excludes Lynch syndrome, except for rare cases associated with PMS2 germ-line mutation. While BRAF V600E mutation has a negative prognostic impact in proficient MMR CRC, data on the role of BRAF in relation to MMR status are scarce and the impact of BRAFV600E mutation on MSI CRCs remains controversial.[5] By contrast, KRAS mutations (in codons 12 or 13) are inversely correlated with MSI-H status.[6]

Clinical presentation, diagnosis and stage/prognosis

The MSI-high (MSI-H) phenotype is characterized by clinical and pathologic features distinct from those observed in microsatellite stable (MSS) CRC. MSI-H CRCs are usually diagnosed at younger age and at an earlier stage than MSS CRC, with a predominance in the right colon. The sporadic form is however characterized by older age at diagnosis than the hereditary one and it's more often associated with

[1] Bray F et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer J for Clin. 2018;68:394-424.
[2] Baretti M, Le DT. DNA mismatch repair in cancer. Pharmacol Ther. 2018 Sep;189:45-62.
[3] Le et al. Mismatch repair deficiency predicts response of solid tumours to PD-1 blockade. Science 2017;357:409–413.
[4] Battaglin F et al. Microsatellite Instability in Colorectal Cancer: Overview of Its Clinical Significance and Novel Perspectives. Clin Adv Hematol Oncol 2018;16(11):735-747.
[5] Cohen R et al. Clinical and molecular characterisation of hereditary and sporadic metastatic colorectal cancers harbouring microsatellite instability/DNA mismatch repair deficiency. Eur J Cancer 2017; 86:266e274.
[6] Gelsomino F et al. The evolving role of microsatellite instability in colorectal cancer:A review. Canc Treat Rev 2016;51:19-26.

female sex and cigarette smoking.[8] Regardless whether hereditary or sporadic, MSI-H CRCs are histologically characterized by great production of mucin with extracellular accumulation, signet ring and medullary types, often admixed, with increased numbers of tumour-infiltrating lymphocytes and prominent Crohn's-like lymphoid reaction.[7]

Patients with Lynch syndrome have an increased risk of synchronous or metachronous tumours, as well as higher risk for the development of extracolonic cancer, in particular endometrial carcinoma, and also cancers of the small bowel, stomach, genitourinary system and biliary tract.

With regard to the molecular diagnosis, MMR or MSI status can be determined by examining either: (1) protein expression by IHC staining for 4 MMR proteins (MLH1/MSH2/MSH6/PMS2) on tumour samples to identify negative or loss of staining (i.e. loss of protein expression) that characterize dMMR as a surrogate for MSI; or (2) molecular DNA testing PCR-based microsatellite instability analysis evaluating a specific panels of microsatellite markers to identify instability in selected loci. In general, tumours are classified as MSI-H (including MMR deficient) when expression of at least 1 of 4 MMR proteins is not detectable by IHC, or when 30% or more of the loci show instability. Both methods are sensitive and specific for MSI detection and have a high concordance rate. Although both IHC- and PCR-based approaches are currently considered the standard for MSI detection, several studies have proposed other methods such as NGS.[6] [8] These tests are performed directly on tumour samples.

International guidelines (ESMO, NCCN, ASCO) recommend MMR/MSI testing with either an MMR protein IHC-based assay or PCR-based MSI loci for all patients with CRC in clinical decision making, and that "IHC for MMR and DNA analysis for MSI are different assays and measure different biological effects caused by deficient mismatch repair function". Patients determined to have defective MMR status are biologically the same population as those with MSI-H status. [9] [10] [11]

Findings from a pooled analysis of four phase 3 studies in participants with metastatic CRC treated with first-line SOC therapies, showed that the median PFS and OS were significantly worse for participants with MSI-H/dMMR CRC compared with participants whose tumours were microsatellite stable (PFS: HR=1.33; 95% CI:1.12–1.57; OS: HR=1.35;95% CI:1.13–1.61)[12] (see table below).

The underlying hypothesis for studies with anti PD-1/PD-L1 antibodies in MSI-H/dMMR cancer is that MSI-H/dMMR cancers are characterized by a high burden of somatic mutation and tumour-specific neoantigen load mediated by MSI and common defects in MMR, which can be recognized by the patient's immune system.[6] In this subset of MSI-H/dMMR cancer patients a large number of activated CD8 positive cytotoxic T cells and a cytokine-rich environment have been observed, associated with upregulated expression of PD-1 and PD-L1 and others checkpoints (e.g. CTLA-4). As a result, the MSI-H/dMMR phenotype represents a unique immunobiology that implicates the role of lymphocyte infiltration, high mutational load, and responsiveness to immune checkpoint blockade that can be addressed by anti-PD-1 therapy. Not all patients with MSI-H tumours, however, respond to immunotherapy, suggesting that a deeper understanding of immune-related mechanisms in MSI-H CRC is required. [13]

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[7] Gatalica Z et al. High microsatellite instability (MSI-H) colorectal carcinoma: a brief review of predictive biomarkers in the era of personalized medicine. Fam Cancer. 2016; 15: 405–412.
[8] Jonathan A Nowak JA et al. Detection of Mismatch Repair Deficiency and Microsatellite Instability in Colorectal Adenocarcinoma by Targeted Next-Generation Sequencing. J Mol Diagn. 2017 Jan;19(1):84-91.
[9] Van Cutsem E et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Ovcol 2016;27:1386-1422.
[10] Balamana J et al. Familial risk-colorectal cancer: ESMO Clinical Practice Guidelines. Ann Oncol 2013;24 (Supplement 6): vi73–vi80.
[11] NCCN Guidelines version 4.2020 Colon Cancer
[12] Venderbosch S, Nagtegaal ID, Maughan TS, Smith CG, Cheadle JP, Fisher D, et al. Mismatch repair status and BRAF mutation status in metastatic colorectal cancer patients: a pooled analysis of the CAIRO, CAIRO2, COIN, and FOCUS studies. Clin Cancer Res. 2014 Oct 15;20(20):5322-30.
[13] Olivera AF et al. Review of PD-1/PD-L1 Inhibitors in Metastatic dMMR/MSI-H Colorectal Cancer. Front Oncol 2019;9:396.

Management

The outcome of patients with mCRC has clearly improved during recent years with median survival now reaching 30 months in clinical trials. The treatment of mCRC patients should be seen as a continuum of care in which the determination of the goals of the treatment is important: prolongation of survival, cure, improving tumour-related symptoms, stopping tumour progression and/or maintaining quality of life.[14]

Patients are treated according to international guidelines for colorectal cancer. Combination chemotherapy of FOLFOX (oxaliplatin, 5-FU, and leucovorin/folinic acid) or FOLFIRI (irinotecan, 5-FU, and leucovorin/folinic acid) are established first-line SOC chemotherapy options for metastatic CRC. Both are partners for biologicals, but have a different toxicity profile, and may be used depending on the physician's recommendation and regional preference. Capecitabine per OS can be used instead of IV 5-FU in combination with oxaliplatin. Monoclonal antibodies against vascular endothelial growth factor VEGF (bevacizumab) and against the epidermal growth factor receptor EGFR (cetuximab, panitumumab) are approved for use in combination with chemotherapy as first-line treatment in CRC, since they improve the outcome of mCRC. A summary of approved treatments for first-line treatment of metastatic CRC is presented in table below.

Although there are currently available treatment options, the presence of additional effective therapies in this targeted advanced setting is welcomed.

Table: "Summary and Pooled Analyses of Clinical Outcomes in First-line dMMR Versus pMMR CRC Patients in Phase 3"

			dMMR	**Efficacy in dMMR CRC**		**Efficacy in pMMR CRC**	
Trial name	**Regimen**	**Agents**	**Prevalence**	**PFS mo. (95% CI)**	**OS mo. (95% CI)**	**PFS mo. (95% CI)**	**OS mo. (95% CI)**
CAIRO	Combination vs. sequential (XELOX, IRI)	Capecitabine, irinotecan, oxaliplatin	18/322 (5.6%)	5.7 (4.2-8.8)	14.8 (12.0-26.0)	6.9 (6.2-7.9)	17.9 (16.1-19.2)
CAIRO2	XELOX+bev vs. XELOX, bev+cetu	Capecitabine, oxaliplatin, bevacizumab, cetuximab	29/516 (5.6%)	7.5 (6.4-10.5)	15.6 (12.9-22.3)	10.5 (9.6-11.4)	22.0 (20.3-24.1)
COIN	XELOX/FOLFOX ± cetu	Capecitabine, oxaliplatin, 5FU, cetuximab	65/1461 (4.4%)	5.7 (5.4-6.1)	10.7 (9.3-13.0)	6.5 (6.2-6.8)	16.0 (15.0-16.9)
FOCUS	Sequential vs. upfront combination doublet (5FU+oxaliplatin or 5FU +irinotecan)	5FU, oxaliplatin, irinotecan	41/764 (5%)	8.1 (6.5-9.1)	16.6 (13.6-21.7)	8.0 (7.4-8.3)	15.5 (14.5-16.6)
Pooled dataset			153/3063 (5%)	6.2 (5.9–7.0)	13.6 (12.4-15.6)	7.6 (7.3-8.0)	16.8 (16.3-17.5)

Data are from Venderbosch et al, 2014.[13]

[14] Van Cutsem E et al. Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25(suppl 3):iii1-iii9.

Table: Summary of First-line Therapies for Metastatic CRC (regardless of MMR status)

Approved Therapies	Regimen	Median OS	Median PFS/TTP	Objective Response Rates	Publication
FOLFOX	Oxaliplatin 5-FU Leucovorin/folinic acid	15 months	TTP 7 months	34%	Colucci G et al. Phase III randomized trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: a multicenter study of the Gruppo Oncologico Dell'Italia Meridionale. J Clin Oncol. 2005 Aug 1;23(22):4866-75.
FOLFIRI	Irinotecan 5-FU Leucovorin/folinic acid	14 months	TTP 7 months	31%	Colucci G et al. Phase III randomized trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: a multicenter study of the Gruppo Oncologico Dell'Italia Meridionale. J Clin Oncol. 2005 Aug 1;23(22):4866-75.
FOLFOX (or XELOX) + Bevacizumab	Oxaliplatin 5-FU Leucovorin/folinic acid Bevacizumab	21.3 months	PFS 9.4 months	49%	Saltz LB, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol. 2008 Apr 20;26(12):2013-9. Erratum in: J Clin Oncol. 2008 Jun;26(18):3110. J Clin Oncol. 2009 Feb 1;27(4):653.
FOLFIRI+ Bevacizumab	Irinotecan 5-FU Leucovorin/folinic acid Bevacizumab	20.3 months 25 months	PFS 10.6 months	44.8% 58%	Heinemann V et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. Lancet Oncol. 2014 Sep;15(10):1065-75. Hurwitz H et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004 Jun 3;350(23):2335-42.
FOLFOX+ Cetuximab	Oxaliplatin 5-FU Leucovorin/folinic acid Cetuximab	18.3 months	PFS 7.2 months	46%	OPUS study
FOLFIRI+ Cetuximab	Irinotecan, 5-FU Leucovorin/folinic acid Cetuximab	19.9 months 28.7 months	PFS 8.9 months	46.9% 62%	Van Cutsem et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med. 2009 Apr 2;360(14):1408-17.
Capecitabine	Monotherapy	392 days	TTP 4.6 months	25.7%	Twelves C. Capecitabine as first-line treatment in colorectal cancer: pooled data from two large, phase III trials. Eur J Cancer. 2002;38:15-20.
Abbreviations: 5-FU=5 fluorouracil; CRC=Colorectal cancer; OS=Overall survival; PFS=Progression-free survival; TTP=Time to progression.					

Table: Overview of Studies in First-line Treatment of Advanced or Metastatic CRC

Treatment Arm	Sample size	Median PFS Months (95% CI)	ORR (95% CI)	Study name
Cetuximab + FOLFIRI	599	8.9 (8.0 - 9.5)	46.9% (42.9 – 51.0)	CRYSTAL
FOLFIRI	599	8.0 (7.6 – 9.0)	38.7% (34.8 – 42.8)	
Panitumumab + FOLFOX4	325 (KRAS WT) 221 (KRAS MT)	10.0 (9.3 – 11.4) 7.4 (6.9 – 8.1)	57% (51.5 – 62.6) 40% (33.4 – 46.9)	PRIME
FOLFOX4	331 (KRAS WT) 219 (KRAS MT)	8.6 (7.5 – 9.5) 9.2 (8.1 – 9.9)	48% (42.0 – 53.1) 41% (34.1 – 47.7)	
Cetuximab + mFOLFOX/ FOLFIRI	578 (KRAS WT)	10.5	59.6%	CALGB80405
Bevacizumab + mFOLFOX/ FOLFIRI	559 (KRAS WT)	10.6	55.2%	
Bevacizumab + FOLFOXIRI	252	12.1 (10.9-13.2)	53.1% (58.8-70.9)	TRIBE
Bevacizumab + FOLFIRI	256	9.7 (9.3-10.9)	65.1% (46.8-59.3)	
Bevacizumab + XELOX/FOLFOX4	699	9.4	47%	NO16966 / XELOX-1,
XELOX/FOLFOX4	701	8.0	49%	
Cetuximab + FOLFIRI	297 (KRAS WT)	10.0 (8.8 – 10.8)	62% (56.2 – 67.5)	FIRE-3 / AIO KRK0306
Bevacizumab + FOLFIRI	295 (KRAS WT)	10.3 (9.8 – 11.3)	58% (52·1 – 63·7)	
FOLFIRI with crossover to FOLFOX6 (upon progression or due to toxicity)	109	8.5 (7.0 – 9.5)	56% (47 – 65)	FRE-GERCOR-C97-3
FOLFOX6 with crossover to FOLFIRI (upon progression or due to toxicity)	111	8.0 (6.2 – 9.4)	54% (45 – 63)	

2.1.2. About the product

Keytruda (pembrolizumab) is a humanized mAb IgG4/kappa isotype directed against PD-1. By blocking the interaction between PD-1 and its ligands PD-L1/2, pembrolizumab enhances T cell lymphocyte activity with consequent stimulation of the immune-mediated anti-tumour activity. 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 non-specifically activate T cells.

Pembrolizumab is currently approved in EU for the treatment of melanoma, NSCLC, RCC, HNSCC, urothelial cancer, and cHL. Pembrolizumab has been approved both as monotherapy and in combination with other agents.

The scope of this variation is to include a new indication for Keytruda for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults. The proposed indication is based on the results from of a single pivotal study, KEYNOTE-177, an ongoing open-label, 2-arm, randomized (1:1), multicentre, international, phase 3 trial evaluating the efficacy and safety of pembrolizumab monotherapy (200 mg Q3W) versus SOC chemotherapies (mFOLFOX6 or FOLFIRI alone or in combination with bevacizumab or cetuximab) as first line treatment for locally confirmed dMMR or MSI-H stage IV CRC. A total of 307 patients were randomized to one of the two treatment arms.

The MAH applied for the following indication:

Keytruda as monotherapy is indicated for the first-line treatment of unresectable or metastatic

microsatellite instability-high (MSI H) or mismatch repair deficient (dMMR) colorectal cancer in adults.

The CHMP agreed to the following indication:

Keytruda as monotherapy is indicated for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults.

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

Scientific advice was obtained from the CHMP on 22-OCT-2015 (EMEA/H/SA/2437/8/2015/II) on the design of KEYNOTE-177 study. With regard to the inclusion/exclusion criteria, the CHMP commented that excluding patients with ECOG PS 2 was not considered necessary. About the comparator, while all the 6 proposed regimens individually were deemed acceptable, it was advised to reduce the number of possible investigator choice chemotherapies to 4 or 2, in order to reduce heterogeneity. The final design however retained all the 6 comparators. PFS was proposed as primary endpoint for the study, with OS as a key secondary endpoint, and collection of PFS2 data was ensured (in the current design PFS and OS are dual primary instead). The CHMP considered this acceptable, provided sufficiently mature OS data were submitted. In this regard, the CHMP recommended to perform the primary PFS analysis with the interim OS analysis after further maturity of the study. The MAH followed such advice, by increasing the maturity of final PFS analysis (i.e. OS IA) compared to the original design.

2.1.4. General comments on compliance with GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH. The assessment of KN177 data did not raise concern over GCP compliance leading to request for GCP inspection.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

2.2.1. Ecotoxicity/environmental risk assessment

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

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Study Number/ Status	Design	Population	Dosage, Regimen	Primary Efficacy Endpoint(s)
KEYNOTE-177 Ongoing	Phase 3, randomized, international-based, multicenter study	Participants who have previously untreated locally advanced unresectable or metastatic (Stage IV) MSI-H CRC (Total enrollment = 307)	Group 1: Pembrolizumab (MK-3475) 200 mg IV Q3W OR Group 2: SOC: Investigator's choice of the following: • mFOLFOX6, or • mFOLFOX6+ bevacizumab, or • mFOLFOX6+ cetuximab, or • FOLFIRI, or • FOLFIRI+ bevacizumab, or • FOLFIRI+ cetuximab	PFS, OS
KEYNOTE-164 Ongoing	Phase 2, multicenter, nonrandomized, open-label multicohort, single-arm study	Patients with locally advanced unresectable or metastatic MSI-H/dMMR CRC must have received 1 line of prior therapy Cohort A (n=61): Participants having received ≥2L prior therapy: prior fluoropyrimidine+oxaliplatin (≥1L) AND prior fluoropyrimidine+ irinotecan(≥1L) Cohort B (n=63): Participants having received ≥1L prior therapy: prior fluoropyrimidine + oxaliplatin OR prior fluoropyrimidine + irinotecan +/-anti-VEGF/EGFR mAb	Pembrolizumab (MK-3475) 200 mg IV Q3W	ORR

Abbreviations: 1L=first-line; 2L=second-line; CRC=Colorectal carcinoma; dMMR=deficient mismatched repair; EGFR=epidermal growth factor receptor; FOLFIRI=Irinotecan (180 mg/m^2)+leucovorin (calcium folinate) 400 mg/m^2+5-fluorouracil 2400 mg/m^2; mFOLFOX6=Oxaliplatin (85 mg/m^2)+leucovorin (calcium folinate) 400 mg/m^2+5-fluorouracil 2400 mg/m^2; IV=Intravenous; mAb=monoclonal antibody; MSI-H=Microsatellite instability-high; n=number; ORR=Objective response rate; OS=Overall survival; PFS=progression-free survival; Q3W=Every 3 weeks; SOC=Standard of care; VEGF=vascular endothelial growth factor.

2.3.2. Pharmacokinetics

Comprehensive review of the key clinical pharmacology findings for pembrolizumab as monotherapy (200 mg Q3W dosing regimen) from melanoma, NSCLC, HNSCC, HL, UC, GEJ adenocarcinoma and HCC indications have been discussed extensively in previous submissions. The key clinical pharmacology characteristics are summarized in the current and EU SmPC.

Clinical pharmacology results specific to this submission include:

• PK data of pembrolizumab at 200 mg Q3W from adults with MSI-/dMMR CRC (KEYNOTE-177).

• A proposed additional dosing regimen of 400 mg Q6W for pembrolizumab selected using Modeling & Simulation analyses, primarily based on PK exposure matching with approved Q3W dosing regimens.

Pharmacokinetics in Subjects with MSI-H/dMMR CRC

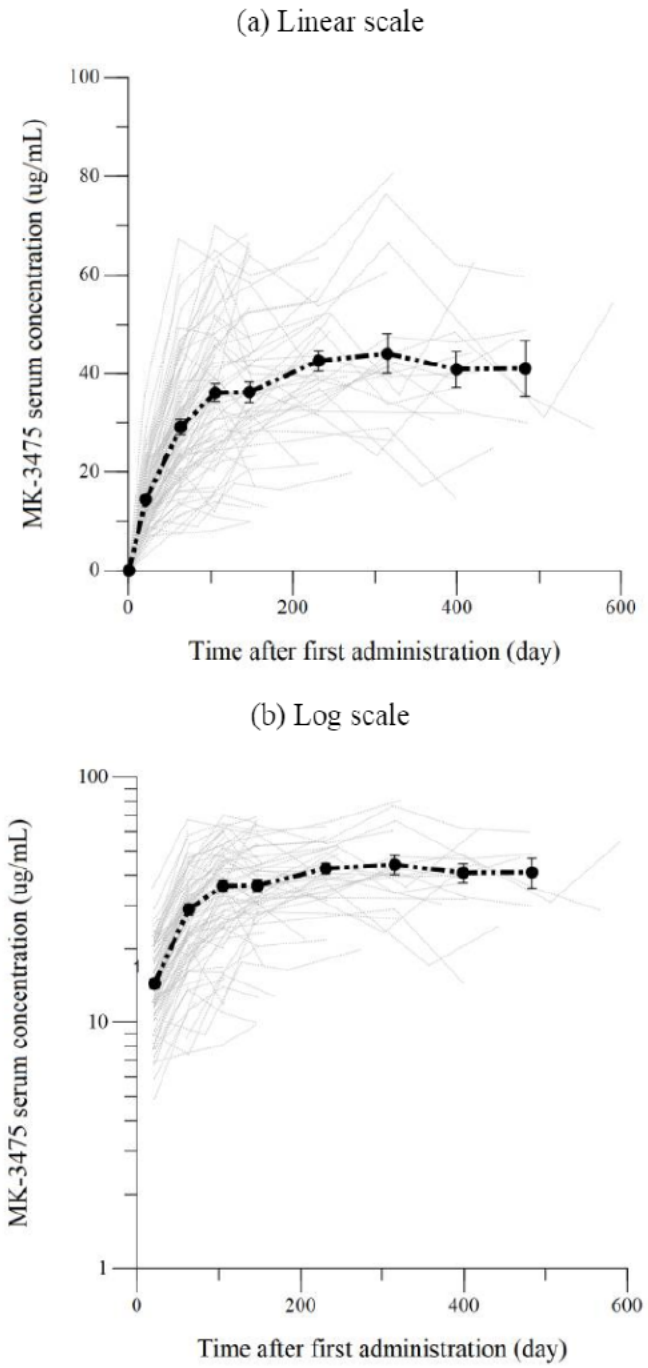
PK samples with a 20-Nov-2017 visit cut-off date were measured for a total of 126 subjects in KEYNOTE-177. The PK analysis was constructed from the final locked SDTM datasets using SAS version 9.4 and contains observed MK-3475 serum concentrations and actual elapsed blood sampling times relative to the corresponding time of dose.

PK sampling schedule in KEYNOTE-177 200 mg Q3W: Pre-dose pembrolizumab serum concentrations (Ctrough) were obtained within 24 hours prior to dosing at cycles 1,2,4,6,8,12 and every 4 cycles thereafter. Post-dose samples (Cmax) were drawn at cycle 1 and cycle 8 within approximately 30 minutes after the end of MK-3475 infusion. Additional PK samples were drawn at 24 hours, between 72 and 168 hours and at 336 hours after cycle 1 dosing. PK samples were also collected at discontinuation of pembrolizumab and 30 days after discontinuation of pembrolizumab.

RESULTS

Individual Predose serum pembrolizumab concentration-time profiles with mean± SE profile overlaid (linear-linear and log-linear scale) and arithmetic mean (SE) predose serum pembrolizumab concentration-time profile following multiple 200 mg IV administration Q3W to subjects in KEYNOTE-177 (linear-linear scale) are shown below:

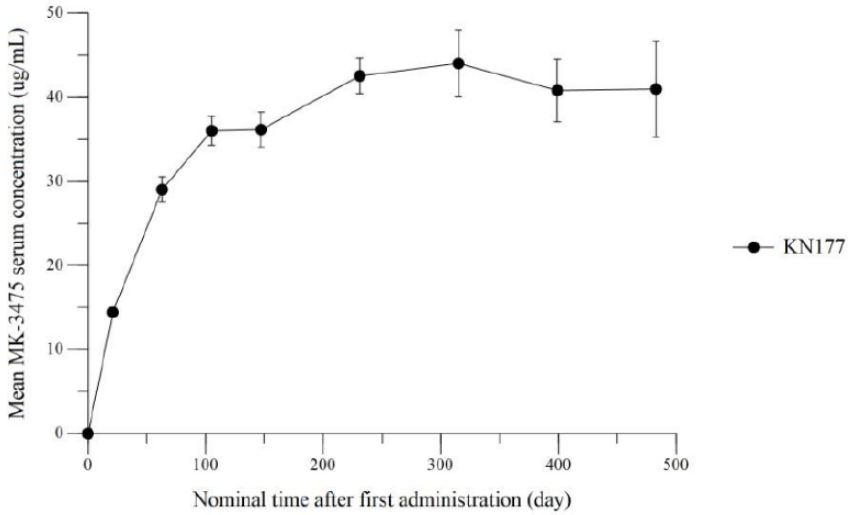
Figure 1 Individual and Arithmetic Mean (±SE) Predose Serum Concentrations of Pembrolizumab Following Multiple 200 mg I.V. Administrations Q3W to Subjects in KEYNOTE-177 (a) Linear scale, (b) Log scale



Note: Grey lines represent individual concentration observations. Black dashed lines represent arithmetic mean concentrations and error bars are associated ± SE. Actual PK drawtimes data were used for this analysis.

Data Source – [05H0W5: analysis-p177crcpkdm03]

Figure 2 **Arithmetic Mean (±SE) Predose Serum Concentrations of Pembrolizumab Following Multiple 200 mg I.V. Administrations Q3W to Subjects in KEYNOTE-177 (Linear scale)**



Note: This plot is Arithmetic mean with SE. X-axis is in days;
Data Source – [05H0W5: analysis-p177crcpkdm03]

Summary descriptive statistics of the PK concentrations by cycle and relative time to pembrolizumab dosing are presented below:

Table 2 **Summary Statistics of Pembrolizumab Predose (C_{trough}), Postdose (C_{max}) and Post Cycle 1 Serum Concentration Values Following Administration of Multiple 200 mg I.V. Doses with a 3 Week Dosing Interval in KEYNOTE-177 Subjects**

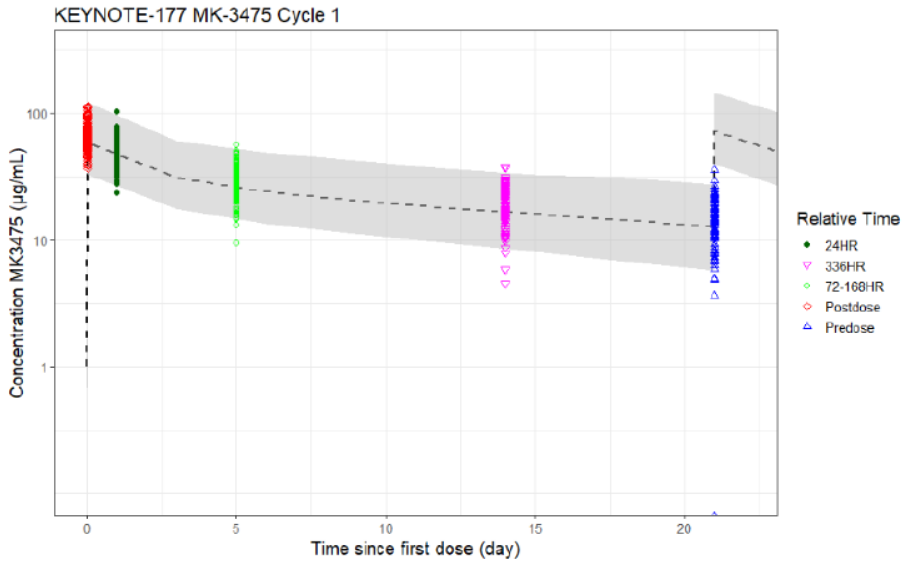
Cycle	NOMTAFD (day)	N	GM(%CV) (µg/mL)	AM(SD) (µg/mL)	Min (µg/mL)	Median (µg/mL)	Max (µg/mL)
Predose (C_{trough})							
Cycle 1 (Week 0)	0	118		0.00 (0.0)	0.00	0.00	0.00
Cycle 2 (Week 3)	21	96	13.2 (46)	14.4 (5.9)	3.64	13.9	35.5
Cycle 4 (Week 9)	63	75	26.0 (51)	28.9 (13)	7.41	27.5	67.2
Cycle 6 (Week 15)	105	70	32.8 (49)	36.0 (15)	8.07	35.4	69.9
Cycle 8 (Week 21)	147	53	32.9 (49)	36.2 (15)	9.76	34.7	68.5
Cycle 12 (Week 33)	231	31	40.9 (31)	42.5 (12)	19.8	41.0	66.3
Cycle 16 (Week 45)	315	18	41.1 (40)	44.0 (17)	17.1	40.6	80.6
Cycle 20 (Week 57)	399	13	38.4 (41)	40.8 (13)	14.5	40.2	62.4
Cycle 24 (Week 69)	483	5	39.5 (31)	41.0 (13)	29.9	35.7	59.6
Postdose (C_{max})							
Cycle 1 (Week 0)	0	115	65.0 (26)	67.1 (17)	36.4	65.7	113
Cycle 8 (Week 21)	147	50	91.6 (42)	98.5 (36)	30.4	91.6	185
Post Cycle 1							
Cycle 1 (Week 0)	1	109	48.8 (27)	50.5 (13)	23.7	48.4	103
	5	112	27.8 (32)	29.1 (9.0)	9.45	27.8	56.7
	14	105	17.7 (37)	18.8 (6.3)	4.55	17.6	37.7

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

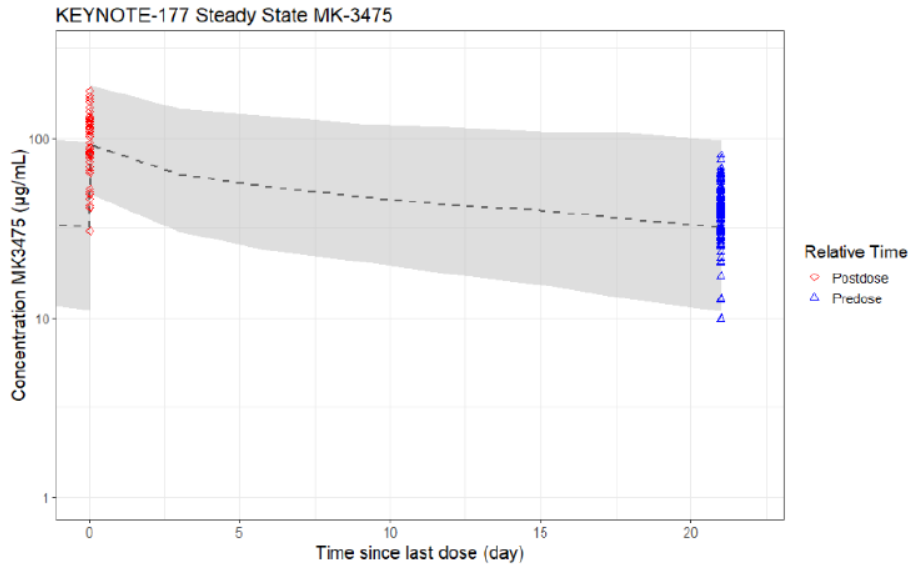
Data Source – [05H0W5: analysis-p177crcpkdm03]

Over the course of clinical development of pembrolizumab, PK has been robustly characterised. Using a dataset with sample size of 2993 participants, a time-dependent PK model was created to describe the PK profile as indicated in the USPI and EU SmPC. This model is used as the reference PK model to support pembrolizumab submissions across indications worldwide. Observed pembrolizumab concentration data in KEYNOTE-177 where pembrolizumab was administered to subjects with microsatellite instability-high colorectal carcinoma are overlaid on the simulated profile using the reference model as shown in the following figure:

Figure 3 Observed Concentration Data in KEYNOTE-177 Subjects Receiving 200 mg Q3W Pembrolizumab with Reference PK Model-Predicted Pharmacokinetic Profile for 200 mg Q3W Dose regimen



a)



b)

Footnote Overlay plot:
Pembrolizumab model predictions and observed concentration data for KEYNOTE-177 subjects after (a) cycle 1 and (b) steady state (at and after cycle 8). Symbols are individual observed data (nominal time) from subjects in KEYNOTE-177; black dashed 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; plots are displayed on log scale. Samples with a time after last dose > 21 days are not included in the plots; RLTVTM = Relative time to dose.
Data Source – [05H0W5: analysis-p177crcpkdm03]

PK Comparison with monotherapy indications

Comparison of KEYNOTE-177 observed concentration values with other monotherapy indications: KEYNOTE-024, KEYNOTE-045, KEYNOTE-048, KEYNOTE-052, KEYNOTE-055, KEYNOTE-087, KEYNOTE-158, KEYNOTE-164, and KEYNOTE-177 subjects.

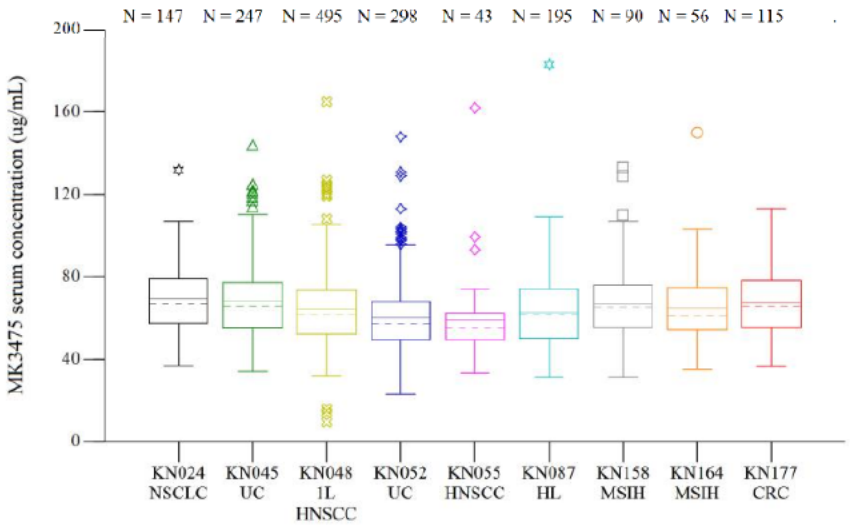
Table 3 Summary Statistics of Pembrolizumab Observed Serum Concentration Values Following Administration of Multiple I.V. Doses of 200 mg Q3W in Studies KN024, KN045, KN048, KN052, KN055, KN087, KN158, KN164 and KN177

Time point	Study/Indication	N	GM (%CV) (µg/mL)	AM (SD) (µg/mL)	Min	Median	Max
Cycle 1 Postdose	KN024 NSCLC	147	67.5 (23)	69.3 (16)	36.6	66.8	132
	KN045 UC	247	65.7 (26)	67.9 (18)	33.9	65.9	144
	KN048 1L HNSCC	495	61.8 (29)	64.2 (18)	9.48	61.7	165
	KN052 UC	298	58.0 (28)	60.2 (17)	22.8	57.4	148
	KN055 HNSCC	43	56.5 (28)	58.9 (21)	33.1	54.9	162
	KN087 HL	195	60.7 (28)	63.1 (18)	31.2	61.3	183
	KN158 MSIH	90	64.4 (27)	66.7 (18)	31.2	65.2	133
	KN164 MSIH	56	62.2 (28)	64.6 (19)	34.9	61.2	150
	KN177 CRC	115	65.0 (26)	67.1 (17)	36.4	65.7	113
Cycle 2 Predose	KN024 NSCLC	132	11.1 (54)	12.3 (4.7)	0.535	12.2	28.5
	KN045 UC	233	13.1 (47)	14.2 (4.9)	0.475	13.9	29.3
	KN048 1L HNSCC	458		13.4 (4.6)	0.00	13.2	29.6
	KN052 UC	286	11.1 (42)	11.9 (4.4)	2.07	11.5	26.2
	KN055 HNSCC	40	10.7 (47)	11.8 (5.2)	3.45	11.6	33.1
	KN087 HL	200	14.4 (40)	15.4 (5.1)	3.06	15.3	30.0
	KN164 MSIH	56	12.5 (35)	13.2 (4.6)	5.44	12.4	25.6
	KN177 CRC	96	13.2 (46)	14.4 (5.9)	3.64	13.9	35.5
Cycle 8 Predose	KN024 NSCLC	82	30.6 (50)	33.6 (13)	5.26	32.7	64.1
	KN045 UC	104	33.4 (64)	37.8 (17)	1.13	37.5	95.6
	KN048 1L HNSCC	235	34.2 (50)	37.5 (15)	1.77	34.8	127
	KN052 UC	59	28.0 (38)	29.9 (10)	8.15	27.9	59.8
	KN055 HNSCC	7	27.8 (41)	29.6 (11)	16.8	24.5	43.3
	KN087 HL	68	43.9 (43)	47.4 (17)	13.9	47.5	92.4
	KN164 MSIH	34	33.6 (43)	36.2 (14)	8.40	33.7	78.8
	KN177 CRC	53	32.9 (49)	36.2 (15)	9.76	34.7	68.5

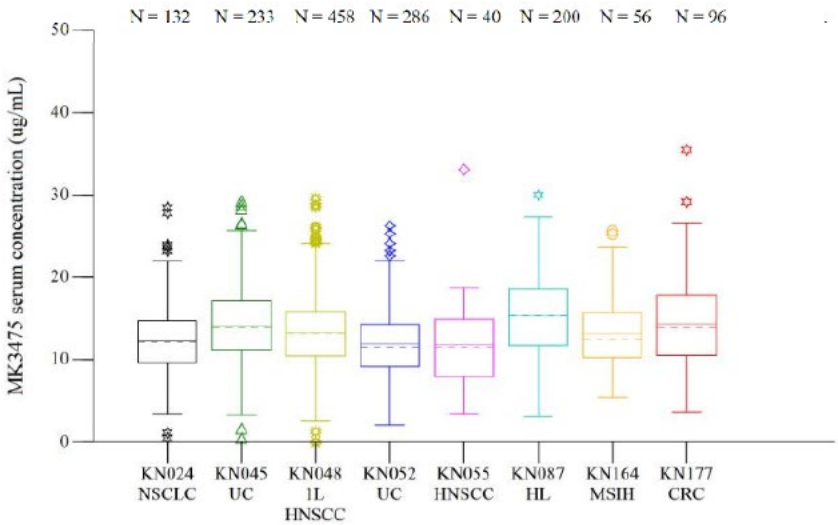
GM = Geometric Mean; %CV = Geometric Coefficient of Variation; SD = Standard Deviation; AM = Arithmetic Mean; Results for time points with N ≥ 3.

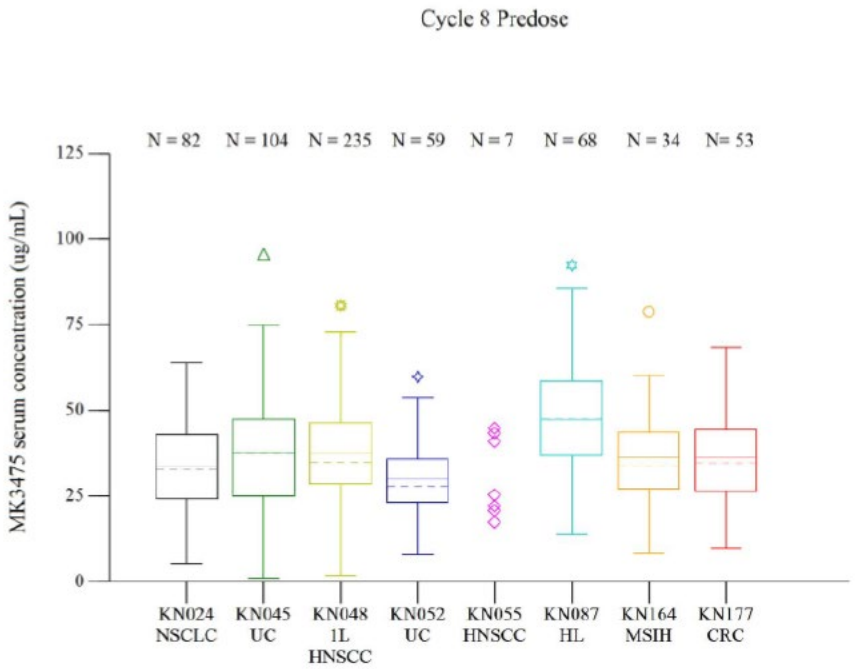
Figure 4 **Boxplots with Serum Concentration Values of Pembrolizumab in Studies KN024, KN045, KN048, KN052, KN055, KN087, KN158, KN164 and KN177**

Cycle 1 Postdose



Cycle 2 Predose





Pembrolizumab serum concentrations in cycle 1, 2 and 8 observed at 200 mg Q3W in MSI-H CRC patients are comparable to the range of concentrations at the same dose levels observed in patients with other types of cancer (Melanoma, NSCLC, HNSCC…).

The observed concentrations in MSI-H CRC generally fall within the range of predicted concentrations, both after first dose and at steady state (at and after cycle 8) indicating that the definitive population TD PK model provides an adequate representation of the pembrolizumab pharmacokinetics in this population, in addition to other indications.

Pharmacokinetic interaction studies

NA

2.3.1. Pharmacodynamics

Dose regimen

The 200 mg Q3W dosing regimen is approved for use in multiple indications globally and is based on a large, integrated body of evidence at this dose level across indications. Furthermore, clinical response in patients from the MSI-H/dMMR CRC trials including treatment arms dosed at 200 mg Q3W (KEYNOTE-177) support the favorable benefit-risk of patient outcomes at the proposed dosing regimen of 200 mg Q3W.

The proposed additional dosing regimen of 400 mg Q6W for pembrolizumab was selected using Modelling & Simulation analyses, primarily based on PK exposure matching with approved Q3W dosing regimens. Specifically, the dosing regimen of 400 mg Q6W is considered adequate, given the following rationale:

• PK simulations demonstrating that in terms of pembrolizumab exposures –

- Cavg over the dosing interval or AUC at 400 mg Q6W are similar to those at the approved 200 mg Q3W dose, thus bridging efficacy between dosing regimens.

- Cmin at 400 mg Q6W are ~12% lower at a mean level compared to that at the lowest clinically tested dose of 2 mg/kg Q3W, at steady state. However, in majority (>99%) of patients, Cmin are generally within the range of clinical experience of Cmin achieved with 2 mg/kg or 200 mg Q3W.

- Cmax and concentrations over the entire PK profile at 400 mg Q6W are well below the Cmax and PK profile for the highest clinically tested dose of 10 mg/kg Q2W. Clinically, the observed safety profiles were similar among 2 mg/kg Q3W, 10 mg/kg Q3W, and 10 mg/kg Q2W in multiple tumour types based on randomized dose comparisons. Since the Cmax,ss (and Cavg through the dosing interval) expected at 400 mg Q6W lies within the range of those achieved at these clinically tested doses, the safety profile is expected to be comparable to the established safety profile of pembrolizumab.

• Exposure-Response for pembrolizumab has been demonstrated to be flat across multiple indications. OS predictions in melanoma and NSCLC demonstrate that efficacy at 400 mg Q6W is expected to be similar to that at 200 mg or 2 mg/kg Q3W, given the similar exposures among these dosing regimens. Thus, 400 mg Q6W is expected to be efficacious across indications where 200 mg (or 2 mg/kg) Q3W have demonstrated efficacy, given the generally similar PK and flat E-R for pembrolizumab across tumour types.

Immunogenicity

The existing immunogenicity assessment for pembrolizumab for the monotherapy setting is based on a sufficiently large dataset of patients across several indications, with low observed rates of total treatment ADA across different pembrolizumab regimens (1.4 – 3.8%) as well as of neutralizing antibodies (0.4 – 1.6%). This analysis has not demonstrated impact on efficacy or safety, as currently summarized in the USPI and EU SmPC. This low rate of immunogenicity has been shown to be consistent across tumour type and no clinically meaningful consequences have been observed in the subjects with a positive immunogenicity reading. Based on the existing robust characterization of immunogenicity potential, alignment has been obtained with the US FDA and EMA that the current assessment of immunogenicity for pembrolizumab is adequate for non-adjuvant monotherapy settings.

2.3.2. Discussion on clinical pharmacology

No dose finding study was conducted for pembrolizumab monotherapy for treatment of MSI-H/dMMR mCRC. The investigated dose and schedule of pembrolizumab monotherapy for treatment of MSI-H/dMMR mCRC is the same as that approved for other monotherapy indications: 200 mg IV infusion over 60 minutes Q3W. This is considered acceptable.

The MAH presented a clinical pharmacology report on a total of 126 patients recruited in study KEYNOTE-177 with a cut-off date of 20-Nov-2017. The following analyses were provided: **i)** descriptive PK concentrations by cycle and relative time to pembrolizumab dosing (Ctrough up to Cycle 24 and Cmax at Cycle 1 and Cycle 8), **ii)** observed pembrolizumab concentrations (both pre-dose and post-dose) at Cycle 1 and at steady-state overlaid on the predictions using the reference model (i.e., a time-dependent PK model constructed using sample size of 2993 participants with melanoma and NSCLC as indicated in the USPI and EU SmPC), and **iii)** a comparison across pembrolizumab monotherapy studies following multiple administrations of 200 mg Q3W dosing, including KEYNOTE-177.

The time course of PK samples following multiple administrations of pembrolizumab 200 mg Q3W in study KEYNOTE-177 shows a progressive increase of Ctrough that plateaued around Cycle 6 (Week 15; median:

35.4 μg/ml), with a slight trend in ongoing accumulation. With respect to the reference PK model, observed concentrations both at Cycle 1 and steady-state generally lay within 90% of prediction interval with only a few outliers, indicating that variability in exposure in patients with CRC is satisfactorily predicted by the definitive population PK model developed on the basis of prior monotherapy studies. Data are confirmed by the comparison across tumour types showing a similar range of peak concentrations at Cycle 1 and similar tough levels at steady state in the different studies, with the only exception for HL that was characterised by a higher level of Cmin at steady-state compared to other tumour types in line with prior findings (40 times higher according with current SmPC).

The MAH proposed an additional dosing regimen of 400 mg Q6W for pembrolizumab. This regimen was approved on 28-MAR-2019 for all monotherapy indications approved at the time based on PK and E-R bridging using M&S analyses (procedure number EMEA/H/C/003820/II/0062). The established flat E-R profiles and the popPK analysis indicate that there are no major differences in pharmacokinetics of pembrolizumab in mCRC compared to other solid tumour types. Therefore, the 400 mg Q6W dosing regimen should have a similar benefit-risk profile as the 200 mg Q3W (or 2 mg/kg Q3W) dosing regimen in the clinical use of pembrolizumab in adult patients with MSI-H/dMMR metastatic CRC.

No additional assessments of the immunogenicity were performed. The observed incidences indicate a low potential of pembrolizumab to elicit anti-drug antibody formation.

2.3.3. Conclusions on clinical pharmacology

The clinical pharmacology profile of pembrolizumab in patients with CRC is consistent with historical data.

2.4. Clinical efficacy

The efficacy data supporting this extension of indication are based on the results of a single pivotal study, **KEYNOTE-177**, an ongoing open-label, 2-arm, randomized (1:1), multicentre, international, phase 3 trial evaluating the efficacy and safety of pembrolizumab monotherapy (200 mg Q3W) versus SOC chemotherapies (mFOLFOX6 or FOLFIRI alone or in combination with bevacizumab or cetuximab) as first line treatment for locally confirmed dMMR or MSI-H stage IV CRC. Subjects randomized to the control arm had the option to crossover and receive pembrolizumab after PD. A total of 307 patients were randomized. Dual primary endpoints were PFS per RECIST 1.1 by BICR and OS. This submission is based on the second interim analysis (i.e. final PFS and interim OS analysis) results with data cutoff date of 19-FEB-2020 (24 months after the last subject was randomized). The median follow-up duration was 28.4 months (range, 0.2 to 48.3) for the pembrolizumab group and 27.2 months (range, 0.8 to 46.6) for the SOC treatment group.

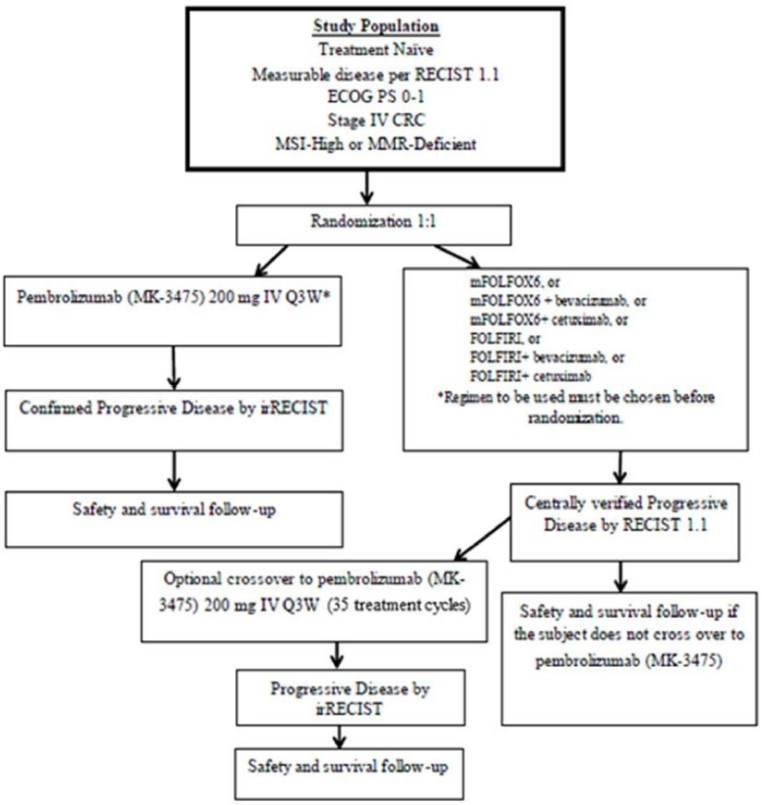
2.4.1. Dose response study(ies)

No dose-response studies were submitted as part of this application.

2.4.2. Main study

Title of Study

A Phase III Study of Pembrolizumab (MK-3475) vs. Chemotherapy in Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Stage IV Colorectal Carcinoma (KEYNOTE-177)



Methods

Study participants

Key Inclusion criteria:

1. Written informed consent

2. Male or female ≥18 years of age

3. Had locally confirmed MSI-H/dMMR Stage IV colorectal carcinoma

4. ECOG performance status of 0 or 1 within 10 days prior to treatment initiation

5. Life expectancy of at least 3 months.

6. Measurable disease at baseline based on RECIST 1.1 as determined by the local site investigator/ radiology assessment

7. Female participants of childbearing potential must have had a negative serum pregnancy test within 72 hours prior to receiving the first dose of study medication

8. Female participants of childbearing potential must have been willing to use an adequate method of contraception

9. Male participants of childbearing potential must have agreed to use an adequate method of contraception

10. Adequate organ function as defined in the study protocol

Key Exclusion criteria:

1. Received prior systemic therapy for Stage IV CRC. Prior adjuvant chemotherapy for CRC completed at least 6 months prior to randomization was allowed

2. Participating and receiving study medication in another study currently or within 4 weeks from randomization

3. Active autoimmune disease that had required systemic treatment in past 2 years. Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) was not considered a form of systemic treatment

4. Diagnosis of immunodeficiency or receiving systemic steroid therapy or other immunosuppressive therapy within 7 days prior to randomization

5. Radiation therapy within 4 weeks prior to randomization and had not recovered to baseline from AE due to radiation therapy. Palliative radiotherapy to peripheral sites (eg, bone metastasis) before 4 weeks have elapsed was allowed but must have had recovered from any acute AEs

6. Known active CNS metastases and/or carcinomatous meningitis. Stable previously treated brain metastases and with no use of steroids for at least 28 days prior to study initiation were allowed (carcinomatous meningitis was excluded regardless of clinical stability)

7. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to randomization

8. Prior therapy with an immune checkpoint inhibitor (e.g., anti-PD-(L)1, anti-PD-L2, anti-CTLA-4 etc)

9. Another malignancy progressing or required active treatment. Exceptions included non-melanomatous skin cancer that has undergone potentially curative therapy and in situ cervical carcinoma

10. Live vaccine within 30 days of planned start of study medication

11. History or current evidence of any condition, therapy, or laboratory abnormality that might have confounded the results of the study, interfered with the participant's participation for the full duration of the study, or was not in the best interest of the participant to participate, in the opinion of the treating investigator

12. Known history of HIV, active chronic or acute Hepatitis B or C

13. Known history of, or evidence of interstitial lung disease or active non-infectious pneumonitis

14. Known history of active tuberculosis

15. Active infection requiring systemic therapy

16. Known psychiatric or substance abuse disorders that would have interfered with cooperation with the requirements of the study

17. Was pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study up to 180 days after the last dose of study medication for SOC or 120 days for pembrolizumab

Treatments

Initial Treatment Phase:

- Experimental arm: Pembrolizumab 200 mg IV Q3W
- Control arm: investigator's choice of one among 6 possible regimens (mFOLFOX6, mFOLFOX6+bevacizumab, mFOLFOX6+cetuximab, FOLFIRI, FOLFIRI+bevacizumab, FOLFIRI+cetuximab).

Study Intervention	Dose/Potency	Route of Administration
Pembrolizumab	200 mg IV Q3W	IV infusion
mFOLFOX6	mFOLFOX6 Q2W: Oxaliplatin 85 mg/m^2 Leucovorin* 400 mg/m^2 5-FU 400 mg/ m^2 bolus, 1200 mg/m^2/day x 2 days continuous infusion	IV infusion
mFOLFOX6 + bevacizumab	mFOLFOX6 Q2W: Oxaliplatin 85 mg/m^2 Leucovorin* 400 mg/m^2 5-FU 400 mg/ m^2 bolus, 1200 mg/m^2/day x 2 days continuous infusion Bevacizumab 5 mg/kg	IV infusion
mFOLFOX6 + cetuximab	mFOLFOX6 Q2W: Oxaliplatin 85 mg/m^2 Leucovorin* 400 mg/m^2 5-FU 400 mg/ m^2 bolus, 1200 mg/m^2/day x 2 days continuous infusion Cetuximab: 400 mg/m^2, then 250 mg/m^2	IV infusion
FOLFIRI	FOLFIRI Q2W: Irinotecan 180 mg/m^2 Leucovorin* 400 mg/m^2 5-FU 400 mg/m^2 bolus, 1200 mg/m^2/day x 2 days continuous infusion	IV infusion
FOLFIRI +bevacizumab	FOLFIRI Q2W: Irinotecan 180 mg/m^2 Leucovorin* 400 mg/m^2 5-FU 400 mg/m^2 bolus, 1200 mg/m^2/day x 2 days continuous infusion Bevacizumab 5 mg/kg IV	IV infusion
FOLFIRI +cetuximab	FOLFIRI Q2W: Irinotecan 180 mg/m^2 Leucovorin* 400 mg/m^2 5-FU 400 mg/m^2 bolus, 1200 mg/m^2/day x 2 days continuous infusion Cetuximab: 400 mg/m^2, then 250 mg/m^2	IV infusion
Q2W: every 2 weeks; Q3W: every 3 weeks; IV: intravenous *or levoleucovorin 200 mg/m^2		

Treatment must be discontinued for confirmed radiographic PD, unacceptable AEs, intercurrent illness that prevents further administration of treatment, consent withdrawal, investigator's decision to discontinue the subject from treatment, confirmed positive serum pregnancy test of the subject, administrative reasons, or the subject completed 35 treatments (2 years) of pembrolizumab.

Discontinuation of pembrolizumab may be considered for subjects with locally confirmed CR after at least 8 cycles (approximately 6 months), and at least 2 treatments beyond the date when the initial CR was declared.

During the study, subjects may undergo resection of the primary tumour and metastasectomy with curative intent if deemed eligible per site institutional standard after achieving a response to study medication converting unresectable to resectable. After surgery, subjects may resume the same pre-operative treatment (SOC or Pembrolizumab) when clinically appropriate.

Second Course Phase (pembrolizumab arm and SOC chemotherapy arm following crossover):

Subjects who stopped pembrolizumab after confirmed CR, or who completed 35 cycles of pembrolizumab with SD, PR or CR, may be eligible for retreatment with pembrolizumab (up to 17 cycles i.e. about 1 year) if they progress after stopping study treatments.

Crossover Phase (SOC chemotherapy arm):

Subjects in the chemotherapy arm with documented PD per RECIST 1.1 confirmed by BICR could be eligible for crossover to pembrolizumab (up to 17 cycles), if meeting eligibility criteria for the Crossover Phase. Surgical subjects who progress post operatively are also eligible to receive pembrolizumab in the Crossover Phase with up to 17 administrations (approximately 1 year) of pembrolizumab.

Imaging assessment

Tumour imaging was performed every 9 weeks during study treatment. All scheduled and unscheduled images for all study subjects from the sites were submitted to the central imaging vendor.

Subjects who undergo surgical resection with curative intent while on study resumed imaging postoperatively when clinically possible to maintain the Q9W imaging schedule.

Local-site investigator assessed 1st PD must be verified by the central imaging vendor. If PD is confirmed centrally by RECIST 1.1, patients on chemotherapy arm may crossover to pembrolizumab (if all criteria for crossover phase are met), while patients on pembrolizumab arm should repeat imaging ≥4 weeks at site to confirm PD. If patient is clinically stable may continue pembrolizumab at investigator discretion while awaiting confirmatory tumour scan. If PD is then verified by site at repeated images, subject should discontinue pembrolizumab (unless deriving clinically meaningful benefit after consultation with the Applicant).

For all subjects, per RECIST 1.1, PR or CR should be confirmed by a repeat tumour imaging assessment.

In subjects who discontinue trial treatment without documented PD, every effort should be made to continue monitoring their disease status by radiologic imaging every 9 weeks until start of new anti-cancer treatment, PD, death, withdrawal of consent, loss to follow-up or the end of the study.

Evaluation of tumour response by RECIST 1.1 per the central imaging vendor is the basis for efficacy assessment in this study. irRECIST is used by site investigator/local radiology review to assess tumour response and progression, and make treatment decisions while subjects are receiving pembrolizumab. irRECIST was used to make treatment decisions beyond progression by RECIST 1.1, allowing treatment after progression if patients derived clinical benefit according to investigator.

Objectives

Primary Objectives

- To compare progression-free survival (PFS) per RECIST 1.1 by central imaging vendor
- To compare overall survival (OS)

Secondary Objectives

- To compare overall response rate (ORR) per RECIST 1.1 by central imaging vendor
- To evaluate the safety and tolerability profiles

Exploratory Objectives

- To evaluate Progression Free Survival 2 (PFS2)
- To evaluate PFS per irRECIST by central imaging vendor
- To evaluate duration of response (DOR) per RECIST 1.1 by central imaging vendor
- To evaluate score change of health-related quality-of-life (HRQoL) using EORTC QLQ-C30 and EORTC QLQ-CR29 from baseline among subjects treated with pembrolizumab compared to SOC chemotherapies
- To characterize utilities using EuroQoL EQ-5D among subjects treated with pembrolizumab compared to SOC chemotherapies.
- To explore the relationship between genetic variation and response to the treatment(s) administered. Variation across the human genome (germline and tumour) will be analyzed for association with clinical data collected in this study.
- To evaluate the surgical conversion rate among subjects treated with pembrolizumab compared to SOC chemotherapies.

Outcomes/endpoints

Primary endpoints (dual-primary)

- PFS per RECIST 1.1 assessed by central imaging vendor: PFS is defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on blinded central imaging vendor review or death due to any cause, whichever occurs first
- OS: OS is defined as the time from randomization to death due to any cause

The study is considered to have met its primary objective if pembrolizumab is superior to SOC chemotherapies in either of the 2 primary endpoints.

Secondary endpoints

- ORR per RECIST 1.1 assessed by central imaging vendor: ORR is defined as the proportion of the subjects in the analysis population who have a complete response or partial response

Exploratory endpoints

- PFS2: PFS2 is defined as the time from randomization to disease progression on the next line of therapy, or death from any cause, whichever occurs first
- PFS per irRECIST by BICR
- DOR per RECIST 1.1 by BICR: for subjects who demonstrated CR or PR, response duration is defined as the time from the date of first response (CR or PR) until the date of first documented disease progression or death.
- Surgical conversion rate: The surgical conversion rate is the rate of subjects who become eligible and undergo resection with curative intent as a result of study therapy.

- Patient Reported Outcome (PRO) endpoints:
  - mean score change from baseline to Week 18 in EQ-5D VAS and utility score
  - mean score change from baseline to Week 18 in QLQ-C30 global health status/QoL
  - mean score change from baseline to Week 18 for QLQ-C30 functional scales (physical, role, emotional, cognitive, and social) and symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties)
  - mean score change from baseline to Week 18 for QLQ-CR29 functional scales (body image, anxiety, weight, etc.) and symptom scales (urinary frequency, blood and mucus in stool, stool frequency, urinary incontinence, dysuria, abdominal pain, buttock pain, bloating, dry mouth, hair loss, taste, flatulence, faecal incontinence, sore skin, embarrassment, etc.)
  - number and proportions of deterioration/stable/improvement from baseline to Week 18 for QLQ-C30 global health status/QoL, functional scales and symptom scales
  - time to deterioration for QLQ-C30 global health status/QoL, physical functioning, social functioning and fatigue
  - time to deterioration for QLQ-CR29 urinary incontinence

Sample size

The study was event-driven and planned to randomize approximately 300 subjects with 1:1 ratio into the two treatment groups: pembrolizumab and SOC.

Two interim efficacy analyses were planned in this study, one for PFS, two for OS and none for ORR. A Lan-DeMets O'Brien-Fleming alpha-spending function was constructed to implement group sequential efficacy boundaries to control the Type I error for each PFS and each OS hypothesis. The sample size calculation for the two primary hypotheses are listed:

(1) With 209 PFS events, there was 98% power to detect a hazard ratio of 0.55 (pembrolizumab vs. SOC) at alpha = 1.25% (one-sided), assuming PFS follows an exponential distribution with a median of 10 months in the control arm, an enrolment period of 30 months from first subject randomized and minimum of 13 months follow-up after enrolment completion. The dropout rate was assumed to be 5% yearly.

(2) With 190 OS events, there was 85% power to detect a hazard ratio of 0.62 (pembrolizumab vs. SOC) at alpha = 1.25% (one-sided) assuming OS follows an exponential distribution with a median of 24 months in the control arm, and an enrolment period of 30 months from first subjects randomized and a minimum of 33.5 months follow-up after enrolment completion. The dropout rate was assumed to be 2% yearly.

For the key secondary endpoint of ORR, which was planned to be tested if either the PFS or the OS hypothesis was rejected, there was 92% power (1-sided 2.5% alpha) to detect an 19% improvement on the experimental arm assuming the true ORR for the control arm ranges between 50%, depending on the actual percentage of subjects without prior SCT are enrolled.

Randomisation

Patients were randomized 1:1 to pembrolizumab or SOC arm centrally using an interactive voice response system/integrated web response system (IVRS/IWRS).

No stratification factors were used.

Blinding (masking)

The study was open-label.

Independent radiologist(s) who centrally reviewed the images had no knowledge of subject treatment assignment.

Statistical methods

Efficacy populations

The analyses of efficacy endpoints were performed on the Intention-to-Treat (ITT) population, which includes all randomized subjects in the treatment group to which they are assigned, whether or not treatment was administered.

For the PRO assessment, the primary analysis was conducted in the quality of life related full analysis set (FAS) population, consisting of all randomized subjects who have received at least one dose of study medication, and have completed at least one PRO assessment. There is one FAS population per PRO instrument scale.

Statistical methods

Table: Summary of Analysis Strategy for Key Efficacy Endpoints in KEYNOTE-177

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoints			
PFS per RECIST 1.1 by BICR[a]	Test: Log-rank test Estimation: Cox model with Efron's tie handling method	ITT	Primary censoring rule[b]
OS	Test: Log-rank test Estimation: Cox model with Efron's tie handling method	ITT	Censored at the date of last known contact
Secondary Endpoint			
ORR per RECIST 1.1 by BICR	Test: Miettinen and Nurminen method	ITT	Subjects with missing data are considered as non-responders.

BICR=Blinded independent central radiology review; ITT=Intention-to-treat; ORR=Objective response rate; OS=Overall survival; PFS=Progression-free survival; RECIST= Response Evaluation Criteria in Solid Tumours.

[a] Surgical participants (ie, those who have surgery with curative intent) will be censored at the surgical date in the PFS analysis. An additional PFS sensitivity analysis, defined as the time from randomization to disease recurrence after surgery, was performed.

[b] Censored at the last disease assessment (before new anticancer treatment, if any).

Sensitivity analysis for primary endpoints

Two sensitivity analyses with different censoring rules for PFS were planned to be performed for the primary analysis, see table below. In comparison to the primary analysis, in the first sensitivity analysis subjects were censored at last disease assessment without PD, when PD/death was documented after more than one missing disease assessment. In the second sensitivity analysis, patients were considered for discontinuation of treatment or initiation of an anticancer treatment subsequent to discontinuation of study-specified treatments to be a PD event for subjects without documented PD or death.

Table: censoring rules for Primary and Sensitivity analyses of PFS

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
No PD and no death; new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment if still on study medication; progressed at treatment discontinuation otherwise
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment before new anticancer treatment	Progressed at date of new anticancer treatment
No PD and no death; ≥ 2 consecutive missed disease assessments	Censored at last disease assessment	Censored at last disease assessment prior to ≥2 consecutive missed visits	Censored at last disease assessment
PD or death documented after ≤ 1 missed disease assessment	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 at any time after ≥ 2 consecutive missed disease assessments	Progressed at date of documented PD or death	Censored at last disease assessment prior to the ≥ 2 consecutive missed disease assessment	Progressed at date of documented PD or death
Note: Surgical subjects will be censored at the surgical date in the PFS primary, sensitivity 1 and 2 analyses, unless the surgery occurs after progression events or censoring points defined above.			

Participants who had curative intent surgery were censored in the PFS analysis at the date of surgery unless a prior PD event had been noted per central review.

Sensitivity analyses for overall survival was performed, where the crossover of patients who switched to pembrolizumab after progressive disease was (1) adjusted for by appropriate methods, and (2) where patients were censored at the start of crossover treatment or the start of first subsequent immune checkpoint inhibitor treatment, whichever occurs first.

Interim Analysis

Two interim analyses were planned. The timing of the interim analyses together with the nominal significance levels are shown in the table below. For the PFS and OS hypotheses, Lan-DeMets O'Brien-Fleming alpha spending function was used to construct group sequential boundaries to control the type I error. For PFS analysis the extended graphical method was planned to be used (Anderson et al, unpublished data, 2018). This means that the actual boundaries were to be adjusted using the Lan-DeMets O'Brien-Fleming spending function with spending time determined by the *minimum* of the actual information fraction and the expected information fraction.

Table: timing, sample size and decision guidance

Analysis	Criteria for Conduct of Analysis	Endpoint	p-value†	Approximate Efficacy Boundary (HR)†
Interim Analysis 1: Interim PFS and interim OS analysis	To be performed after 1) approximately 162 PFS events have occurred; and 2) 6 months after last subject randomized Expected OS events: ~95	PFS	0.0046	0.66
		OS	0.0004	0.50
Interim Analysis 2: Final PFS and interim OS analysis	To be performed after approximately 209 PFS events have occurred or 24 months after last subject randomized, whichever occurs first. Expected OS events:~135	PFS	0.0111	0.73
		OS	0.0029	0.62
Final Analysis: Final OS analysis	To be performed after approximately 190 OS events have occurred or 12 months after Interim Analysis 2, whichever occurs first.	OS	0.0115	0.72
†The "p value" and "Approximate Efficacy Boundary (HR)" for efficacy assume no re-distribution of initially assigned type I error.				

<u>Multiplicity</u>

The family-wise type I error rate for this study was controlled at 2.5% (one-sided), whereby the allocation to the different hypotheses was defined as shown in the following figure by Maurer and Bretz (2013):

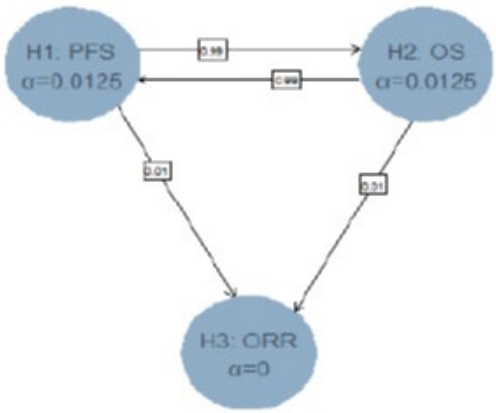


Table: Efficacy Boundaries and Properties for Progression-Free Survival Analyses

Analysis	Value	α=0.0125	α=0.0249
IA1: 78%[a] N: 300 Events: 162 Month: 36	Z	2.6082	2.2959
	p (1-sided)[b]	0.0046	0.0108
	HR at bound[c]	0.6631	0.6971
	P(Cross) if HR=1[d]	0.0046	0.0108
	P(Cross) if HR=0.55[e]	0.8842	0.9354
IA2 (PFS FA) N: 300 Events: 209 Month: 46	Z	2.2860	2.0198
	p (1-sided)[b]	0.0111	0.0217
	HR at bound[c]	0.7283	0.7562
	P(Cross) if HR=1[d]	0.0125	0.0249
	P(Cross) if HR=0.55[e]	0.9800	0.9902

[a] Percentage of total number of required events needed at the interim analysis
[b] The nominal α for testing.
[c] The approximated HR required to reach an efficacy bound.
[d] The probability of crossing a bound under the null hypothesis.
[b] The probability of crossing a bound under the alternative hypothesis.

Table: Efficacy Boundaries and Properties for Overall Survival Analyses

Analysis	Value	α=0.0125	α=0.0249
IA1: 50%[a] N: 300 Events: 95 Month: 36	Z	3.3446	2.9649
	p (1-sided)[b]	0.0004	0.0015
	HR at bound[c]	0.5025	0.5442
	P(Cross) if HR=1[d]	0.0004	0.0015
	P(Cross) if HR=0.62[e]	0.1552	0.2649
IA2: 71%[a] N: 300 Events: 135 Month: 46	Z	2.7589	2.4427
	p (1-sided)[b]	0.0029	0.0073
	HR at bound[c]	0.6211	0.6567
	P(Cross) if HR=1[d]	0.0030	0.0078
	P(Cross) if HR=0.62[e]	0.5100	0.6382
Final: N: 300 Events: 190 Month: 63.5	Z	2.2724	2.0057
	p (1-sided)[b]	0.0115	0.0224
	HR at bound[c]	0.7185	0.7475
	P(Cross) if HR=1[d]	0.0125	0.0249
	P(Cross) if HR=0.62[e]	0.8500	0.9061

[a] Percentage of total number of required events needed at the interim analysis
[b] The nominal α for testing.
[c] The approximated HR required to reach an efficacy bound.
[d] The probability of crossing a bound under the null hypothesis.
[b] The probability of crossing a bound under the alternative hypothesis.

The trial initially allocates 0% to the ORR hypothesis. If null hypotheses for both OS and PFS are rejected, an ORR benefit may be tested at the 2.5% 1-sided level. If only one of the OS and PFS null hypotheses is rejected, ORR would be tested at the 0.0125% 1-sided level. The p-value from IA1 will be used to compare with α-levels, considering ORR data will be mature at IA1.

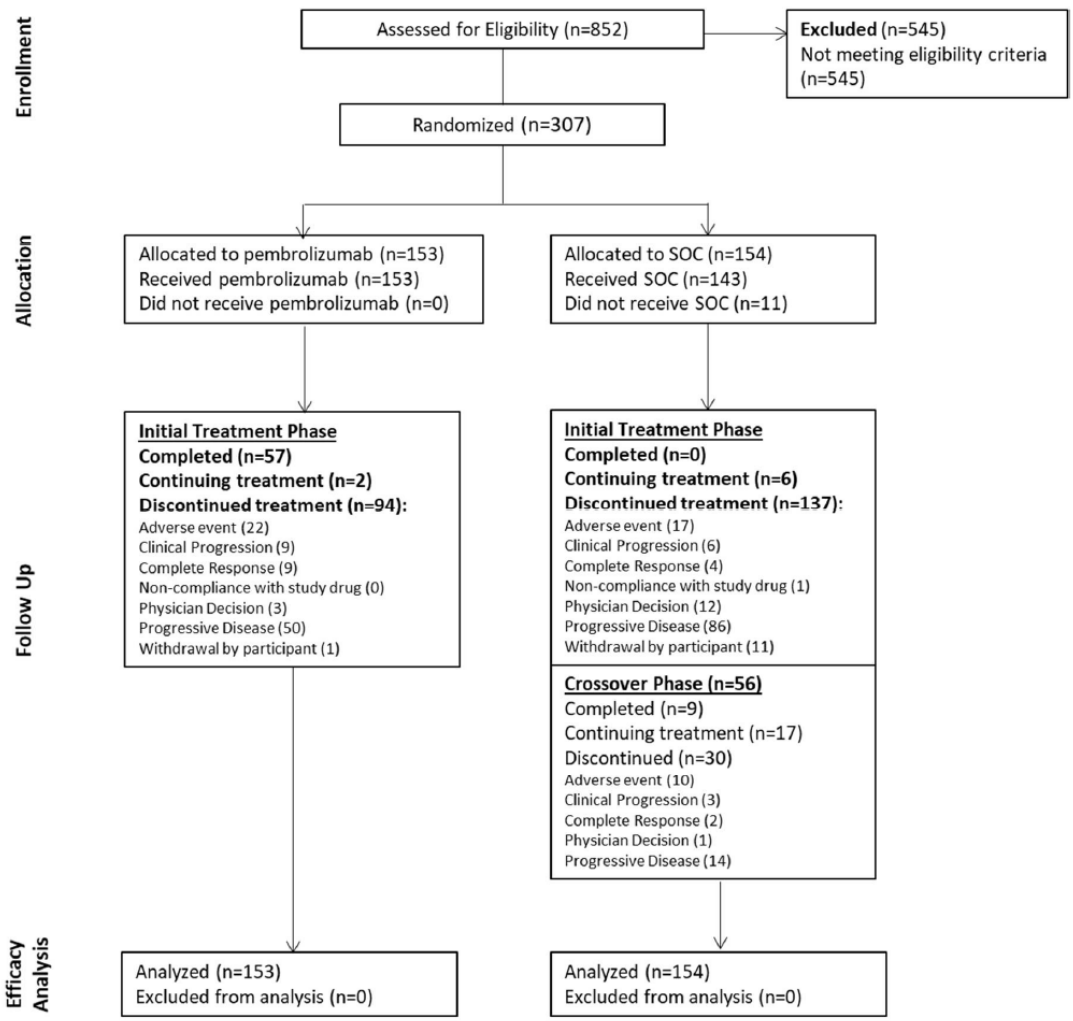
Table: Possible α-levels and Approximate ORR Difference Required to Demonstrate Efficacy for ORR

α	Power	~ΔORR[1]
0.0125%	0.38	20.37%
2.5%	0.92	10.90%
[1] ΔORR = ORR treatment arm − ORR control arm, where ORR on control arm is assumed to be 0.50.		

Results

This submission is based on IA2 with a data cutoff date of 19-FEB-2020, which is 24 months after the last subject was randomized and after 195 PFS events had occurred.

Participant flow



Overall, 545 patients did not meet eligibility criteria of Keynote-177. Most of the patients were not MSI-

H/dMMR (n=471 (86.4%)), 4.4% had received prior systemic therapy for stage IV CRC and 3.1 % had no measurable disease at baseline.

All but 1 (in the SOC group) enrolled participants were MSI-H/dMMR.

Table: Disposition of Subjects (ITT Population)

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	153		154		307	
Status for Trial						
Discontinued	58	(37.9)	75	(48.7)	133	(43.3)
Death	56	(36.6)	66	(42.9)	122	(39.7)
Lost To Follow-Up	2	(1.3)	0	(0.0)	2	(0.7)
Withdrawal By Subject	0	(0.0)	9	(5.8)	9	(2.9)
Subjects Ongoing	95	(62.1)	79	(51.3)	174	(56.7)
Status for Study Medication in Trial Segment Treatment						
Started	153		143		296	
Completed	57	(37.3)	0	(0.0)	57	(19.3)
Discontinued	94	(61.4)	137	(95.8)	231	(78.0)
Adverse Event	22	(14.4)	17	(11.9)	39	(13.2)
Clinical Progression	9	(5.9)	6	(4.2)	15	(5.1)
Complete Response	9	(5.9)	4	(2.8)	13	(4.4)
Non-Compliance With Study Drug	0	(0.0)	1	(0.7)	1	(0.3)
Physician Decision	3	(2.0)	12	(8.4)	15	(5.1)
Progressive Disease	50	(32.7)	86	(60.1)	136	(45.9)
Withdrawal By Subject	1	(0.7)	11	(7.7)	12	(4.1)
Subjects Ongoing	2	(1.3)	6	(4.2)	8	(2.7)
Status for Study Medication in Trial Segment Crossover						
Started	0		56		56	
Completed	0	(0.0)	9	(16.1)	9	(16.1)
Discontinued	0	(0.0)	30	(53.6)	30	(53.6)
Adverse Event	0	(0.0)	10	(17.9)	10	(17.9)
Clinical Progression	0	(0.0)	3	(5.4)	3	(5.4)
Complete Response	0	(0.0)	2	(3.6)	2	(3.6)
Physician Decision	0	(0.0)	1	(1.8)	1	(1.8)
Progressive Disease	0	(0.0)	14	(25.0)	14	(25.0)
Subjects Ongoing	0	(0.0)	17	(30.4)	17	(30.4)
Database Cutoff Date: 19FEB2020.						

Eleven participants who were randomized to the SOC group withdrew from the study prior to starting treatment. The reasons for withdrawal were unknown (5 participants), randomized to the SOC arm (5), and administrative issues (1).

Among participants who received treatment during the initial treatment phase, more participants in the SOC group than in the pembrolizumab group discontinued due to withdrawal of consent (11 vs 1) and physician decision (12 vs 3). The reasons for withdrawal of consent in the SOC group were unknown (6 participants), no longer wanted therapy (3 participants), and pursuing surgical intervention (2 participants). The reasons for discontinuation due to physician decision included surgical resection (7 participants), status of subject not conducive to continue treatment (3 participants), and additional therapy required (2 participants).

Out of 4 patients who received second-course treatment with pembrolizumab, one achieved PR upon retreatment. Out of 3 patients who stopped for progression, one had PR when retreated. The patient who discontinued due to CR had SD at retreatment. One patient who stopped pembrolizumab due to an AE (not specified) was rechallenged with SD.

Table: Summary of Subsequent Therapies (ITT Population)

	Pembrolizumab (N=153) n (%)	SOC (N=154) n (%)
Subjects Who Crossed Over from SOC to Pembrolizumab	0 (0.0)	56 (36.4)
Subjects Who Did Not Crossed Over but Received Subsequent Anti-Cancer Therapies*	44 (28.8)	44 (28.6)
Anti-PD1/PDL1 Therapies	9 (5.9)	35 (22.7)
Antimuscarinic / Non disease related medication	2 (1.3)	0 (0.0)
CD40 inhibitor	0 (0.0)	1 (0.6)
CTLA-4 Inhibitor	0 (0.0)	4 (2.6)
Chemotherapy	35 (22.9)	18 (11.7)
EGFR inhibitor	8 (5.2)	4 (2.6)
Estrogen derivative / Non disease related medication	1 (0.7)	0 (0.0)
Folic Acid derivative	24 (15.7)	12 (7.8)
ICOS inhibitor	1 (0.7)	1 (0.6)
Nucleoside Analog / Thymidine Phosphorylase inhibitor	1 (0.7)	2 (1.3)
TIM3 inhibitor	1 (0.7)	1 (0.6)
VEGF inhibitor	22 (14.4)	11 (7.1)

*Including second course treatment for subjects randomized to pembrolizumab arm.
Database Cutoff Date: 19FEB2020

Recruitment

A total of 307 patients (153 in the pembrolizumab arm and 154 in the SOC arm) were randomized in 120 centers in 23 countries worldwide (Australia, Europe, Asia, America, South Africa). First patient first visit was on 30-NOV-2015.

KEYNOTE-177 study is ongoing; this report is based on the second interim analysis (i.e. final for PFS, IA for OS) with data cutoff date of 19-FEB-2020 (database lock date 16-MAR-2020).

Median duration of follow-up at the time of data cutoff was 28.4 months (range: 0.2, 48.3 months) and 27.2 months (range: 0.8, 46.6 months) in the pembrolizumab and SOC groups, respectively.

Conduct of the study

Protocol amendments

The original protocol is dated 11 Sep 2015. Up to the data cut-off date for this submission (19 Feb 2020), there have been 5 protocol amendments, the first 2 amendments were country-specific, while amendments 3, 4 and 5 were global.

Table: Summary of Key Changes in Protocol Amendments

Amendment Number	Global or Local	Date	Key changes	Rationale
01	France	17-MAR-2016	• Required subjects to discontinue pembrolizumab after confirmed disease progression. • Clarified exclusion criterion to address contraindications to standard of care options.	As per French Health Authority (ANSM) request.

			• Addresses the need for a subject to discontinue the study if there is progression/recurrence/occurrence of another malignancy that requires active treatment	
02	UK	16-MAR-2016	• Clarified exclusion criterion to address contraindications to standard of care options. • Added prohibited medications for all standard of care agents according to respective SmPCs. • Added cautionary information for 5-FU • Added assessments for physical exam for subjects assigned to FOLFOX-based regimens	As per UK Regulatory Agency (MHRA) request.
03	Global	20-NOV-2017	• Primary objective was changed from a single PFS endpoint to dual endpoints of PFS and OS. • Sample size was increased to 300. • Interim and final analysis timing was updated and one IA for PFS and OS was added.	The revisions were based on desire to add OS as a dual primary endpoint. OS power was increased to 85% to increase probability of success for this primary hypothesis. Timing of analyses changed to allow for more mature PFS and OS data to account for a potential delayed separation in survival curves observed in immune-oncology studies, while adding an interim analysis to allow for earlier stopping if this is not the case.
04	Global	30-APR-2018	• The timing component of IA1 and IA2 was prolonged by 3 additional months and the alpha spending method for PFS was modified.	For PFS analysis, the alpha spending function to control the Type-I error based on information fraction was replaced by a function of the minimum of the actual event information fraction and the expected event information fraction. The timing component for conducting both interim analysis 1 and interim analysis 2 was prolonged by 3 additional months. This change was made due to emerging results from multiple immunotherapy trials in which delayed treatment effects have been observed for time to event endpoints. To account for this potential effect, the timing of interim analyses 1 and 2 was changed to allow for a longer follow-up time, and the alpha spending method was modified accordingly.
05	Global	17-DEC-2019	• The timing of IA2 and FA was changed. IA2 will be performed when approximately 209 PFS events have occurred or 24 months after last participant randomized, whichever occurs first. FA will be performed after approximately 190 OS events have occurred or 12 months after IA2, whichever occurs first.	In the event that PFS or OS events accrue slower than expected as has been shown with immunotherapy in biomarker selected populations, alternate maximum time periods are specified for the conduct of the final PFS analysis and the final OS analysis.
Note: Table includes protocol amendments implemented up to the data cutoff date 19-FEB-2020				

Protocol deviations

Protocol deviations were classified as per the ICH E3 classification as:

- important (those that may significantly impact the quality or integrity of key study data or that may significantly affect a participant's rights, safety, or well-being)

    - clinically important (deviations that may compromise critical data analyses pertaining to primary efficacy and/or safety endpoints or the participant's safety)

    - not clinically important

- not important

Patients with one or more important protocol deviations were 13 (8.5%) in the pembrolizumab arm and 17 (11%) in the SOC arm; most of these deviations pertained to reportable safety events or follow-up safety information that was reported outside the safety reporting window (6.5% and 9.1% in the pembrolizumab and SOC group, respectively). Important protocol deviations considered to be clinically important occurred in 1 patient in each arm: one clinically important deviation occurred in a participant who had a positive MSI-H status upon entering the study, but when retested centrally had a negative MSI-H status. This has been reported as due to a problem on the device used locally to perform the MSI test. The other clinically important deviation was noted in a participant who did not have measurable disease upon entering the study.

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

Baseline data

Table: subjects characteristics (ITT population)

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	153		154		307	
Gender						
Male	71	(46.4)	82	(53.2)	153	(49.8)
Female	82	(53.6)	72	(46.8)	154	(50.2)
Age (Years)						
<65	80	(52.3)	83	(53.9)	163	(53.1)
>=65	73	(47.7)	71	(46.1)	144	(46.9)
Subjects with data	153		154		307	
Mean	61.9		60.6		61.2	
SD	14.9		14.8		14.8	
Median	63.0		62.5		63.0	
Range	24 to 93		26 to 90		24 to 93	
Age (Years)						
<=70	105	(68.6)	112	(72.7)	217	(70.7)
>70	48	(31.4)	42	(27.3)	90	(29.3)
Race						
ASIAN	24	(15.7)	26	(16.9)	50	(16.3)
BLACK OR AFRICAN AMERICAN	9	(5.9)	5	(3.2)	14	(4.6)
WHITE	113	(73.9)	116	(75.3)	229	(74.6)

Missing	7	(4.6)	7	(4.5)	14	(4.6)
Ethnicity						
HISPANIC OR LATINO	11	(7.2)	10	(6.5)	21	(6.8)
NOT HISPANIC OR LATINO	128	(83.7)	131	(85.1)	259	(84.4)
NOT REPORTED	10	(6.5)	10	(6.5)	20	(6.5)
UNKNOWN	2	(1.3)	2	(1.3)	4	(1.3)
Missing	2	(1.3)	1	(0.6)	3	(1.0)
Geographic Region						
Asia	22	(14.4)	26	(16.9)	48	(15.6)
Western Europe/North America	109	(71.2)	113	(73.4)	222	(72.3)
Rest of World	22	(14.4)	15	(9.7)	37	(12.1)
ECOG						
0	75	(49.0)	84	(54.5)	159	(51.8)
1	78	(51.0)	70	(45.5)	148	(48.2)
Site of Primary Tumour*						
Right	102	(66.7)	107	(69.5)	209	(68.1)
Left	46	(30.1)	42	(27.3)	88	(28.7)
Other	4	(2.6)	5	(3.2)	9	(2.9)
Missing	1	(0.7)	0	(0.0)	1	(0.3)
Metastases Location						
Hepatic or pulmonary	86	(56.2)	73	(47.4)	159	(51.8)
Other Metastases	67	(43.8)	81	(52.6)	148	(48.2)
Metastases Location						
Pulmonary	36	(23.5)	34	(22.1)	70	(22.8)
Other	117	(76.5)	120	(77.9)	237	(77.2)
Diagnosed Stage						
Recurrent	80	(52.3)	74	(48.1)	154	(50.2)
Newly diagnosed stage	73	(47.7)	80	(51.9)	153	(49.8)
Prior Systemic Therapy						
Adjuvant only	33	(21.6)	37	(24.0)	70	(22.8)
Neoadjuvant only	2	(1.3)	3	(1.9)	5	(1.6)
Neoadjuvant and adjuvant	3	(2.0)	5	(3.2)	8	(2.6)
None	115	(75.2)	109	(70.8)	224	(73.0)
Mutation Status**						
BRAF/KRAS/NRAS all wild type	34	(22.2)	35	(22.7)	69	(22.5)
KRAS/NRAS mutant and BRAF V600E not mutant	33	(21.6)	38	(24.7)	71	(23.1)
BRAF V600E mutant and KRAS/NRAS not mutant	34	(22.2)	40	(26.0)	74	(24.1)
BRAF V600E and KRAS/NRAS mutant	0	(0.0)	3	(1.9)	3	(1.0)
Other	52	(34.0)	38	(24.7)	90	(29.3)
MSI-High Status#						
Positive	153	(100.0)	153	(99.4)	306	(99.7)
Negative	0	(0.0)	1	(0.6)	1	(0.3)
Oncologic Surgery with Curative Intent##						

Received surgery with curative-intent	14	(9.2)	13	(8.4)	27	(8.8)
Did not receive surgery with curative-intent	139	(90.8)	141	(91.6)	280	(91.2)
Prior Radiation Therapy						
Yes	11	(7.2)	13	(8.4)	24	(7.8)
No	142	(92.8)	141	(91.6)	283	(92.2)
Sum of IRC Target Lesions at Baseline[###]						
<= Median	68	(44.4)	91	(59.1)	159	(51.8)
> Median	85	(55.6)	63	(40.9)	148	(48.2)
Baseline CEA Group						
N	50	(32.7)	61	(39.6)	111	(36.2)
H	86	(56.2)	74	(48.1)	160	(52.1)
L	1	(0.7)	1	(0.6)	2	(0.7)
Missing	16	(10.5)	18	(11.7)	34	(11.1)
Lynch Syndrome						
Yes	28	(18.3)	36	(23.4)	64	(20.8)
No	114	(74.5)	104	(67.5)	218	(71.0)
Unknown	11	(7.2)	14	(9.1)	25	(8.1)

[*] If there were primary tumours in both left side and right side, the subject would be categorized into Other.

[**] When none of BRAF V600E, KRAS and NRAS was mutant, if at least one of the mutation statuses was undetermined or missing, or the type of BRAF mutation was not V600E, the subject was categorized into Other.

[#] MSI status by PCR test or IHC test at local site laboratory.

[##] Oncologic surgery that was with curative intent and occurred after subject randomization and before initiation of new anti-cancer therapy, crossover treatment and second course treatment.

[###] Subjects without baseline tumour size per BICR are categorized as baseline tumour size <=median.

Database Cutoff Date: 19FEB2020.

Sites of metastases:

Hepatic or pulmonary 86 (56.2) vs 73 (47.4); hepatic only 50 (32.7%) vs 39 (25.3%); pulmonary only 15 (9.8%) vs 19 (12.3%); hepatic and pulmonary 21 (13.7%) vs 15 (9.7%); pulmonary (alone or with other sites) 36 (23.5%) vs 34 (22%), in pembrolizumab vs SOC arm, respectively.

Table: Investigator's Choice of Standard of Care Treatment (ASaT Population)

	SOC (N=143)	
	n	(%)
FOLFIRI	16	11.2
FOLFIRI + BEVACIZUMAB	36	25.2
FOLFIRI + CETUXIMAB	11	7.7
mFOLFOX6	11	7.7
mFOLFOX6 + BEVACIZUMAB	64	44.8
mFOLFOX6 + CETUXIMAB	5	3.5

Database Cutoff Date: 19FEB2020

Determination of MSI-H/dMMR status

IHC testing was used for the majority of participants (105 pembrolizumab, 97 SOC) with far fewer participants assessed using PCR (16 participants in each treatment group) or PCR and IHC (32 pembrolizumab, 40 SOC).

Numbers analysed

The ITT population includes 307 participants, 153 in the pembrolizumab arm and 154 in the SOC arm, which were analysed for efficacy.

Outcomes and estimation

Table: summary of efficacy results for KEYNOTE-177

	Pembrolizumab N=153	**SOC N=154**
PFS (BICR per RECIST 1.1)		
Number of events (%)	82 (53.6)	113 (73.4)
Median in months (95% CI)	16.5 (5.4, 32.4)	8.2 (6.1, 10.2)
HR (95% CI)	0.60 (0.45, 0.80)	
P-value	0.0002	
PFS rate at 12 months (95% CI)	55.3 (47.0, 62.9)	37.3 (29.0, 45.5)
PFS rate at 18 months (95% CI)	49.1 (40.7, 57.0)	26.7 (19.2, 34.7)
PFS rate at 24 months (95% CI)	48.3 (39.9, 56.2)	18.6 (12.1, 26.3)
OS		
Number of events (%)	56 (36.6)	69 (44.8)
Median in months (95% CI)	NR (NR, NR)	34.8 (26.3, NR)
HR (95% CI)	0.77 (0.54, 1.09)	
P-value	0.0694	
OS rate at 12 months (95% CI)	77.8 (70.3, 83.6)	74.0 (66.2, 80.3)
OS rate at 18 months (95% CI)	71.2 (63.4, 77.7)	65.9 (57.7, 72.9)
OS rate at 24 months (95% CI)	68.0 (59.9, 74.7)	59.8 (51.5, 67.2)
ORR (BICR per RECIST 1.1, with confirmation)		
% (95% CI)	43.8 (35.8, 52.0)	33.1 (25.8, 41.1)
Complete Responses %	11.1	3.9
Partial Responses %	32.7	29.2
Stable Disease %	20.9	42.2
Progressive Disease %	29.4	12.3
DOR (Confirmed CR or PR, BICR per RECIST 1.1)		
Number of responders	67	51
Median in months (range)	NR (2.3+ - 41.4+)	10.6 (2.8 - 37.5+)

	Pembrolizumab N=153	SOC N=154
Median time to response (range)	2.2 (1.8-18.8)	2.1 (1.7-24.9)
Number (KM %) With Extended Response Duration (⩾6 months)	61 (96.9)	43 (87.9)
Progression-free Survival 2		
Median in months (95% CI)	NR (NR, NR)	23.5 (95% CI: 16.6, 32.6)
HR (95% CI)	0.63 (95% CI: 0.45, 0.88)	
P-value	p=0.0031*	
PRO		
QLQ-C30 global health status/QoL mean score change from baseline to prespecified Week 18 (95% CI)	+3.33 points (-0.05, 6.72)	-5.63 points (-9.32, -1.94)
LS mean difference in global health status/QoL score (95% CI)	8.96 points (4.24, 13.69) p=0.0002*	
Time to deterioration# in global health status/QoL	HR=0.61 (95% CI 0.38-0.98) p=0.0195*	
Time to deterioration# in physical functioning	HR=0.50 (95% CI 0.32-0.81) p=0.0016*	
Time to deterioration# in social functioning	HR=0.53 (95% CI 0.32-0.87) p=0.0050*	
Time to deterioration# in fatigue	HR=0.48 (95% CI 0.33-0.69) p<0.0001*	
Time to deterioration# in urinary incontinence	HR=0.43 (95% CI 0.14-1.31) p=0.0637*	

Abbreviations: BICR=Blinded independent central review; CI=Confidence interval; CR=Complete response; DOR=Duration of response; HR=Hazard ratio; KM=Kaplan-Meier; LS=least squares; N=Number; NR=Not reached; ORR=Objective response rate; OS=Overall survival; PFS=Progression-free survival; PR=Partial response; PRO=Patient-reported outcomes; QLQ=Quality of life questionnaire; QoL=Quality of Life; RECIST 1.1=Response Evaluation Criteria in Solid Tumours Version 1.1; SOC=Standard of care.
* not controlled for multiplicity
# deterioration defined as the time to first onset of a decrease of >10 points with confirmation
Database Cutoff Date: 19FEB2020.
Data Source: [Ref. 5.3.5.1: P177V01MK3475: Table 11-2], [Ref. 5.3.5.1: P177V01MK3475: Table 11-8], [Ref. 5.3.5.1: P177V01MK3475: Table 11-9], [Ref. 5.3.5.1: P177V01MK3475: Table 11-10], [Ref. 5.3.5.1: P177V01MK3475: Table 14.2-9], [Ref. 5.3.5.1: P177V01MK3475: Table 14.2-18], [Ref. 5.3.5.1: P177V01MK3475: Table 14.2-19], [Ref. 5.3.5.1: P177V01MK3475: Table 14.2-20], [Ref. 5.3.5.1: P177V01MK3475: Table 14.2-21], [Ref. 5.3.5.1: P177V01MK3475: Table 14.2-22], [Ref. 5.3.5.1: P177V01MK3475: Table 14.2-23], [Ref. 5.3.5.1: P177V01MK3475: Table 14.2-30].

Primary endpoints (dual primary)

- Progression Free Survival (PFS)

At the IA2 (i.e. final analysis for PFS), pembrolizumab provided a statistically significant and clinically meaningful improvement in PFS per RECIST 1.1 by BICR compared to SOC.

Table: Analysis of Progression-Free Survival (Primary Analysis) By Central Imaging Vendor 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 Month 12 in % † (95% CI)
Pembrolizumab	153	82 (53.6)	2238.8	3.7	16.5 (5.4, 32.4)	55.3 (47.0, 62.9)
SOC	154	113 (73.4)	1487.3	7.6	8.2 (6.1, 10.2)	37.3 (29.0, 45.5)
					Hazard Ratio‡ (95% CI)‡	p-Value§
Pembrolizumab vs. SOC					0.60 (0.45, 0.80)	0.0002

† 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.
§ One-sided p-value based on log-rank test.
Database Cutoff Date: 19FEB2020.

Table: Summary of Event and Censoring Description for Progression-Free Survival (Primary Analysis) By Central Imaging Vendor per RECIST 1.1 (ITT Population)

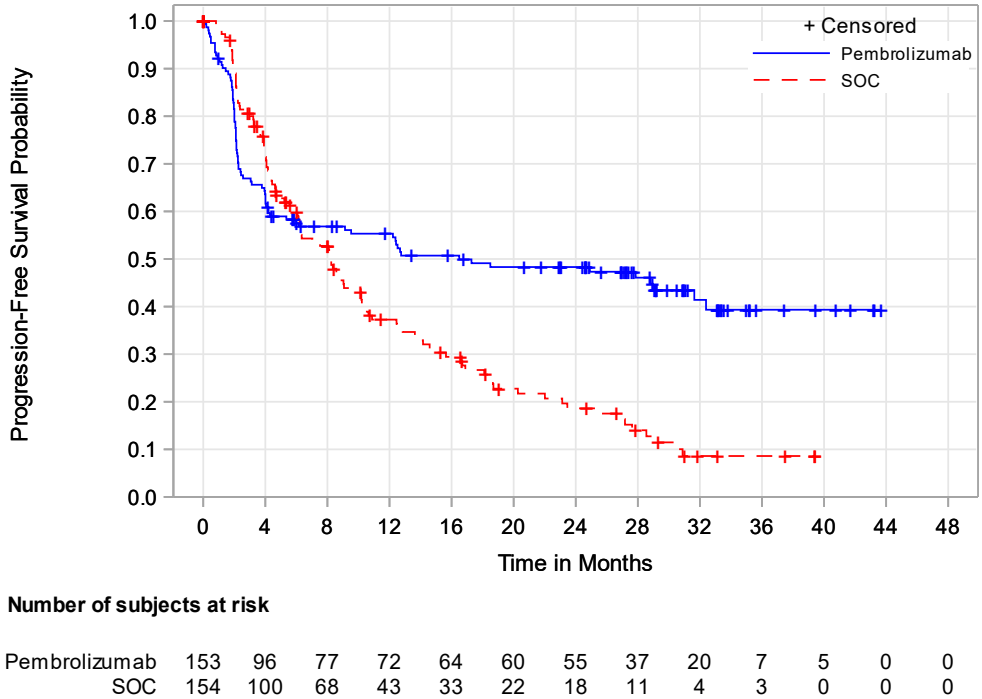
	Pembrolizumab (N=153) n (%)	SOC (N=154) n (%)
Subjects with Events	82 (53.6)	113 (73.4)
Documented progression	65 (42.5)	86 (55.8)
Death	17 (11.1)	27 (17.5)
Subjects Censored	71 (46.4)	41 (26.6)
Curative-intent surgery	12 (7.8)	12 (7.8)
New anti-cancer therapy	5 (3.3)	15 (9.7)
Last radiologic assessment showing no progression	53 (34.6)	10 (6.5)
No adequate post-baseline imaging assessment	1 (0.7)	4 (2.6)
Database Cutoff Date: 19FEB2020.		

Table: analysis of PFS rate over time (primary analysis) by central imaging vendor per RECIST 1.1 (ITT population)

	Pembrolizumab (N=153) % (95% CI)†	SOC (N=154) % (95% CI)†
Progression-Free Survival rate at time point		
6 months	57.6 (49.3, 65.0)	59.7 (51.1, 67.3)
9 months	56.8 (48.5, 64.3)	45.5 (36.9, 53.7)
12 months	55.3 (47.0, 62.9)	37.3 (29.0, 45.5)
18 months	49.1 (40.7, 57.0)	26.7 (19.2, 34.7)
24 months	48.3 (39.9, 56.2)	18.6 (12.1, 26.3)

† From product-limit (Kaplan-Meier) method for censored data.
Database Cutoff Date: 19FEB2020.

Figure: Kaplan-Meier Estimates of Progression-Free Survival (Primary Analysis) By Central Imaging Vendor per RECIST 1.1 (ITT Population)



Database Cutoff Date: 19FEB2020.

- Overall Survival (OS)

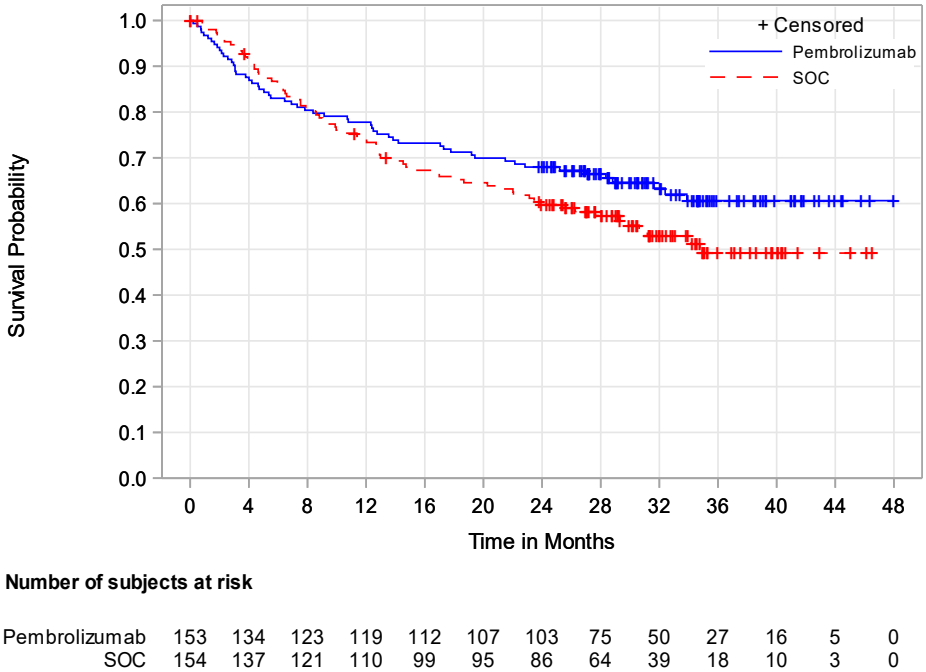
At the IA2 (i.e. interim analysis for OS), the statistical significance criterion for OS was not met when compared to the p-value boundary of 0.0053.

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 Month 12 in % † (95% CI)
Pembrolizumab	153	56 (36.6)	3794.5	1.5	NR (NR, NR)	77.8 (70.3, 83.6)
SOC	154	69 (44.8)	3430.2	2.0	34.8 (26.3, NR)	74.0 (66.2, 80.3)
					Hazard Ratio‡ (95% CI)‡	p-Value§
Pembrolizumab vs. SOC					0.77 (0.54, 1.09)	0.0694

† 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.
§ One-sided p-value based on log-rank test.
NR = Not reached.
Database Cutoff Date: 19FEB2020.

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



Database Cutoff Date: 19FEB2020.

Key secondary endpoint

- Overall Response Rate (ORR)

Based on protocol-specified multiplicity strategy, if ORR by BICR per RECIST 1.1 was not significant at IA1, ORR at IA1 could be tested following a statistically significant PFS or OS hypothesis test at IA2 or final analysis. Because PFS was statistically significant at IA2, ORR at IA1 was formally tested and statistical significance was not demonstrated, as the p-value of 0.0582 for ORR at IA1 was above the p-value boundary of 0.000125.

Only 2 cases of pseudoprogression were identified in the pembrolizumab arm.

Table: Analysis of Best Overall Response By Central Imaging Vendor per RECIST 1.1 (ITT Population)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI*)	Difference in % vs. SOC	
				Estimate (95% CI)†	p-Value‡
Pembrolizumab	153	67	43.8 (35.8,52.0)	10.7 (-0.2,21.3)	0.0275
SOC	154	51	33.1 (25.8,41.1)		

Only confirmed responses are included.
* Based on binomial exact confidence interval method.
† Based on Miettinen & Nurminen method.
‡ One-sided p-value for testing H0: difference in % = 0 versus H1: difference in % > 0.
Database Cutoff Date: 19FEB2020.

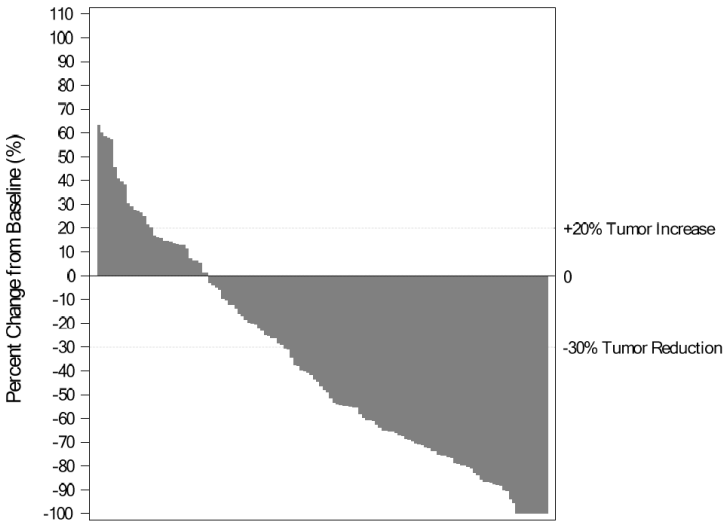
Table: Summary of Best Overall Response By Central Imaging Vendor per RECIST 1.1 (ITT Population)

Response Evaluation	Pembrolizumab (N=153)			SOC (N=154)		
	n	%	95% CI†	n	%	95% CI†
Complete Response (CR)	17	11.1	(6.6, 17.2)	6	3.9	(1.4, 8.3)
Partial Response (PR)	50	32.7	(25.3, 40.7)	45	29.2	(22.2, 37.1)
Objective Response (CR+PR)	**67**	**43.8**	**(35.8, 52.0)**	**51**	**33.1**	**(25.8, 41.1)**
Stable Disease (SD)	32	20.9	(14.8, 28.2)	65	42.2	(34.3, 50.4)
Disease Control (CR+PR+SD)	**99**	**64.7**	**(56.6, 72.3)**	**116**	**75.3**	**(67.7, 81.9)**
Progressive Disease (PD)	45	29.4	(22.3, 37.3)	19	12.3	(7.6, 18.6)
Not Evaluable	3	2.0	(0.4, 5.6)	2	1.3	(0.2, 4.6)
No Assessment	6	3.9	(1.5, 8.3)	17	11.0	(6.6, 17.1)

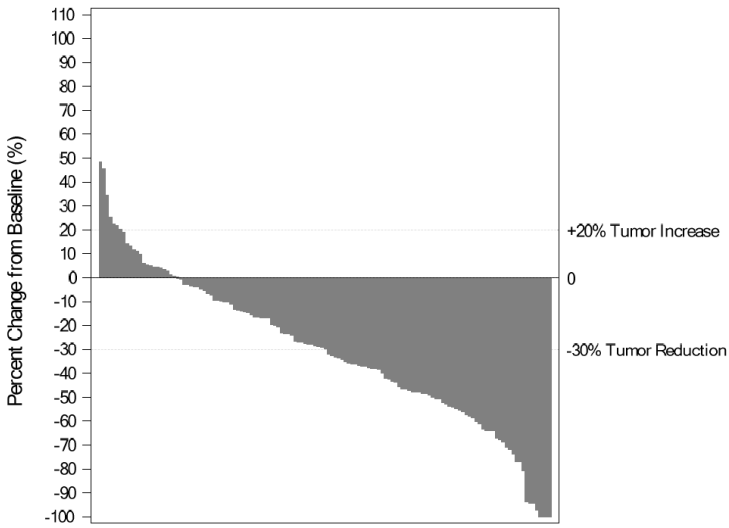
Only confirmed responses are included.
† Based on binomial exact confidence interval method.
No Assessment: subject had no post-baseline imaging.
Database Cutoff Date: 19FEB2020.

Figures: Waterfall Plot of Maximum Target Lesion Change from Baseline By Central Imaging Vendor per RECIST 1.1 (ITT Population)

Pembrolizumab arm



SOC arm



Exploratory endpoints

Duration of response

Table: Summary of Time to Response and Duration of Response in Subjects with Confirmed Response By Central Imaging Vendor per RECIST 1.1 (ITT Population)

	Pembrolizumab (N=153)	SOC (N=154)
Number of subjects with response†	67	51
Time to Response (months)		

Mean (SD)	4.0 (3.7)	3.6 (4.1)
Median (Range)	2.2 (1.8-18.8)	2.1 (1.7-24.9)
Response Duration‡ (months)		
Median (Range)	NR (2.3+ - 41.4+)	10.6 (2.8 - 37.5+)
Number (%‡) of Subjects with Extended Response Duration:		
≥6 months	61 (96.9)	43 (87.9)
≥9 months	55 (91.9)	27 (59.9)
≥12 months	50 (85.1)	19 (43.8)
≥18 months	45 (85.1)	11 (35.3)
≥24 months	29 (82.6)	9 (35.3)

† 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: 19FEB2020.

	Pembrolizumab (N=153)	SOC (N=154)
Number of Subjects with Response†	67	51
Subjects Who Progressed or Died‡ (%)	**13 (19.4)**	**32 (62.7)**
Range of DOR (months)	3.3 to 27.0	2.8 to 28.8
Censored Subjects (%)	**54 (80.6)**	**19 (37.3)**
Subjects who received oncologic surgery with curative intent	8 (11.9)	2 (3.9)
Subjects who missed 2 or more consecutive disease assessments	3 (4.5)	1 (2.0)
Subjects who started new anti-cancer treatment	1 (1.5)	6 (11.8)
Subjects who were lost to follow-up	0 (0.0)	0 (0.0)
Subjects whose last adequate assessment was ≥ 5 months prior to data cutoff date	4 (6.0)	1 (2.0)
Ongoing response§	38 (56.7)	9 (17.6)
≥6 months	38 (56.7)	9 (17.6)
≥9 months	38 (56.7)	8 (15.7)
≥12 months	38 (56.7)	8 (15.7)
≥18 months	34 (50.7)	8 (15.7)
≥24 months	24 (35.8)	6 (11.8)
Range of DOR (months)	15.7+ to 41.4+	6.2+ to 37.5+

† Includes subjects with a confirmed complete response or partial response.

‡ Includes subjects who progressed or died without previously missing 2 or more consecutive disease assessments.

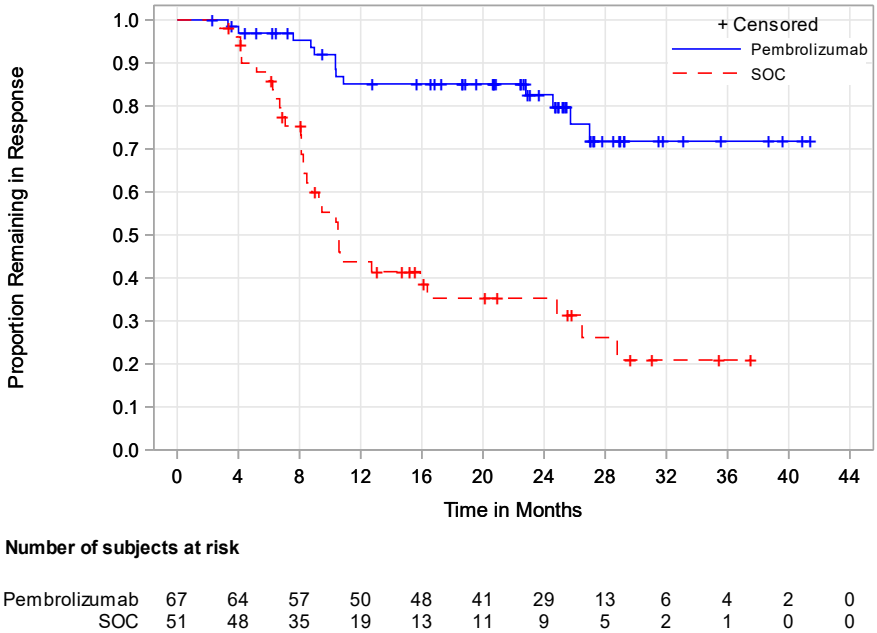
§ Includes subjects who are alive, have not progressed, have not received oncologic surgery with curative intent, have not initiated new anti-cancer treatment, are not lost to follow-up, and whose last disease assessment was <5 months prior to data cutoff date.

For censored subjects who met multiple criteria for censoring and do not have ongoing response, subjects are included in the censoring criterion that occurred earliest.

'+' indicates there was no progressive disease by the time of last disease assessment.

Database Cutoff Date: 19FEB2020.

Figure: Kaplan-Meier Estimates of Duration of Response in Subjects with Confirmed Response By Central Imaging Vendor per RECIST 1.1 (ITT Population)



Database Cutoff Date: 19FEB2020.

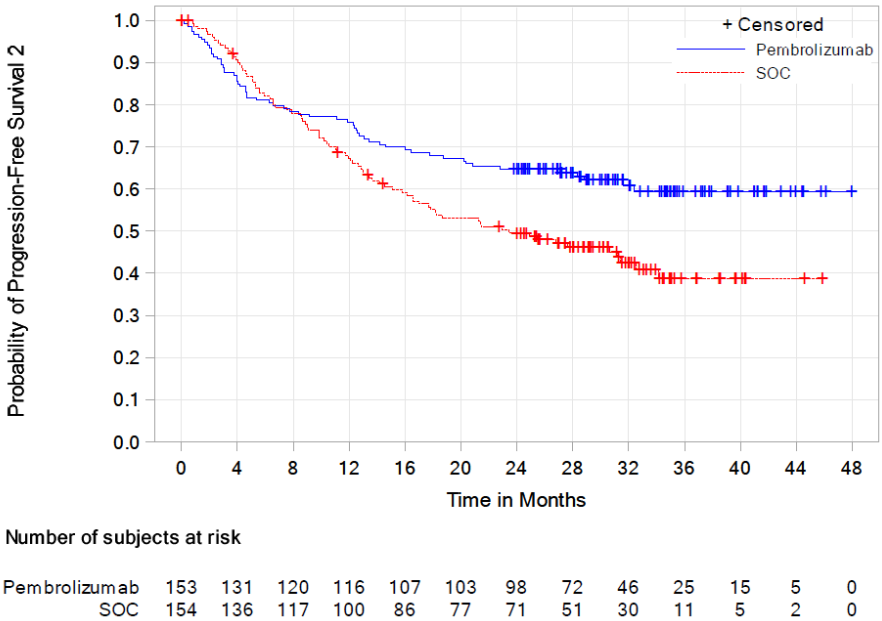
Progression Free Survival 2

Table: Analysis of Progression-Free Survival 2 By Investigator per RECIST 1.1 (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS2 † (Months) (95% CI)	PFS2 Rate at Month 12 in % † (95% CI)
Pembrolizumab	153	59 (38.6)	3650.3	1.6	NR (NR, NR)	75.8 (68.2, 81.8)
SOC	154	84 (54.5)	3026.4	2.8	23.5 (16.6, 32.6)	67.4 (59.2, 74.2)
					Hazard Ratio‡ (95% CI)‡	p-Value§
Pembrolizumab vs. SOC					0.63 (0.45, 0.88)	0.0031

† 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.
§ One-sided p-value based on log-rank test.
NR = Not reached.
Progression-Free Survival 2 (PFS2) is defined as the time from randomization to disease progression on the next line of therapy, or death from any cause, whichever occurs first.
Database Cutoff Date: 19FEB2020.

Figure: Kaplan-Meier Estimates of Progression-Free Survival 2 By Investigator per RECIST 1.1 (ITT Population)



Database Cutoff Date: 19FEB2020.

Patient Reported Outcome (PRO)

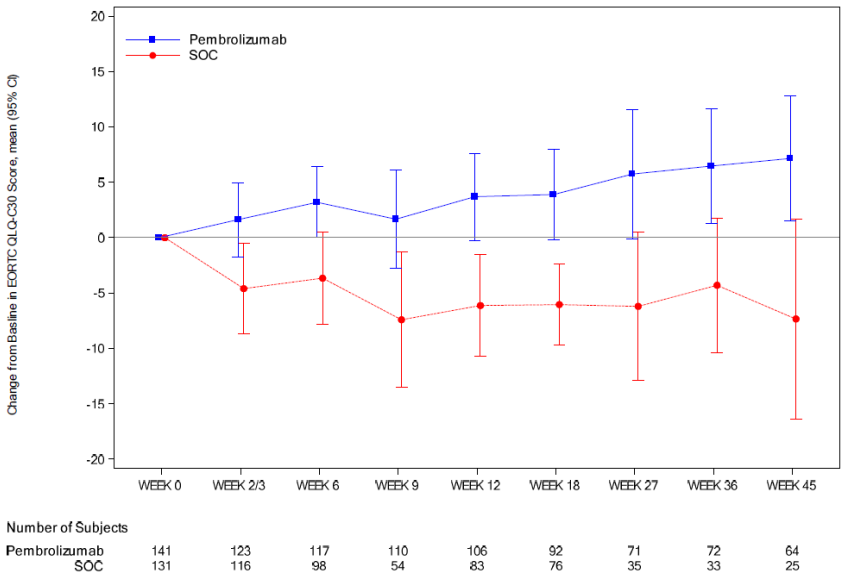
At baseline, the compliance rates for the EORTC QLQ-C30 were similar and above 90% in both treatment groups (92.8% vs 92.9%, respectively) and remained high at prespecified Week 18 (87.9% vs 76.6%, respectively). Compliance rates at baseline through Week 18 were similar for the EORTC QLQ-CR29 and EQ-5D.

Baseline global health status/QoL scores were similar between treatment groups. At prespecified Week 18, the mean change from baseline in the global health status/QoL score showed improvement (LS mean = 3.33 points [95% CI: -0.05, 6.72]) in the pembrolizumab group, and a decline (LS mean = -5.63 points [95% CI: -9.32, -1.94]) in the SOC group. The difference in LS means between pembrolizumab and the SOC group at Week 18 was 8.96 points (95% CI: 4.24, 13.69; two-sided nominal p=0.0002, not adjusted for multiplicity).

In the PRO FAS population with baseline assessments, based on the EORTC QLQ-C30, for participants in the pembrolizumab group compared to those in the SOC group, prolonged TTD was observed in global health status/QoL score (HR 0.61; 95% CI 0.38-0.98; one-sided nominal p=0.0195, not adjusted for multiplicity).

A greater proportion of participants in the pembrolizumab group showed improvement in global health status/QoL score and all functioning and symptom scores (except insomnia) compared to those in the SOC group, while a greater proportion of participants in the SOC group showed deterioration in global health status/QoL score and all functioning and symptom scores compared to those in the pembrolizumab group.

Figure: Mean Change from Baseline and 95% CI for the EORTC QLQ-C30 Global Health Status/QoL Over Time (FAS Population with Baseline and Post-Baseline Assessment)



Database Cutoff Date: 19FEB2020.

Figure: Kaplan-Meier Estimates of Time to Deterioration for EORTC QLQ-C30 Global Health Status/QOL (FAS Population with Baseline)

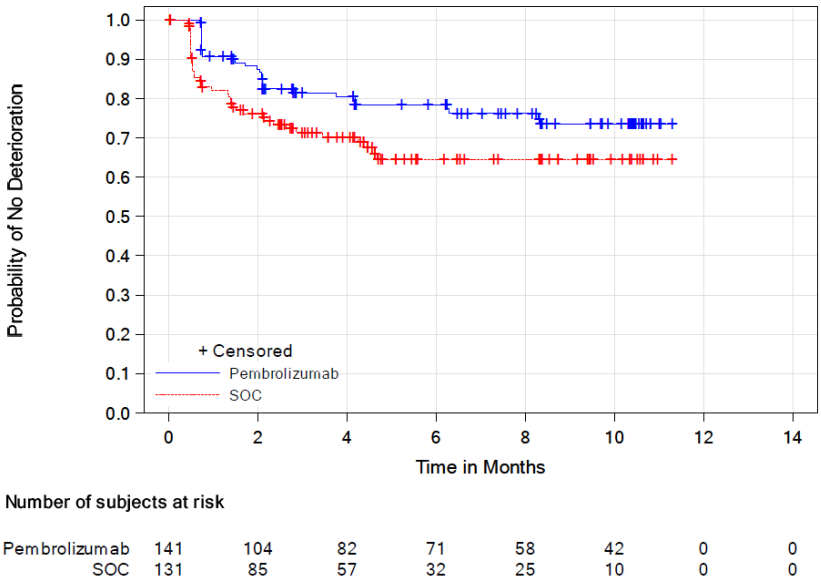


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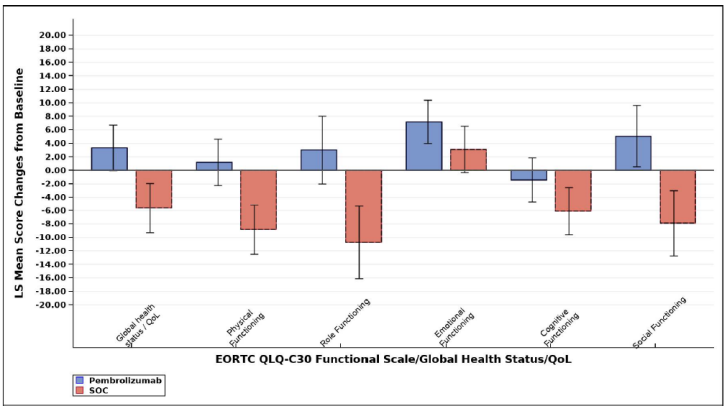
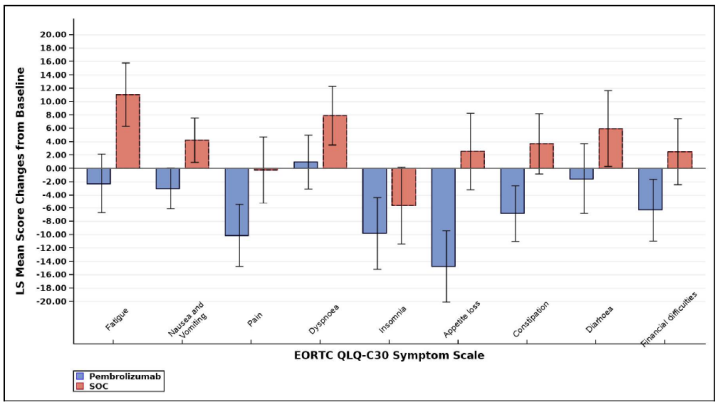
Figure: Change from Baseline for EORTC QLQ-C30 scores at Week 18 LS Mean Change and 95% CI (FAS Population)

Functional Scale/Global Health Status/QoL



For global health status/quality of life score and all functional scales, a higher score denotes better HRQOL or function.

Symptom Scale

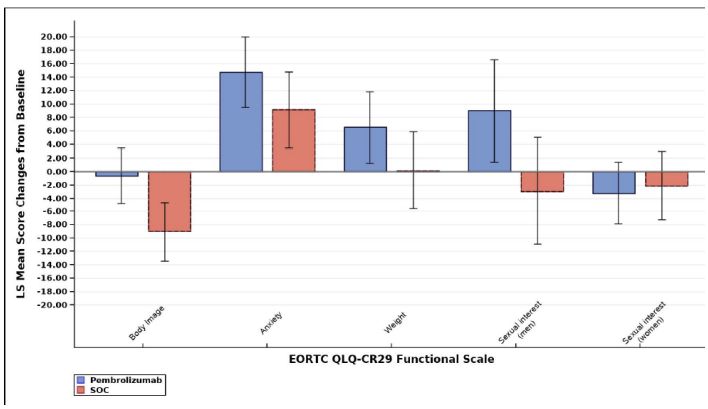


For symptoms scales, a higher score denotes worse symptoms.

Database Cutoff Date: 19FEB2020.

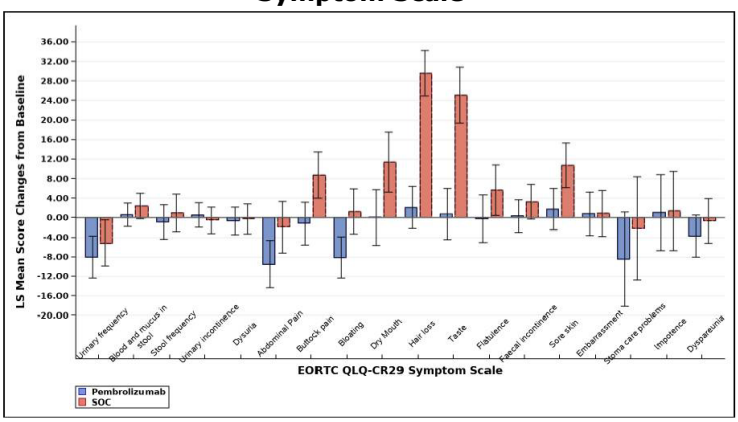
Figure: Change from Baseline for EORTC QLQ-CR29 scores at Week 18 LS Mean Change and 95% CI (FAS Population)

Functional Scale



For global health status/quality of life score and all functional scales, a higher score denotes better HRQOL or function.

Symptom Scale



For symptoms scales, a higher score denotes worse symptoms.

Database Cutoff Date: 19FEB2020.

Baseline EQ-5D VAS and utility scores were similar between treatment groups. At prespecified Week 18, the mean change from baseline in the EQ-5D VAS score showed improvement (LS mean = 4.50 points [95% CI: 1.16, 7.83]) in the pembrolizumab group, and a decline (LS mean = -2.88 points [95% CI: -6.46, 0.69]) in the SOC group. The difference in LS means between pembrolizumab and the SOC group at Week 18 was 7.38 points (95% CI: 2.82, 11.93; two-sided nominal p=0.0016, not adjusted for multiplicity), a clinically important difference. For the EQ-5D utility score, the mean change from baseline to Week 18 showed improvement (LS mean = 0.04 points [95% CI: 0.00, 0.08]) in the pembrolizumab group, and a decline (LS mean = -0.01 points [95% CI: -0.05, 0.02]) in the SOC group, although the difference was not clinically meaningful (difference in LS means = 0.05; 95% CI: 0.00, 0.10; two-sided nominal p=0.0311, not adjusted for multiplicity).

Ancillary analyses (pre-specified)

Sensitivity analyses for PFS

- *Sensitivity analysis using time to disease recurrence after curative-intent surgery:* because some patients received surgery with curative intent (9.2% in the pembrolizumab group and 8.4% in the SOC group), a PFS sensitivity analysis (defined as PFS using time from randomization to disease recurrence after surgery for surgical participants) was performed: PFS HR= 0.60, 95%CI 0.45, 0.80.

- *PFS sensitivity analysis 1* (censors at the last disease assessment without PD when PD or death is documented after >1 missed disease assessment): PFS HR=0.62, 95%CI 0.46, 0.84.

- *PFS sensitivity analysis 2* (considers discontinuation of treatment or initiation of an anticancer treatment subsequent to discontinuation of study-specified treatments, whichever occurs later, to be a PD event for participants without documented PD or death): PFS HR=0.61, 95%CI 0.48, 0.79.

Sensitivity analysis for OS – adjustment for crossover

Sensitivity analyses were carried out to assess the impact of crossover on overall survival. Subjects in SOC arm who initiated subsequent anti-PD1/PDL1 treatment include those who crossed over from SOC to Pembrolizumab (n=56) and those who did not cross over but received subsequent anti-PD1/PDL1 treatment (n=35).

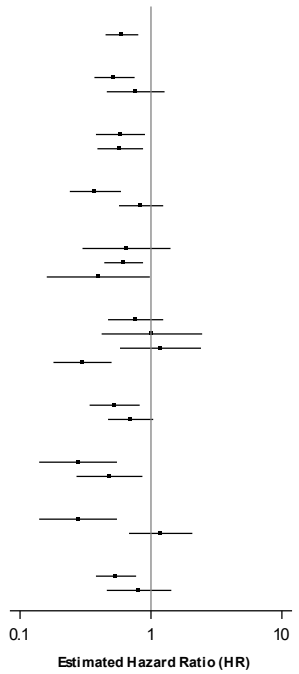
- inverse probability of censoring weighting model (IPCW): OS HR = 0.54 (95% CI: 0.27, 1.39)

- rank preserving structural failure time model (RPSFT): OS HR = 0.72 (95% CI: 0.47, 1.11)

Subgroup analyses

Figure: Analysis of Progression-Free Survival by Subgroup Factors By Central Imaging Vendor per RECIST 1.1 (ITT Population)

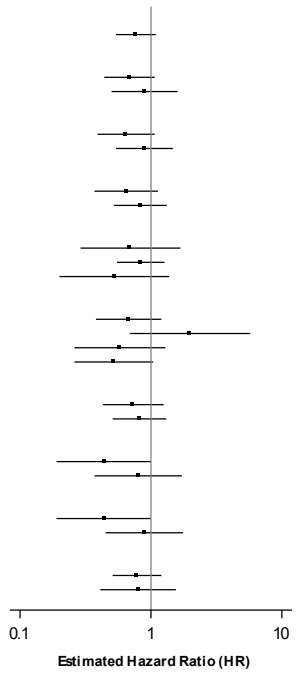
	# event/N		Median (Months)		HR	95% CI
	Pembrolizumab	SOC	Pembrolizumab	SOC		
Overall	82/153	113/154	16.5	8.2	0.60	(0.45, 0.80)
Age						
<= 70 years	51/105	81/112	28.8	10.2	0.52	(0.37, 0.75)
> 70 years	31/48	32/42	6.1	6.3	0.77	(0.46, 1.27)
Gender						
Male	35/71	56/82	28.8	10.6	0.59	(0.38, 0.90)
Female	47/82	57/72	12.5	5.2	0.58	(0.39, 0.87)
ECOG						
0	29/75	61/84	NR	9.1	0.37	(0.24, 0.59)
1	53/78	52/70	4.3	6.3	0.84	(0.57, 1.24)
Geographic Region						
Asia	10/22	18/26	NR	10.4	0.65	(0.30, 1.41)
Western Europe/North America	61/109	85/113	12.5	8.1	0.62	(0.44, 0.87)
Rest of World	11/22	10/15	31.6	6.1	0.40	(0.16, 0.98)
Metastases						
Hepatic metastases	35/50	33/39	4.8	6.2	0.76	(0.47, 1.24)
Pulmonary metastases	9/15	12/19	2.6	10.9	1.02	(0.42, 2.46)
Hepatic and pulmonary metastases	16/21	15/15	2.2	6.1	1.18	(0.58, 2.41)
Other metastases	22/67	53/81	NR	9.0	0.30	(0.18, 0.50)
Diagnosis						
Recurrent	37/80	50/74	31.6	10.6	0.53	(0.34, 0.82)
Newly diagnosed stage IV CRC	45/73	63/80	6.0	5.9	0.70	(0.47, 1.04)
BRAF						
BRAF/KRAS/NRAS all Wild type	13/34	28/35	NR	10.2	0.28	(0.14, 0.55)
BRAF V600E	18/34	33/43	14.5	6.2	0.48	(0.27, 0.86)
KRAS/NRAS						
BRAF/KRAS/NRAS all Wild type	13/34	28/35	NR	10.2	0.28	(0.14, 0.55)
KRAS or NRAS Mutant	23/33	28/41	4.0	10.4	1.19	(0.68, 2.07)
Site of Primary Tumor (Right vs. Left)						
Right	53/102	84/107	16.5	8.1	0.54	(0.38, 0.77)
Left	26/46	24/42	17.3	10.3	0.81	(0.46, 1.43)



Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
Database Cutoff Date: 19FEB2020.

Table: Analysis of Overall Survival by Subgroup Factors (ITT Population)

	# event/N		Median (Months)		HR	95% CI
	Pembrolizumab	SOC	Pembrolizumab	SOC		
Overall	56/153	69/154	NR	34.8	0.77	(0.54, 1.09)
Age						
<= 70 years	33/105	47/112	NR	NR	0.69	(0.44, 1.07)
> 70 years	23/48	22/42	NR	22.0	0.89	(0.50, 1.60)
Gender						
Male	24/71	39/82	NR	30.6	0.64	(0.39, 1.07)
Female	32/82	30/72	NR	NR	0.90	(0.54, 1.47)
ECOG						
0	21/75	32/84	NR	NR	0.65	(0.37, 1.13)
1	35/78	37/70	NR	29.9	0.83	(0.52, 1.32)
Geographic Region						
Asia	8/22	13/26	NR	NR	0.69	(0.29, 1.68)
Western Europe/North America	40/109	47/113	NR	NR	0.83	(0.55, 1.27)
Rest of World	8/22	9/15	31.6	16.1	0.53	(0.20, 1.38)
Metastases						
Hepatic metastases	23/50	25/39	NR	22.0	0.68	(0.38, 1.20)
Pulmonary metastases	8/15	6/19	12.5	NR	1.99	(0.69, 5.74)
Hepatic and pulmonary metastases	13/21	13/15	27.0	12.0	0.58	(0.26, 1.29)
Other metastases	12/67	25/81	NR	NR	0.52	(0.26, 1.04)
Diagnosis						
Recurrent	25/80	29/74	NR	NR	0.73	(0.43, 1.25)
Newly diagnosed stage IV CRC	31/73	40/80	NR	30.6	0.82	(0.51, 1.31)
BRAF						
BRAF/KRAS/NRAS all Wild type	9/34	16/35	NR	34.2	0.44	(0.19, 1.00)
BRAF V600E	11/34	16/43	NR	NR	0.80	(0.37, 1.72)
KRAS/NRAS						
BRAF/KRAS/NRAS all Wild type	9/34	16/35	NR	34.2	0.44	(0.19, 1.00)
KRAS or NRAS Mutant	14/33	20/41	NR	31.2	0.89	(0.45, 1.76)
Site of Primary Tumor (Right vs. Left)						
Right	37/102	47/107	NR	34.8	0.78	(0.51, 1.20)
Left	17/46	18/42	NR	NR	0.80	(0.41, 1.55)

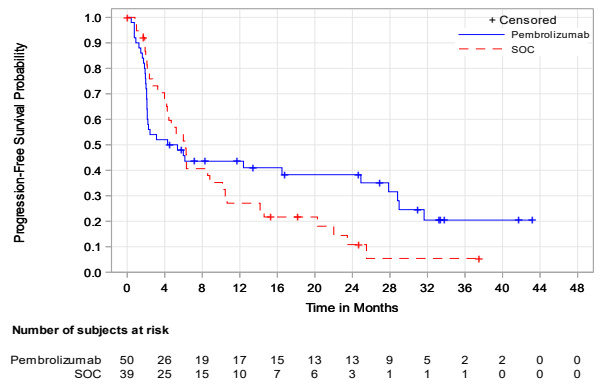


Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
Database Cutoff Date: 19FEB2020.

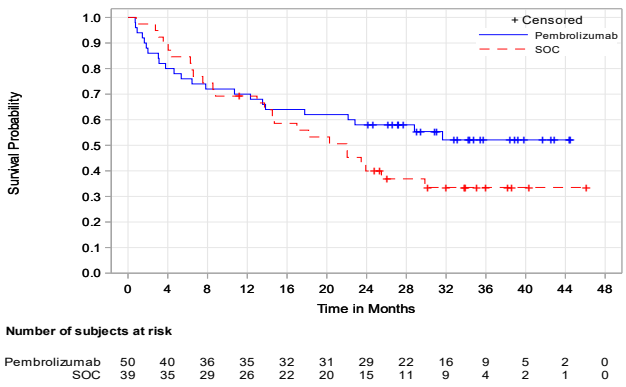
Efficacy data according to site of metastases

Hepatic metastases only (50 vs 39 patients)

PFS (HR 0.76, 95%CI 0.47, 1.24)



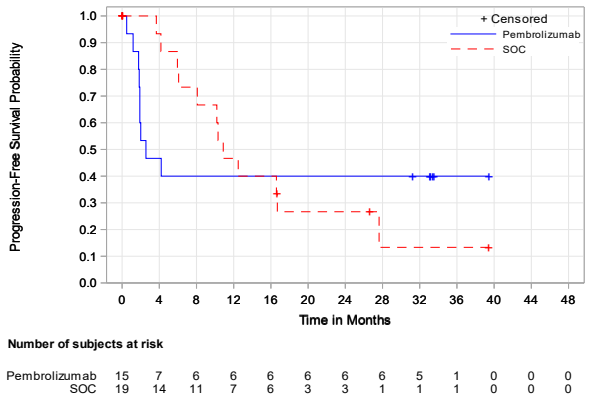
OS (HR 0.68, 95%CI 0.28, 1.20)

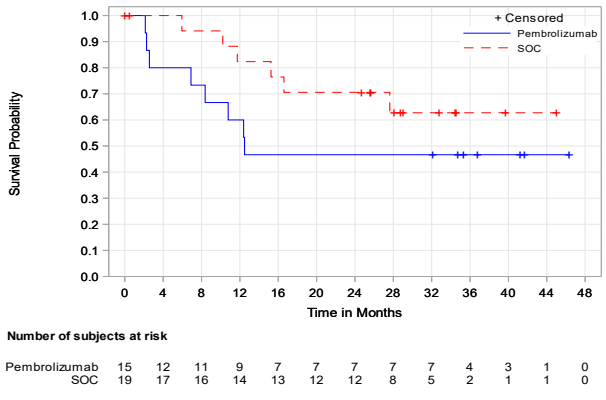


Pulmonary metastases only (15 vs 19 patients)

PFS (HR 1.02, 95%CI 0.42, 2.46)

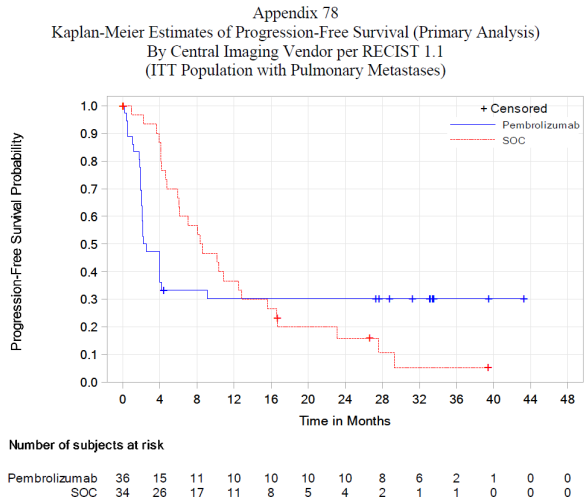
OS (HR 1.99, 95%CI 0.69, 5.44)

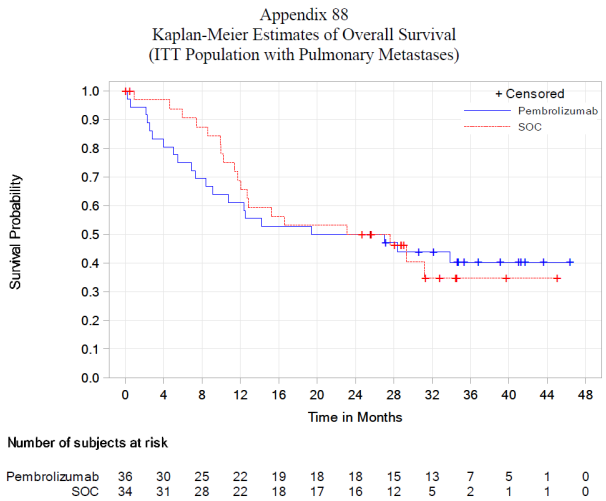




Pulmonary metastases (+/- hepatic metastases) (36 vs 34 patients)

PFS (HR 1.13, 95% CI, 0.65, 1.96) (median 2.4 months vs 8.5 months)	OS (HR 1.05, 95% CI, 0.56, 1.97) (median 23.2 months vs 25.4 months)

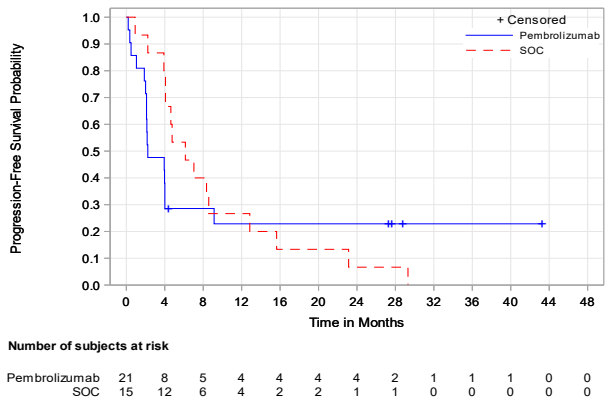


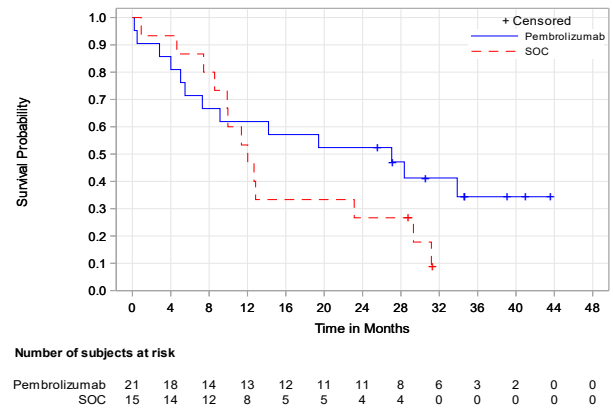


ORR: 25.0% vs 41.2%

Hepatic and pulmonary metastases (21 vs 15 patients)

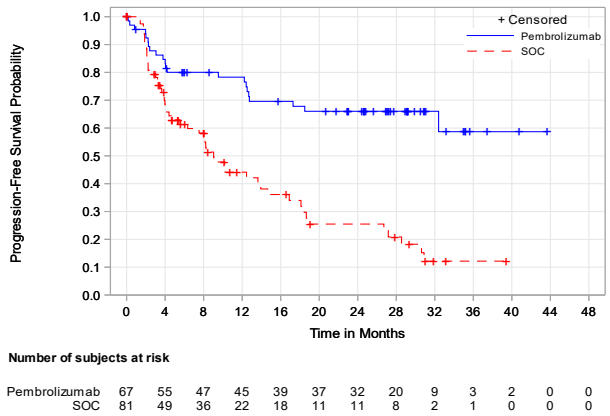
PFS (HR 1.18, 95%CI 0.58, 2.41)	OS (HR 0.58, 95%CI 0.26, 1.29)

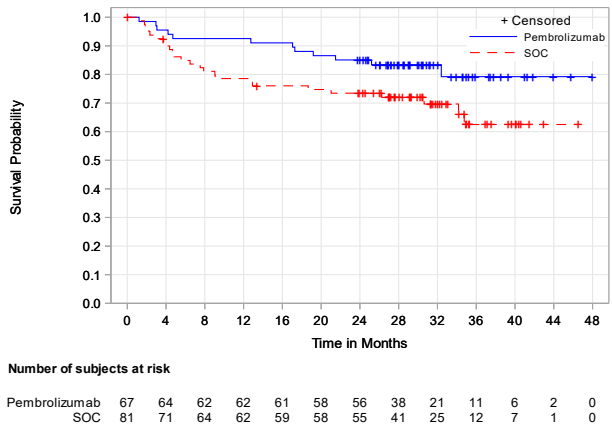




Other metastases (67 vs 81 patients)

PFS (HR 0.30, 95%CI 0.18, 0.50)	OS (HR 0.52, 95%CI 0.26, 1.04)

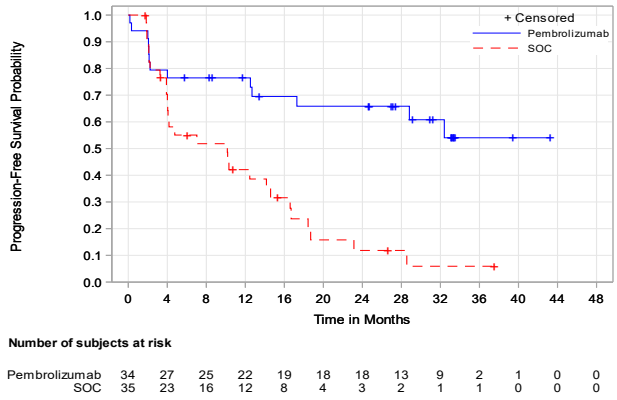




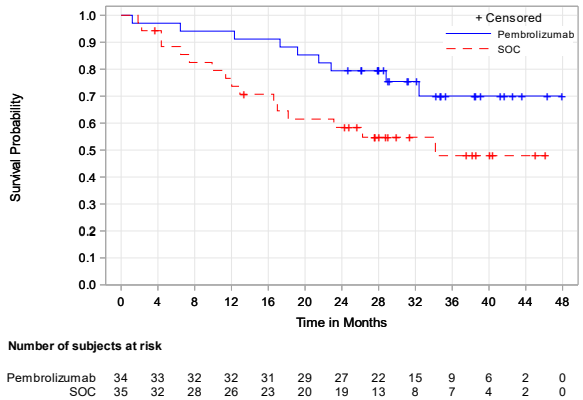
Efficacy data according to mutational status

BRAF/KRAS/NRAS All Wild Type (34 vs 35 patients)

PFS (HR 0.14, 95%CI 0.14, 0.55)

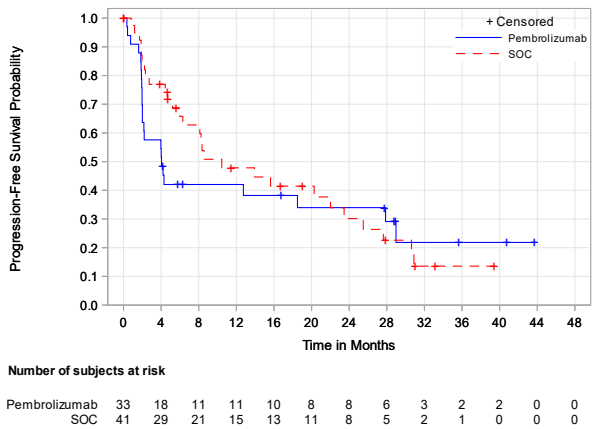


OS (HR 0.44, 95%CI 0.19, 1.00)

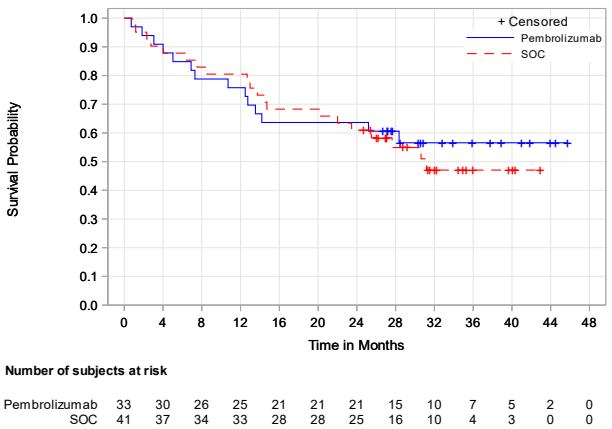


KRAS/NRAS Mutant (33 vs 41 patients)

PFS (HR 1.19, 95%CI 0.68, 2.07)

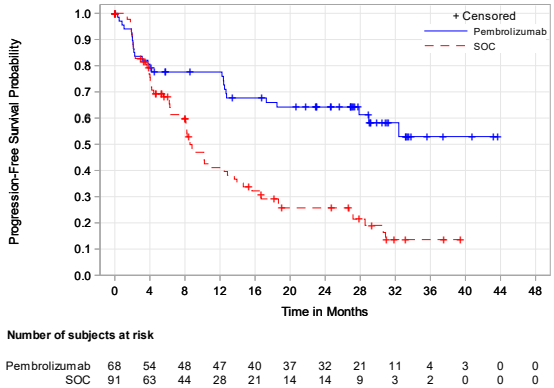
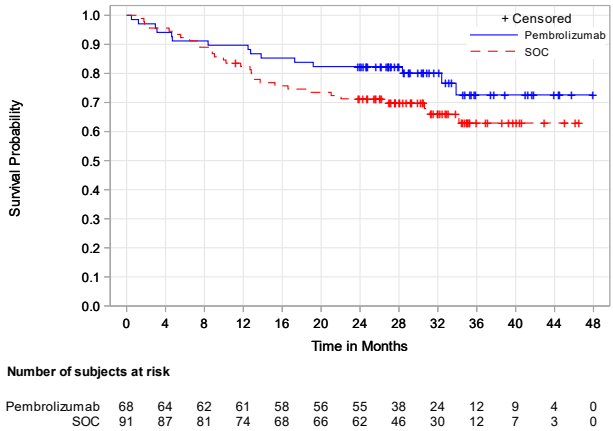
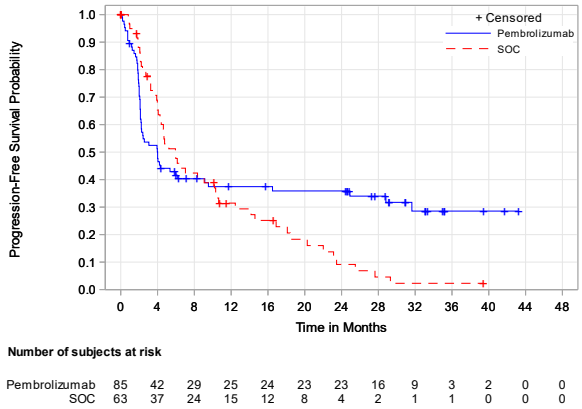
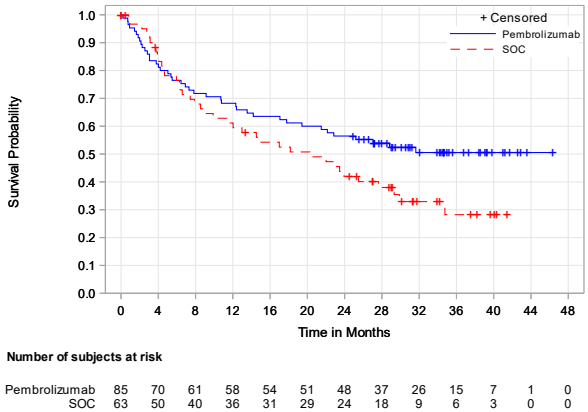


OS (0.89, 95%CI 0.45, 1.55)



ORR: 30.3% vs 26.8%

Efficacy data according to tumour burden at baseline

Tumour burden less than or equal to the median (69 vs 91 patients)	
PFS HR 0.36 (95% CI: 0.23, 0.58)	OS HR 0.63 (95% CI: 0.34, 1.17)
	
ORR: 57.4% (95% CI: 44.8, 69.3) vs 34.1% (95%CI: 24.5, 44.7) (CR 20.6% vs 6.6%)	
Tumour burden above the median	
PFS HR 0.78 (95%CI 0.53, 1.15)	OS HR 0.67 (95% CI: 0.43, 1.04)
	
ORR: 32.9% (95% CI: 23.1, 44.0) vs 31.7% (95% CI: 20.6, 44.7) (CR 3.5% vs 0%) in pembrolizumab vs SOC	

<u>Efficacy results in patients with Lynch syndrome (28 vs 36 patients):</u>
PFS: HR 0.57 (95% CI: 0.27, 1.20)
OS: HR 0.42 (95% CI: 0.15, 1.17)
ORR: 46.4% (27.5, 66.1) vs 33.3% (18.6, 51.0)

<u>Multivariate Cox Regression analysis of PFS</u>

A multivariate Cox regression analysis of PFS was performed to further investigate potential covariates of prognostic interest in CRC. Two-sided p-values of <0.05 were observed for treatment by ECOG interaction and treatment by KRAS/NRAS status interaction. Multivariate Cox regression analysis was adjusted for ECOG, KRAS/NRAS status, treatment by ECOG interaction and treatment by KRAS/NRAS status interaction. The results of this analysis may suggest evidence of an interaction effect. However,

this analysis was not prespecified or adjusted for multiplicity and is underpowered due to the small sample size among participants with known KRAS/NRAS mutations (N = 74), as well as the fraction of the study population (29% of participants) whose KRAS/NRAS results were either undetermined or missing.

Table: Summary of Multivariate Cox Regression Analysis for Progression-Free Survival By Central Imaging Vendor per RECIST 1.1 (ITT Population)

Parameter	p-Value‡
Treatment	
Pembrolizumab vs. SOC (reference)	0.8439
Age: <= 70 years vs. > 70 years (reference)	0.6719
Treatment * Age	0.0958
ECOG: 0 vs. 1 (reference)	0.8471
Treatment * ECOG	0.0200
BRAF Status: BRAF V600E vs. Other† (reference)	0.3260
Treatment * BRAF Status	0.2222
KRAS/NRAS Status: KRAS/NRAS Mutant vs. Other¶ (reference)	0.1522
Treatment * KRAS/NRAS Status	0.0018
Baseline CEA: <= Median vs. > Median (reference)	0.2086
Treatment * Baseline CEA	0.3270
Baseline Tumour Size: <= Median vs. > Median (reference)	0.1403
Treatment * Baseline Tumour Size	0.1080
Metastases: Hepatic Metastases vs. Pulmonary Metastases vs. Hepatic and Pulmonary Metastases vs. Other Metastases (reference)	0.5173
Treatment * Metastases	0.2106

† Other includes BRAF status of wild type, undetermined, missing or non-V600E mutation.

¶ Other includes KRAS and/or NRAS wild type, undetermined or missing, i.e., all subjects whose KRAS and NRAS are not mutant.

‡ Based on multivariate Cox regression model with treatment, age, ECOG, BRAF status, KRAS/NRAS status, baseline CEA, baseline tumour size, metastases, treatment by age, ECOG, BRAF status, KRAS/NRAS status, baseline CEA, baseline tumour size and metastases interactions as covariates. Two-sided p-value based on joint test.

CEA: Carcinoembryonic Antigen

Database Cutoff Date: 19FEB2020.

Table: Multivariate Cox Regression Analysis for Progression-Free Survival By Central Imaging Vendor per RECIST 1.1 (ITT Population)

Parameter	Hazard Ratio‡ (95% CI)‡	p-Value‡
Treatment		
Pembrolizumab vs. SOC (reference)		0.0321
ECOG: 0 vs. 1 (reference)		0.2334
KRAS/NRAS Status: KRAS/NRAS Mutant vs. Other¶ (reference)		0.1559
Treatment * ECOG		0.0362
Treatment * KRAS/NRAS Status		0.0069
Pembrolizumab vs. SOC for Subjects with ECOG = 0 and KRAS/NRAS Mutant	0.81 (0.42, 1.58)	
Pembrolizumab vs. SOC for Subjects with ECOG = 0 and KRAS/NRAS Status = Other	0.33 (0.21, 0.53)	
Pembrolizumab vs. SOC for Subjects with ECOG = 1 and KRAS/NRAS Mutant	1.52 (0.84, 2.76)	
Pembrolizumab vs. SOC for Subjects with ECOG = 1 and KRAS/NRAS Status = Other	0.62 (0.40, 0.96)	

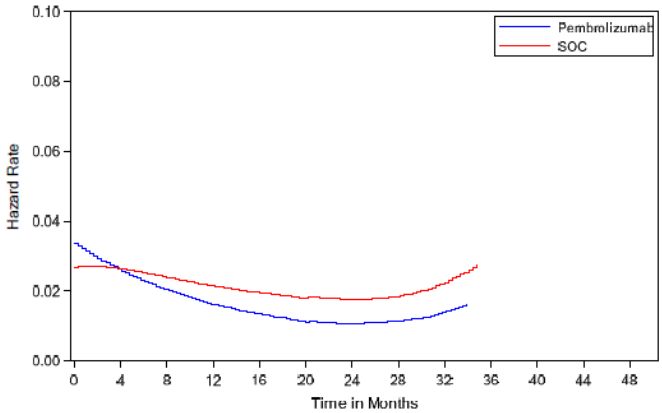
¶ Other includes KRAS and/or NRAS wild type, undetermined or missing, i.e., all subjects whose KRAS and NRAS are not mutant.

‡ Based on multivariate Cox regression model with treatment, ECOG, KRAS/NRAS status, treatment by ECOG, KRAS/NRAS status interactions as covariates. Two-sided p-value based on joint test.

Database Cutoff Date: 19FEB2020.

Analysis of the first part of the OS curves

Figure 5
Smoothed Hazard Rate Estimates for Overall Survival
(ITT Population)



Database Cutoff Date: 19FEB2020.
Source: [P177V01MK3475: adam-adsl; adtte]

Table 15
Piecewise Hazard Ratios for Overall Survival
(ITT Population)

Month	Pembrolizumab (N=153)		SOC (N=154)		Hazard Ratio
	Event	Rate	Event	Rate	
4	19	0.033	13	0.022	1.49
4-8	11	0.022	16	0.031	0.69
> 8	26	0.010	40	0.017	0.56

Database Cutoff Date: 19FEB2020.

Baseline characteristics of the 32 participants (19 in the pembrolizumab group and 13 in the SOC group) with early OS events within the first 4 months are provided in the table below:

Table: Subject Characteristics (ITT Population with Early OS Events)

	Pembrolizumab		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	19		13		32	
Gender						
Male	9	(47.4)	6	(46.2)	15	(46.9)
Female	10	(52.6)	7	(53.8)	17	(53.1)
Age (Years)						
<65	6	(31.6)	7	(53.8)	13	(40.6)

>=65	13	(68.4)	6	(46.2)	19	(59.4)
Subjects with data	19		13		32	
Mean	68.5		65.6		67.3	
SD	13.3		14.0		13.5	
Median	71.0		63.0		68.0	
Range	28 to 85		39 to 87		28 to 87	
Age (Years)						
<=70	9	(47.4)	9	(69.2)	18	(56.3)
>70	10	(52.6)	4	(30.8)	14	(43.8)
Race						
ASIAN	2	(10.5)	1	(7.7)	3	(9.4)
WHITE	16	(84.2)	12	(92.3)	28	(87.5)
Missing	1	(5.3)	0	(0.0)	1	(3.1)
Ethnicity						
HISPANIC OR LATINO	0	(0.0)	1	(7.7)	1	(3.1)
NOT HISPANIC OR LATINO	15	(78.9)	12	(92.3)	27	(84.4)
NOT REPORTED	2	(10.5)	0	(0.0)	2	(6.3)
UNKNOWN	2	(10.5)	0	(0.0)	2	(6.3)
Geographic Region						
Asia	2	(10.5)	1	(7.7)	3	(9.4)
Western Europe/North America	14	(73.7)	11	(84.6)	25	(78.1)
Rest of World	3	(15.8)	1	(7.7)	4	(12.5)
ECOG						
0	2	(10.5)	3	(23.1)	5	(15.6)
1	17	(89.5)	10	(76.9)	27	(84.4)
Site of Primary Tumour*						
Right	11	(57.9)	9	(69.2)	20	(62.5)
Left	6	(31.6)	4	(30.8)	10	(31.3)
Other	1	(5.3)	0	(0.0)	1	(3.1)
Missing	1	(5.3)	0	(0.0)	1	(3.1)
Metastases Location						
Hepatic or pulmonary	16	(84.2)	5	(38.5)	21	(65.6)
Other Metastases	3	(15.8)	8	(61.5)	11	(34.4)
Metastases Location						
Pulmonary	6	(31.6)	1	(7.7)	7	(21.9)
Other	13	(68.4)	12	(92.3)	25	(78.1)
Diagnosed Stage						
Recurrent	5	(26.3)	3	(23.1)	8	(25.0)
Newly diagnosed stage	14	(73.7)	10	(76.9)	24	(75.0)
Prior Systemic Therapy						
Adjuvant only	2	(10.5)	1	(7.7)	3	(9.4)
Neoadjuvant and adjuvant	0	(0.0)	1	(7.7)	1	(3.1)
None	17	(89.5)	11	(84.6)	28	(87.5)
Mutation Status**						
BRAF/KRAS/NRAS all wild type	1	(5.3)	2	(15.4)	3	(9.4)

KRAS/NRAS mutant and BRAF V600E not mutant	3	(15.8)	2	(15.4)	5	(15.6)
BRAF V600E mutant and KRAS/NRAS not mutant	7	(36.8)	3	(23.1)	10	(31.3)
BRAF V600E and KRAS/NRAS mutant	0	(0.0)	2	(15.4)	2	(6.3)
Other	8	(42.1)	4	(30.8)	12	(37.5)
MSI-High Status[#]						
Positive	19	(100.0)	13	(100.0)	32	(100.0)
Oncologic Surgery with Curative Intent[##]						
Did not receive surgery with curative-intent	19	(100.0)	13	(100.0)	32	(100.0)
Prior Radiation Therapy						
Yes	1	(5.3)	0	(0.0)	1	(3.1)
No	18	(94.7)	13	(100.0)	31	(96.9)
Sum of IRC Target Lesions at Baseline[###]						
<= Median	4	(21.1)	4	(30.8)	8	(25.0)
> Median	15	(78.9)	9	(69.2)	24	(75.0)
Baseline CEA Group						
N	3	(15.8)	5	(38.5)	8	(25.0)
H	15	(78.9)	6	(46.2)	21	(65.6)
Missing	1	(5.3)	2	(15.4)	3	(9.4)

[*] If there were primary tumours in both left side and right side, the subject would be categorized into Other.

[**] When none of BRAF V600E, KRAS and NRAS was mutant, if at least one of the mutation statuses was undetermined or missing, or the type of BRAF mutation was not V600E, the subject was categorized into Other.

[#] MSI status by PCR test or IHC test at local site laboratory.

[##] Oncologic surgery that was with curative intent and occurred after subject randomization and before initiation of new anti-cancer therapy, crossover treatment and second course treatment.

[###] Subjects without baseline tumour size per BICR are categorized as baseline tumour size <=median.

Database Cutoff Date: 19FEB2020.

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-177

Title: A Phase III Study of Pembrolizumab (MK-3475) vs. Chemotherapy I Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Stage IV Colorectal Carcinoma (KEYNOTE-177)		
Study identifier	EudraCT: 2015-002024-89; IND: 123,482	
Design	Phase 3, two-arm, multicenter, international, randomized, open-label, controlled study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	FPFV 30 Nov 2015. Study ongoing. NA NA
Hypothesis	Superiority	

Treatments groups	Pembrolizumab (n=153)		200 mg IV Q3W
	SOC (Investigator's choice) (n=154)		mFOLFOX6 mFOLFOX6+bevacizumab mFOLFOX6+cetuximab FOLFIRI FOLFIRI+bevacizumab FOLFIRI+cetuximab
Endpoints and definitions	Dual Primary endpoint	PFS (per RECIST 1.1 by BICR)	Time from randomization to the first documented disease progression per RECIST 1.1 based on blinded central imaging vendor review or death due to any cause, whichever occurs first.
	Dual primary endpoint	OS	Time from randomization to death due to any cause.
	Secondary endpoint	ORR	Per RECIST 1.1 by BICR (confirmed CR/PR)
	Exploratory endpoints	PFS2, DOR, PRO (etc)	
Data cut-off Database lock	19 Feb 2020 16 Mar 2020		

Results and Analysis

Analysis description	**Interim analysis 2 (i.e. final analysis for PFS, interim analysis for OS)**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab	SOC
	Number of subject	153	154
	PFS (median in months)	16.5	8.2
	95%CI	(5.4, 32.4)	(6.1, 10.2)
	OS (median in months)	NR	34.8
	95%CI	NR, NR	(26.3, NR)
	ORR	43.8 %	33.1 %
	95%CI	(35.8, 52.0)	(25.8, 41.1)
	DOR (median in months)	NR	10.6
	range	(2.3+ - 41.4+)	(2.8 - 37.5+)
Effect estimate per comparison	Dual Primary endpoint	Pembrolizumab vs SOC	PFS
		HR	0.60
		95%CI	(0.45, 0.80)
		P-value	0.0002
	Dual Primary endpoint	Pembrolizumab vs SOC	OS
		HR	0.77
		95%CI	(0.54, 1.09)
		P-value	0.0694
	Key Secondary endpoint	Pembrolizumab vs SOC	ORR
		Difference in %	10.7
		95%CI	(-0.2,21.3)
		P-value	0.0275
Notes	Dual primary endpoints: at the IA2, PFS was statistically significant; OS did not reach statistical significance. Secondary endpoint (included in the multiplicity strategy): ORR did not reach statistical significance.		

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

N/A

Clinical studies in special populations

Age

Table: Efficacy Results by Age Categories (ITT Population)

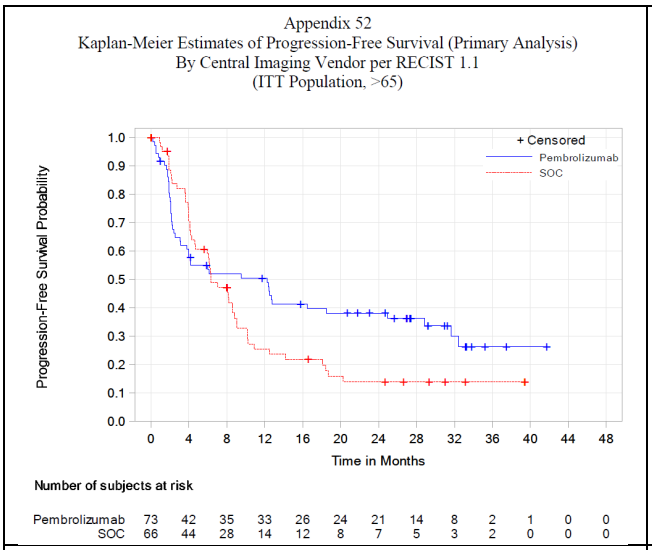
Endpoint	Age Category	N (Pembrolizumab, SOC)	Number of Events (OS and PFS) or Number of Objective Responses (ORR) (Pembrolizumab (%), SOC (%))	Hazard Ratio (95% CI)† (OS and PFS) or Difference in % (95% CI)‡ (ORR) for Pembrolizumab vs. SOC
PFS	<65 years	80, 83	35 (43.8), 59 (71.1)	0.46 (0.30, 0.71)
	65-74 years	43, 40	27 (62.8), 32 (80.0)	0.63 (0.38, 1.06)
	75-84 years	22, 24	15 (68.2), 18 (75.0)	1.00 (0.50, 2.00)
	>=85 years	8, 7	5 (62.5), 4 (57.1)	0.91 (0.24, 3.40)
OS	<65 years	80, 83	20 (25.0), 34 (41.0)	0.53 (0.31, 0.93)
	65-74 years	43, 40	20 (46.5), 17 (42.5)	1.19 (0.63, 2.28)
	75-84 years	22, 24	12 (54.5), 14 (58.3)	0.90 (0.41, 1.94)
	>=85 years	8, 7	4 (50.0), 4 (57.1)	0.78 (0.19, 3.11)
ORR	<65 years	80, 83	39 (48.8), 25 (30.1)	18.63 (3.60, 32.90)
	65-74 years	43, 40	18 (41.9), 15 (37.5)	4.36 (-16.64, 24.88)
	75-84 years	22, 24	6 (27.3), 9 (37.5)	-10.23 (-35.98, 17.21)
	>=85 years	8, 7	4 (50.0), 2 (28.6)	21.43 (-28.51, 61.77)

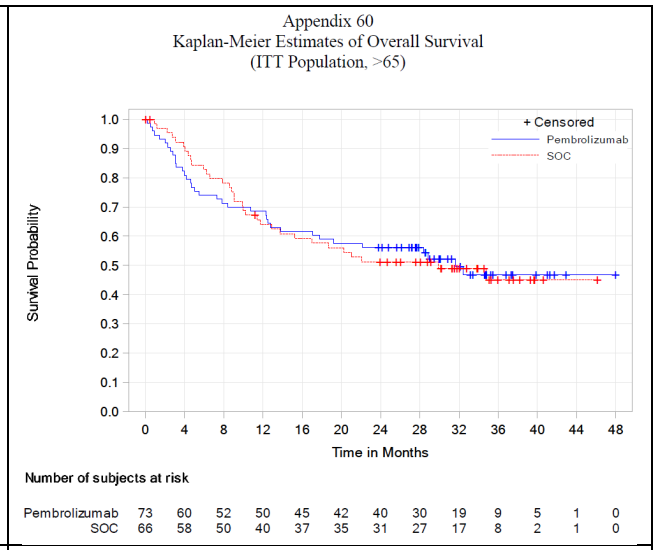
† Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
‡ Based on Miettinen & Nurminen method.
Database Cutoff Date: 19FEB2020

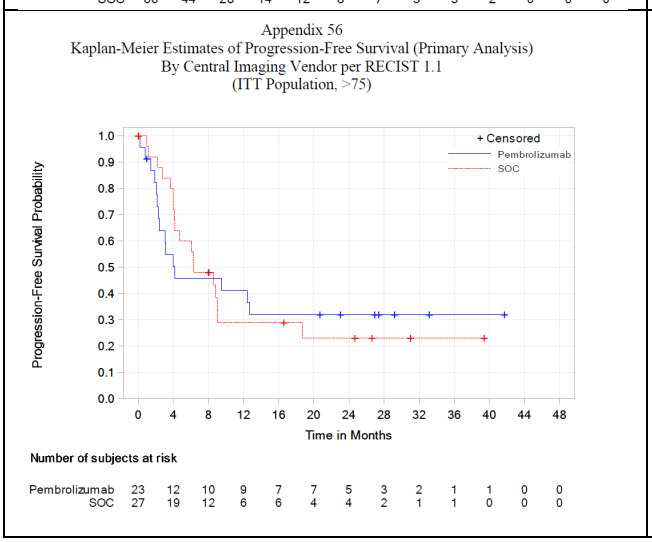
Table 24
Efficacy Results by Age Categories
(ITT Population)

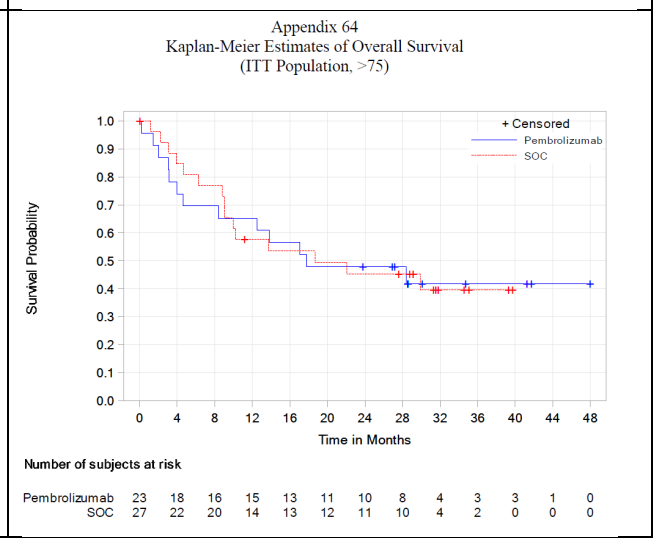
Endpoint	Age Category (years)	N (Pembrolizumab, SOC)	Number of Events (OS and PFS) or Number of Objective Responses (ORR) (Pembrolizumab (%), SOC (%))	Hazard Ratio (95% CI)† (OS and PFS) Pembrolizumab vs. SOC
PFS	≤65	80, 88	35 (43.8), 63 (71.6)	0.47 (0.30, 0.71)
	>65	73, 66	47 (64.4), 50 (75.8)	0.73 (0.49, 1.10)
	≤75	130, 127	67 (51.5), 95 (74.8)	0.54 (0.39, 0.74)
	>75	23, 27	15 (65.2), 18 (66.7)	1.01 (0.51, 2.02)
OS	≤65	80, 88	20 (25.0), 36 (40.9)	0.54 (0.31, 0.93)
	>65	73, 66	36 (49.3), 33 (50.0)	0.99 (0.62, 1.58)
	≤75	130, 127	43 (33.1), 54 (42.5)	0.73 (0.49, 1.08)
	>75	23, 27	13 (56.5), 15 (55.6)	1.03 (0.49, 2.16)
ORR	≤65	80, 88	39 (48.8), 26 (29.5)	N/A
	>65	73, 66	28 (38.4), 25 (37.9)	N/A
	≤75	130, 127	59 (45.4), 42 (33.1)	N/A
	>75	23, 27	8 (34.8), 9 (33.3)	N/A

† Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
Database Cutoff Date: 19FEB2020
Source: [Appendix 49] through [Appendix 68]









Supportive study(ies)

N/A

The MAH included in the dossier (but not presented as supportive) the CSR of KEYNOTE-164, a phase II single arm study of pembrolizumab in subjects with previously treated dMMR or MSI-H CRC, which included overall 124 adult, of whom 61 in Cohort A (patients previously treated with at least 2 lines of standard of care therapies), and 63 in Cohort B (patients previously treated with at least 1 line of systemic standard of care therapy). ORR per RECIST by IRC was the primary endpoint. Treatment with pembrolizumab resulted in an ORR of 32.8% (95%CI 21.3, 46) for Cohort A and 34.9% (95%CI 23.3, 48) for Cohort B, with 4.9% and 12.7% of complete responses in Cohort A and B, respectively With a median follow-up time of 31.4 months for Cohort A and 36.1 months for Cohort B, the median DOR was not reached in either cohort. 95% of responding patients have a response lasting ≥ 12 months.

Of note, although advanced unresectable disease was formally included in KEYNOTE-164, according to baseline characteristics 100% of the patients had Stage IV mCRC (Cohort A and B).

2.4.3. Discussion on clinical efficacy

The MAH is seeking an extension of indication for Keytruda (pembrolizumab) as monotherapy for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal carcinoma in adults, based on the results of the **pivotal KEYNOTE-177 study**, an ongoing phase 3 open-label randomized (1:1) study of pembrolizumab vs investigator's choice SOC chemotherapy. Patients in the SOC arm had the option to crossover to pembrolizumab at BICR-confirmed radiographic PD.

Design and conduct of clinical studies

The randomized 1:1 active controlled design of KEYNOTE-177 study is acceptable. The open label design is acknowledged in view of the marked differences of the treatments in the two arms.

The inclusion/exclusion criteria are considered overall appropriate to define the target population, although mostly reflecting relatively fit patients (ECOG 0-1). Patients with ECOG 2/3 account for more than 30% of the mCRC patients. In MSI-H/dMMR this proportion seems to be even higher (Aasebø et al. 2019). Information that only patients with ECOG 0 or 1 were enrolled is however included in the SmPC.

The population proposed to be included in the initially sought indication was "unresectable or metastatic", although only patients with stage IV disease (i.e. metastatic) were included in KEYNOTE-177. During the procedure, the indication was updated to include "metastatic" patients only, reflecting the population treated in the study.

Inclusion was based on locally determined MSI/MMR testing by PCR or ICH, respectively, which is considered acceptable in general, taking into account that testing is already recommended by international guidelines in routine clinical practice and the acceptable concordance between PCR and IHC. In KEYNOTE-177 only 16 MSI-H tumours were detected via PCR. IHC testing was used for the majority of participants (105 pembrolizumab, 97 SOC) with far fewer participants assessed using PCR (16 participants in each treatment group) or PCR and IHC (32 pembrolizumab, 40 SOC); therefore, considering the differences in the number of participants within each group, caution should be used when comparing across groups. Data provided for PCR detected (MSI-H) tumours are too limited to draw conclusions but given the reported data it could be that PCR-test with a 3 poly-A panel used in this study is not adequate in terms of specificity to detect MSI-H tumours. However, this is considered to be not clinically relevant in this specific indication due to the predominant use of IHC test in CRC.

The comparator arm consisted of an investigator's choice treatment (chosen before randomization) among 6 different polychemotherapy regimens, each acceptable as 1L regimen: 45% of the patients received mFOLFOX6+bevacizumab, followed by FOLFIRI+bevacizumab (25%), less than 20% of subjects received chemotherapy alone, and about 11% was treated with chemotherapy in combination with cetuximab. A consistent OS and PFS benefit of pembrolizumab vs each SOC (alone or grouped) was generally observed when analysed separately. Data for FOLFIRI/FOLFOX6 and cetuximab are too limited to draw any conclusion, nevertheless, contrary to worse OS, PFS was in favour of pembrolizumab. Further, due to the favourable safety profile of the pembrolizumab monotherapy, the use of several different regimen does not raise relevant concern of heterogeneity in the control arm.

The study had PFS per RECIST 1.1 by BICR and OS as dual primary endpoint, i.e. the study was considered to have met its primary objective if pembrolizumab is superior to SOC chemotherapies in either of the 2 primary endpoints. ORR was a secondary endpoint, and PFS2 and DOR among the exploratory endpoint. The use of central imaging review is endorsed in view of the open-label design.

A justification for the assumptions made for median PFS (10 months) and median OS (24 months) in the control arm, which the sample size calculation was based on, has not been found, although it seems

congruent with the available historical data of chemotherapy in 1L CRC setting. Overall, statistical methods appeared standard and not controversial.

The timing of the interim analyses was postponed several times. The MAH explained that the reason for postponing interim analysis 2 in amendment 5 by 8 months was motivated by the slow number of PFS events observed after interim analysis 1. The results for the timing defined in Amendment 4 however are consistent with the results of the final Amendment 5, which is reassuring.

While in the original protocol PFS was the solely primary endpoint, OS was upgraded from key secondary to (dual) primary endpoint with Amendment 3 on 20.11.2017, which occurred before enrolment closure (on 19.02.2018) and before IA1 (on 19.10.2018). The MAH stated that revisions occurred to allow for more mature PFS and OS data to account for a potential delayed separation in survival curves observed in immuno-oncology studies, indeed all the study referenced were published before Amendment 3 was released. The argumentation that the changes were implemented solely based on emerging data from other immunotherapy trials outside of KEYNOTE-177 can be therefore followed.

The MAH explained the procedure of IA1, which is acceptable. There seem to be no association between IA1 and the motivation of protocol amendment 5. PFS results are significant for both approaches of p-value boundaries, the expected and the observed event fraction.

Overall, the rate of protocol deviations was similar in both arms and no concern is raised over possible impact of protocol deviations on efficacy results.

Efficacy data and additional analyses

A total of 307 patients were randomized to pembrolizumab (n=153) vs SOC arm (n=154). Compared to the pembrolizumab arm, a higher number of patients did not receive the SOC treatment assigned at randomization (0 vs 11 patients) as well as discontinued SOC treatment for subject's or physician's decision (4 vs 23). In this regard, the MAH presented 2 worst-case scenarios for PFS and OS. 34 participants in the SOC arm who were not treated, or withdrawn by physician's decision, or withdrew by participant's choice follow the PFS/OS pattern in the pembrolizumab arm. The results show consistency with the primary PFS and OS analysis.

On the contrary, it is noted that, apparently unexpectedly, a higher number of patients in the pembrolizumab than in the control arm discontinued treatment due to AEs (22 vs 17). However, based on the safety data, this could be related to a longer duration of exposure (see clinical safety).

The MAH presented the results of the 2nd interim analysis (i.e. final PFS and interim OS analysis) having data cut-off date of 19-FEB-2020 (24 months after the last subject was randomized), with a median survival follow-up duration of about 28 months.

The baseline characteristics appeared mostly balanced between the two treatment arms, with the exception (differences ≥5% between arms) of: gender (male 46.4% vs 54.2%), ECOG (ECOG 0 49% vs 54.5%), hepatic or pulmonary metastases (56.2% vs 47.4%), mutation status (KRAS/NRAS mutations 21.6% vs 26.6%, BRAF V600E 22.2% vs 27.9%), in pembrolizumab vs SOC arm, respectively. It is noted that no stratification factors at randomization were used. It is reassuring that the results of the multivariate cox regression analyses adjusted for unbalanced baseline factors were similar to the overall study results (PFS HR=0.60, OS HR=0.77). BRAF/KRAS/NRAS mutations were mutually exclusive in almost all tested patients. Unfortunately, about 30% of subjects had unknown mutational status, as this was not mandatory for enrolment. Tumour burden was more commonly higher than the median in the pembrolizumab arm, which is not expected to have favoured the pembrolizumab arm.

Per protocol, tissue was not collected in KEYNOTE-177, and therefore, no data are available to permit assessment of PD-L1 expression and TMB scores. The MAH mentioned that expression of PD-L1 was not found to be significantly associated with survival in KEYNOTE-016 study, but the number of patients with PD-L1 data available in this phase II study was very limited (n=30). No data on smoking status have been collected.

Efficacy analyses were carried out in the ITT population. Pembrolizumab showed statistically significant and clinically meaningful improvement in **PFS** by BICR per RECIST 1.1 (final analysis) compared to SOC, with HR 0.60 (95%CI 0.45, 0.80), p=0.0002. Median PFS was 16.5 (95%CI 5.4, 32.4) vs 8.2 (95%CI 6.1, 10.2) months. PFS events occurred in 53.6% vs 73.5% of subjects in pembrolizumab vs SOC arm. The pembrolizumab PFS KM curve is slightly below/overlap the SOC one, but after month 6 the two curves demonstrate an increasingly pronounced separation (PFS rate at 12 months 55.3% vs 37.3%, PFS rate at 24 months 48.3% vs 18.6%). Censoring from month 22-24 preclude the interpretation of the tail of the curve. PFS sensitivity analyses were consistent with the primary analysis result. Overall, the PFS benefit of pembrolizumab over SOC can be considered clinically relevant.

On the contrary, **OS** (interim analysis) was not statistically significant, although a trend toward a survival advantage for pembrolizumab over SOC is noted: HR 0.77 (95%CI 0.54, 1.09), p=0.0694. Number of OS events were 36.6% vs 44.8% in pembrolizumab vs SOC arm, respectively, which is considered a reasonable maturity. Curves are however no more interpretable after 24 months due to high rate of censoring. Median OS was not reached in the pembrolizumab arm, vs 34.8 months (95%CI 26.3, NR) in the control arm, the latter being far higher compared to what originally expected with standard treatments (mOS 24 months). It is acknowledged that the high crossover rate to anti-PD(L)1 in the SOC arm (59%) could be implicated in this observation. Indeed, sensitivity analyses carried out to assess the impact of crossover on OS indicated possibly lower HRs compared to the primary OS analysis. However, no definitive conclusions can be drawn with respect to a possible effect on OS although pembrolizumab is not expected to be associated with a detrimental effect with respect to OS.

As repeatedly observed with anti-PD(L)1 vs chemotherapy, an initial crossing of KM overall survival curves up to month 8 is seen, after that point curves diverge (about 5-10% difference in favour of pembrolizumab arm). Hazard rates were greater in the pembrolizumab arm compared with the SOC arm for the first 4 months. Baseline characteristics of the 32 participants (19 in the pembrolizumab group and 13 in the SOC group) with early OS events within the first 4 months showed the largest difference between treatment groups included presence of hepatic or pulmonary metastases, age over 70 and high baseline CEA value, occurred in a higher proportion of participants in the pembrolizumab group. However, due to the limited number of patients, it is not possible to clearly define one or more characteristics as risk factors of early death with pembrolizumab. Text in the SmPC section 4.4 reporting that "in KEYNOTE-177, the hazard rates for overall survival events were greater for pembrolizumab compared with chemotherapy for the first 4 months of treatment, followed by a long-term survival benefit for pembrolizumab" has been added.

The MAH agreed to include interim OS analysis data in the SmPC and in the EPAR. Final OS analysis for KEYNOTE-177 will be submitted by the MAH (estimated Q3 2021) as Annex II condition to confirm interim OS data.

An advantage in **PFS2** further support that pembrolizumab is not expected to be associated with a detrimental effect with respect to subsequent therapies (HR 0.63, 95%CI 0.45, 0.88).

ORR was a key secondary endpoint, adjusted for multiplicity. Statistical significance was not reached, however. ORR was also in favour of pembrolizumab compared to the standard chemotherapy: 43.8% (95% CI: 35.8, 52.0) vs 33.1% (95% CI: 25.8, 41.1), including higher CR rate (11.1% versus 3.9%). On the contrary, pembrolizumab more rarely induced disease stabilization, and progressive disease as best response were more than doubled with pembrolizumab than with chemotherapy (29.4% vs 12.3%).

Withdrawal from study treatment was the main cause of the higher number of patients in the SOC compared to pembrolizumab arm not having the first radiological assessment.

By looking at the waterfall plot, it seems that the maximum target lesion change (both tumour increase and reduction) is more pronounced with pembrolizumab. Patients who responded to pembrolizumab have generally long duration of response (median DOR not reached in the pembrolizumab group vs 10.6 months in the SOC group), as also shown by a relevant proportion of patients who responded to pembrolizumab reaching DOR ≥12 months (85.1% vs 43.8%). As observed in other indications, pembrolizumab seems to induce prolonged and deep responses in patients who responded, but if patients did not respond the disease is rarely controlled and patient progress, which is also probably also linked to the early crossing of the KM OS/PFS curves.

Patients were allowed to undergo resection of primary tumour or metastases with curative intent if deemed eligible after responding to treatment. The possibility to be treated with curative intent after systemic treatment-induced response is considered clinically relevant as this can result in long term survival. The MAH clarified that a total of 13 patients underwent curative surgery in the SOC arm, vs 14 patients in the pembrolizumab arm. It is concluded that, despite a higher objective response rate and apparently deeper response achieved in the pembrolizumab arm compared to SOC, disappointingly the possibility to undergo curative surgery with pembrolizumab treatment did not seem to increase.

No significant deterioration in health status is observed with pembrolizumab, with a trend toward improvement in QoL and most of the functioning and symptoms score compared to SOC. Overall, PRO data are supporting the benefit of pembrolizumab over the chemotherapy regimens in KEYNOTE-177 study in terms of efficacy and safety. However, the open-label design of the study and the lack of multiplicity control does not allowt upholding formal superiority claims. PROs data have not been included in the SmPC.

Subgroup analyses showed overall consistent results with the exception of subgroups by metastatic sites and mutational status.

Based upon ad-hoc exploratory sub-group analyses, patients with hepatic and/or pulmonary metastases seem to achieve less benefit from pembrolizumab vs chemotherapy compared to a clearer advantage in patients with metastases other than hepatic and pulmonary. In particular, this seems to be observed in subjects with lung metastases: as the only site of metastases (15 vs 19, ca. 10% of the randomized patient population (PFS 1.02, OS 1.99), or with other sites (36 vs 34, ca. 23% of patients, PFS 1.13, OS 1.05, ORR 25% vs 41.2%). It is acknowledged that the concern regarding a reduced efficacy in patients with lung metastases is based on a limited dataset of only 34 patients and that conclusions based on this sample size are prone to uncertainties. In view of this, it can be considered acceptable that information on the uncertain benefit for patients with lung metastases are not to be included in the SmPC. Nevertheless, there is a common observation that patients with more advanced disease with high tumour burden may not have sufficient time to respond on immunotherapeutics (20% of the patients with lung metastases died in the first 4 month in KEYNOTE-177). The inclusion of OS KM curves in section 5.1 as well as text in section 4.4 of the SmPC (see above) are considered appropriate.

The benefit of pembrolizumab over SOC seems somewhat more limited in RAS mutant disease compared to wild type tumours. In the subgroup KRAS/NRAS mutant (n=74), no advantage of pembrolizumab over SOC was apparent in PFS (HR 1.19). For OS (HR 0.89) KM curves are overlapping until month 24 (after this point they seem to diverge in favour of pembrolizumab but there are too many censored patients), but no detriment is observed (HR 0.89), and ORR was also similar. Limitations in the interpretation of subgroup analyses are acknowledged, also related to small number of patients in some subgroups, and

the lack of information on mutational status in 30% of subjects. Further, a multivariate Cox regression analysis of PFS suggested interaction between treatment and RAS status.

Higher tumour burden may confer worse prognosis in line with historical data in mCRC. Benefit of pembrolizumab over chemotherapy was seen regardless of tumour burden but much more pronounced in smaller tumours. Patients with prior radiation therapy seem not to benefit from pembrolizumab monotherapy treatment, but number of patients was too low (11 vs 13) to draw conclusion. Pembrolizumab improved PFS and OS over SOC regardless having or not received prior neoadjuvant treatment.

Heterogeneity has been suggested in MSI-H/dMMR CRC based on MSI aetiology. A benefit of pembrolizumab over SOC is however seen also in the small subgroup of patients with Lynch syndrome.

A trend toward more limited efficacy of pembrolizumab compared to SOC is seen in older patients compared to younger ones (≤65 vs >65, ≤75 vs >75). For patients over 75 years of age (n=50), pembrolizumab and SOC seems to perform similarly in OS, PFS and ORR. The pembrolizumab safety profile could however represent an advantage over SOC in this aged population (lower incidence of drug-related AEs, G3-5 AEs, drug-related G3-5 AEs, drug-related SAE and discontinuation due to drug-related SAE is reported in pembrolizumab compared to SOC arm in patients ≥75, see safety section). The MAH has reflected in the SmPC section 4.2 the fact that that a limited number of patients >75 have been included in KN-177 study.

2.4.4. Conclusions on the clinical efficacy

Pembrolizumab demonstrated a statistically significant and clinically meaningful improvement in PFS compared to SOC chemotherapies as first line treatment for patients with metastatic colorectal cancer MSI-H/dMMR in KEYNOTE-177 study. During the procedure, the MAH updated the indication to include "metastatic" patients only to reflect the studied population. The benefit of pembrolizumab was supported by PFS sensitivity analyses. Although not statistically significant, a trend toward OS advantage in pembrolizumab treated patients, analysed at an interim analysis having a reasonable maturity level, is considered supportive of the PFS results, notwithstanding the crossing of the OS KM curves, as seen in several studies of anti-PD(L)1 antibodies. An advantage in PFS2 further support the data. Increased ORR is seen, although not statistically significant, but CR rate is higher and responses appear durable.

The MAH agreed to submit the final OS analysis for KEYNOTE-177 as part of the final CSR when available (estimated Q3 2021) as an Annex II condition in the Product Information in order to confirm interim OS data.

2.5. Clinical safety

Introduction

Pembrolizumab monotherapy safety data presented in the current submission are from the randomized, controlled, open-label Phase 3 study KEYNOTE-177, which is the pivotal study supporting the intended use of pembrolizumab for the first-line treatment of patients with unresectable or metastatic MSI-H or dMMR CRC. Safety analyses are presented by the treatment group (pembrolizumab vs investigator's choice of SOC chemotherapy, consisting in either mFOLFOX6 or FOLFIRI or respective combinations with bevacizumab or cetuximab) in participant who received treatment (ASaT population, n=153 in pembrolizumab and n=143 in SOC arm,) up to the data cutoff date of 19-FEB-2020. Adverse events were graded according to the NCI CTCAE, version 4.03. AEs were coded using MedDRA Version 22.1.

In addition, the new pembrolizumab safety data from KEYNOTE-177 have been compared to the established safety profile for pembrolizumab monotherapy from the Reference Safety Dataset. Thus, the following 4 datasets are presented side by side:

1. KEYNOTE-177 Dataset - Pembrolizumab (N=153): Participants with unresectable or metastatic MSI-H/dMMR CRC, who received pembrolizumab in KEYNOTE-177.
2. KEYNOTE-177 Dataset - SOC (N=143): Participants with unresectable or metastatic MSI-H/dMMR CRC who received SOC therapy in KEYNOTE-177.
3. Pembrolizumab Monotherapy Reference Safety Dataset (N = 5884): includes participants who received pembrolizumab in the following populations and studies: melanoma (n=2076) in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006 and KEYNOTE-054; NSCLC (n=2022) in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, KEYNOTE-010, KEYNOTE-024 and KEYNOTE-42; HNSCC (n=909) in KEYNOTE-012, KEYNOTE-040, KEYNOTE-048 and KEYNOTE-055; HL (n=241) in KEYNOTE-013 and KEYNOTE-087; Bladder (n=636) in KEYNOTE-045 and KEYNOTE-052. This dataset represents the established safety profile for pembrolizumab.
4. Cumulative Running Pembrolizumab Monotherapy Safety Dataset (N=8098): Cumulative pembrolizumab safety data from all studies reported to a regulatory authority for which a submission occurred at least 6 weeks prior to the database lock date for KEYNOTE-177. Participants from KEYNOTE-177 (pembrolizumab arm), the RSD, and participants treated with pembrolizumab in KEYNOTE-012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer), KEYNOTE-013 Cohort 3 (Hodgkin Lymphoma), KEYNOTE-013 Cohort 4A (PMBCL), KEYNOTE-017, KEYNOTE-024, KEYNOTE-028 Cohort A4 (Esophageal Cancer), Cohort B4 (Cervical Cancer) and Cohort C1 (SCLC), KEYNOTE-040, KEYNOTE-042, KEYNOTE-045, KEYNOTE-048, KEYNOTE-052, KEYNOTE-054, KEYNOTE-055, KEYNOTE-057, KEYNOTE-059 Cohort 1 (Gastric Cancer), KEYNOTE-062, KEYNOTE-087, KEYNOTE-158 Cohort E (Cervical Cancer) and Cohort G (SCLC), KEYNOTE-158 with TMB-H, KEYNOTE-164 Cohort A (CRC), KEYNOTE-170, KEYNOTE-180, KEYNOTE-181, KEYNOTE-224, and KEYNOTE-427.

Statistical Methods for Key Safety Analyses: The analysis of safety results followed a tiered approach. "Tier 1" safety endpoints were subject to inferential testing for statistical significance with p-values and 95% CI provided for between-group comparisons. Other safety parameters were considered Tier 2 or Tier 3. Tier 2 parameters were assessed via point estimates with 95% CI for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. There are no Tier 1 events in KEYNOTE-177 study. The between-treatment difference were analyzed using the Miettinen and Nurminen method.

Patient exposure

Table: Summary of Drug Exposure (ASaT Population)

	KN177 Data for Pembrolizumab[††] (N=153)	KN177 Data for SOC[¶¶] (N=143)	Reference Safety Dataset for Pembrolizumab[‡‡] (N=5884)	Cumulative Running Safety Dataset for Pembrolizumab[§§] (N=8098)
Duration on therapy (month)				
Mean	13.3	8.3	7.1	7.0
Median	11.1	5.7	4.9	4.2
SD	10.25	8.01	6.55	7.10
Range	0.0 to 30.6	0.1 to 39.6	0.0 to 32.5	0.0 to 53.4
Number of Administration				

Mean	19.0	68.7	11.4	11.2
Median	16.0	50.0	8.0	7.0
SD	14.08	62.09	9.87	10.52
Range	1.0 to 35.0	4.0 to 296.0	1.0 to 59.0	1.0 to 72.0

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

Duration of Exposure is calculated as last dose date - first dose date + 1.

[††] Includes all subjects who received at least one dose of pembrolizumab in KN177.

[¶¶] Includes all subjects who received at least one dose of SOC in KN177.

[‡‡] 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 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN054, 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 (cHL) and KN013 Cohort 4A (PMBCL); KN024; KN028 Cohort A4 (Esophageal), Cohort B4 (Cervical) and Cohort C1 (SCLC); KN040; KN042; KN045; KN048; KN052; KN054; KN055; KN057; KN059 Cohort 1; KN062; KN087; KN158 Cohort E (Cervical), Cohort G (SCLC) and TMB-H; KN164 Cohort A; KN170; KN177; KN180; KN181; KN224; KN427; P017.

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

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

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

Database cutoff date for Gastric (KN012-Cohort D: 26APR2016, KN059-Cohort 1: 08AUG2018, KN062: 26MAR2019)

Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 25SEP2016)

Database cutoff date for Bladder (KN012-Cohort C: 01SEP2015, KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for CRC (KN164-Cohort A: 03AUG2016, KN177: 19FEB2020)

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

Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158-Cohort E: 27JUN2019)

Database cutoff date for HCC (KN224: 15MAY2018)

Database Cutoff Date for Merkel Cell (P017: 06FEB2018)

Database cutoff date for Esophageal (KN028: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)

Database cutoff date for RCC (KN427: 07SEP2018)

Database cutoff date for TMB-H (KN158: 27JUN2019)

Database cutoff date for SCLC (KN028-Cohort C1: 31JUL2018, KN158-Cohort G: 27JUN2019)

Database cutoff date for NMIBC (KN057: 24MAY2019)

Table: Drug Exposure by Duration (ASaT Population)

	KN177 Data for Pembrolizumab[††] (N=153)			KN177 Data for SOC[¶¶] (N=143)			Reference Safety Dataset for Pembrolizumab[‡‡] (N=5884)			Cumulative Running Safety Dataset for Pembrolizumab[§§] (N=8098)		
	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years
Duration of exposure												
>0 m	153	(100.0)	(169.0)	143	(100.0)	(98.6)	5,884	(100.0)	(3,465.2)	8,098	(100.0)	(4,622.0)
>=1 m	134	(87.6)	(168.5)	133	(93.0)	(98.3)	5,033	(85.5)	(3,437.0)	6,808	(84.1)	(4,577.7)
>=3 m	112	(73.2)	(165.0)	104	(72.7)	(93.4)	3,620	(61.5)	(3,201.8)	4,768	(58.9)	(4,241.1)
>=6 m	96	(62.7)	(158.7)	65	(45.5)	(78.8)	2,610	(44.4)	(2,835.0)	3,332	(41.1)	(3,722.4)
>=12 m	73	(47.7)	(141.7)	32	(22.4)	(54.7)	1,196	(20.3)	(1,760.2)	1,595	(19.7)	(2,418.7)

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

Duration of Exposure is calculated as last dose date - first dose date + 1.

Safety populations: distribution of gender, race, and ECOG performance status were generally similar across the KEYNOTE-177 pembrolizumab safety dataset and the SOC Safety Dataset. Compared with the RSD, the KEYNOTE-177 pembrolizumab safety dataset had a lower proportion of male participants and a greater proportion of EU participants.

Adverse events

Table: Adverse Event Summary (ASaT Population)

	KN177 Data for Pembrolizumab[††]		KN177 Data for SOC[¶¶]		Reference Safety Dataset for Pembrolizumab[‡‡]		Cumulative Running Safety Dataset for Pembrolizumab[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	153		143		5,884		8,098	
with one or more adverse events	149	(97.4)	142	(99.3)	5,687	(96.7)	7,812	(96.5)
with no adverse event	4	(2.6)	1	(0.7)	197	(3.3)	286	(3.5)
with drug-related[†] adverse events	122	(79.7)	141	(98.6)	4,123	(70.1)	5,581	(68.9)
with toxicity grade 3-5 adverse events	86	(56.2)	111	(77.6)	2,813	(47.8)	3,941	(48.7)
with toxicity grade 3-5 drug-related adverse events	33	(21.6)	94	(65.7)	909	(15.4)	1,297	(16.0)
with serious adverse events	62	(40.5)	75	(52.4)	2,252	(38.3)	3,094	(38.2)
with serious drug-related adverse events	25	(16.3)	41	(28.7)	650	(11.0)	912	(11.3)
who died	6	(3.9)	7	(4.9)	311	(5.3)	446	(5.5)
who died due to a drug-related adverse event	0	(0.0)	1	(0.7)	39	(0.7)	60	(0.7)
discontinued drug due to an adverse event	21	(13.7)	17	(11.9)	783	(13.3)	1,041	(12.9)
discontinued drug due to a drug-related adverse event	15	(9.8)	8	(5.6)	405	(6.9)	542	(6.7)
discontinued drug due to a serious adverse event	12	(7.8)	13	(9.1)	570	(9.7)	756	(9.3)
discontinued drug due to a serious drug-related adverse event	7	(4.6)	5	(3.5)	244	(4.1)	327	(4.0)

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

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.

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

	Event Count and Rate (Events/100 person-years)[†]			
	KN177 Data for Pembrolizumab[††]	KN177 Data for SOC[¶¶]	Reference Safety Dataset for Pembrolizumab[‡‡]	Cumulative Running Safety Dataset for Pembrolizumab[§§]
Number of subjects exposed	153	143	5884	8098
Total exposure[‡] in person-years	181.34	109.95	3894.24	5224.94
Total events (rate)				
adverse events	2298 (1267.26)	3308 (3008.65)	60934 (1564.72)	81335 (1556.67)
drug-related[§] adverse events	671 (370.03)	2021 (1838.11)	19159 (491.98)	24615 (471.11)
toxicity grade 3-5 adverse events	227 (125.18)	380 (345.61)	6129 (157.39)	8765 (167.75)
toxicity grade 3-5 drug-related adverse events	50 (27.57)	219 (199.18)	1370 (35.18)	1959 (37.49)
serious adverse events	115 (63.42)	148 (134.61)	4071 (104.54)	5523 (105.70)
serious drug-related adverse events	30 (16.54)	55 (50.02)	911 (23.39)	1261 (24.13)
adverse events leading to death	6 (3.31)	7 (6.37)	318 (8.17)	455 (8.71)
drug-related adverse events leading to death	0 (0.00)	1 (0.91)	39 (1.00)	60 (1.15)
adverse events resulting in drug discontinuation	21 (11.58)	18 (16.37)	855 (21.96)	1122 (21.47)
drug-related adverse events resulting in drug discontinuation	15 (8.27)	9 (8.19)	442 (11.35)	583 (11.16)
serious adverse events resulting in drug discontinuation	12 (6.62)	13 (11.82)	606 (15.56)	796 (15.23)
serious drug-related adverse events resulting in drug discontinuation	7 (3.86)	5 (4.55)	257 (6.60)	343 (6.56)

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

For subjects who received second course treatment, adverse events which occurred in second course phase 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.

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

Table: Exposure-Adjusted AE by Observation Period (Including Multiple Occurrences of Events) (Incidence ≥ 10% in One or More Treatment Groups) (Excerpt)

Observation period of drug exposure	Event Count and Rate (Events/100 person-months)[†]							
	Pembrolizumab				SOC			
	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[‡]	153	122	103	77	143	114	80	36
Total exposure[§] person-months	419.19	333.15	527.28	896.40	407.25	288.80	322.08	301.26
Total events (rate)	796 (189.9)	366 (109.9)	525 (99.6)	611 (68.2)	1704 (418.4)	687 (237.9)	557 (172.9)	360 (119.5)

Adverse events (all grades)

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

	KN177 Data for Pembrolizumab[††]		KN177 Data for SOC[¶¶]		Reference Safety Dataset for Pembrolizumab[‡‡]		Cumulative Running Safety Dataset for Pembrolizumab[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	153		143		5,884		8,098	
with one or more adverse events	149	(97.4)	142	(99.3)	5,687	(96.7)	7,812	(96.5)
with no adverse events	4	(2.6)	1	(0.7)	197	(3.3)	286	(3.5)
Diarrhoea	68	(44.4)	89	(62.2)	1,193	(20.3)	1,628	(20.1)
Fatigue	58	(37.9)	72	(50.3)	1,878	(31.9)	2,491	(30.8)
Nausea	47	(30.7)	85	(59.4)	1,203	(20.4)	1,653	(20.4)
Abdominal pain	37	(24.2)	42	(29.4)	477	(8.1)	786	(9.7)
Decreased appetite	36	(23.5)	58	(40.6)	1,132	(19.2)	1,587	(19.6)
Vomiting	33	(21.6)	53	(37.1)	726	(12.3)	1,030	(12.7)
Arthralgia	28	(18.3)	7	(4.9)	846	(14.4)	1,083	(13.4)
Pyrexia	28	(18.3)	20	(14.0)	734	(12.5)	1,008	(12.4)
Anaemia	27	(17.6)	32	(22.4)	834	(14.2)	1,231	(15.2)
Back pain	26	(17.0)	24	(16.8)	654	(11.1)	895	(11.1)
Constipation	26	(17.0)	45	(31.5)	992	(16.9)	1,373	(17.0)
Cough	26	(17.0)	23	(16.1)	1,138	(19.3)	1,484	(18.3)
Pruritus	25	(16.3)	12	(8.4)	1,053	(17.9)	1,371	(16.9)
Aspartate aminotransferase increased	24	(15.7)	12	(8.4)	380	(6.5)	604	(7.5)
Dizziness	24	(15.7)	27	(18.9)	428	(7.3)	559	(6.9)
Alanine aminotransferase increased	22	(14.4)	16	(11.2)	388	(6.6)	567	(7.0)
Blood alkaline phosphatase increased	22	(14.4)	6	(4.2)	238	(4.0)	385	(4.8)
Dyspnoea	21	(13.7)	15	(10.5)	984	(16.7)	1,232	(15.2)
Headache	21	(13.7)	22	(15.4)	706	(12.0)	871	(10.8)
Abdominal pain upper	20	(13.1)	11	(7.7)	211	(3.6)	331	(4.1)
Nasopharyngitis	20	(13.1)	10	(7.0)	344	(5.8)	459	(5.7)
Rash	20	(13.1)	16	(11.2)	896	(15.2)	1,116	(13.8)
Asthenia	19	(12.4)	31	(21.7)	663	(11.3)	922	(11.4)
Dry skin	19	(12.4)	13	(9.1)	302	(5.1)	403	(5.0)
Hypertension	19	(12.4)	16	(11.2)	294	(5.0)	393	(4.9)
Hypothyroidism	19	(12.4)	3	(2.1)	647	(11.0)	860	(10.6)
Oedema peripheral	18	(11.8)	12	(8.4)	510	(8.7)	716	(8.8)
Pain in extremity	18	(11.8)	11	(7.7)	389	(6.6)	489	(6.0)
Dry mouth	17	(11.1)	9	(6.3)	283	(4.8)	386	(4.8)
Upper respiratory tract infection	16	(10.5)	8	(5.6)	371	(6.3)	490	(6.1)
Urinary tract infection	14	(9.2)	16	(11.2)	382	(6.5)	515	(6.4)
Hypokalaemia	13	(8.5)	24	(16.8)	270	(4.6)	387	(4.8)
Alopecia	11	(7.2)	29	(20.3)	85	(1.4)	114	(1.4)
Stomatitis	10	(6.5)	43	(30.1)	144	(2.4)	204	(2.5)
Dyspepsia	9	(5.9)	16	(11.2)	148	(2.5)	227	(2.8)
Mucosal inflammation	7	(4.6)	27	(18.9)	92	(1.6)	121	(1.5)
Weight decreased	7	(4.6)	17	(11.9)	560	(9.5)	747	(9.2)
Neutropenia	3	(2.0)	30	(21.0)	49	(0.8)	79	(1.0)
Peripheral sensory neuropathy	3	(2.0)	31	(21.7)	62	(1.1)	87	(1.1)

Epistaxis	2	(1.3)	23	(16.1)	82	(1.4)	99	(1.2)
Neutrophil count decreased	2	(1.3)	33	(23.1)	37	(0.6)	55	(0.7)
Neuropathy peripheral	1	(0.7)	27	(18.9)	114	(1.9)	149	(1.8)
Palmar-plantar erythrodysaesthesia syndrome	1	(0.7)	25	(17.5)	19	(0.3)	24	(0.3)
White blood cell count decreased	1	(0.7)	17	(11.9)	56	(1.0)	81	(1.0)

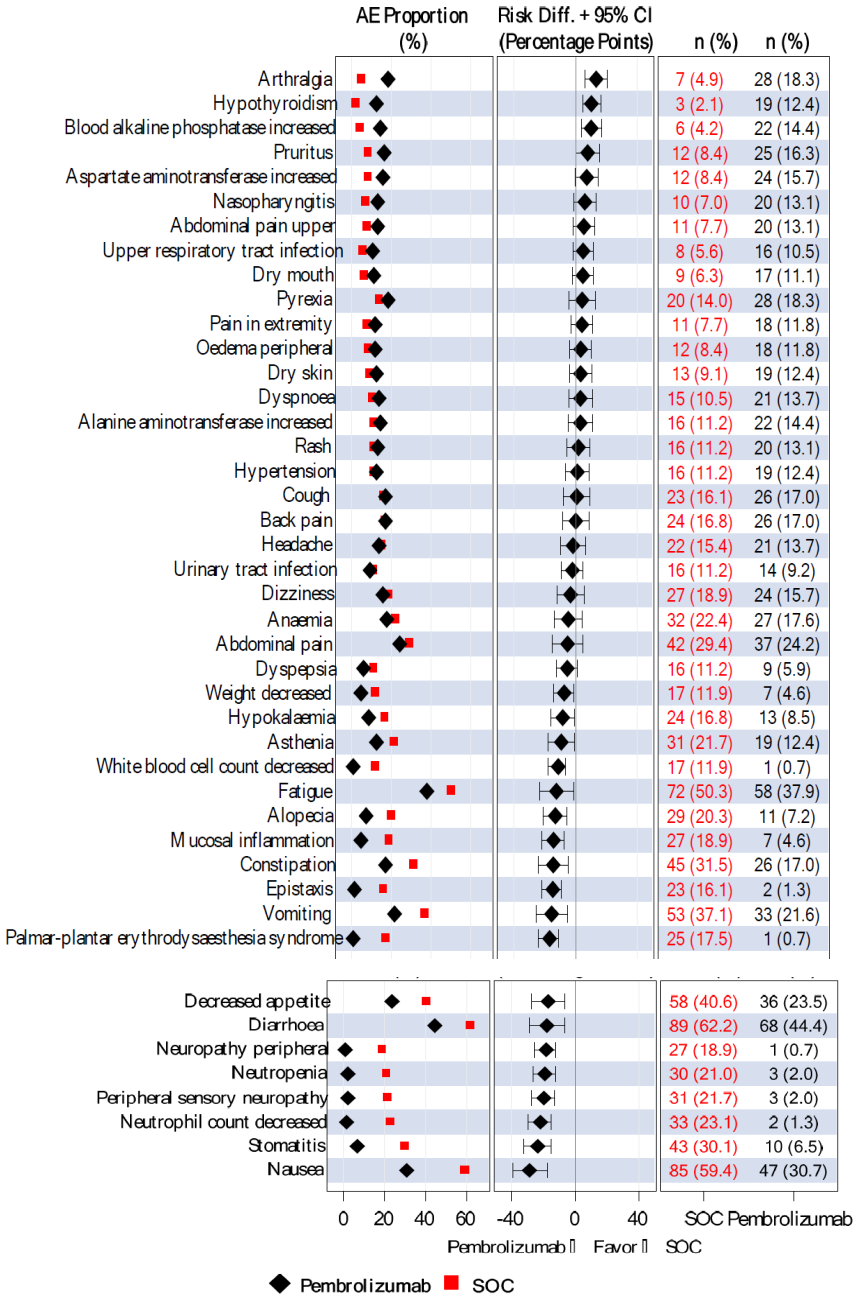
Every subject is counted a single time for each applicable row and column.

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 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.

Figure: Between-Treatment Comparisons in AEs (Incidence >= 10% in One or More Treatment Groups)



Adverse events (grade 3-5)

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

	KN177 Data for Pembrolizumab[††]		KN177 Data for SOC[¶¶]		Reference Safety Dataset for Pembrolizumab[‡‡]		Cumulative Running Safety Dataset for Pembrolizumab[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	153		143		5,884		8,098	
with one or more adverse events	86	(56.2)	111	(77.6)	2,813	(47.8)	3,941	(48.7)
with no adverse events	67	(43.8)	32	(22.4)	3,071	(52.2)	4,157	(51.3)
Hypertension	11	(7.2)	7	(4.9)	101	(1.7)	132	(1.6)
Diarrhoea	9	(5.9)	16	(11.2)	78	(1.3)	112	(1.4)
Abdominal pain	8	(5.2)	8	(5.6)	42	(0.7)	87	(1.1)
Anaemia	8	(5.2)	15	(10.5)	234	(4.0)	376	(4.6)
Hyponatraemia	8	(5.2)	4	(2.8)	153	(2.6)	221	(2.7)
Gamma-glutamyltransferase increased	7	(4.6)	1	(0.7)	35	(0.6)	62	(0.8)
Fatigue	6	(3.9)	13	(9.1)	144	(2.4)	199	(2.5)
Pneumonia	5	(3.3)	3	(2.1)	238	(4.0)	314	(3.9)
Alanine aminotransferase increased	4	(2.6)	3	(2.1)	60	(1.0)	99	(1.2)
Aspartate aminotransferase increased	4	(2.6)	3	(2.1)	65	(1.1)	126	(1.6)
Blood alkaline phosphatase increased	4	(2.6)	2	(1.4)	48	(0.8)	86	(1.1)
Nausea	4	(2.6)	6	(4.2)	50	(0.8)	72	(0.9)
Asthenia	3	(2.0)	6	(4.2)	58	(1.0)	100	(1.2)
Colitis	3	(2.0)	0	(0.0)	60	(1.0)	85	(1.0)
Hyperglycaemia	3	(2.0)	1	(0.7)	63	(1.1)	97	(1.2)
Infection	3	(2.0)	0	(0.0)	10	(0.2)	15	(0.2)
Pulmonary embolism	3	(2.0)	5	(3.5)	91	(1.5)	124	(1.5)
Syncope	3	(2.0)	0	(0.0)	34	(0.6)	49	(0.6)
Abdominal pain upper	2	(1.3)	1	(0.7)	9	(0.2)	20	(0.2)
Acute kidney injury	2	(1.3)	2	(1.4)	51	(0.9)	74	(0.9)
Adrenal insufficiency	2	(1.3)	0	(0.0)	18	(0.3)	25	(0.3)
Autoimmune colitis	2	(1.3)	0	(0.0)	1	(0.0)	3	(0.0)
Back pain	2	(1.3)	1	(0.7)	63	(1.1)	90	(1.1)
Dehydration	2	(1.3)	5	(3.5)	62	(1.1)	93	(1.1)
Delirium	2	(1.3)	0	(0.0)	7	(0.1)	16	(0.2)
Hepatitis	2	(1.3)	0	(0.0)	17	(0.3)	26	(0.3)
Hypokalaemia	2	(1.3)	9	(6.3)	58	(1.0)	83	(1.0)
Intestinal obstruction	2	(1.3)	2	(1.4)	12	(0.2)	25	(0.3)
Psoriasis	2	(1.3)	0	(0.0)	4	(0.1)	6	(0.1)
Small intestinal obstruction	2	(1.3)	5	(3.5)	9	(0.2)	19	(0.2)
Subileus	2	(1.3)	0	(0.0)	0	(0.0)	2	(0.0)
Vomiting	2	(1.3)	7	(4.9)	42	(0.7)	68	(0.8)
Weight increased	2	(1.3)	0	(0.0)	6	(0.1)	13	(0.2)
Deep vein thrombosis	1	(0.7)	2	(1.4)	16	(0.3)	26	(0.3)
Dyspnoea	1	(0.7)	0	(0.0)	133	(2.3)	171	(2.1)
Febrile neutropenia	1	(0.7)	7	(4.9)	7	(0.1)	11	(0.1)
Hypophosphataemia	1	(0.7)	2	(1.4)	39	(0.7)	59	(0.7)
Ileus	1	(0.7)	3	(2.1)	9	(0.2)	19	(0.2)
Influenza	1	(0.7)	2	(1.4)	7	(0.1)	10	(0.1)
Large intestinal obstruction	1	(0.7)	2	(1.4)	3	(0.1)	4	(0.0)
Pleural effusion	1	(0.7)	0	(0.0)	68	(1.2)	95	(1.2)
Urinary tract infection	1	(0.7)	4	(2.8)	73	(1.2)	98	(1.2)
Blood creatinine increased	0	(0.0)	2	(1.4)	11	(0.2)	23	(0.3)
Cholangitis	0	(0.0)	2	(1.4)	1	(0.0)	4	(0.0)
Decreased appetite	0	(0.0)	7	(4.9)	74	(1.3)	107	(1.3)
Device related infection	0	(0.0)	2	(1.4)	8	(0.1)	10	(0.1)
Embolism	0	(0.0)	7	(4.9)	14	(0.2)	22	(0.3)
Intestinal perforation	0	(0.0)	2	(1.4)	3	(0.1)	3	(0.0)
Lymphocyte count decreased	0	(0.0)	2	(1.4)	30	(0.5)	53	(0.7)
Neurotoxicity	0	(0.0)	3	(2.1)	0	(0.0)	0	(0.0)
Neutropenia	0	(0.0)	22	(15.4)	15	(0.3)	28	(0.3)

Neutrophil count decreased	0	(0.0)	24	(16.8)	8	(0.1)	17	(0.2)
Oedema peripheral	0	(0.0)	2	(1.4)	19	(0.3)	26	(0.3)
Peripheral sensory neuropathy	0	(0.0)	3	(2.1)	1	(0.0)	2	(0.0)
Pneumonitis	0	(0.0)	0	(0.0)	82	(1.4)	97	(1.2)
Proteinuria	0	(0.0)	2	(1.4)	1	(0.0)	3	(0.0)
Skin ulcer	0	(0.0)	2	(1.4)	3	(0.1)	3	(0.0)
Stomatitis	0	(0.0)	6	(4.2)	9	(0.2)	9	(0.1)
Urosepsis	0	(0.0)	2	(1.4)	22	(0.4)	25	(0.3)
White blood cell count decreased	0	(0.0)	6	(4.2)	4	(0.1)	5	(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.

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.

Drug-related adverse events (all grades)

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

	KN177 Data for Pembrolizumab[††]		KN177 Data for SOC[¶¶]		Reference Safety Dataset for Pembrolizumab[‡‡]		Cumulative Running Safety Dataset for Pembrolizumab[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	153		143		5,884		8,098	
with one or more adverse events	122	(79.7)	141	(98.6)	4,123	(70.1)	5,581	(68.9)
with no adverse events	31	(20.3)	2	(1.4)	1,761	(29.9)	2,517	(31.1)
Diarrhoea	38	(24.8)	75	(52.4)	628	(10.7)	832	(10.3)
Fatigue	32	(20.9)	63	(44.1)	1,166	(19.8)	1,503	(18.6)
Pruritus	21	(13.7)	7	(4.9)	831	(14.1)	1,063	(13.1)
Nausea	19	(12.4)	79	(55.2)	532	(9.0)	672	(8.3)
Aspartate aminotransferase increased	17	(11.1)	7	(4.9)	217	(3.7)	337	(4.2)
Rash	17	(11.1)	11	(7.7)	669	(11.4)	829	(10.2)
Arthralgia	16	(10.5)	2	(1.4)	434	(7.4)	567	(7.0)
Hypothyroidism	16	(10.5)	0	(0.0)	561	(9.5)	748	(9.2)
Alanine aminotransferase increased	15	(9.8)	10	(7.0)	232	(3.9)	333	(4.1)
Blood alkaline phosphatase increased	12	(7.8)	3	(2.1)	84	(1.4)	130	(1.6)
Decreased appetite	12	(7.8)	49	(34.3)	461	(7.8)	604	(7.5)
Asthenia	11	(7.2)	25	(17.5)	363	(6.2)	483	(6.0)
Dry mouth	11	(7.2)	6	(4.2)	142	(2.4)	182	(2.2)
Pyrexia	11	(7.2)	7	(4.9)	256	(4.4)	342	(4.2)
Anaemia	9	(5.9)	17	(11.9)	202	(3.4)	278	(3.4)
Colitis	8	(5.2)	0	(0.0)	84	(1.4)	123	(1.5)
Stomatitis	8	(5.2)	43	(30.1)	71	(1.2)	103	(1.3)
Dry skin	7	(4.6)	10	(7.0)	174	(3.0)	232	(2.9)
Abdominal pain	6	(3.9)	10	(7.0)	113	(1.9)	156	(1.9)
Alopecia	5	(3.3)	28	(19.6)	44	(0.7)	61	(0.8)
Vomiting	5	(3.3)	40	(28.0)	196	(3.3)	259	(3.2)
Dizziness	4	(2.6)	15	(10.5)	83	(1.4)	102	(1.3)
Mucosal inflammation	4	(2.6)	25	(17.5)	48	(0.8)	64	(0.8)
Hypokalaemia	3	(2.0)	8	(5.6)	36	(0.6)	45	(0.6)
Weight decreased	3	(2.0)	8	(5.6)	138	(2.3)	164	(2.0)
Constipation	2	(1.3)	10	(7.0)	156	(2.7)	201	(2.5)
Dysgeusia	2	(1.3)	13	(9.1)	60	(1.0)	80	(1.0)
Platelet count decreased	2	(1.3)	9	(6.3)	32	(0.5)	47	(0.6)
Proteinuria	2	(1.3)	10	(7.0)	14	(0.2)	26	(0.3)
Hypertension	1	(0.7)	9	(6.3)	32	(0.5)	45	(0.6)
Neuropathy peripheral	1	(0.7)	25	(17.5)	40	(0.7)	53	(0.7)
Neutrophil count decreased	1	(0.7)	33	(23.1)	26	(0.4)	34	(0.4)
Paronychia	1	(0.7)	8	(5.6)	2	(0.0)	3	(0.0)

White blood cell count decreased	1	(0.7)	17	(11.9)	28	(0.5)	38	(0.5)
Epistaxis	0	(0.0)	20	(14.0)	6	(0.1)	8	(0.1)
Neutropenia	0	(0.0)	30	(21.0)	30	(0.5)	49	(0.6)
Palmar-plantar erythrodysaesthesia syndrome	0	(0.0)	25	(17.5)	15	(0.3)	18	(0.2)
Peripheral sensory neuropathy	0	(0.0)	29	(20.3)	28	(0.5)	36	(0.4)
Temperature intolerance	0	(0.0)	8	(5.6)	4	(0.1)	5	(0.1)

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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.

Drug-related adverse events (grade 3-5)

Table: 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)

	KN177 Data for Pembrolizumab[††]		KN177 Data for SOC[¶¶]		Reference Safety Dataset for Pembrolizumab[‡‡]		Cumulative Running Safety Dataset for Pembrolizumab[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	153		143		5,884		8,098	
with one or more adverse events	33	(21.6)	94	(65.7)	909	(15.4)	1,297	(16.0)
with no adverse events	120	(78.4)	49	(34.3)	4,975	(84.6)	6,801	(84.0)
Alanine aminotransferase increased	3	(2.0)	1	(0.7)	34	(0.6)	54	(0.7)
Colitis	3	(2.0)	0	(0.0)	53	(0.9)	75	(0.9)
Diarrhoea	3	(2.0)	14	(9.8)	55	(0.9)	75	(0.9)
Fatigue	3	(2.0)	13	(9.1)	63	(1.1)	88	(1.1)
Anaemia	2	(1.3)	7	(4.9)	29	(0.5)	50	(0.6)
Aspartate aminotransferase increased	2	(1.3)	1	(0.7)	35	(0.6)	60	(0.7)
Autoimmune colitis	2	(1.3)	0	(0.0)	1	(0.0)	3	(0.0)
Gamma-glutamyltransferase increased	2	(1.3)	0	(0.0)	15	(0.3)	21	(0.3)
Hepatitis	2	(1.3)	0	(0.0)	14	(0.2)	22	(0.3)
Hyponatraemia	2	(1.3)	1	(0.7)	29	(0.5)	45	(0.6)
Psoriasis	2	(1.3)	0	(0.0)	4	(0.1)	6	(0.1)
Acute kidney injury	1	(0.7)	2	(1.4)	8	(0.1)	14	(0.2)
Hypertension	1	(0.7)	6	(4.2)	10	(0.2)	13	(0.2)
Hypokalaemia	1	(0.7)	4	(2.8)	10	(0.2)	11	(0.1)
Asthenia	0	(0.0)	5	(3.5)	22	(0.4)	35	(0.4)
Decreased appetite	0	(0.0)	3	(2.1)	21	(0.4)	28	(0.3)
Dehydration	0	(0.0)	2	(1.4)	8	(0.1)	14	(0.2)
Febrile neutropenia	0	(0.0)	6	(4.2)	0	(0.0)	1	(0.0)
Intestinal perforation	0	(0.0)	2	(1.4)	0	(0.0)	0	(0.0)
Lymphocyte count decreased	0	(0.0)	2	(1.4)	7	(0.1)	14	(0.2)
Nausea	0	(0.0)	3	(2.1)	13	(0.2)	16	(0.2)
Neurotoxicity	0	(0.0)	3	(2.1)	0	(0.0)	0	(0.0)
Neutropenia	0	(0.0)	22	(15.4)	9	(0.2)	20	(0.2)
Neutrophil count decreased	0	(0.0)	24	(16.8)	4	(0.1)	8	(0.1)
Peripheral sensory neuropathy	0	(0.0)	3	(2.1)	1	(0.0)	2	(0.0)
Pneumonitis	0	(0.0)	0	(0.0)	77	(1.3)	91	(1.1)
Proteinuria	0	(0.0)	2	(1.4)	0	(0.0)	1	(0.0)
Pulmonary embolism	0	(0.0)	2	(1.4)	9	(0.2)	13	(0.2)
Stomatitis	0	(0.0)	6	(4.2)	5	(0.1)	5	(0.1)
Vomiting	0	(0.0)	5	(3.5)	10	(0.2)	11	(0.1)
White blood cell count decreased	0	(0.0)	6	(4.2)	1	(0.0)	1	(0.0)

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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.

Adverse Drug Reactions (ADR) in section 4.8 of the SmPC

Table: Adverse Reactions in Patients Treated with Pembrolizumab

		Monotherapy (N=6185)	
		All AEs % (n)	Gr 3-5 AEs n
Infections and infestations			
Common	Pneumonia	7.3% (451)	255
Blood and lymphatic system disorders			
Very common	Anaemia	14.1% (872)	247
Common	Thrombocytopenia	1.6% (100)	21
Common	Neutropenia	1.0% (62)	19
Common	Lymphopenia	1.2% (72)	17
Uncommon	Leukopenia	0.7% (46)	7
Uncommon	Eosinophilia	0.6% (40)	0
Rare	Immune thrombocytopenia	0.097% (6)	5
Rare	Haemolytic anaemia	0.02% (1)	1
Rare	Haemophagocytic lymphohistiocytosis[#]	(0)	0
Rare	Pure red cell aplasia[#]	(0)	0
Immune system disorders			
Common	Infusion Reactions[a]	2.4% (149)	14
Uncommon	Sarcoidosis	0.2% (10)	0
Not known	solid organ transplant rejection[*]	Not Calculated	
Endocrine disorders			
Very common	hypothyroidism[b]	11.3% (699)	7
Common	Hyperthyroidism	4.2% (261)	7
Common	Thyroiditis[c]	1.0% (62)	1
Uncommon	Adrenal Insufficiency[d]	0.8% (52)	25
Uncommon	Hypophysitis[e]	0.6% (38)	20
Metabolism and nutrition disorders			
Very common	Decreased appetite	19.1% (1181)	74
Common	Hyponatraemia	5.8% (356)	161
Common	Hypokalaemia	4.6% (286)	61
Common	Hypocalcaemia	1.9% (120)	9
Uncommon	Type 1 Diabetes Mellitus[f]	0.3% (21)	20
Psychiatric disorders			
Common	Insomnia	7.2% (448)	8
Nervous system disorders			
Very common	Headache	12.1% (747)	18
Common	Dizziness	7.4% (460)	11
Common	Neuropathy peripheral	2.0% (123)	4
Common	Lethargy	1.2% (74)	3
Common	Dysgeusia	1.9% (116)	1
Uncommon	Epilepsy	0.2% (11)	7
Rare	Encephalitis[g]	0.06% (4)	3
Rare	Guillain-Barre Syndrome[h]	0.06% (4)	2
Rare	Myelitis[i]	0.03% (2)	2
Rare	Myasthenic Syndrome[j]	0.05% (3)	1
Rare	meningitis (aseptic)[k]	0.05% (3)	3

Eye disorders			
Common	Dry eye	1.7% (108)	0
Uncommon	Uveitis[l]	0.4% (23)	2
Rare	Vogt-Koyanagi-Harada syndrome[#]	(0)	0
Cardiac disorders			
Common	cardiac arrhythmia (including atrial fibrillation)[m]	3.3% (204)	46
Uncommon	Myocarditis	0.1% (7)	6
Uncommon	Pericardial effusion	0.8% (52)	25
Uncommon	Pericarditis	0.1% (9)	5
Vascular disorders			
Common	Hypertension	5.1% (316)	113
Respiratory, thoracic and mediastinal disorders			
Very common	Dyspnoea	16.5% (1021)	133
Very common	Cough	19.4% (1199)	10
Common	Pneumonitis[n]	4.6% (286)	99
Gastrointestinal disorders			
Very common	Diarrhoea	21.0% (1297)	91
Very common	abdominal pain[o]	13.0% (807)	67
Very common	Nausea	20.7% (1281)	54
Very common	Vomiting	12.7% (785)	46
Very common	Constipation	16.7% (1032)	24
Common	Colitis[p]	2.0% (121)	72
Common	Dry mouth	4.9% (304)	1
Uncommon	Pancreatitis[q]	0.3% (21)	12
Uncommon	gastrointestinal ulceration[r]	0.1% (8)	5
Rare	Small intestinal perforation	0.03% (2)	1
Hepatobiliary disorders			
Uncommon	Hepatitis[s]	0.99% (61)	49
Skin and subcutaneous tissue disorders			
Very common	rash[t]	19.5% (1209)	2
Very common	pruritus[u]	18.5% (1146)	2
Common	Severe Skin Reactions[v]	1.6% (102)	78
Common	Erythema	2.9% (177)	2
Common	Dermatitis	1.0% (62)	1
Common	Dry skin	5.3% (327)	0
Common	vitiligo[w]	4.0% (245)	0
Common	Alopecia	1.6% (99)	0
Common	Eczema	1.6% (97)	0
Common	Dermatitis acneiform	1.3% (78)	0
Uncommon	Psoriasis	0.7% (43)	7
Uncommon	lichenoid keratosis[x]	0.4% (23)	4
Uncommon	Papule	0.4% (27)	1
Uncommon	Hair colour changes	0.3% (20)	0
Rare	stevens-johnson syndrome	0.05% (3)	2
Rare	Erythema nodosum	0.05% (3)	0
Rare	Toxic epidermal necrolysis[#]	(0)	0
Musculoskeletal and connective tissue disorders			
Very common	musculoskeletal pain[y]	19.1% (1182)	100
Very common	Arthralgia	14.4% (892)	39
Common	myositis[z]	7.6% (467)	18
Common	Pain in extremity	6.8% (422)	18
Common	arthritis[aa]	2.3% (143)	9

Uncommon	tenosynovitis[bb]	0.5% (32)	1
Rare	Sjogren's syndrome	0.05% (3)	1
Renal and urinary disorders			
Uncommon	Nephritis[cc]	0.4% (25)	17
General disorders and administration site conditions			
Very common	Fatigue	31.8% (1965)	150
Very common	Asthenia	11.2% (693)	61
Very common	oedema[dd]	11.6% (719)	42
Very common	Pyrexia	13.0% (803)	29
Common	Influenza like illness	3.9% (244)	1
Common	Chills	4.2% (260)	0
Investigations			
Common	Aspartate aminotransferase increased	6.8% (420)	70
Common	Alanine aminotransferase increased	6.9% (428)	67
Common	Blood alkaline phosphatase increased	4.3% (266)	52
Common	Hypercalcaemia	3.0% (185)	51
Common	Blood bilirubin increased	2.2% (134)	23
Common	Blood creatinine increased	4.3% (268)	12
Uncommon	Amylase increased	0.3% (20)	10

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

[*] Adverse reaction frequencies presented 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.

[#] The “rule of 3” has been applied in calculation.

a. Infusion Reactions (anaphylactic reaction, anaphylactoid reaction, cytokine release syndrome, drug hypersensitivity, hypersensitivity, infusion related reaction)

b. hypothyroidism (hypothyroidism, myxoedema)

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

d. Adrenal Insufficiency (addison's disease, adrenal insufficiency, adrenocortical insufficiency acute, secondary adrenocortical insufficiency)

e. Hypophysitis (hypophysitis, hypopituitarism)

f. Type 1 Diabetes Mellitus (diabetic ketoacidosis, type 1 diabetes mellitus)

g. Encephalitis (encephalitis, encephalitis autoimmune)

h. Guillain-Barre Syndrome (axonal neuropathy, demyelinating polyneuropathy, guillain-barre syndrome)

i. Myelitis (myelitis, myelitis transverse)

j. Myasthenic Syndrome (myasthenia gravis, myasthenic syndrome)

k. meningitis (aseptic) (meningitis, meningitis noninfective)

l. Uveitis (chorioretinitis, iridocyclitis, iritis, uveitis)

m. cardiac arrhythmia (including atrial fibrillation) (adams-stokes syndrome, arrhythmia, arrhythmia supraventricular, atrial fibrillation, atrial flutter, atrial tachycardia, atrioventricular block, atrioventricular block complete, atrioventricular block first degree, bundle branch block left, bundle branch block right, electrocardiogram qt prolonged, electrocardiogram repolarisation abnormality, heart rate irregular, paroxysmal arrhythmia, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, supraventricular tachycardia, tachyarrhythmia, ventricular extrasystoles, ventricular fibrillation, ventricular tachycardia, wolff-parkinson-white syndrome)

n. Pneumonitis (interstitial lung disease, organising pneumonia, pneumonitis)

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

p. Colitis (autoimmune colitis, colitis, colitis microscopic, enterocolitis, immune-mediated enterocolitis)

q. Pancreatitis (autoimmune pancreatitis, pancreatitis, pancreatitis acute)

r. gastrointestinal ulceration (duodenal ulcer, gastric ulcer)

s. Hepatitis (autoimmune hepatitis, drug-induced liver injury, hepatitis, hepatitis acute, immune-mediated hepatitis)

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

u. pruritus (pruritus, pruritus genital, urticaria, urticaria papular)

v. Severe Skin Reactions (dermatitis bullous, dermatitis exfoliative, dermatitis exfoliative generalised, erythema

multiforme, exfoliative rash, lichen planus, oral lichen planus, pemphigoid, pemphigus, pruritus, pruritus genital, rash, rash erythematous, rash maculo-papular, rash pruritic, rash pustular, skin necrosis, stevens-johnson syndrome, toxic skin eruption)

w. vitiligo (hypopigmentation of eyelid, skin depigmentation, skin hypopigmentation, vitiligo)

x. lichenoid keratosis (lichen planus, lichen sclerosus, lichenoid keratosis)

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

z. myositis (myalgia, myopathy, myositis, necrotising myositis, polymyalgia rheumatica, rhabdomyolysis)

aa. arthritis (arthritis, joint effusion, joint swelling, polyarthritis)

bb. tenosynovitis (synovitis, tendon pain, tendonitis, tenosynovitis)

cc. Nephritis (acute kidney injury, autoimmune nephritis, glomerulonephritis, glomerulonephritis membranous, nephritis, nephrotic syndrome, renal failure, tubulointerstitial nephritis)

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

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 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177 and KN204.

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

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

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

Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KM204: 16JAN2020)

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

Database cutoff date for CRC (KN177: 19FEB2020)

Serious adverse event/deaths/other significant events

Serious Adverse Events

Table: 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)

	KN177 Data for Pembrolizumab[††]		KN177 Data for SOC[¶]		Reference Safety Dataset for Pembrolizumab[‡‡]		Cumulative Running Safety Dataset for Pembrolizumab[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	153		143		5,884		8,098	
with one or more adverse events	62	(40.5)	75	(52.4)	2,251	(38.3)	3,093	(38.2)
with no adverse events	91	(59.5)	68	(47.6)	3,633	(61.7)	5,005	(61.8)
Abdominal pain	7	(4.6)	2	(1.4)	27	(0.5)	51	(0.6)
Diarrhoea	4	(2.6)	9	(6.3)	58	(1.0)	81	(1.0)
Pyrexia	4	(2.6)	0	(0.0)	66	(1.1)	91	(1.1)
Acute kidney injury	3	(2.0)	2	(1.4)	50	(0.8)	82	(1.0)
Colitis	3	(2.0)	0	(0.0)	59	(1.0)	79	(1.0)
Pneumonia	3	(2.0)	2	(1.4)	243	(4.1)	315	(3.9)
Adrenal insufficiency	2	(1.3)	0	(0.0)	18	(0.3)	25	(0.3)
Autoimmune colitis	2	(1.3)	0	(0.0)	0	(0.0)	3	(0.0)
Hepatitis	2	(1.3)	0	(0.0)	9	(0.2)	18	(0.2)
Infection	2	(1.3)	0	(0.0)	5	(0.1)	9	(0.1)
Intestinal obstruction	2	(1.3)	2	(1.4)	12	(0.2)	25	(0.3)
Small intestinal obstruction	2	(1.3)	5	(3.5)	10	(0.2)	20	(0.2)
Squamous cell carcinoma	2	(1.3)	0	(0.0)	24	(0.4)	28	(0.3)
Subileus	2	(1.3)	0	(0.0)	0	(0.0)	3	(0.0)
Anaemia	1	(0.7)	2	(1.4)	59	(1.0)	86	(1.1)
Dyspnoea	1	(0.7)	0	(0.0)	83	(1.4)	96	(1.2)

Febrile neutropenia	1	(0.7)	6	(4.2)	4	(0.1)	8	(0.1)
Ileus	1	(0.7)	3	(2.1)	10	(0.2)	19	(0.2)
Influenza	1	(0.7)	2	(1.4)	11	(0.2)	15	(0.2)
Large intestinal obstruction	1	(0.7)	2	(1.4)	3	(0.1)	5	(0.1)
Pneumonitis	1	(0.7)	0	(0.0)	116	(2.0)	140	(1.7)
Pulmonary embolism	1	(0.7)	4	(2.8)	71	(1.2)	94	(1.2)
Vomiting	1	(0.7)	4	(2.8)	28	(0.5)	42	(0.5)
Cholangitis	0	(0.0)	2	(1.4)	1	(0.0)	4	(0.0)
Decreased appetite	0	(0.0)	3	(2.1)	18	(0.3)	28	(0.3)
Dehydration	0	(0.0)	4	(2.8)	42	(0.7)	59	(0.7)
Device related infection	0	(0.0)	2	(1.4)	5	(0.1)	7	(0.1)
Fatigue	0	(0.0)	3	(2.1)	23	(0.4)	30	(0.4)
Hypokalaemia	0	(0.0)	2	(1.4)	8	(0.1)	11	(0.1)
Intestinal perforation	0	(0.0)	2	(1.4)	4	(0.1)	4	(0.0)
Neutropenia	0	(0.0)	3	(2.1)	3	(0.1)	4	(0.0)
Pleural effusion	0	(0.0)	0	(0.0)	83	(1.4)	107	(1.3)
Tumour associated fever	0	(0.0)	2	(1.4)	2	(0.0)	3	(0.0)
Urinary tract infection	0	(0.0)	1	(0.7)	59	(1.0)	79	(1.0)
Urosepsis	0	(0.0)	2	(1.4)	24	(0.4)	26	(0.3)

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.

Table: 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)

	KN177 Data for Pembrolizumab[††]		KN177 Data for SOC[¶¶]		Reference Safety Dataset for Pembrolizumab[‡‡]		Cumulative Running Safety Dataset for Pembrolizumab[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	153		143		5,884		8,098	
with one or more adverse events	25	(16.3)	41	(28.7)	650	(11.0)	912	(11.3)
with no adverse events	128	(83.7)	102	(71.3)	5,234	(89.0)	7,186	(88.7)
Colitis	3	(2.0)	0	(0.0)	51	(0.9)	69	(0.9)
Acute kidney injury	2	(1.3)	2	(1.4)	10	(0.2)	18	(0.2)
Autoimmune colitis	2	(1.3)	0	(0.0)	0	(0.0)	3	(0.0)
Diarrhoea	2	(1.3)	9	(6.3)	38	(0.6)	52	(0.6)
Hepatitis	2	(1.3)	0	(0.0)	8	(0.1)	15	(0.2)
Pyrexia	2	(1.3)	0	(0.0)	17	(0.3)	28	(0.3)
Pneumonitis	1	(0.7)	0	(0.0)	110	(1.9)	133	(1.6)
Decreased appetite	0	(0.0)	3	(2.1)	5	(0.1)	10	(0.1)
Fatigue	0	(0.0)	3	(2.1)	8	(0.1)	12	(0.1)
Febrile neutropenia	0	(0.0)	5	(3.5)	0	(0.0)	1	(0.0)
Intestinal perforation	0	(0.0)	2	(1.4)	0	(0.0)	0	(0.0)
Neutropenia	0	(0.0)	3	(2.1)	1	(0.0)	2	(0.0)
Vomiting	0	(0.0)	2	(1.4)	9	(0.2)	10	(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 preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

Deaths Due to Adverse Events

The proportion of participants with AEs resulting in death was similar in the KEYNOTE-177 pembrolizumab and SOC safety datasets (6 participants [3.9%] vs 7 participants [4.9%]).

All AEs leading to a fatal outcome were reported in a single participant. In the pembrolizumab arm: abdominal sepsis, death, diarrhoea, duodenal perforation, failure to thrive, pseudobulbar palsy; in the SOC arm: aortic dissection, aspiration, cardiac arrest, cholangitis, intestinal perforation, pulmonary embolism, upper gastrointestinal haemorrhage. None of the deaths were attributed to a drug-related AEs by investigator, vs one death considered due to a drug-related AE in the SOC arm.

Additionally, 3 subjects in the pembrolizumab crossover phase experienced AEs leading to death: recurrent lung carcinoma, pulmonary embolism, respiratory failure. All AEs leading to death were considered not related to pembrolizumab by the investigator.

Adverse Events of Special Interest (AEOSI)

The analysis of AEOSIs is the primary method of assessing immune-related AEs (irAEs) and infusion-related reactions for this study. The frequency and maximum severity of AEOSI analyses are based on a predefined list of preferred AE terms deemed clinically consistent with the identified risks of pembrolizumab (AEOSIs) and potentially associated with an immune etiology. This list was developed by the Sponsor and includes AEOSI terms identified to allow consistent assessment of AEOSIs across pembrolizumab studies. The list of terms is updated periodically based on emerging pembrolizumab safety data.

Table: Adverse Event Summary AEOSI (ASaT Population)

	KN177 Data for Pembrolizumab[††]		KN177 Data for SOC[¶¶]		Reference Safety Dataset for Pembrolizumab[‡‡]		Cumulative Running Safety Dataset for Pembrolizumab[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	153		143		5,884		8,098	
with one or more adverse events	47	(30.7)	18	(12.6)	1,464	(24.9)	1,957	(24.2)
with no adverse event	106	(69.3)	125	(87.4)	4,420	(75.1)	6,141	(75.8)
with drug-related[†] adverse events	42	(27.5)	15	(10.5)	1,272	(21.6)	1,708	(21.1)
with toxicity grade 3-5 adverse events	14	(9.2)	3	(2.1)	377	(6.4)	516	(6.4)
with toxicity grade 3-5 drug-related adverse events	12	(7.8)	3	(2.1)	329	(5.6)	455	(5.6)
with serious adverse events	16	(10.5)	1	(0.7)	378	(6.4)	502	(6.2)
with serious drug-related adverse events	14	(9.2)	1	(0.7)	335	(5.7)	449	(5.5)
who died	0	(0.0)	0	(0.0)	11	(0.2)	17	(0.2)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	11	(0.2)	17	(0.2)
discontinued drug due to an adverse event	10	(6.5)	0	(0.0)	227	(3.9)	303	(3.7)
discontinued drug due to a drug-related adverse event	10	(6.5)	0	(0.0)	224	(3.8)	300	(3.7)
discontinued drug due to a serious adverse event	6	(3.9)	0	(0.0)	155	(2.6)	199	(2.5)
discontinued drug due to a serious drug-related adverse event	6	(3.9)	0	(0.0)	153	(2.6)	197	(2.4)

Table: Exposure-adjusted AEOSI

	Event Count and Rate (Events/100 person-YEARS)[†]			
	KN177 Data for Pembrolizumab[††]	KN177 Data for SOC[¶¶]	Reference Safety Dataset for Pembrolizumab[‡‡]	Cumulative Running Safety Dataset for Pembrolizumab[§§]
Number of subjects exposed	153	143	5884	8098
Total exposure[‡] person-YEARS	181.33	109.95	3894.13	5224.80
Total events (rate)	65 (35.85)	29 (26.38)	2127 (54.62)	2800 (53.59)

Table: AEOSI by grade

	KN177 Data for Pembrolizumab[††]		KN177 Data for SOC[¶¶]		Reference Safety Dataset for Pembrolizumab[‡‡]		Cumulative Running Safety Dataset for Pembrolizumab[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	153		143		5,884		8,098	
with one or more adverse events	47	(30.7)	18	(12.6)	1,464	(24.9)	1,957	(24.2)
Grade 1	12	(7.8)	4	(2.8)	364	(6.2)	470	(5.8)
Grade 2	21	(13.7)	11	(7.7)	723	(12.3)	971	(12.0)
Grade 3	12	(7.8)	3	(2.1)	321	(5.5)	442	(5.5)
Grade 4	2	(1.3)	0	(0.0)	45	(0.8)	57	(0.7)
Grade 5	0	(0.0)	0	(0.0)	11	(0.2)	17	(0.2)
with no adverse events	106	(69.3)	125	(87.4)	4,420	(75.1)	6,141	(75.8)

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

	KN177 Data for Pembrolizumab[††]		KN177 Data for SOC[¶¶]		Reference Safety Dataset for Pembrolizumab[‡‡]		Cumulative Running Safety Dataset for Pembrolizumab[§§]	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	153		143		5,884		8,098	
with one or more adverse events	47	(30.7)	18	(12.6)	1,464	(24.9)	1,957	(24.2)
with no adverse events	106	(69.3)	125	(87.4)	4,420	(75.1)	6,141	(75.8)
Adrenal Insufficiency	**4**	**(2.6)**	**0**	**(0.0)**	**47**	**(0.8)**	**66**	**(0.8)**
Colitis	**10**	**(6.5)**	**0**	**(0.0)**	**110**	**(1.9)**	**163**	**(2.0)**
Encephalitis	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.0)**	**4**	**(0.0)**
Guillain-Barre Syndrome	**0**	**(0.0)**	**0**	**(0.0)**	**4**	**(0.1)**	**6**	**(0.1)**
Hepatitis	**4**	**(2.6)**	**0**	**(0.0)**	**55**	**(0.9)**	**82**	**(1.0)**
Hyperthyroidism	**6**	**(3.9)**	**0**	**(0.0)**	**245**	**(4.2)**	**348**	**(4.3)**
Hypophysitis	**2**	**(1.3)**	**0**	**(0.0)**	**36**	**(0.6)**	**44**	**(0.5)**
Hypothyroidism	**19**	**(12.4)**	**3**	**(2.1)**	**648**	**(11.0)**	**864**	**(10.7)**
Infusion Reactions	**3**	**(2.0)**	**11**	**(7.7)**	**135**	**(2.3)**	**165**	**(2.0)**
Myasthenic Syndrome	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.1)**	**4**	**(0.0)**
Myelitis	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.0)**	**2**	**(0.0)**
Myocarditis	**0**	**(0.0)**	**1**	**(0.7)**	**5**	**(0.1)**	**7**	**(0.1)**
Myositis	**1**	**(0.7)**	**0**	**(0.0)**	**19**	**(0.3)**	**32**	**(0.4)**
Nephritis	**1**	**(0.7)**	**0**	**(0.0)**	**23**	**(0.4)**	**36**	**(0.4)**
Pancreatitis	**1**	**(0.7)**	**0**	**(0.0)**	**18**	**(0.3)**	**31**	**(0.4)**
Pneumonitis	**6**	**(3.9)**	**1**	**(0.7)**	**259**	**(4.4)**	**326**	**(4.0)**
Sarcoidosis	**0**	**(0.0)**	**0**	**(0.0)**	**10**	**(0.2)**	**11**	**(0.1)**
Severe Skin Reactions	**2**	**(1.3)**	**2**	**(1.4)**	**95**	**(1.6)**	**125**	**(1.5)**
Thyroiditis	**2**	**(1.3)**	**0**	**(0.0)**	**57**	**(1.0)**	**75**	**(0.9)**
Type 1 Diabetes Mellitus	**1**	**(0.7)**	**0**	**(0.0)**	**20**	**(0.3)**	**29**	**(0.4)**
Uveitis	**0**	**(0.0)**	**0**	**(0.0)**	**20**	**(0.3)**	**25**	**(0.3)**

Table: summary of outcome for AEOSI (excerpt)

	Outcome	KN177 Data for Pembrolizumab†† n	(%)	KN177 Data for SOC¶¶ n	(%)	Reference Safety Dataset for Pembrolizumab‡‡ n	(%)	Cumulative Running Safety Dataset for Pembrolizumab§§ n	(%)
Subjects in population		153		143		5884		8098	
With one or more AEOSI	**Overall**	**47**	**(30.7)**	**18**	**(12.6)**	**1464**	**(24.9)**	**1957**	**(24.2)**
	Fatal	0	(0.0)	0	(0.0)	11	(0.8)	17	(0.9)
	Not Resolved	23	(48.9)	2	(11.1)	689	(47.1)	912	(46.6)
	Resolving	2	(4.3)	1	(5.6)	99	(6.8)	153	(7.8)
	Unknown	0	(0.0)	0	(0.0)	27	(1.8)	29	(1.5)
	Sequelae	2	(4.3)	0	(0.0)	31	(2.1)	42	(2.1)
	Resolved	20	(42.6)	15	(83.3)	607	(41.5)	804	(41.1)

Colitis

Table: Adverse Event Summary AEOSI – Colitis (ASaT Population)

	KN177 Data for Pembrolizumab†† n	(%)	KN177 Data for SOC¶¶ n	(%)	Reference Safety Dataset for Pembrolizumab‡‡ n	(%)	Cumulative Running Safety Dataset for Pembrolizumab§§ n	(%)
Subjects in population	153		143		5,884		8,098	
with one or more adverse events	10	(6.5)	0	(0.0)	110	(1.9)	163	(2.0)
with no adverse event	143	(93.5)	143	(100.0)	5,774	(98.1)	7,935	(98.0)
with drug-related† adverse events	10	(6.5)	0	(0.0)	97	(1.6)	141	(1.7)
with toxicity grade 3-5 adverse events	5	(3.3)	0	(0.0)	67	(1.1)	95	(1.2)
with toxicity grade 3-5 drug-related adverse events	5	(3.3)	0	(0.0)	60	(1.0)	85	(1.0)
with serious adverse events	5	(3.3)	0	(0.0)	66	(1.1)	93	(1.1)
with serious drug-related adverse events	5	(3.3)	0	(0.0)	58	(1.0)	81	(1.0)
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 drug due to an adverse event	4	(2.6)	0	(0.0)	30	(0.5)	42	(0.5)
discontinued drug due to a drug-related adverse event	4	(2.6)	0	(0.0)	30	(0.5)	42	(0.5)
discontinued drug due to a serious adverse event	2	(1.3)	0	(0.0)	18	(0.3)	26	(0.3)

Of the 5 patients who had Grade 3-5 colitis (3.3%), 3 cases were grade 3 (2%) and 2 cases grade 4 (1.3%), vs 1.1% and 0.1% Grade 3 and grade 4, respectively, in the RSD.

Table: exposure adjusted event rates (events/100 person-years) (include PTs of colitis and autoimmune colitis) *table made by assessor*

	KN177 Pembro	RSD Pembro	KN177 SOC
Colitis, all grade	6.4	4.1	0.0
Colitis, Grade 3-5 AEs	2.8	1.7	0.0

Table: Colitis by grade (excerpt)

Colitis	**10**	**(6.5)**	**0**	**(0.0)**	**110**	**(1.9)**	**163**	**(2.0)**
Grade 1	3	(2.0)	0	(0.0)	11	(0.2)	20	(0.2)
Grade 2	2	(1.3)	0	(0.0)	32	(0.5)	48	(0.6)
Grade 3	3	(2.0)	0	(0.0)	64	(1.1)	89	(1.1)
Grade 4	2	(1.3)	0	(0.0)	3	(0.1)	6	(0.1)

Table: time to onset and duration of AEOSI colitis

	KN177 Data for Pembrolizumab††		KN177 Data for SOC¶¶		Reference Safety Dataset for Pembrolizumab‡‡		Cumulative Running Safety Dataset for Pembrolizumab§§	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	153		143		5884		8098	
Subjects with Colitis	10	(6.5)	0		110	(1.9)	163	(2.0)
Time to Onset of First Colitis (days)†								
Mean (Std)	256.9 (172.1)		0		187.5 (160.8)		187.9 (166.9)	
Median	186.0		0.0		132.0		125.0	
Range	95 to 560		0 to 0		7 to 739		7 to 739	
Total episodes of Colitis	11		0		155		211	
Average Episodes per patient	1.10		0		1.41		1.29	
Episode duration (days)‡								
Median	71.0		0		27.0		32.0	
Range	15 to 378		0 to 0		1 to 266+		1 to 642	

Out of the 10 participants with colitis events in the KEYNOTE-177 pembrolizumab safety dataset, 8 were treated with systemic corticosteroids (vs 58% in the RSD).

As of the data cutoff date, 9 of 10 participants with colitis AEOSIs had resolved events. One participant had an unresolved Grade 1 event; however, this participant experienced disease progression resulting in the participant's death.

Laboratory findings

In KEYNOTE-177, the only laboratory test that was >10% points higher in the pembrolizumab group relative to the SOC group was blood bilirubin increased, with most of the toxicities being Grade 1 or 2.

The incidence of laboratory abnormalities with clinically meaningful (Grade 3 to 4 events) worsening from baseline was similar in the pembrolizumab safety dataset compared with the SOC safety dataset, except for lower rates (≥10% lower incidence) of neutrophils decreased reported in the pembrolizumab safety dataset compared with the SOC safety dataset (2.7% vs 34.5%), known to be associated with cytotoxic chemotherapies.

The incidences of laboratory abnormalities with clinically meaningful worsening from baseline in the KEYNOTE-177 pembrolizumab safety dataset were generally consistent with the RSD.

None of the participants in KEYNOTE-177 (in either arm) had laboratory values that satisfied the protocol-specified criteria for potential drug-induced liver injury.

Safety in special populations

Age

Table: Adverse Event Summary by Age Category (ASaT Population)

- Keynote 177 - Pembrolizumab vs SOC

	KN177 Data for Pembrolizumab[††]								KN177 Data for SOC[¶¶]							
	<65		65-74		75-84		>=85		<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	80		43		22		8		76		38		23		6	
with one or more adverse events	79	(98.8)	41	(95.3)	21	(95.5)	8	(100.0)	76	(100.0)	37	(97.4)	23	(100.0)	6	(100.0)
with no adverse event	1	(1.3)	2	(4.7)	1	(4.5)	0	(0.0)	0	(0.0)	1	(2.6)	0	(0.0)	0	(0.0)
with drug-related[†] adverse events	66	(82.5)	33	(76.7)	16	(72.7)	7	(87.5)	76	(100.0)	36	(94.7)	23	(100.0)	6	(100.0)
with toxicity grade 3-5 adverse events	39	(48.8)	27	(62.8)	12	(54.5)	8	(100.0)	53	(69.7)	31	(81.6)	21	(91.3)	6	(100.0)
with toxicity grade 3-5 drug-related adverse events	16	(20.0)	6	(14.0)	5	(22.7)	6	(75.0)	41	(53.9)	28	(73.7)	20	(87.0)	5	(83.3)
with serious adverse events	25	(31.3)	22	(51.2)	8	(36.4)	7	(87.5)	34	(44.7)	24	(63.2)	14	(60.9)	3	(50.0)
with serious drug-related adverse events	12	(15.0)	5	(11.6)	3	(13.6)	5	(62.5)	12	(15.8)	14	(36.8)	13	(56.5)	2	(33.3)
who died	1	(1.3)	3	(7.0)	1	(4.5)	1	(12.5)	3	(3.9)	2	(5.3)	1	(4.3)	1	(16.7)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	9	(11.3)	5	(11.6)	5	(22.7)	2	(25.0)	8	(10.5)	3	(7.9)	5	(21.7)	1	(16.7)
discontinued drug due to a drug-related adverse event	8	(10.0)	3	(7.0)	3	(13.6)	1	(12.5)	3	(3.9)	0	(0.0)	4	(17.4)	1	(16.7)
discontinued drug due to a serious adverse event	4	(5.0)	4	(9.3)	2	(9.1)	2	(25.0)	6	(7.9)	2	(5.3)	4	(17.4)	1	(16.7)
discontinued drug due to a serious drug-related adverse event	3	(3.8)	2	(4.7)	1	(4.5)	1	(12.5)	1	(1.3)	0	(0.0)	3	(13.0)	1	(16.7)
CNS (confusion/extrapyramidal)	7	(8.8)	4	(9.3)	3	(13.6)	3	(37.5)	11	(14.5)	7	(18.4)	2	(8.7)	0	(0.0)
AE related to falling	7	(8.8)	8	(18.6)	4	(18.2)	2	(25.0)	7	(9.2)	3	(7.9)	8	(34.8)	1	(16.7)
CV events	16	(20.0)	8	(18.6)	6	(27.3)	5	(62.5)	23	(30.3)	14	(36.8)	13	(56.5)	2	(33.3)
Cerebrovascular events	1	(1.3)	2	(4.7)	1	(4.5)	0	(0.0)	2	(2.6)	0	(0.0)	2	(8.7)	0	(0.0)
Infections	52	(65.0)	28	(65.1)	10	(45.5)	4	(50.0)	48	(63.2)	21	(55.3)	12	(52.2)	2	(33.3)

- Pembrolizumab monotherapy RSD and CSD

	Reference Safety Dataset for Pembrolizumab[‡‡]								Cumulative Running Safety Dataset for Pembrolizumab[§§]							
	<65		65-74		75-84		>=85		<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	3,385		1,737		663		99		4,598		2,445		918		137	
with one or more adverse events	3,266	(96.5)	1,677	(96.5)	646	(97.4)	98	(99.0)	4,434	(96.4)	2,351	(96.2)	891	(97.1)	136	(99.3)
with no adverse event	119	(3.5)	60	(3.5)	17	(2.6)	1	(1.0)	164	(3.6)	94	(3.8)	27	(2.9)	1	(0.7)
with drug-related[†] adverse events	2,358	(69.7)	1,223	(70.4)	467	(70.4)	75	(75.8)	3,132	(68.1)	1,711	(70.0)	635	(69.2)	103	(75.2)
with toxicity grade 3-5 adverse events	1,489	(44.0)	891	(51.3)	373	(56.3)	60	(60.6)	2,112	(45.9)	1,241	(50.8)	507	(55.2)	81	(59.1)
with toxicity grade 3-5 drug-related adverse events	452	(13.4)	311	(17.9)	128	(19.3)	18	(18.2)	646	(14.0)	440	(18.0)	181	(19.7)	30	(21.9)
with serious adverse events	1,168	(34.5)	719	(41.4)	315	(47.5)	50	(50.5)	1,615	(35.1)	988	(40.4)	425	(46.3)	66	(48.2)
with serious drug-related adverse events	339	(10.0)	214	(12.3)	85	(12.8)	12	(12.1)	464	(10.1)	310	(12.7)	119	(13.0)	19	(13.9)
who died	143	(4.2)	103	(5.9)	54	(8.1)	11	(11.1)	201	(4.4)	153	(6.3)	79	(8.6)	13	(9.5)
who died due to a drug-related adverse event	21	(0.6)	12	(0.7)	5	(0.8)	1	(1.0)	27	(0.6)	22	(0.9)	10	(1.1)	1	(0.7)
discontinued drug due to an adverse event	392	(11.6)	246	(14.2)	131	(19.8)	14	(14.1)	511	(11.1)	336	(13.7)	173	(18.8)	21	(15.3)
discontinued drug due to a drug-related adverse event	202	(6.0)	135	(7.8)	62	(9.4)	6	(6.1)	260	(5.7)	185	(7.6)	86	(9.4)	11	(8.0)
discontinued drug due to a serious adverse event	285	(8.4)	174	(10.0)	100	(15.1)	11	(11.1)	375	(8.2)	237	(9.7)	129	(14.1)	15	(10.9)
discontinued drug due to a serious drug-related adverse event	122	(3.6)	81	(4.7)	38	(5.7)	3	(3.0)	159	(3.5)	111	(4.5)	52	(5.7)	5	(3.6)
CNS (confusion/extrapyramidal)	247	(7.3)	157	(9.0)	46	(6.9)	16	(16.2)	335	(7.3)	215	(8.8)	62	(6.8)	22	(16.1)
AE related to falling	225	(6.6)	152	(8.8)	70	(10.6)	20	(20.2)	295	(6.4)	206	(8.4)	99	(10.8)	26	(19.0)
CV events	649	(19.2)	395	(22.7)	160	(24.1)	25	(25.3)	869	(18.9)	516	(21.1)	208	(22.7)	34	(24.8)
Cerebrovascular events	61	(1.8)	40	(2.3)	20	(3.0)	3	(3.0)	76	(1.7)	53	(2.2)	29	(3.2)	3	(2.2)
Infections	1434	(42.4)	773	(44.5)	308	(46.5)	44	(44.4)	1866	(40.6)	1048	(42.9)	404	(44.0)	63	(46.0)

Sex

Table: Adverse Event Summary by Gender (Male, Female) (ASaT Population)

	KN177 Data for Pembrolizumab[††]				KN177 Data for SOC[¶¶]				Reference Safety Dataset for Pembrolizumab[‡‡]				Cumulative Running Safety Dataset for Pembrolizumab[§§]			
	M		F		M		F		M		F		M		F	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	71		82		75		68		3,887		1,997		5,406		2,692	
with one or more adverse events	69	(97.2)	80	(97.6)	74	(98.7)	68	(100.0)	3,754	(96.6)	1,933	(96.8)	5,203	(96.2)	2,609	(96.9)
with no adverse event	2	(2.8)	2	(2.4)	1	(1.3)	0	(0.0)	133	(3.4)	64	(3.2)	203	(3.8)	83	(3.1)
with drug-related[†] adverse events	55	(77.5)	67	(81.7)	73	(97.3)	68	(100.0)	2,703	(69.5)	1,420	(71.1)	3,680	(68.1)	1,901	(70.6)
with toxicity grade 3-5 adverse events	34	(47.9)	52	(63.4)	55	(73.3)	56	(82.4)	1,884	(48.5)	929	(46.5)	2,649	(49.0)	1,292	(48.0)
with toxicity grade 3-5 drug-related adverse events	17	(23.9)	16	(19.5)	46	(61.3)	48	(70.6)	626	(16.1)	283	(14.2)	908	(16.8)	389	(14.5)
with serious adverse events	25	(35.2)	37	(45.1)	37	(49.3)	38	(55.9)	1,525	(39.2)	727	(36.4)	2,100	(38.8)	994	(36.9)
with serious drug-related adverse events	13	(18.3)	12	(14.6)	16	(21.3)	25	(36.8)	443	(11.4)	207	(10.4)	638	(11.8)	274	(10.2)
who died	2	(2.8)	4	(4.9)	4	(5.3)	3	(4.4)	220	(5.7)	91	(4.6)	326	(6.0)	120	(4.5)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	1	(1.3)	0	(0.0)	25	(0.6)	14	(0.7)	40	(0.7)	20	(0.7)
discontinued drug due to an adverse event	7	(9.9)	14	(17.1)	7	(9.3)	10	(14.7)	526	(13.5)	257	(12.9)	713	(13.2)	328	(12.2)
discontinued drug due to a drug-related adverse event	6	(8.5)	9	(11.0)	4	(5.3)	4	(5.9)	276	(7.1)	129	(6.5)	376	(7.0)	166	(6.2)
discontinued drug due to a serious adverse event	5	(7.0)	7	(8.5)	5	(6.7)	8	(11.8)	385	(9.9)	185	(9.3)	521	(9.6)	235	(8.7)

Region

Table: Adverse Event Summary by Region (EU, Ex-EU) (ASaT Population)

	KN177 Data for Pembrolizumab[††]				KN177 Data for SOC[¶¶]				Reference Safety Dataset for Pembrolizumab[‡‡]				Cumulative Running Safety Dataset for Pembrolizumab[§§]			
	EU		Ex-EU		EU		Ex-EU		EU		Ex-EU		EU		Ex-EU	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	78		75		81		62		2,091		3,793		2,831		5,267	
with one or more adverse events	75	(96.2)	74	(98.7)	81	(100.0)	61	(98.4)	2,012	(96.2)	3,675	(96.9)	2,720	(96.1)	5,092	(96.7)
with no adverse event	3	(3.8)	1	(1.3)	0	(0.0)	1	(1.6)	79	(3.8)	118	(3.1)	111	(3.9)	175	(3.3)
with drug-related[†] adverse events	64	(82.1)	58	(77.3)	80	(98.8)	61	(98.4)	1,426	(68.2)	2,697	(71.1)	1,901	(67.1)	3,680	(69.9)
with toxicity grade 3-5 adverse events	44	(56.4)	42	(56.0)	58	(71.6)	53	(85.5)	952	(45.5)	1,861	(49.1)	1,346	(47.5)	2,595	(49.3)
with toxicity grade 3-5 drug-related adverse events	21	(26.9)	12	(16.0)	46	(56.8)	48	(77.4)	312	(14.9)	597	(15.7)	439	(15.5)	858	(16.3)
with serious adverse events	36	(46.2)	26	(34.7)	43	(53.1)	32	(51.6)	786	(37.6)	1,466	(38.7)	1,096	(38.7)	1,998	(37.9)
with serious drug-related adverse events	18	(23.1)	7	(9.3)	22	(27.2)	19	(30.6)	235	(11.2)	415	(10.9)	321	(11.3)	591	(11.2)
who died	4	(5.1)	2	(2.7)	3	(3.7)	4	(6.5)	108	(5.2)	203	(5.4)	158	(5.6)	288	(5.5)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	12	(0.6)	27	(0.7)	18	(0.6)	42	(0.8)
discontinued drug due to an adverse event	13	(16.7)	8	(10.7)	12	(14.8)	5	(8.1)	263	(12.6)	520	(13.7)	356	(12.6)	685	(13.0)
discontinued drug due to a drug-related adverse event	9	(11.5)	6	(8.0)	5	(6.2)	3	(4.8)	148	(7.1)	257	(6.8)	190	(6.7)	352	(6.7)
discontinued drug due to a serious adverse event	10	(12.8)	2	(2.7)	8	(9.9)	5	(8.1)	191	(9.1)	379	(10.0)	259	(9.1)	497	(9.4)

Immunogenicity

No new immunogenicity data are available.

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 and other metabolizing enzymes, are not expected to interfere with the metabolism of an IgG antibody.

Studies evaluating PD drug interactions with pembrolizumab have not been conducted. No relationship was observed between prolonged use of systemic corticosteroids and pembrolizumab exposure. Nevertheless, given the study design, exclusion criteria, and immunomodulatory mechanism of action, the use of systemic corticosteroids (at doses greater than physiologic replacement), or other immunosuppressants before the start of pembrolizumab treatment, is not recommended, but can be used to treat immune-related adverse reactions.

Discontinuation due to adverse events

Treatment discontinuation

In the KEYNOTE-177 safety dataset, discontinuation due to AE (all causality) occurred in 21 (13.7%) vs 17 (11.9%) patients in pembrolizumab vs SOC arm, respectively. After adjustment for exposure, the incidence of AEs leading to discontinuation remained consistent in the KEYNOTE-177 pembrolizumab safety dataset relative to the SOC safety dataset (11.58 vs 16.37 events/100 person-years).

The proportion of participants who experienced AEs leading to pembrolizumab discontinuation in the KEYNOTE-177 pembrolizumab safety dataset (13.7%) was consistent with the RSD (13.3%)

The incidence of drug-related AEs leading to treatment discontinuation 9.8% (15 patients) in the KEYNOTE-177 pembrolizumab safety dataset and 5.6% (8 patients) in the SOC safety dataset. After adjustment for exposure, the incidence of drug-related AEs leading to treatment discontinuation was similar in the pembrolizumab safety dataset relative to the SOC safety dataset (8.27 vs 8.19 events/100 person-years). The drug-related AEs leading to treatment discontinuation in the pembrolizumab arm were: Autoimmune colitis, Colitis, Hepatitis, Alanine aminotransferase increased (2 patients each), Autoimmune hepatitis, Immune-mediated hepatitis, Aspartate aminotransferase increased, Hypophysitis, Acute kidney injury, Pneumonitis, Psoriasis (1 patient each).

The proportion of participants who experienced drug-related AEs leading to pembrolizumab discontinuation in the KEYNOTE-177 pembrolizumab safety dataset (9.8%) was generally consistent with the RSD (6.9%). Compared to the RSD, a higher frequency of discontinuation due to gastrointestinal and hepatic events was observed. After adjustment for exposure, the incidence of drug-related AEs leading to discontinuation remained similar in the KEYNOTE-177 pembrolizumab safety dataset relative to the RSD (8.27 vs 11.35 events/100 person-years).

Treatment interruption

A lower proportion of participants in the KEYNOTE-177 pembrolizumab safety dataset experienced an AE as well as drug-related AEs resulting in treatment interruption than in the SOC safety dataset (AEs: 37.9% vs 69.2%; drug-related AEs 22.9% vs 58.7%).

Compared to the RSD, the proportion of participants who experienced AEs and drug-related AEs leading to treatment interruption in the KEYNOTE-177 pembrolizumab safety dataset was higher than the RSD (AEs: 37.9% vs 25.2%; drug-related AEs: 22.9% vs 14.2%).

Drug-related AEs leading to treatment interruption that occurred more frequently (≥2% difference) in the KEYNOTE-177 pembrolizumab safety dataset versus the RSD were aspartate aminotransferase increased (3.3% vs 0.7%), diarrhea (3.3% vs 1.4%), and colitis (2.6% vs 0.5%).

Safety in Participants Who Crossed Over to Pembrolizumab Monotherapy

There were 56 participants from the SOC group who crossed over to pembrolizumab monotherapy within the study. Of the 56 participants who crossed over to pembrolizumab, 94.6% experienced at least 1 AE after initiating crossover treatment. The incidences of drug-related AEs, drug-related Grade 3 to 5 AEs, SAEs, and drug-related SAEs were similar to those in the pembrolizumab group in the initial treatment phase.

Review of listings of events in participants who crossed over to pembrolizumab did not identify any new safety concerns. The summary safety data observed for participants who crossed over from SOC to

pembrolizumab treatment were generally consistent with the summary AE data in the pembrolizumab group in the initial treatment phase.

Table: AE Summary Cross-over Phase (ASaT Population Who Crossed Over From Standard of Care to Pembrolizumab)

	Pembrolizumab	
	n	(%)
Subjects in population*	56	
with one or more adverse events	53	(94.6)
with no adverse event	3	(5.4)
with drug-related† adverse events	41	(73.2)
with toxicity grade 3-5 adverse events	33	(58.9)
with toxicity grade 3-5 drug-related adverse events	9	(16.1)
with serious adverse events	26	(46.4)
with serious drug-related adverse events	7	(12.5)
who died	3	(5.4)
who died due to a drug-related adverse event	0	(0.0)
discontinued‡ drug due to an adverse event	10	(17.9)
discontinued‡ drug due to a drug-related adverse event	5	(8.9)
discontinued‡ drug due to a serious adverse event	8	(14.3)
discontinued‡ drug due to a serious drug-related adverse event	3	(5.4)

* Subjects who were originally assigned to SOC arm and then crossed over to Pembrolizumab.
† Determined by the investigator to be related to the drug.
‡ All study medications withdrawn.
Grades are based on NCI CTCAE version 4.03.
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: 19FEB2020.

Post marketing experience

The safety profile of pembrolizumab was summarized in the PSUR (period from 04-SEP-2018-03 to SEP-2019). There are no records of any pembrolizumab registration being revoked or withdrawn for safety reasons in any country.

2.5.1. Discussion on clinical safety

The evaluation of the safety profile of pembrolizumab in the sought extension of indication for Keytruda as first line treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer is based on the pivotal phase III study KEYNOTE-177 IA2 results (n=153 patients in the pembrolizumab group vs n=143 patients in the SOC chemotherapy mFOLFOX6 or FOLFIRI or respective combinations with bevacizumab or cetuximab). Data have been presented side by side with the Reference Safety Dataset (RSD, n=5884) and the Cumulative Running Pembrolizumab Monotherapy Safety Dataset (N=8098), in order to assess the consistency of the pembrolizumab monotherapy safety in the intended indication with its already established safety profile in the other indications.

Median **exposure** to treatment was longer for the pembrolizumab group than for the SOC group (11.1 vs 5.7 months). It was also longer compared to the RSD (11.1 vs 4.9 months), with more than twice the median number of administrations in KN177 (median 16 vs 8). Patients exposed to pembrolizumab ≥12 months were 47.7% in KN177, vs 20.3% in the RSD.

Regarding the **summary of adverse events**, pembrolizumab treatment was generally well-tolerated when compared to SOC treatment.

The overall incidence of **AEs** was similar in pembrolizumab (97.4%) and SOC safety datasets (99.3%), as well as in the RSD (96.5%). The most frequent (>20% incidence) AEs in the KN177 pembrolizumab arm were diarrhoea, fatigue, nausea, abdominal pain, decreased appetite and vomiting. Diarrhoea, nausea and fatigue were also the most common ARs in the SOC arm, although at higher frequency (>50%). On the contrary, AEs with a ≥10% point difference in KN177 pembrolizumab compared with the SOC group were arthralgia, hypothyroidism, and blood alkaline phosphatase increased. When compared to the established pembrolizumab safety profile of the RSD, AEs more frequently (≥10% point difference) reported in the KN177 pembrolizumab safety dataset than RSD were diarrhoea (44.4% vs 20.3%), abdominal pain (24.2% vs 8.1%), and nausea (30.7% vs 20.4%). Higher rates of diarrhoea and abdominal pain compared to RSD are still observed after adjusting for exposure. Overall, the above events appear more commonly reported in both arms of KN177 study; they can be considered expected in patients with colon cancer.

The incidence of **grade 3-5 AEs** was lower in the KEYNOTE-177 pembrolizumab compared with the SOC safety dataset (56.2% vs 77.6%), which was driven by the higher incidences of haematological toxicities in the chemotherapy arm. But it was higher when compared to the RSD (48.7%). However, the difference between pembrolizumab in KN177 and in RSD is no more evident after adjusting for exposure. The most common G3-5 AEs was hypertension (7.2%, vs 4.9% in the SOC and 1.7% in the RSD). The MAH stated that all participants with a reported event of G3-5 hypertension had a medical history of hypertension at the time of enrolment. In addition, the frequency of hypertension is markedly lower at 0.7%, lower than the SOC (4.2%) and in line with the RSD (0.2%) when treatment-related G3-5 AEs are considered. This is reassuring.

The most frequently (>10%) reported **drug-related AEs** in KN177 pembrolizumab arm were diarrhoea, fatigue, pruritus, nausea, AST increased, rash, arthralgia and hypothyroidism. Among them, diarrhoea, fatigue and nausea were detected at higher incidence in the SOC arm. Diarrhoea was the drug-related AR reported more frequently (>10% point difference) in the KN177 pembrolizumab safety dataset vs the RSD (24.8% vs 10.7%). Diarrhoea, colitis, ALT increase and fatigue were the most commonly reported **G3-5 drug-related AEs** (2% each) in the KN177 pembrolizumab arm; all were more common in KN177 than in the RSD, and colitis and ALT increase were also more frequent than in the SOC arm (0% and 0.7% respectively).

Incidence of **SAE** was lower in the pembrolizumab than in the SOC arm of KN177 study (40.5% vs 52.4%) and in line with the RSD (38.3%). The most frequently reported (>2%) SAEs in the KN177 pembrolizumab safety dataset were abdominal pain, diarrhoea, and pyrexia. Abdominal pain was higher in the KN177 pembrolizumab safety dataset (4.6%) compared to SOC (1.4%) as well as to pembrolizumab RSD (0.6%). The MAH stated that medical review of abdominal pain events indicate that these AEs were associated with the underlying colon cancer disease. Diarrhoea was on the contrary less common in the pembrolizumab than in the SOC arm (2.6% vs 6.3%), but higher compared to the RSD (0.6%).

The overall incidence of **drug-related SAE** in the KN177 pembrolizumab safety dataset was lower compared with the SOC safety dataset (16.3% vs 28.7%). On the contrary, when compared to RSD the incidence in KN177 was slightly higher (16.3% vs 11.3%), but this trend reversed when adjusted for exposure (rate 16.34 vs 24.13). The most common drug-related SAE was colitis (2%, in 3 patients), followed by acute kidney injury, autoimmune colitis, diarrhoea, hepatitis and pyrexia (1.3%, 2 patients each). Colitis was not reported in the SOC, and it was reported at higher incidence than in the RSD (2% vs 0.9% for colitis, 1.3% vs 0% for autoimmune colitis).

As expected, the overall incidence of **AEOSI** was higher in the KN177 pembrolizumab compared with the SOC safety dataset (30.7% vs 12.6%), the most common (≥2% incidence) being hypothyroidism, colitis, hyperthyroidism, pneumonitis, adrenal insufficiency, hepatitis, and infusion reactions. The frequency of

AEOSI was higher for pembrolizumab-treated patients in KN177 compared to RSD (30.7% vs 24.9%), but it is reassuring that this trend reverted when adjusted for exposure (rate 35.85 vs 53.39). While the most common AEOSI was hypothyroidism in both pembrolizumab KN177 arm and RSD at a similar frequency (12.4% vs 10.7%), it can be observed an higher incidence of colitis (6.5% vs 2%), adrenal insufficiency (2.6% vs 0.8%) and hepatitis (2.6% vs 1%) in KN177 pembrolizumab arm than in RSD. When adjusted for exposure, the above differences tended to be reduced. Most of the AEOSI were grade 1 and 2, with no fatal AEOSI reported. Approximately half of the AEOSI were not resolved as of the data cut-off date. The highest rate of not-resolved AEOSI was hypothyroidism, as expected due to long term hormone thyroid replacement.

Treatment discontinuation due to AEs (all causality and drug related) were more frequently reported in the pembrolizumab arm compared to patients receiving chemotherapy in the SOC arm, as well as compared to pembrolizumab RSD (discontinuation due to drug-related AE: 9.8% vs 5.6% vs 6.9%, respectively). However, after adjusting for exposure, discontinuations in the pembrolizumab KN177 arm were lower than the other two datasets. Of the 15 patients who discontinued pembrolizumab due to drug related AEs, 13 were due to gastrointestinal and hepatic events.

The proportion of participants with **AEs resulting in death** was similar in the KN177 pembrolizumab and SOC safety datasets (6 participants [3.9%] vs 7 participants [4.9%]). Additionally, 3 deaths were reported in patients receiving pembrolizumab in the crossover phase. None of the deaths were considered related to pembrolizumab by investigator. Clarifications have been requested regarding two AEs leading to death: for the first one "pseudobulbar palsy", the MAH stated that pseudobulbar palsy is impacted by the confounding factor of amyotrophic lateral sclerosis, although this diagnosis is not included in the past medical history and it is unclear whether this diagnosis was made during the study. With regard to a subjects who died due to aggravating diarrhoea "without infection focus", from a regulatory and retrospective perspective, it appears that the patient experienced autoimmune hepatitis, worsening of pre-existing autoimmune disease (psoriasis) and very likely also immune-related colitis, the latter however was not further investigated (e.g. colonoscopy) and no immunosuppressive therapy was initiated, so this cannot be finally determined. Nonetheless, the MAH's interpretation that this event is unlikely related to pembrolizumab is not shared. The omission of further diagnostic and therapeutic intervention during the course of non-infectious, aggravating and finally fatal diarrhoea remains worrisome and underlines that physicians' awareness of the risk of potential autoimmune colitis appears clinically relevant (see colitis below).

The MAH performed a separate analysis for the events of **colitis**. In the pembrolizumab KN177 arm 10 patients experienced colitis (6.5%), vs none in the SOC arm. The incidence of colitis was higher also compared to the RSD (2%). Half (n=5) of the colitis events were G3-4, which is however similar to what observed in the RSD (60% were G3-4) (but when taking into account G4 only events these are more common in KN177 study). Difference remains after adjusting for exposure although less pronounced, but still incidences of all grade and severe colitis are about 50% higher for patients with CRC than in the RSD. On one side, it might not be fully appropriate to argue the clinical relevance of higher colitis AEs away by referring to the lower differences in exposure-adjusted event rates (since most of the AEs overall are expected to occur during the early treatment phase). On the other side, the longer exposure could be important in the incidence of colitis, taking into account that the median time to onset of colitis was approximately 6 months (range 3 to 18 months). Four G4 colitis events were considered treatment-related SAEs, and colitis led to pembrolizumab discontinuation in four patients. The median duration was about 2.4 months (range 15 days to 1 year). Corticosteroids were administered in 8/10 cases. It is reassuring that in 9/10 patients, colitis was resolved at the cut-off date. The argument that the role of metastatic CRC as a risk factor for colitis is unclear is understood. Nonetheless, while colitis is a known AEOSI to pembrolizumab already included in the SmPC, higher incidences were observed for pembrolizumab in Study KEYNOTE-177 compared to the RSD, and physicians should be informed about

this. Awareness might be especially relevant in the context of the underlying disease, since clinical symptoms of colitis might be more easily misinterpreted (and remain untreated). The observed incidences of all grade and Grade 3-5 colitis events in patients with CRC in KEYNOTE-177 has been included by the MAH in the SmPC section 4.8, immune-related colitis.

The MAH was requested to discuss **hepatic toxicity**. In the KN177 pembrolizumab arm, among the AEOSI, 4 patients experienced hepatitis (2.6%), all grade 3 and all leading to treatment discontinuation. Reassuringly, all the 4 events of hepatitis resolved at the data cut-off date. In the RSD, the incidence of hepatitis was lower (1%), but when adjusted for exposure, hepatitis was similar between pembrolizumab arm in KN-177 and RSD (all grades and grade 3-5). Hepatitis is a known AEOSI associated to pembrolizumab and reported in the SmPC. None of the participants in KN177 (in either arm) had laboratory values that satisfied the protocol-specified criteria for potential drug-induced liver injury, however participants in the KEYNOTE-177 pembrolizumab safety dataset compared with the RSD reported a higher frequency of ALT increased (14.4% vs 6.6%), AST increased (15.7% vs 6.5%), and blood bilirubin increased (4.6% vs 2.1%). When adjusted for exposure, the difference was overall comparable. The incidence of liver investigation abnormalities does not seem to be related with the liver metastases. Based on the overall data, no change in the SmPC is warranted.

No major concerns are raised based on the analysis of safety **by subgroups** based on intrinsic factors (age, sex, ECOG).

A higher incidence (≥12% point) of Grade 3 to 5 AEs and SAEs was noted in the ≥65 years age group of the KEYNOTE-177 pembrolizumab safety dataset compared to the participants <65 years of age. A less pronounced difference was observed between the age groups in the RSD. However, AE incidences for pembrolizumab in the higher age group did not exceed the rates of those in the SOC arm.

2.5.2. Conclusions on clinical safety

Overall, the safety profile of pembrolizumab remains unchanged and no new safety concerns were identified in the KEYNOTE-177 study. Pembrolizumab showed a favourable safety overall relative to polychemotherapy SOC, with a different AE profile as expected.

Compared to the known safety profile of pembrolizumab in RSD, in some cases a trend toward worse toxicity and higher rate of discontinuations were observed in the CRC MSI-H pembrolizumab treated population of KN177. However, in most cases this appears to be due to the longer exposure, which was almost doubled in the KN177 dataset compared to RSD, as shown based on exposure-adjusted safety analyses. The safety profile of pembrolizumab was characterized by an increased gastrointestinal toxicity, especially diarrhoea and abdominal pain, compared to the known pembrolizumab safety profile. The incidence of immune-related colitis observed in CRC patients in KEYNOTE-177 study is included in the SmPC section 4.8.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 29 is acceptable.

The CHMP endorsed the Risk Management Plan version 29 with the following content:

Safety concerns

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

No new safety concerns have been identified from the submitted data supporting the new indication.

Existing pharmacovigilance plan and risk minimisations measures remain sufficient to mitigate the risks of the product in all approved indications.

Pharmacovigilance plan

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					
Planned	Cumulative review of literature, clinical trial and post-marketing cases for the risk of GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	To monitor, identify and evaluate reports of 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

Risk minimisation measures

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

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

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

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Important Potential Risks		
For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab	Routine risk minimisation measures: • For Hematologic malignancies: the increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab is described in the SmPC, Section 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk. No additional risk minimisation measures warranted	Routine pharmacovigilance activities Additional pharmacovigilance including: • Safety monitoring in the ongoing HL trials (KN087, KN204).
GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	Routine risk minimisation measures: • GVHD after pembrolizumab administration in patients with a history of allogeneic SCT is described in the SmPC, Section 4.4 and appropriate advice is provided to the prescriber to minimize the risk. No additional risk minimisation measures warranted	Routine pharmacovigilance activities Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumour types • Cumulative review of literature, clinical trial and post-marketing cases of GVHD after pembrolizumab administration in patients with a history of allogeneic SCT with PSUR submission in 2019.

2.7. Changes to 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 Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The changes to the package leaflet are limited; in particular, the key messages for the safe use of the medicinal product are not impacted. Furthermore, the design, layout and format of the package leaflet will not be affected by the proposed revisions. Therefore, these proposed revisions do not constitute

significant changes that would require the need to conduct a new user consultation or abridged focus testing.

2.7.2. Additional monitoring

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The final indication is *"KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults"*

3.1.2. Available therapies and unmet medical need

Combination chemotherapy in the form of FOLFOX (oxaliplatin, 5-FU, and leucovorin/folinic acid) or FOLFIRI (irinotecan, 5-FU, and leucovorin/folinic acid) has been established as first-line SOC chemotherapy options for metastatic CRC and may be used interchangeably depending on the physician's recommendation and regional preference.

The treatment of mCRC patients should be seen as a continuum of care in which the determination of the goals of the treatment is important: prolongation of survival, cure, improving tumour-related symptoms, stopping tumour progression and/or maintaining quality of life[15].

3.1.3. Main clinical studies

KEYNOTE-177 is an ongoing, two-arm, multicenter, international, randomized, open-label, controlled study of pembrolizumab monotherapy vs standard chemotherapy in participants with Stage IV MSI-H/dMMR CRC. The dual primary objectives of the study are PFS per RECIST 1.1 by BICR and OS. A total of 307 participants were randomized in a 1:1 ratio to receive pembrolizumab 200 mg Q3W (n=153) or investigator's choice of SOC (6 regimens allowed: mFOLFOX6 or FOLFIRI alone or in combination with bevacizumab or cetuximab) (n=154).

The MAH submitted the Interim Analysis 2 (i.e. final PFS and interim OS analysis) results with data cutoff date of 19-FEB-2020 (median survival follow-up 27 months).

3.2. Favourable effects

- Statistically significant and clinically relevant PFS advantage of pembrolizumab vs SOC: HR 0.60 (95%CI 0.45, 0.80), p=0.0002, median PFS 16.5 (95%CI 5.4, 32.4) vs 8.2 (95%CI 6.1, 10.2) months. Kaplan-Meier PFS curves demonstrate an increasingly pronounced separation after month 6

[15] Van Cutsem E et al. Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25(suppl 3):iii1-iii9.

(PFS rate at 12 months 55.3% vs 37.3%, PFS rate at 24 months 48.3% vs 18.6%). PFS results were consistent across sensitivity analyses.

- A favourable OS trend was observed: HR 0.77 (95% CI 0.54, 1.09), p=0.0694, median OS NR vs 34.8 months (95%CI 26.3, NR).
- A trend toward higher ORR with pembrolizumab compared to SOC was seen [43.8% (95% CI: 35.8, 52.0) vs 33.1% (95% CI: 25.8, 41.1], including higher CR rate (11.1% versus 3.9%).
- Durable responses with pembrolizumab compared to SOC: median DOR NR in the pembrolizumab vs 10.6 months in the SOC group, proportion of patients with DOR ≥12 months 85.1% vs 43.8%.
- PFS2 advantage is seen with pembrolizumab compared to SOC (HR 0.63, 95%CI 0.45, 0.88).
- Trend toward improvement in QoL and most of the functioning and symptoms score in the pembrolizumab arm compared to SOC, supporting the overall efficacy and safety data.

3.3. Uncertainties and limitations about favourable effects

- A crossing of the OS KM curves up to month 8, with greater Hazard rates in the pembrolizumab arm compared with the SOC arm for the first 4 months, is observed. Number of patients is too small to firmly identify risk factors of early death. Text in the SmPC section 4.4 reporting that "in Keynote-177, the hazard rates for overall survival events were greater for pembrolizumab compared with chemotherapy for the first 4 months of treatment, followed by a long-term survival benefit for pembrolizumab" has been added, and OS KM curves are shown in section 5.1 of the SmPC.
- Similar efficacy of pembrolizumab and SOC is observed, but with better safety profile in patients beyond the age of 75 years. Data in this age group is however limited. This is reflected in the SmPC.

3.4. Unfavourable effects

- Drug-related AEs were reported in 79.7% of pembrolizumab treated MSI-H CRC patients in KN177 study. The most commonly (>10%) observed drug-related AEs were diarrhoea (24.8%), fatigue (20.9%), pruritus (13.7%), nausea (12.1%), AST increased (11.1%), rash (11.1%), arthralgia (10.5%) and hypothyroidism (10.5%).
- Drug-related G3-5 AEs occurred in 21.6% of subjects, being ALT increase, colitis, diarrhoea and fatigue the most frequent (2% each).
- The incidence of drug-related SAEs was 16.3%, with colitis as the most frequent (2%).
- AEOSI occurred in 30.7% of patients, most common being hypothyroidism (12.4%) and colitis (6.5%).
- Drug-related AEs leading to discontinuation of pembrolizumab in 9.8% (n=15) of patients. Autoimmune colitis, Colitis, Hepatitis and ALT increase cause discontinuation of treatment in 2 patients each.
- Compared to the known pembrolizumab safety profile, an increased frequency of gastrointestinal toxicity, in particular diarrhoea and abdominal pain, as well as a higher incidence of the AEOSI colitis was evident in KN177. The argument that the role of metastatic CRC as a risk factor for colitis is unclear is understood. Difference in incidence of colitis between arms is reduced when adjusted for exposure, but still awareness might be especially relevant in the context of the underlying disease, since clinical symptoms of colitis might be more easily misinterpreted (and remain untreated). The

incidence of immune-related colitis in CRC patients from KEYNOTE-177 has been added by the MAH in the SmPC section 4.8.

3.5. Uncertainties and limitations about unfavourable effects

No new uncertainties have been introduced with this application (see RMP).

3.6. Effects Table

Table 2. Effects Table for Keytruda in first line metastatic MSI-H/dMMR CRC (data cut-off: 19-FEB-2020)

Effect	Short description	Unit	Treatment Pembro 200 mg Q3W	Control Investigator's choice SOC	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS (by BICR per RECIST 1.1)	Time from randomization to first documented disease progression per RECIST 1.1 based on BICR or death due to any cause, whichever occurs first	months (95% CI)	16.5 (5.4, 32.4)	8.2 (6.1, 10.2)	Statistically significant and clinically relevant advantage in PFS. Consistent sensitivity analyses results / apparent reduced efficacy in patients with lung metastases, but limited number to draw conclusion	CSR KN-177
		HR 0.60 (95%CI 0.45, 0.80) p-value 0.0002 (boundary ⩽ 0.0117)				
OS	Time from randomization to death due to any cause	months (95% CI)	NR (NR, NR)	34.8 (26.3, NR)	Trend toward OS benefit although not statistically significant (60% of crossover in SOC arm) /early crossing of OS curves	
		HR 0.77 (95%CI 0.54, 1.09) P-value0.0694 (boundary ⩽ 0.0053)				
ORR	Confirmed CR or PR (by BICR per RECIST 1.1)	% (95% CI)	43.8 (35.8, 52.0)	33.1 (25.8, 41.1)	Trend toward higher ORR and CR/ less SD and more PD	
DOR	Time from first response to PD or death due to any cause, whichever occurs first, in subjects who achieve a PR or CR	months (range)	NR (2.3+ -41.4+)	10.6 (2.8 -37.5+)	Durable responses	
PFS2	Time from randomization to disease progression on the next line of therapy, or death from any cause, whichever occurs first	months (95% CI)	NR (NR, NR)	23.5 (16.6, 32.6)	Advantage in PFS2	
Unfavourable Effects						
AE summary	AE	%	97.4	99.3	Pembrolizumab safety profile compared favourably with SOC. Higher discontinuation due to AE in pembrolizumab than SOC arm possibly due to longer exposure. Consistent safety profile compared to the reference safety dataset, with the exception of a higher incidence of colitis. No new safety concerns identified.	CSR KN-177
	drug related AE	%	79.7	98.6		
	G3-5 AE	%	56.2	77.6		
	drug related G3-5 AE	%	21.6	65.7		
	SAE	%	40.5	52.4		
	drug related SAE	%	16.3	28.7		
	death due to AE	%	3.9	4.9		
	death due to drug related AE	%	0	0.7		
	discontinuation due to AE	%	13.7	11.9		
	discontinuation due to drug related AE	%	9.8	5.6		
AEOSI	hypothyroidism	%	12.4	2.1		
	colitis	%	6.5	0		

Abbreviations: PFS: progression free survival; OS: overall survival; ORR: objective response rate; DOR: duration of response; RECIST: BICR: blinded central imaging review; NR: not reached; CI: confidence interval; AE: adverse event; SAE: serious adverse event; AEOSI: Adverse Events of Special Interest; CRS: clinical study report

Notes:

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In the open-label study KEYNOTE-177, pembrolizumab demonstrated a statistically significant and clinically meaningful PFS benefit for patients with metastatic MSI-H/ dMMR mCRC. The median PFS in the pembrolizumab arm was almost doubled compared to the SOC arm, with a gain of about 8 months.

OS curves showed initial crossing with greater hazard rates in the pembrolizumab arm compared with the SOC arm for the first 4 months. Some imbalances in baseline characteristics of patients who died early in the two arms are observed, although the small number of patients prevent to identify risk factors for early death with pembrolizumab. OS KM curves in section 5.1 as well as text in section 4.4 of the SmPC have been included to inform prescribers.

Safety analyses broadly confirmed the already well-known and different toxicity profiles of pembrolizumab, which compared favourably to polychemotherapy regimens. An increased incidence of GI toxicity was on reported, in particular the AEOSI of Colitis.

3.7.2. Balance of benefits and risks

The efficacy data of pembrolizumab monotherapy as demonstrated in study KEYNOTE-177 support its benefit as first line treatment of metastatic MSI-H/dMMR CRC outweighing the established risks of treatment. The wording of the indication was updated to include only patients actually enrolled in the clinical trial (i.e. metastatic).

3.7.3. Additional considerations on the benefit-risk balance

The MAH is requesting to approve the 400 mg Q6W as alternative dose for the sought indication, as done for the other pembrolizumab monotherapy indications, which is considered acceptable.

3.8. Conclusions

The overall B/R of Keytruda is positive.

The following measures are considered necessary to address issues related to efficacy:

The MAH agreed to submit the final OS analysis for KEYNOTE-177 as part of the final CSR when available (estimated Q3 2021), as an Annex II condition in the Product Information in order to confirm interim OS data.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

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

C.I.6 -Extension of indication to include first-line treatment of metastatic microsatellite instability-high (MSI H) or mismatch repair deficient (dMMR) colorectal cancer in adults for Keytruda based on the results from KEYNOTE-177 (an international, randomised, open-label Phase 3 trial of pembrolizumab versus chemotherapy in MSI-H or dMMR Stage IV Colorectal Carcinoma). 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, a minor correction has been made in section 4.4, "Immune related endocrinopathies" subsection. Version 29.0 of the RMP has also been submitted.

Amendments to the marketing authorisation

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

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Keytruda-H-C-3820-II-0091'.