24 March 2022
EMA/224161/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: pembrolizumab

Procedure No. EMEA/H/C/003820/II/0109

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
AE	Adverse event(s)
AEOSI	Adverse event(s) of special interest
ASaT	All subjects as treated
ASCO	American Society of Clinical Oncology
BORR	Best overall response rate
CCA	Cholangiocarcinoma
cHL	Classic Hodgkin's Lymphoma
CI	Confidence interval
CL	Clearance
CR	Complete response
CRC	Colorectal Cancer
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
dMMR	Mismatch repair deficiency
DOR	Duration of response
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EORTC-QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D	European Quality of Life Five Dimensions Questionnaire
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
HCC	Hepatocellular carcinoma
HNSCC	Head and neck squamous cell carcinoma
HTA	Health Technology Assessment
IHC	Immunohistochemistry
IRC	Independent central radiologic review
ISS	Integrated Summary of Safety
KM	Kaplan-Meier
mAb	Monoclonal antibody
mCRC	Metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
MSI-H	Microsatellite instability-high
NCCN	National Comprehensive Cancer Network
NGS	Next generation sequencing

Abbreviation	Definition
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed cell death-1
PD-L1	Programmed cell death-1 ligand-1
PD-L2	Programmed cell death-1 ligand-2
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic
PMBCL	Primary mediastinal large B-cell lymphoma
PR	Partial response
PRO	Patient-reported outcome
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q6W	Every 6 weeks
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumours
RSD	Reference Safety Dataset
SAE	Serious adverse event(s)
sBLA	Supplemental biologics license application
SOC	Standard of care
sSAP	Supplemental statistical analysis plan
UK	United Kingdom
US	United States
Vd	Volume of distribution
XELIRI	Irinotecan (180 mg/m^2); capecitabine (1000 mg/m^2)

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 2021 an application for a variation.

The following changes were proposed:

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

Extension of indication for Keytruda as monotherapy in the treatment of unresectable or metastatic MSI-H or dMMR colorectal, endometrial, gastric, small intestine, biliary, or pancreatic cancer in adults who have received prior therapy. The proposed indication is based on the results from the KEYNOTE-164 (KN164) and KEYNOTE-158 (KN158) trials.
As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. An updated version of the RMP (Version 34.1) has been submitted.

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

Information on paediatric requirements

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

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

The Paediatric Investigation Plan (EMEA-001474-PIP01-13-M01) covering the condition "Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue)" and the final compliance check have been provided in the dossier. Additionally, the PIP covering the condition 'Treatment of Hodgkin Lymphoma' (EMEA -001474-PIP02-16-M01) and the partial compliance check, completed on 1 February 2019, has been also provided for completeness.

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 application included a critical report addressing the possible similarity with authorised orphan medicinal products (Pemazyre).

Scientific advice

The MAH received in 2015 EMA-HTA Parallel Scientific Advice for KEYNOTE-158 (EMEA/H/SAH/039/3/2015/II) and EMA Scientific Advice on MSI-H CRC indication (KEYNOTE-164 and KEYNOTE-177) (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 2021
Start of procedure	17 July 2021
CHMP Rapporteur's preliminary assessment report circulated on	24 September 2021
PRAC preliminary assessment report circulated on	28 September 2021
CHMP Co-Rapporteur Critique circulated on	01 October 2021
PRAC RMP advice and assessment overview adopted by PRAC on	30 September 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report circulated on	8 October 2021
Request for supplementary information adopted by the CHMP on	14 October 2021
MAH's responses submitted to the CHMP on	21 December 2021
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	3 February 2022
2nd Request for supplementary information adopted by the CHMP on	24 February 2022
MAH's responses submitted to the CHMP on	1 March 2022
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	11 March 2022
Updated CHMP Rapporteur's assessment report on the MAH's responses circulated on	18 March 2022
CHMP opinion	24 March 2022
The CHMP adopted a report on similarity of Keytruda with Pemazyre of the authorised orphan medicinal product(s)	24 March 2022

2. Scientific discussion

2.1. Introduction

The scope of this variation is to include a new indication for KEYTRUDA as monotherapy for the treatment of unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR) CRC, endometrial, gastric, small intestine, biliary, or pancreatic cancer in adults who have received prior therapy.

The proposed indication is based on the results from the final analysis of KEYNOTE-164 and interim analysis 11 (IA11) of KEYNOTE-158 (Cohort K) trials. KEYNOTE-164 is a single-arm study of pembrolizumab as monotherapy in participants with previously-treated locally advanced unresectable or metastatic MSI-H/dMMR colorectal cancer (CRC). KEYNOTE-158 is a single-arm basket study of pembrolizumab as monotherapy in participants with advanced Non-Colorectal (non-CRC) MSI-H/dMMR solid tumours (Cohort K of this study).

2.1.1. Problem statement

Disease or condition

Targeted conditions are six solid tumours (CRC, endometrial, gastric, small intestine, biliary, and pancreatic cancer) with microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR) in advanced stage following prior treatments.

State the claimed the therapeutic indication

"KEYTRUDA as monotherapy is indicated for the treatment of unresectable or metastatic MSI-H or dMMR CRC, endometrial, gastric, small intestine, biliary, or pancreatic cancer in adults who have received prior therapy."

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

"Keytruda as monotherapy is indicated for the treatment of the following MSI-H or dMMR tumours in adults with:

- unresectable or metastatic colorectal cancer after previous fluoropyrimidine-based combination therapy;

- advanced or recurrent endometrial carcinoma, who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation;

- unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy."

Epidemiology

The prevalence of MSI-H across different tumours varied widely by tumour type and by disease stage.

Several tumour types, including endometrial, colorectal, and gastric cancers were consistently found to have the highest MSI-H prevalence, generally above 10%[1], which includes also the Lynch syndrome associated tumour types. For most other cancers, MSI-H prevalence was below 5%[2]. Among the 6 tumour types included in the claimed indication, colorectal, endometrial, and gastric cancers (with the highest MSI-H prevalence) are also the most frequently diagnosed. Although not frequently diagnosed cancers, MSI-H prevalence in small intestine cancer is about 10%, while pancreatic cancer and biliary cancer have a low MSI-H prevalence of <3%. Additionally, the prevalence of MSI-H in late-stage disease is generally lower than in earlies cancer stages[3].

The epidemiology specific for each selected tumours included in the claimed indication is presented below:

CRC: Overall, colorectal cancer ranks third in terms of incidence (33.6 per 100,000 in Northern Europe) and second in terms of mortality[4]. Less than 30% of CRC have metastases at diagnosis. MSI-H is present in approximately 10% to 15% of patients with CRC overall, but it's less frequent in the more advanced stage (4-8%)[5] [6].

Endometrial cancer: Endometrial cancer was the second most common and the fourth leading cause of death due to gynaecological cancer among women worldwide in 2020[6], with highest incidence in EU observed in Central and Eastern Europe (incidence rate 20.2 per 100,000). Patients are less frequently diagnosed at late stage III or IV (<20%, 7-8% with metastases at diagnosis). In sporadic endometrial cancer MSI-H is observed in 11% to 32% of the patients, with lower MSI-H prevalence of 6% to 11% in patients with advanced stage disease [3] [7].

Gastric Cancer: Gastric cancer is the fifth most frequently diagnosed cancer and the fourth leading cause of cancer death, with the highest incidence rates in Eastern Asia in particular, in Europe in Central and Eastern Europe (incidence rate 11.3 per 100,000)[6]. Gastric cancer patients are most commonly diagnosed at stage IV (46-57%). MSI-H is present in approximately 9% to 20% of patients with gastric cancer. The MSI-H prevalence is the lower the higher the stage is (between 5-8% in stage IV)[3] [4] [8] [9].

Small Intestine Cancer: Small intestine adenocarcinoma is a rare malignancy (incidence rate of 2.4 per 100,000) that is often diagnosed at an advanced stage[10]. About 10% of patients with small intestine cancer is MSI-H, being 2-6% in patients with advanced stage small intestine cancer as compared with 7-15% in patients with early-stage disease [5] [11].

[1] Bonneville R, Krook MA, Kautto EA, Miya J, Wing MR, Chen HZ, et al. Landscape of Microsatellite Instability Across 39 Cancer Types. JCO Precision Oncology 2017:1, 1-15.
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[11] Xia M, Singhi AD, Dudley B, Brand R, Nikiforova M, Pai RK. Small bowel adenocarcinoma frequently exhibits lynch syndrome-associated mismatch repair protein deficiency but does not harbor sporadic MLH1 deficiency. Appl Immunohistochem Mol Morphol. 2017 Jul;25(6):399-406

Pancreatic Cancer: Pancreatic cancer is the twelfth most common cancer in the world, with highest incidence rate in Western Europe (8.6 per 100,000 people), but the fourth for mortality[6]. In approximately 70% of the cases, pancreatic cancer is diagnosed at stage IV. The reported prevalence of MSI-H in patients with pancreatic cancer is <2%[5] [12].

Biliary Cancer: Biliary tract cancer incidence rate varies between 2-5 per 100,000 people. Biliary adenocarcinoma includes gallbladder cancer, the most common in the biliary tract. Cholangiocarcinomas (CCAs) are a diverse group of malignancies (usually adenocarcinoma) arising from the biliary epithelium, typically classified as either intrahepatic or extrahepatic CCA. The reported prevalence of MSI-H in patients with biliary cancer is 1% to 3%[5].

Biologic features, aetiology and pathogenesis

The DNA mismatch repair (MMR) system repairs damaged DNA through base pair and small insertion-deletion corrections that are erroneously generated during DNA replication. MLH1, MSH2, MSH6 and PMS2 proteins are known MMR gene product. Mutations in the MMR genes cause dysfunctional MMR proteins incapable of recognising DNA mismatch in coding regions of repetitive nucleotide sequences called microsatellites; as a result DNA damage fails to be repaired and may lead to generation of non-functional protein. This form of genomic instability is called microsatellite instability (MSI)[13]. Inactivation of MMR gene can either be somatic (sporadic) or of germline origin (e.g. Lynch syndrome). Lynch syndrome (LS) is a hereditary disorder with an autosomal dominant transmission that primarily predisposes to colorectal and endometrial cancer, but is also associated with other extra-colonic malignancies, such as stomach, small bowel, pancreatic, bladder, prostate, and biliary tract cancers[14].

MSI-H cancers are usually characterized by a high mutational burden and tumour-specific neoantigen load mediated by MSI and common defects in MMR, and can demonstrate highly upregulated expression of PD-1 and PD-L1, as well as other immune checkpoints, thereby providing a scientific rationale for PD-1 blockade with pembrolizumab for the management of patients with MSI-H cancer[15]. In a series of 11,348 patients, approximately 70% of MSI-H cases were TMB-high, but only 26% of MSI-H cases were PD-L1 positive. The overlap between TMB, MSI, and PD-L1 differed among cancer types. Only 0.6% of the cases were positive for all three markers[16]. Not all patients with MSI-H tumours, respond to immunotherapy, suggesting that a deeper understanding of immune-related mechanisms in MSI-H is required.

In literature, some characteristics features have been described for some MSI-H tumours. MSI-H CRC 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[17]. 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[18]. Women with endometrial tumours that had MMR defects were likely to have higher-grade cancers and more frequent lymphovascular space invasion[9]. Patients with MSI-H gastric cancer tend to be

[12] Hu ZI, Shia J, Stadler ZK, Varghese AM, Capanu M, Salo-Mullen E, et al. Evaluating mismatch repair deficiency in pancreatic adenocarcinoma: challenges and recommendations. Clin Cancer Res. 2018 Mar 15;24(6):1326-36.
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older, female, to have distal tumour location, intestinal type of Lauren classification, and differentiated histological type[11].

Clinical presentation, diagnosis and stage/prognosis

MMR or MSI status can be determined by examining either (1) protein expression by IHC of 4 MMR proteins (MLH1/MSH2/MSH6/PMS2) or (2) 3 to 5 tumour microsatellite loci by using a PCR assay. 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 at least 2 allelic size shifts among 3 to 5 analyzed microsatellite markers are detected by PCR. Current MMR/MSI testing with an MMR protein IHC based assay, PCR-based MSI loci testing, or a validated NGS panel is recommended by the NCCN, ESMO, and ASCO for patients with CRC[19] [20] [21].

The prognostic effect of MSI-H/dMMR status varies by tumour type and by stage:

- While MSI-H/dMMR CRC patients with early-stage disease have a survival advantage, patients with MSI-H/dMMR mCRC have a poorer prognosis and in general a trend toward worse survival outcome compared to microsatellite stable mCRC was highlighted[22] [23] [24] [25]. No unanimous views are found in literature though, e.g. Price[26] did not detect an association between DFS or OS with MSI status in mCRC patients undergoing curative resection.

- Similarly, MSI-H/dMMR endometrial tumours have been associated with a favorable prognosis value of dMMR in early stage, but a poorer survival outcome in some studies in later stages, although there is no definitive evidence of a significant association between MMR status and detrimental survival[27] [28].

- Patients with MSI-H/dMMR early stage/resected gastric cancer generally have an overall favourable prognosis[29] [30]. Less is reported in literature regarding the advanced setting, e.g. the MSI status seems to have worse prognostic value[31], so the evidence supporting the prognostic value of MSI status in the advanced gastric cancer setting are limited to date.

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[20] Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol. 2016 Aug;27(8):1386-422.
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[31] Kubota Y, Kawazoe A, Sasaki A, Mishima S, Sawada K, Nakamura Y, et al. The impact of molecular subtype on efficacy of chemotherapy and checkpoint inhibition in advanced gastric cancer. Clin Cancer Res. 2020 Jul 15;26(14):3784-90.

- In small intestine cancer, most literature data are showing an association between dMMR status and survival[32] [33] [34] [35], while few do not indicate influence on survival[36] [37]. However, almost all available literature evidence in small bowel cancer referred to resected disease, while very few cases of MSI-H referred to metastatic disease. No conclusion can be drawn on the prognostic value of MSI status in small intestine cancer in an advanced setting. The literature data always referred to the histologic type of adenocarcinoma.

- There is limited evidence in the literature to conclude on the prognostic value of MSI status in biliary cancer. Some references reported longer OS[38] [39], other no association with survival [40] [41], but the conclusion is hampered by the low number of MSI-H patients identified.

- A more favourable prognosis was seen in pancreatic MSI-H cancer after surgical resection[42] [43]. In the meta-analysis by Luchini et al[44], potential association between MSI/dMMR and prognosis in PDAC was not found, highlighting however that data are too few to draw any definitive conclusion. Evidence is too limited to date to conclude on the prognostic value of MSI-H status in pancreatic cancer in the advanced/metastatic setting.

Management

To date, the only approved treatment options in the EU for patients with MSI-H/dMMR cancers are dostarlimab for MSI-H/dMMR recurrent or advanced endometrial cancer that has progressed after platinum-based chemotherapy, pembrolizumab in MSI-H/dMMR metastatic colorectal cancer (mCRC) as first line treatment, nivolumab in combination with ipilimumab for adult patients with mCRC after prior fluoropyrimidine-based combination chemotherapy.

The approval of dostarlimab in MSI-H/dMMR endometrial cancer in April 2021 was based on results from the Phase I GARNET trial in 108 patients, showing an ORR of 43.5% (95% CI 34%, 53.4%), and median DOR not reached (range 2.6, 28.1+). The incidence of treatment-related AEs of Grade 3 or higher was 13.2%[45].

Pembrolizumab was approved in the EU in January 2021 as first line treatment for patients with CRC MSI-H/dMMR metastatic CRC based on the results of the pivotal phase III study KEYNOTE-177. A total of 307 patients were randomized to pembrolizumab compared to standard chemotherapy (FOLFOX/FOLFIRI +/-

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cetuximab or bevacizumab). Pembrolizumab showed statistically significant PFS improvement over standard chemotherapy [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)], supported by a favourable OS trend [HR 0.77 (95% CI 0.54, 1.09), p=0.0694, median OS NR vs 34.8 months (95%CI 26.3, NR)] and higher ORR (43.8% vs 33.1%) with durable responses (median DOR NR vs 10.6 months)[46].

The combination nivolumab and ipilimumab in MSI-H/dMMR CRC was approved in June 2021 based on the results of the single arm phase 2 study CheckMate 142. Based on 119 patients, the combination showed an ORR of 61.3% (95%CI 52, 70.1) by BICR, with median DOR not reached. Grade 3-4 drug-related AEs occurred in 31.9% of the population[47].

Where there is no approved MSI-H-specific therapy, patients with MSI-H cancer are managed with the same Standard of Care (SOC) treatments that are used to treat other cancers regardless the molecular alteration. The MAH has provided a summary of efficacy results for the currently available and recommended treatment in the 2L+ setting relative to the 6 tumour types selected (see tables below). To further contextualize the results of pembrolizumab, the MAH has conducted a systematic literature review (SLR) and meta-analysis to provide a better estimate of the efficacy of historical comparator. All analyses have been provided for an MSI unselected population due to the general lack of data in this particular subset. The methodology of the SLR/meta-analysis is considered appropriate. It is to note however that the meta-analysis is heterogeneous, especially for the selection of included studies. The results of such meta-analyses, although cannot be regarded as strong evidence, are considered a useful indication to contextualize the data provided within each tumour type.

Table 1: Range of Efficacy Outcomes Reported in Phase 3 Clinical Studies

Tumour types Line of therapy	ORR (%)	DOR (months)	PFS (months)	OS (months)	Reference
Metastatic or advanced CRC					
Phase 3 2L (9 studies)	3.3-24.2	5.5-5.7	2.5-8.4	10.0-21.5	
Phase 3 3L (9 studies)	1.0-22.9	2.0-11.4	1.5-4.4	6.1-10.4	
Metastatic or advanced endometrial					
Phase 3 2L (1 study)	15.2-15.7	NR	3.4-4.0	10.9-12.3	
Metastatic or advanced gastric					
Phase 3 2L (13 studies)	0-28.0	2.8-5.2	2.1-4.8	3.6-14.0	
Phase 3 3L (1 study)	2.2-4.3	5.5	1.4-2.7	4.6-5.0	
Metastatic or advanced small intestine					
Phase 2/3 2L	NR	NR	NR	NR	
Retrospective study (1 study)	20	NR	3.2	10.5	
Metastatic or advanced pancreatic					
Phase 3 2L (6 studies)	1.0-20.6	NR	1.5-3.9	3.3-9.9	
Metastatic or advanced biliary					

[46] European Medicine Agency: EMA/CHMP/33664/2021 – EPAR Keytruda, https://www.ema.europa.eu/en/documents/variation-report/keytruda-h-c-3820-ii-0091-epar-assessment-report-variation_en.pdf, September 2021.
[47] European Medicine Agency: EMA/314215/2021 – EPAR Opdivo, https://www.ema.europa.eu/en/documents/variation-report/opdivo-h-c-3985-ws-1840-epar-assessment-report-variation_en.pdf, September 2021.

Tumour types Line of therapy	ORR (%)	DOR (months)	PFS (months)	OS (months)	Reference
Phase 3 2L (1 study)	5	NR	4.0	5.3-6.2	

Abbreviations: 2L=Second line; 3L=Third line; CRC=Colorectal carcinoma; DOR=Duration of response; NR=Not reported; ORR=Objective response rate; OS=Overall survival; PFS=Progression-free survival.

Table 2: Range of Efficacy Outcomes Reported in Phase 3 Clinical Studies Assessing Standard of Care Therapies per ESMO Guideline

Tumour types Line of therapy	SOC therapies per ESMO guideline	ORR (%)	DOR (months)	PFS (months)	OS (months)	References
Metastatic or advanced CRC						
Phase 3 2L	FOLFOX or CAPOX or FOLFIRI +/-bevacizumab; or aflibercept or ramucirumab with FOLFIRI; cetuximab or panitumumab	3.3-24.2	5.5-5.7	2.5-8.4	10.0-21.5	
Phase 3 3L+	Regorafenib/TAS-102	1.0-4.0	2.0-4.8	1.9-3.2	6.4-8.8	
Metastatic or advanced endometrial						
Phase 3 2L	None	N/A	N/A	N/A	N/A	N/A
Metastatic or advanced gastric						
Phase 3 2L	taxane (docetaxel, paclitaxel) or irinotecan or ramucirumab as single agent or combo with paclitaxel	0-28.0	2.8-5.2	2.1-4.8	5.2-14.0	
Phase 3 3L+	None	N/A	N/A	N/A	N/A	N/A
Metastatic or advanced small intestine						
Phase 3 2L	None	N/A	N/A	N/A	N/A	N/A
Metastatic or advanced pancreatic						
Phase 3 2L	5FU/folinic acid/oxaliplatin; Nanoliposomal irinotecan/5FU	1.0-16.0	NR	1.5-3.1	3.3-9.9	
Metastatic or advanced biliary						
Phase 3 2L	None	N/A	N/A	N/A	N/A	N/A

Abbreviations: 2L=Second line; 3L=Third line; CRC=Colorectal carcinoma; DOR=Duration of response; N/A=Not applicable; NR=Not reported; ORR=Objective response rate; OS=Overall survival; PFS=Progression-free survival

Results of Systematic Literature Review and Meta-Analysis of Standard Therapies

Main results are summarized below.

In addition, the MAH provided a summary of the available literature data for immunotherapy in MSI-H selected solid tumours.

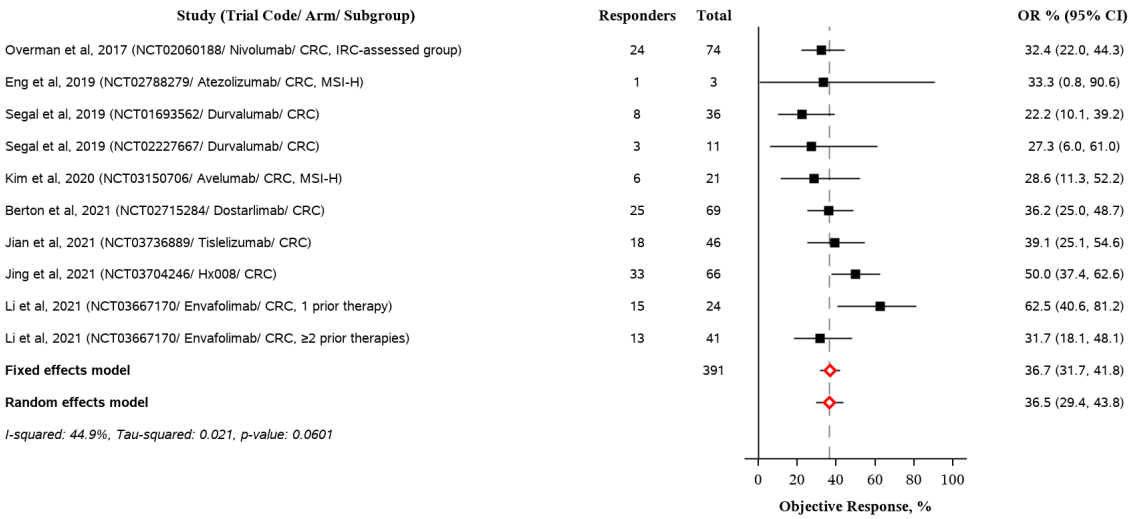
Colorectal cancer

Table 3: Comparison of Efficacy Between SLR/meta-analysis and KEYNOTE-164 (CRC)

	CRC			
	SLR/meta-analysis		KEYNOTE-164 [a]	
	Unselected Population	I/O (mono) in MSI-H/dMMR Population	Cohort A	Cohort B
ORR, % (95% CI)	17.5 (14.2, 21.0)	36.5 (29.4, 43.8)	32.8 (21.3, 46.0)	34.9 (23.3, 48.0)
Median PFS, months (95% CI)	6.0 (5.6, 6.7)	8.3 (4.1, 10.7)	2.3 (2.1, 8.1)	4.1 (2.1,18.9)
PFS rate, % at 6 Months	50.1	54.7	42.6	48.9
PFS rate, % at 12 Months	18.5	39.9	34.4	40.6
PFS rate, % at 24 Months	3.1	21.3	31.0	36.7
Median OS, months (95% CI)	13.1 (12.1, 14.0)	18.1 (12.4-19.1)	31.4	47.0 (19.2, NR)
OS rate, % at 6 Months	79.8	79.4	86.9	84.1
OS rate, % at 12 Months	59.0	65.1	72.1	76.2
OS rate, % at 24 Months	23.5	38.6	55.3	63.0

Abbreviations: I/O=immunotherapy; NA=not available NR=not reached ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

Figure: Meta-Analysis of Objective Response for Colorectal Cancer ⩾2L Immunotherapies (Monotherapy) Among Clinical Trials (MSI-H/dMMR Population)



Endometrial cancer

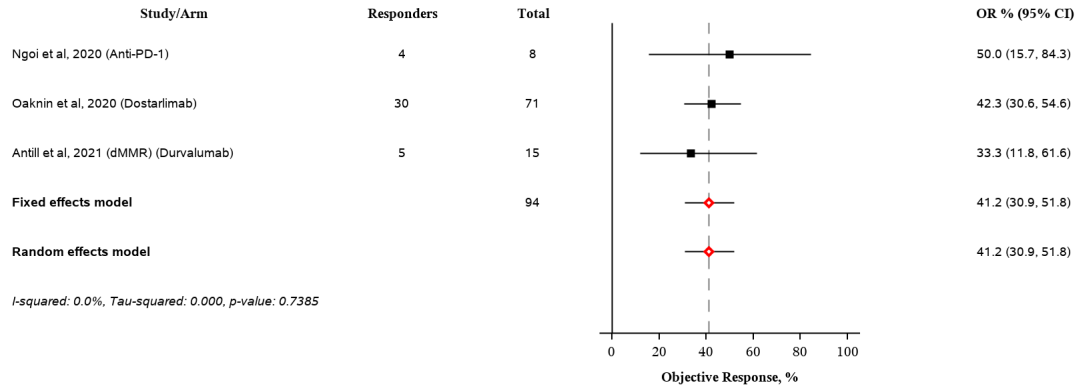
Table 4: Comparison of Efficacy Between SLR/meta-analysis and KEYNOTE-158 (Endometrial Cancer)

	Endometrial	
	SLR/meta-analysis	**KEYNOTE-158[a]**
ORR, % (95% CI)	14.6 (10.7, 18.9)	50.6 (39.4, 61.8)
Median PFS, months (95% CI)	3.2 (2.8, 3.9)	13.1 (4.9, 25.7)
PFS rate, % at 6 Months	25.5	60.0
PFS rate, % at 12 Months	10.3	50.9
PFS rate, % at 24 Months	0.2	39.0
Median OS, months (95% CI)	11.2 (8.3, 12.3)	NR (48.0, NR)
OS rate, % at 6 Months	70.9	85.5
OS rate, % at 12 Months	45.9	73.3
OS rate, % at 24 Months	13.1	67.2

Abbreviations: NR=not reached; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

a Database cutoff date: 15OCT2021;

Figure: Meta-analysis of Objective Response for Endometrial Cancer ⩾2L Immunotherapies (Monotherapy) among Clinical Trials and Observational Studies (MSI-H/dMMR Population)



Gastric cancer

Table 5: Comparison of Efficacy Between SLR/meta-analysis and KEYNOTE-158 (Gastric Cancer)

	Gastric	
	SLR/meta-analysis	**KEYNOTE-158[a]**
ORR, % (95% CI)	15.0 (12.7, 17.5)	37.3 (24.1, 51.9)
Median PFS, months (95% CI)	3.5 (3.2, 3.7)	4.1 (2.1, 24.6)
PFS rate, % at 6 Months	25.7	47.1
PFS rate, % at 12 Months	7.1	41.1
PFS rate, % at 24 Months	0.6	38.5
Median OS, months (95% CI)	7.9 (7.4, 8.5)	26.9 (6.6, NR)
OS rate, % at 6 Months	62.5	66.7
OS rate, % at 12 Months	30.4	54.8
OS rate, % at 24 Months	6.7	50.0

Abbreviations: NR=not reached; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

a Database cutoff date: 15OCT2021

Biliary cancer

Table 6: Comparison of Efficacy Between SLR/meta-analysis and KEYNOTE-158 (Biliary Cancer)

	Biliary	
	SLR/meta-analysis	**KEYNOTE-158 [a]**
ORR, % (95% CI)	6.6 (4.1, 9.7)	40.9 (20.7, 63.6)
Median PFS, months (95% CI)	3.1 (2.5, 3.8)	4.2 (2.1, 24.9)
PFS rate, % at 6 Months	26.7	45.5
PFS rate, % at 12 Months	6.9	36.4
PFS rate, % at 24 months	NA [b]	31.8
Median OS, months (95% CI)	6.8 (5.9, 7.5)	19.4 (6.5, 44.8)
OS rate, % at 6 Months	55.3	81.8
OS rate, % at 12 Months	24.6	63.6
OS rate, % at 24 Months	2.0	50.0

Abbreviations: NR=not reached; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.
[a] Database cutoff date: 15OCT2021.

Small intestine cancer

Table 7: Comparison of Efficacy Between SLR/meta-analysis and KEYNOTE-158 (Small Intestine/Small Bowel Adenocarcinoma)

	Small Intestine/Small Bowel Adenocarcinoma	
	SLR/meta-analysis [48]	**KEYNOTE-158 [a]**
ORR, % (95% CI)	20 (N/A)	55 (35.3, 74.5)
Median PFS, months (95% CI)	3.2 (2.1, NR)	23.4 (4.3, NR)
Median OS, months (95% CI)	10.9 (7.0, NR)	NR (16.2, NR)

Abbreviations: N/A=not applicable; NR=not reached; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

[a] Database cutoff date: 15OCT2021;

Pancreatic cancer

Table 8: Comparison of Efficacy Between SLR/meta-analysis and KEYNOTE-158 (Pancreatic Adenocarcinoma)

	Pancreatic	
	SLR/meta-analysis	**KEYNOTE-158[a]**
ORR, % (95% CI)	6.8 (4.5, 9.4)	18.2 (5.2, 40.3)
Median PFS, months (95% CI)	2.8 (2.4, 3.3)	2.1 (1.9, 3.4)
PFS rate, % at 6 Months	23.2	20.8
PFS rate, % at 12 Months	6.8	15.6
PFS rate, % at 24 Months	0.5	10.4
Median OS, months (95% CI)	6.2 (5.3, 7.1)	3.7 (2.1, 9.8)
OS rate, % at 6 Months	51.9	36.4
OS rate, % at 12 Months	20.7	22.7
OS rate, % at 24 Months	3.1	22.7

Abbreviations: ORR=objective response rate; OS=overall survival; PFS=progression-free survival.
a Database cutoff date: 15OCT2021;

[48] Overman MJ, Adam L, Raghav K, Wang J, Kee B, Fogelman D, et al. Phase II study of nab-paclitaxel in refractory small bowel adenocarcinoma and CpG island methylator phenotype (CIMP)-high colorectal cancer. Ann Oncol. 2018;29(1):139-44. Erratum in: Ann Oncol. 2019;30:495.

Real-world Evidence

The associated lack or limited MSI-H/dMMR testing across various cancers prior to global approval of immunotherapies for specific or multiple MSI-H/dMMR cancers has presented a challenge with gathering real-world evidence on clinical outcomes for SOC treatments for MSI-H/dMMR cancers. The real-world evidence on clinical outcomes for SOC and immunotherapies for MSI-H/dMMR cancers is limited and mostly pertaining colon cancer, and has been summarized by the MAH below.

A retrospective study conducted in 18 centers in France included MSI-H/dMMR metastatic CRC patients diagnosed between 2007 and 2017[49]. Overall, 342 patients with MSI-H/dMMR metastatic CRC were included, of which 220 (64.3%), 136 (39.8%) and 56 (16.4%) patients received 1L, 2L and 3L chemotherapy with or without targeted therapy, respectively. The primary endpoint was PFS in patients receiving 1L chemotherapy. PFS and OS were also reported across various lines. Median PFS and OS on 1L chemotherapy plus targeted therapy were 6.0 months (95% CI: 5.0, 7.8) and 26.3 months (95% CI: 21.5, 35.2), respectively. Median PFS and OS in the 2L setting for chemotherapy with or without targeted therapy were 4.4 months (95% CI: 3.5, 5.4) and 21.6 months (95% CI: 14.2, 25.3), respectively. For 3L chemotherapy with or without targeted therapy, median PFS and OS were 3.6 months (95% CI: 2.3, 4.6) and 13.7 months (95% CI: 8.6, 20.8), respectively.

Another retrospective chart review study conducted at 2 tertiary French University hospitals evaluated real-world clinical outcomes in patients diagnosed with stage IV MSI-H/dMMR CRC and treated with 2 or more prior lines of SOC therapy[50]. Key exclusion criterion was prior or current treatment for 3L with immune checkpoint inhibitors. OS from the start of 3L treatment (index date) was reported along with BORR, CR and PR. For the 36 MSI-H/dMMR mCRC patients that were included, the median OS for patients receiving 3L chemotherapy-based treatments was 9.0 months (95% CI: 4.0, 14.1). Median OS decreased to 4.1 months (95% CI: 4.0, 9.0) when survival data of patients receiving immune checkpoint inhibitors at fourth or later lines was censored at progression date of prior treatment line. For 3L treatment BORR was 5.7% (2 patients with PRs).

Another study representing real-world evidence for immunotherapies, assessed clinical outcomes in patients with MSI-H solid tumours treated with pembrolizumab monotherapy after May 2017, following the FDA approval[51]. Patients with MSI-H solid tumours were selected from the US Flatiron Health-Foundation Medicine clinico-genomic database, a nationwide de-identified electronic health record - derived database linked to comprehensive genomic profiling data. Time to treatment discontinuation and OS from first pembrolizumab use were estimated with KM analyses of all patients and those with the most common tumour types. A total of 129 MSI-H patients across 33 tumour types, with CRC (N=36) and endometrial cancer (N=39) being the most common, received pembrolizumab. Median OS exceeded 1 year across all tumour types, including CRC, endometrial, and other tumours (see table below).

[49] Tougeron D, Sueur B, Zaanan A, de la Fouchardiere C, Sefrioui D, Lecomte T, et al. Prognosis and chemosensitivity of deficient MMR phenotype in patients with metastatic colorectal cancer: an AGEO retrospective multicenter study. Int J Cancer. 2020;147:285-96.
[50] Cohen R, Andre T, Roset M, Amonkar M, Renna P, Lara N, et al. Real-world clinical outcomes for third-line standard of care regimens in deficient mismatch repair or microsatellite instability-high metastatic colorectal cancer in France [abstract]. Presented at: European Society for Medical Oncology (ESMO) 22nd World Congress on Gastrointestinal Cancer; 2020 Jul 1-4; [online meeting]. Ann Oncol. 2020;31(suppl 3):S170-1.
[51] Snow T, Swaminathan A, Snider J, Schrock AB, Li G, Alexander BM, et al. Characteristics and outcomes of real-world (RW) patients (pts) with microsatellite instability-high (MSI-H) solid tumours treated with pembrolizumab monotherapy (P)after FDA approval [abstract]. Presented at: 2020 American Society of Clinical Oncology (ASCO) Virtual Scientific Program; 2020 May 29-31; [online meeting]. J Clin Oncol. 2020;38(15 suppl). Abstract no.3060.

Table 9: Real-world Effectiveness of Pembrolizumab Across 33 MSI-H tumour types[34]

	N	Median TTD, month [95% CI]	Median OS, month [95% CI]	12-month OS, % [95% CI]
All tumours	129	5.5 [4.1-7.6]	NR [14.6-NR]	62.7 [53.3-73.7]
CRC	36	4.5 [2.8-9.2]	NR [12.9-NR]	71.8 [55.0-93.7]
Endometrial	39	6.2 [3.0-11.0]	NR [11.0-NR]	58.4 [42.9-79.5]
Other tumours [a]	54	6.1 [2.8-8.2]	17.3 [9.9-NR]	60.3 [46.7-78.0]

Abbreviations: CI=confidence interval; CRC=colorectal cancer; OS=overall survival; TTD=Time to treatment discontinuation.

[a] Tumours included (largest to smallest N): gastric, occult/unknown primary, prostate, esophageal/gastroesophageal junction, breast, hepatobiliary, small intestine, non-small cell lung, pancreatic, ovarian.

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.

In the EU, pembrolizumab is currently approved (as monotherapy and in combination with other agents) for the treatment of melanoma, NSCLC, RCC, HNSCC, urothelial cancer, esophageal cancer, triple negative breast cancer, endometrial carcinoma and cHL. In January 2021 pembrolizumab as monotherapy was approved 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

- EMA-HTA Parallel Scientific Advice for KEYNOTE-158, 06-OCT-2015 (EMEA/H/SAH/039/3/2015/II):

- The proposal to conduct a basket study in multiple rare tumours was discussed, which was considered "acceptable by the CHMP at this stage, based on available data showing the potential broad activity of pembrolizumab across histologies, and the potential to identify predictive biomarkers of clinical utility across histologies. While exploratory in nature, it cannot be excluded in principle that such a study could be considered for registration, taking into account the rarity and the poor treatment alternatives. However, provided that convincing results will emerge from the proposed study in the selected tumours, it will mostly depend on the type and strength of background information available at the time of filing, coming from the overall clinical development plan."

- It was discussed that "before starting such a basket trial in rare tumours, moreover aimed to support a regulatory approval, one (or more?) biomarker with proven predictive value regardless of histology are already identified in more common malignancies" and the MAH was "strongly encouraged to use predictive biomarker data from the extensive (external) pembrolizumab development programme to inform the basket study, in addition to the data generated from within the current basket study".

- With regard to rare tumours, it was "recommended that TTP on prior treatment is carefully captured in order to allow for intra-patient comparisons that could further support the efficacy of pembrolizumab in these rare tumours". Such analysis has been provided (see clinical efficacy section).

- The CHMP further noted that, "whilst the exploratory nature of the trial at inception is well understood, it is likely to be necessary, at some point, to more closely define the hypothesis that is subject to 'confirmatory 'test'', i.e. that at some point before full recruitment a decision to draw inferences based on histology-selected / histology-unselected / biomarker-selected /biomarker-unselected populations should be taken and 'confirmed' prospectively as the study continues." The study seems however to be exploratory in nature with any confirmatory part missing.

- The CHMP finally commented that "The strength of evidence supporting the use of the predictive biomarker(s) is fundamental for the interpretation of study results. Of note ORR may be a poor overall measure of patient benefit probably underestimating the effects on PFS/OS." In order to "understand the prevalence of these biomarkers of interest and their association with OS to further characterize the prognostic value of these biomarkers", the MAH proposed "a retrospective molecular epidemiology study from Danish National Registries and prospective/retrospective data from EORTC SPECTA (Screening Patients for Efficient Clinical Trial Access)". This was considered acceptable, although recommended that data used are not too far back. The MAH informed that the molecular epidemiology studies from Danish National Registries and EORTC SPECTA were cancelled for reasons beyond the control of the MAH. As a result, no data were available from these sources.

- PRO were also discussed, but the CHMP highlighted that "the interpretation of data will be limited by the uncontrolled setting and the rather heterogeneous patient population that will be enrolled in the study".

- EMA Scientific Advice on MSI-H CRC indication (KEYNOTE-164 and KEYNOTE-177), 22-OCT-2015 (EMEA/H/SA/2437/8/2015/II):

Regarding KEYNOTE-164, CHMP highlighted that "the number of patients (60) appears limited, and there is a risk for overestimation of the response particularly since this is a single-arm trial, so an increase in the sample size could be considered. To grant an indication, a truly high rate of durable responses with an acceptable safety profile is expected". At the time of the Advice, KEYNOTE-177 was proposed to extend an MSI-H CRC indication in first line; however, pembrolizumab monotherapy has been already approved in EU in 1L based on KEYNOTE-177 results (January 2021).

2.1.4. General comments on compliance with GCP

The Clinical trials were performed in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human participants in biomedical research as claimed by the MAH. Clinical trials carried out outside of the European Union meet the ethical requirements of Directive 2001/20/EC as claimed by the MAH.

The assessment of KN158 and KN164 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 ID	Phase	Country/ Region	Study Title	Study design	Dosing regimen	Study population	Participant exposure
- 3475-158 [Ref. 5.3.5.2: P158V09MK3475]	2	- Australia, Brazil, Canada, Colombia, Denmark, France, Germany, Israel, Italy, Japan, Mexico, Netherlands, Norway, Republic of Korea, Russian Federation, Spain, South Africa, USA	- A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predicitive Biomarkers in Subjects with Advanced Solid Tumors (KEYNOTE-158)	- Open-label, multicenter, non-randomized, multi-group, interventional study	- Pembrolizumab 200 mg IV Q3W	- Males/females - Age: 18 and older Cohort K: participants with any unresectable and/or metastatic solid tumor that is MSI-H, excluding colorectal carcinoma	- 351 participants were treated

Study ID	Phase	Country / Region	Study Title	Study design	Dosing regimen	Study population	Participant exposure
3475-164 [Ref. 5.3.5.2: P164V04MK3475]	2	Australia Belgium Canada France Germany Israel Japan Republic of Korea Spain USA	A Phase II Study of Pembrolizumab (MK-3475) as Monotherapy in Subjects with Previously Treated Locally Advanced Unresectable or Metastatic (Stage IV) Mismatched Repair Deficient or Microsatellite Instability-High Colorectal Carcinoma (KEYNOTE-164)	Single-arm, multi-cohort, open-label, multi-site clinical trial	Pembrolizumab 200 mg IV Q3W	Men and women, ≥18 years of age, with locally advanced unresectable or metastatic dMMR or MSI-H CRC	124 participants treated with pembrolizumab

2.3.2. Pharmacokinetics

Pembrolizumab PK disposition has been characterized via pooled population PK analyses using serum concentration-time data contributed from subjects across various clinical studies using a time-dependent PK (TDPK) model. The PK reference dataset for monotherapy includes all available PK data from subjects enrolled on KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, KEYNOTE-010, and KEYNOTE-024, with an overall sample size of 2993. This serves as the PK reference analysis to support descriptions of pembrolizumab pharmacokinetics in the EU SmPC.

Based on the existing robust characterization of pembrolizumab PK, a comparison of observed PK for the current indication, MSI-H cancer, with the predictions from the TDPK reference model is provided with this EoI.

Absorption

Pembrolizumab is dosed via the intravenous route and therefore is immediately and completely bioavailable.

Distribution

Consistent with a limited extravascular distribution, the volume of distribution of pembrolizumab at steady state is small (6.0 L; coefficient of variation [CV]: 20%). As expected for an antibody, pembrolizumab does not bind to plasma proteins in a specific manner.

Elimination

Pembrolizumab CL is approximately 23% lower (geometric mean, 195 mL/day [CV%: 40%]) after achieving maximal change at steady state compared with the first dose (252 mL/day [CV%: 37%]); this decrease in CL with time is not considered clinically meaningful. The geometric mean value (CV%) for the terminal half-life is 22 days (32%) at steady-state.

Pharmacokinetic in Subjects with MSI-H Cancer

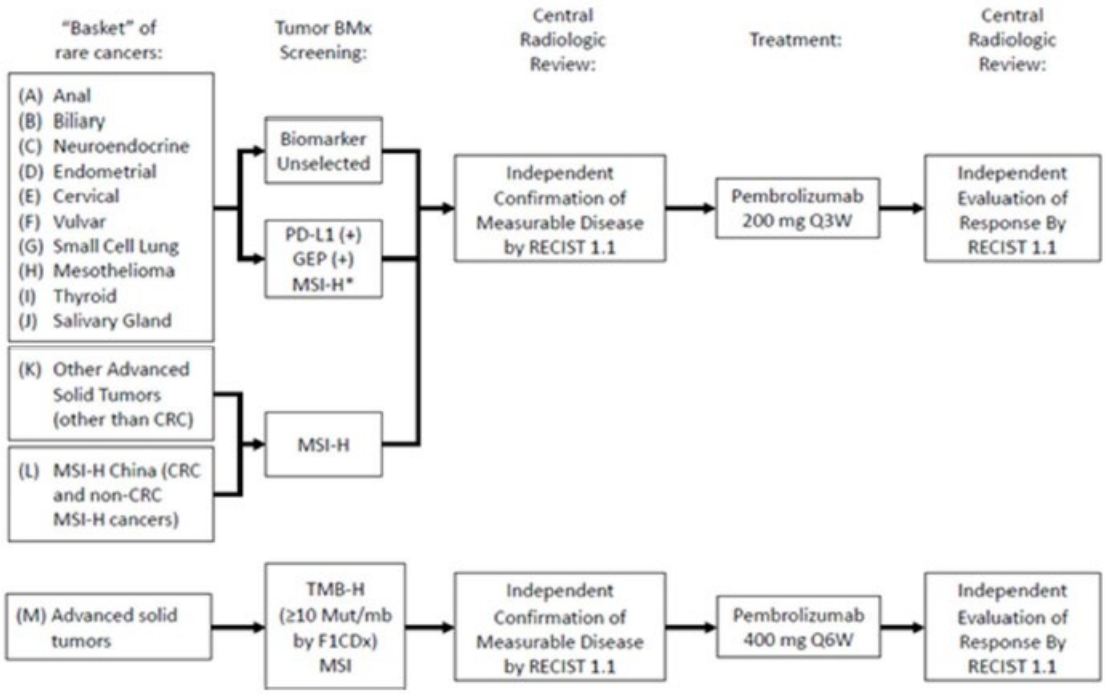
The updated clinical pharmacology results specific to this submission include:

- PK data from subjects with MSI-H cancer from KEYNOTE-158 and KEYNOTE-164, receiving pembrolizumab 200 mg Q3W as monotherapy agent.
- A comparison of KN158 and KN164 observed PK data with reference model (TDPK) predicted PK.

PK Data KEYNOTE-158

KEYNOTE-158 is *an ongoing*, non-randomized, single arm, multi-site, open-label study of pembrolizumab in previously treated participants who have locally advanced unresectable or metastatic rare cancers for whom prior standard first-line treatment had failed. Eligible participants received pembrolizumab 200 mg IV Q3W.

Figure 9-1
Study Design



*Selection of BMx(s) for biomarker enrichment may occur after interim analyses.

Abbreviations: BMx=Biomarker; CRC=Colorectal carcinoma; GEP=Gene expression profile; MSI-H=Microsatellite instability-high; PD L1=Programmed Cell Death-Ligand 1; Q3W=Every 3 weeks; RECIST=Response Evaluation Criteria in Solid Tumors.

For Cohort M, MSI= MSI-H excluded.

The Pharmacokinetic objective of study KEYNOTE-158 was to evaluate serum concentrations of pembrolizumab in patients with unresectable or metastatic, microsatellite-instability–high cancer (MSI-H) (KEYNOTE 158).

The table below shows an Overview of Pembrolizumab Cohorts Included in KEYNOTE-158 PK Analysis:

Table 1: Overview of Pembrolizumab Cohorts Included in KEYNOTE-158 PK Analysis

Indication	Cohort	Treatment	Number of Subjects providing PK [a]	Total	Data cut off
MSI-H	Endometrial Carcinoma	200 mg Q3W	7	93	28-Apr-2017
	Cervical Carcinoma	200 mg Q3W	2		
	Mesothelioma	200 mg Q3W	1		
	Salivary Gland Carcinoma	200 mg Q3W	1		
	Non-CRC MSI-H	200 mg Q3W	82		

[a] number of unique subject numbers in dataset
Data Source: [05Q8NM: analysis-p158pkdm25msih]

Among 93 subjects providing PK sampling, 92 subjects with evaluable samples were considered in the final analysis and 10 samples were excluded from pembrolizumab PK analysis.

PK sample schedule in KEYNOTE-158: Predose pembrolizumab serum concentrations (Ctrough) were obtained within 24 hours prior to dosing at Cycles 1 and 4. Postdose serum concentrations (Cmax) were drawn within approximately 30 minutes after the end of the infusion in Cycle 1.

Phoenix™ WinNonlin® (Version 6.3.0.395) software was used for pharmacokinetic analysis.
Summary statistics of the observed pembrolizumab trough (pre-dose) and post-dose concentrations in MSI- H subjects from KN0158 study are presented in the table below:

Table 2 Summary Statistics of Pembrolizumab Predose (C_{trough}) and Postdose (C_{max}) Serum Concentration Values Following Administration of Multiple I.V. Doses 200 mg Q3W in KEYNOTE-158 MSI-H

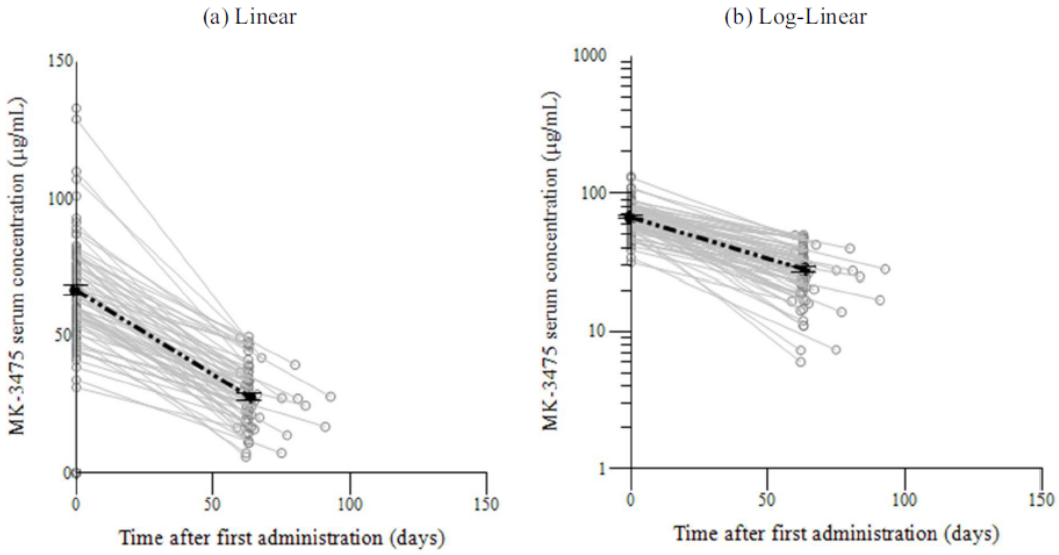
Cycle	NOMTAFD	N	GM (%CV)	GM (SD)	AM (SD)	Min	Median	Max
	day		(µg/mL)					
Predose (C_{trough})								
Cycle 4 (Week 9)	63	69	25.4 (50)	25.4 (11)	27.9 (11)	6.01	27.0	49.7
Postdose (C_{max}) (within 30 min post end of infusion)								
Cycle 1 (Week 0)	0	90	64.4 (27)	64.4 (18)	66.7 (18)	31.2	65.2	133

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

[05Q8NM: analysis-p158pkdm25msih]

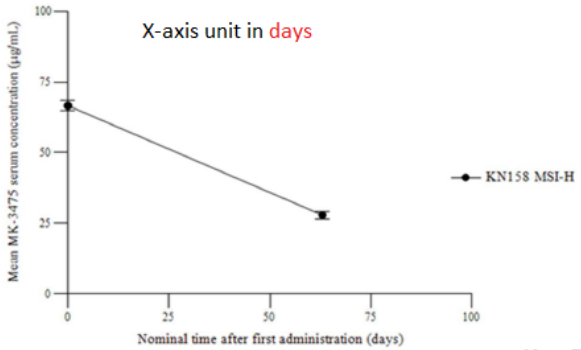
The following figures show the individual and Arithmetic Mean (SE) Pembrolizumab Concentration - Time Profiles Following Multiple I.V. Doses of 200 mg Q3W:

Individual and Arithmetic Mean (SE) Pembrolizumab Concentration - Time Profiles Following Multiple I.V. Doses of 200 mg Q3W in Study KEYNOTE-158 MSI-H (a) Linear scale, (b) Log scale

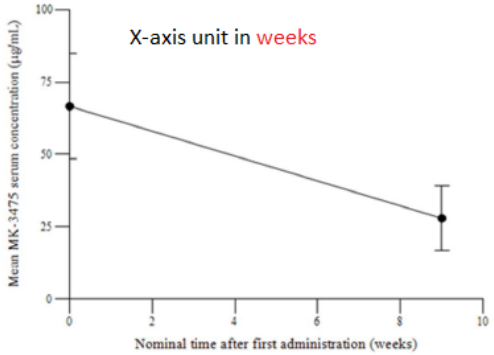


Note: Grey lines represent individual concentration observations. Black dashed lines represent arithmetic mean concentrations and error bars are associated +/- SE (Standard Error).
Data Source: [05Q8NM: analysis-p158pkdm25msih]

Arithmetic Mean (SE) Pembrolizumab Concentration -Time Profiles Following Multiple I.V. Doses of 200 mg Q3W to Subjects in Study KEYNOTE-158 MSI-H (Linear scale)



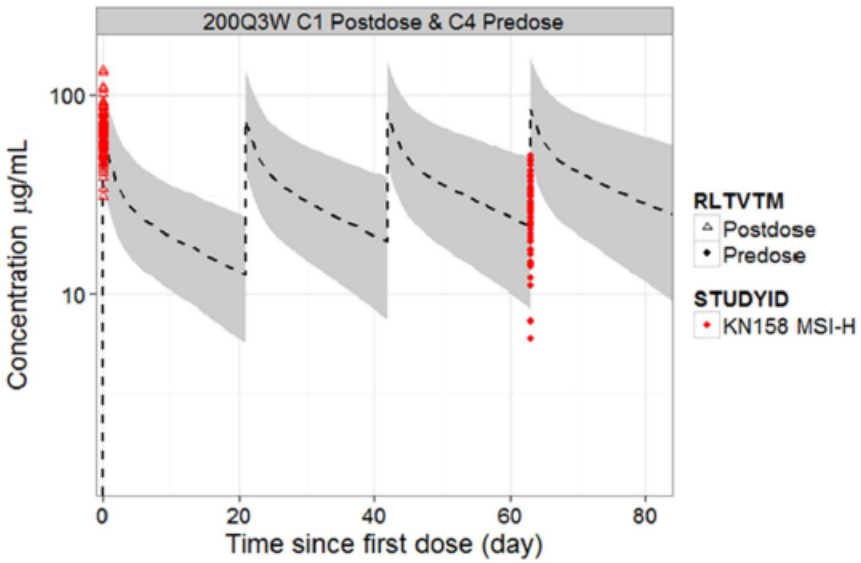
Note: This plot is Arithmetic Mean with Standard Error (SE). X-axis unit is in days.
Data Source: [05Q8NM: analysis-p158pkdm25msih]



Note: This plot is Arithmetic Mean with Standard Deviation (SD). X-axis unit is in weeks.
Data Source: [05Q8NM: analysis-p158pkdm25msih]

The observed and predicted pembrolizumab concentration-time profiles following 200 mg Q3W administration after 1rst dose and at Cycle 4 (9 weeks) are illustrated in the following figure:

Observed Concentration Data in KEYNOTE-158 MSI-H Subjects Receiving 200 mg Q3W Pembrolizumab with Reference Model-Predicted Pharmacokinetic Profile for 200 mg Q3W Dose Regimen

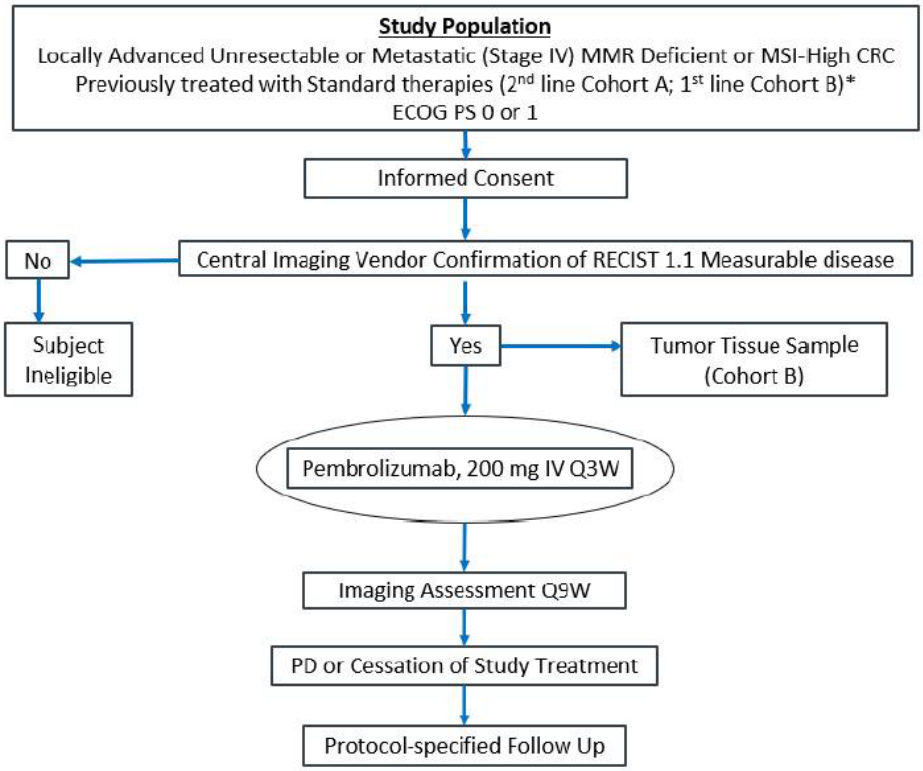


After 1st dose and at Cycle 4 (9 weeks) on log scale. Red symbols are individual observed data (nominal time) from subjects with MSI-H cancer in KEYNOTE-158; black line is median predicted concentrations from the model for a regimen of 200 mg Q3W and the grey shaded area represents the 90% prediction interval.
Data Source: [05Q8NM: analysis-p158pkdm25msih]

PK Data KEYNOTE-164

KEYNOTE-164 is an open-label, single-arm, multicenter, multicohort, Phase 2 study of pembrolizumab in previously treated participants with locally advanced unresectable or metastatic (Stage IV) MSI-H CRC.

Study Design for KEYNOTE-164



Abbreviations: CRC=Colorectal carcinoma; ECOG=Eastern Cooperative Oncology Group; IV=Intravenous; MMR=Mismatch repair; MSI-H=Microsatellite instability-high; PD=Progressive disease; PS=Performance status; Q3W=Every 3 weeks; Q9W=Every 9 weeks; RECIST=Response Evaluation Criteria in Solid Tumors.
* Line of therapy refers to prior standard treatment received.

The pharmacokinetics objective of this study was to evaluate pembrolizumab serum concentrations from KEYNOTE-164 mismatched repair (MMR) deficient or microsatellite-instability high (MSI-H) colorectal carcinoma (CRC) subjects.

The table below shows an Overview of Pembrolizumab Cohorts Included in KEYNOTE-164 PK Analysis:

Indication	Study	Treatment	Number of Subjects providing PK[a]	Data cut off
MSIH-CRC	KEYNOTE-164	200 mg Q3W	60	10-Feb-2017

[a] number of unique subject numbers in dataset
Data Source: [05Q8NM: analysis-p164pkdm10]

PK sample schedule in KEYNOTE-164: Predose pembrolizumab serum concentrations (Ctrough) were obtained within 24 hours prior to dosing at Cycles 1, 2, 4, 6, 8 and every 4 cycles (12 weeks) thereafter. Postdose serum concentrations (Cmax) were drawn within approximately 30 minutes after the end of the infusion in Cycle 1 and Cycle 8. Additional PK samples were drawn at 24 hours (day 1), between 72 and 168 hours (3-7 days) and 336 hours (day 14) after Cycle 1 dosing.

Phoenix™ WinNonlin® (Version 6.3.0.395) software was used for pharmacokinetic analysis.
Summary statistics of the observed pembrolizumab trough (pre-dose) and post-dose concentrations following Administration of Multiple I.V. Doses 200 mg Q3W in KEYNOTE-164 are presented in the table below:

Summary Statistics of Pembrolizumab Predose (C_{trough}), Postdose (C_{max}) and Post Cycle 1 Serum Concentration Values Following Administration of Multiple I.V. Doses 200 mg Q3W in KEYNOTE-164

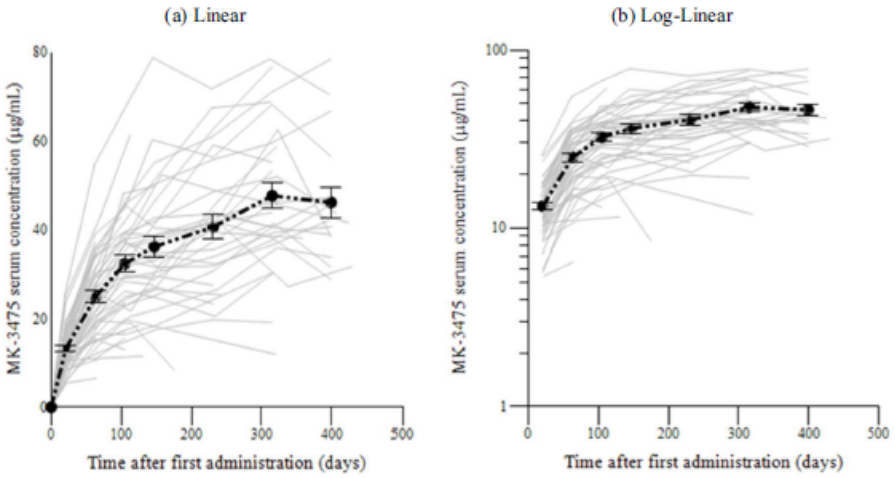
Cycle	NOMTAFD	N	GM (%CV)	GM (SD)	AM (SD)	Min	Median	Max
	day		(µg/mL)					
Predose (C_{trough})								
Cycle 2 (Week 3)	21	56	12.5 (35)	12.5 (5)	13.2 (5)	5.44	12.4	25.6
Cycle 4 (Week 9)	63	51	23.1 (42)	23.1 (9)	24.9 (9)	6.52	23.4	54.7
Cycle 6 (Week 15)	105	43	30.1 (41)	30.1 (12)	32.4 (12)	11.5	31.8	67.4
Cycle 8 (Week 21)	147	34	33.6 (43)	33.6 (14)	36.2 (14)	8.40	33.7	78.8
Cycle 12 (Week 33)	231	31	37.7 (43)	37.7 (15)	40.6 (15)	11.9	41.6	71.8
Cycle 16 (Week 45)	315	29	45.3 (34)	45.3 (15)	47.7 (15)	19.1	43.9	78.5
Cycle 20 (Week 57)	399	17	44.3 (29)	44.3 (14)	46.2 (14)	28.8	42.5	78.5
Postdose (C_{max}) (within 30 min post end of infusion)								
Cycle 1 (Week 0)	0	56	62.2 (28)	62.2 (19)	64.6 (19)	34.9	61.2	150
Cycle 8 (Week 21)	147	30	95.7 (27)	95.7 (26)	98.9 (26)	53.2	96.1	162
Post Cycle 1								
24 hours post C1	1	57	46.3 (27)	46.3 (16)	48.1 (16)	27.6	45.9	133
72-168 hours post C1	5	56	25.3 (27)	25.3 (7)	26.2 (7)	13.7	25.1	43.9
336 hours post C1	14	56	16.0 (35)	16.0 (5)	16.9 (5)	4.30	16.2	31.4

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

Data Source: [05Q8NM: analysis-p164pkdm10]

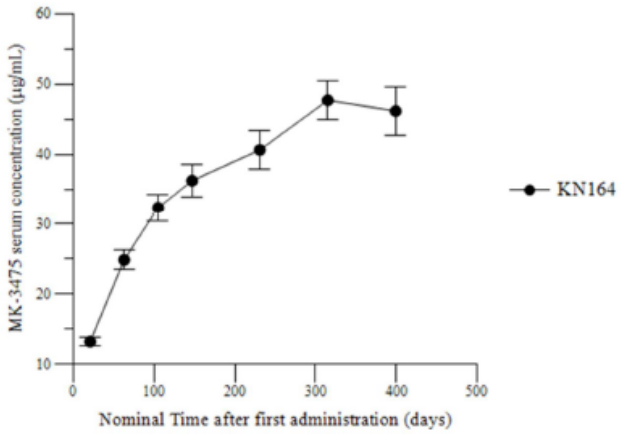
The following figures show the individual and mean C_{trough} concentration-time profiles:

Individual and Arithmetic Mean (SE) Pembrolizumab C_{trough} -Time Profiles Following Multiple I.V. Doses of 200 mg Q3W in Study KEYNOTE-164 (a) Linear scale, (b) Log scale



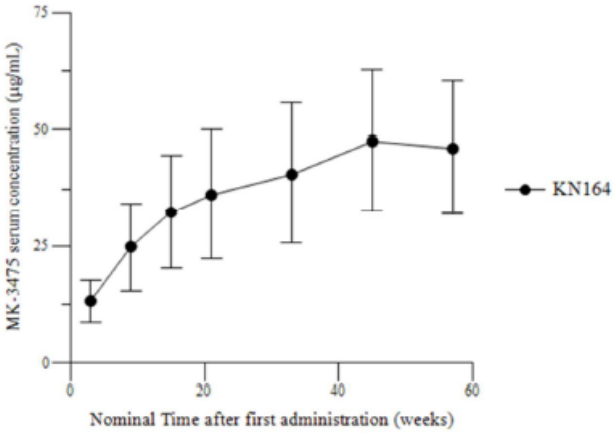
Note: Grey lines represent individual concentration observations. Black dashed lines represent arithmetic mean concentrations and error bars are associated +/- SE (Standard Error).
Data Source: Data Source: [05Q8NM: analysis-p164pkdm10]

Arithmetic Mean (SE) Pembrolizumab C_{trough}-Time Profiles Following Multiple I.V. Doses of 200 mg Q3W to Subjects in Study KEYNOTE-164 (Linear scale)



Note: This plot is Arithmetic Mean with Standard Error (SE). X-axis unit is in days.
Data Source: [05Q8NM: analysis-p164pkdm10]

Arithmetic Mean (SD) Pembrolizumab C_{trough}-Time Profiles Following Multiple I.V. Administrations of 200 mg Q3W to Subjects in Study KEYNOTE-164 (Linear scale)

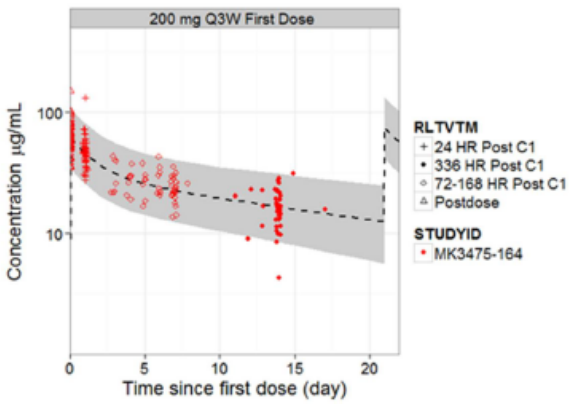


Note: This plot is Arithmetic Mean with Standard Deviation (SD). X-axis unit is in weeks.
Data Source: [05Q8NM: analysis-p164pkdm10]

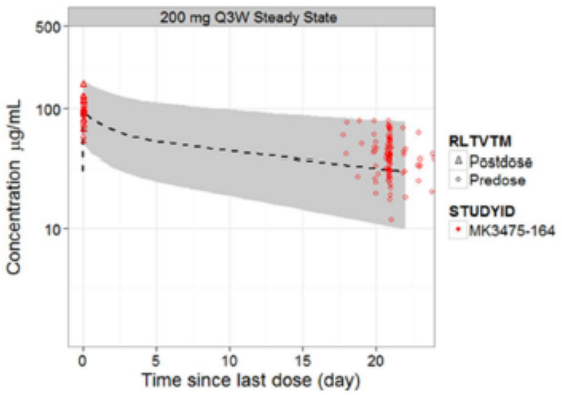
The observed and predicted pembrolizumab concentration-time profiles following 200 mg Q3W administration after 1rst dose and at and after cycle 8 (21 weeks) are illustrated in the following figure:

Observed Concentration Data in KEYNOTE-164 Subjects Receiving 200 mg Q3W Pembrolizumab with Reference Model-Predicted Pharmacokinetic Profile for 200 mg Q3W Dose Regimen

a)



b)



a) After 1st dose on log scale; b) At and after cycle 8 (21 weeks) on log scale. Red symbols are individual observed data (actual time) from subjects with MSI-H cancer in KEYNOTE-164; black line is median predicted concentrations from the model for a regimen of 200 mg Q3W and the grey shaded area represents the 90% prediction interval.

Data Source: [05Q8NM: analysis-p164pkdm10]

PK Comparison with monotherapy indications

A comparison of KEYNOTE-158 and KEYNOTE-164 observed concentration values with other monotherapy indications: KEYNOTE-024, KEYNOTE-045, KEYNOTE-052, KEYNOTE-055, and KEYNOTE-087 has been also provided, as shown in the following table and graph:

Geometric Mean Serum Concentration Values of Pembrolizumab Following Administration of Multiple IV 200 mg Q3W Fixed Doses in NSCLC, UC, HNSCC, HL, and MSIH CRC cancer

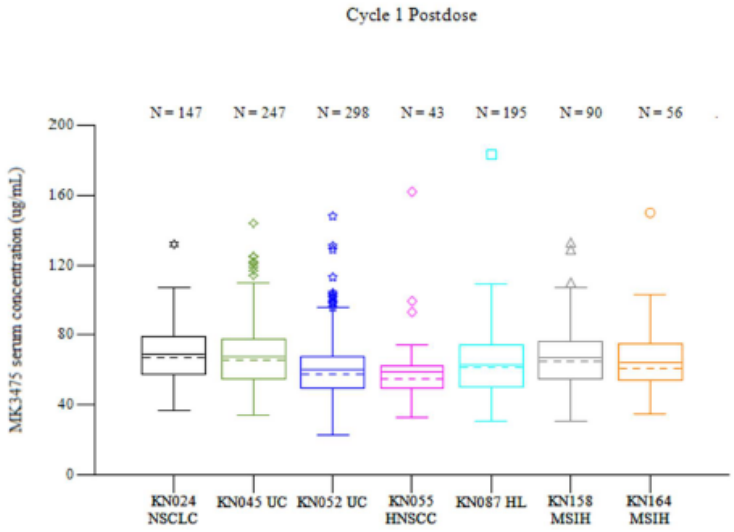
Time point	Study/Indication	N	GM(%CV) (µg/mL)	AM(SD) (µg/mL)	Min (µg/mL)	Median (µg/mL)	Max (µg/mL)
Cycle 1 Postdose	KN024 NSCLC	147	67.5 (23)	69.3 (16)	36.6	66.8	132
	KN045 UC	247	65.7 (26)	67.9 (18)	33.9	65.9	144
	KN052 UC	298	58.0 (28)	60.2 (17)	22.8	57.4	148
	KN055 HNSCC	43	56.5 (28)	58.9 (21)	33.1	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
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
	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
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
	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

GM = Geometric Mean; %CV = Geometric Coefficient of Variation; AM = Arithmetic Mean; SD = Standard Deviation; NSCLC = non-small cell lung cancer; UC = urothelial cancer; HNSCC = head and neck squamous cell carcinoma; HL = Hodgkin lymphoma; MSIH = micro satellite instability high cancer, colorectal cancer;

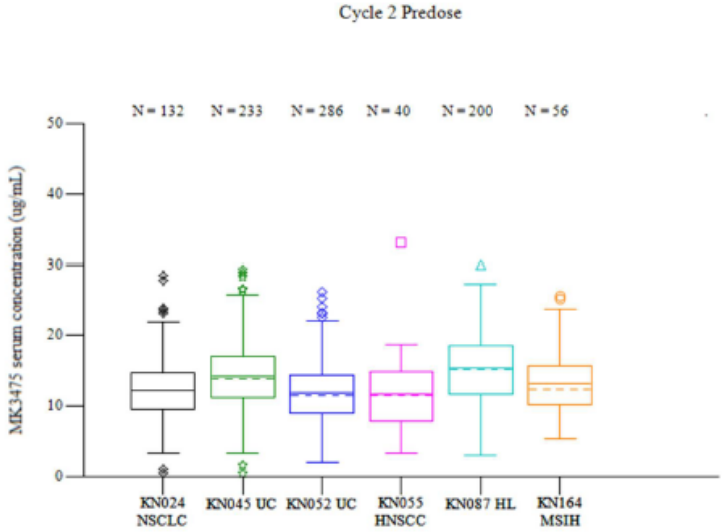
Data Source: [05Q8NM: analysis-p164pkdm10, p158pkdm25msih, p24p45p52p55p87p158msihp164200f01]

Observed Serum Concentration Values of Pembrolizumab in KEYNOTE-158 and KEYNOTE-164 MSI-H Subjects Compared with Historical Data from Monotherapy Studies with Dosing Regimen of 200 mg Q3W Pembrolizumab. (a) Cycle 1 Postdose, (b) Cycle 2 Predose, (c) Cycle 8 Predose

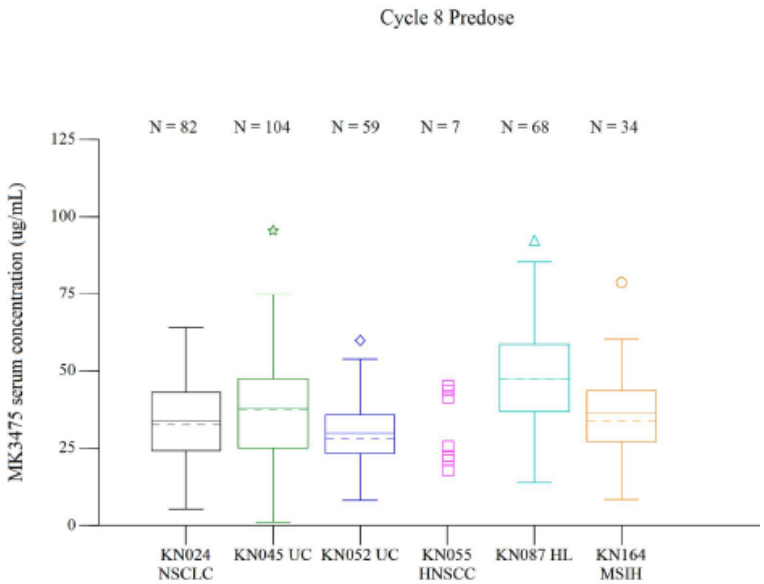
a)



b)



c)



Data Source: [05Q8NM: analysis-p164pkdm10, p158pkdm25msih, p24p45p52p55p87p158msihp164200f01]

The observed pembrolizumab serum concentrations from KEYNOTE-158 and KEYNOTE-164 in subjects with MSI-H cancer 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.

2.3.3. Pharmacodynamics

Dose regimen selection

Pembrolizumab is approved at a 2 mg/Kg, 200 mg Q3W and 400 mg Q6W dosing regimens for use in multiple indications globally as monotherapy as well as in combination with small molecule or chemotherapy

A dosing regimen of 200 mg Q3W or 400 mg Q6W is recommended for pembrolizumab in the treatment of adult subjects with MSI-H cancer.

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

Immunogenicity

The existing immunogenicity assessment for pembrolizumab for the monotherapy setting is based on a sufficiently large dataset of patients across several indications, with very low observed rates of total treatment 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.

No new ADA data are provided in this submission based on the robust characterization of immunogenicity potential with trials in non-adjuvant monotherapy setting.

2.3.4. Discussion on clinical pharmacology

The updated clinical pharmacology results specific to this submission include:

1) PK data from subjects with MSI-H cancer from KEYNOTE-158 and KEYNOTE-164, receiving pembrolizumab 200 mg Q3W as monotherapy agent.
2) A comparison of KN158 and KN164 observed PK data with reference model (TDPK) predicted PK.

The MAH presented a clinical pharmacology report on a total of 93 patients recruited in study KEYNOTE-158 with a cut-off date of 28-April-2017 and 60 patients in study KEYNOTE-164 with a cut-off date of 10 February 2017.

The reference PK/PD model is used to support pembrolizumab submission also in this therapeutic indication.

Observed Pembrolizumab (MK-3475) concentration-time profiles at 200 mg Q3W in subjects with MSI-H cancer in KEYNOTE-158 were in line with the model predicted median concentrations based on Population PK Model using the reference dataset both at cycle 1 (after first dose) and cycle 4 (up to day 84). However, it is of note that in KEYNOTE-158, concentrations at cycle 4 are not likely to have reached the steady state (half- life 22 days).

PK samples in KEYNOTE-164 were collected also at cycle 8 and beyond (at steady state) and the observed Pembrolizumab (MK-3475) concentration-time profiles in this study were in line with the model predicted median concentrations and 90% prediction interval (PI) at cycle 1 (after first dose) and at steady state at cycle 8 and beyond (at and after 21 weeks).

Summarizing, the PK in subjects with MSI-H cancer in both trials follows a similar profile as predicted based on the TDPK reference model over the dosing interval, both after first dose as well as at steady state (cycle 8 and beyond). The majority of the observed concentrations both at Cycle 1 and steady-state generally lay within 90% of prediction interval of the reference PK model, with only a few outliers.

A comparison of KEYNOTE-158 and KEYNOTE-164 observed concentration values with other monotherapy indications such as KEYNOTE-024, KEYNOTE-045, KEYNOTE-052, KEYNOTE-055, and KEYNOTE-087 were provided. The comparison trough box plots and tables with statistical analysis showed that pembrolizumab serum concentration are similar among different tumour types.

No dose finding study was conducted for pembrolizumab monotherapy for treatment of unresectable or metastatic MSI-H or dMMR colorectal, endometrial, gastric, small intestine, biliary, or pancreatic cancer in adults. The investigated dose and schedule of pembrolizumab monotherapy in the above reported indication is the same as that approved for other monotherapy indications: 200 mg IV infusion over 60 minutes Q3W. This is considered acceptable.
No new information regarding PK/PD modelling for pembrolizumab is available within this extension of indication.

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

2.3.5. Conclusions on clinical pharmacology

The clinical pharmacology profile of pembrolizumab in patients with unresectable or metastatic MSI-H or dMMR colorectal, endometrial, gastric, small intestine, biliary, or pancreatic cancer who have received prior therapy is consistent with historical data.

2.4. Clinical efficacy

The efficacy data in this submission are based on the data from 2 global single arm studies, KEYNOTE-158 (Cohort K) and KEYNOTE-164. All patients received pembrolizumab 200 mg Q3W IV.

2.4.1. Dose response study(ies)

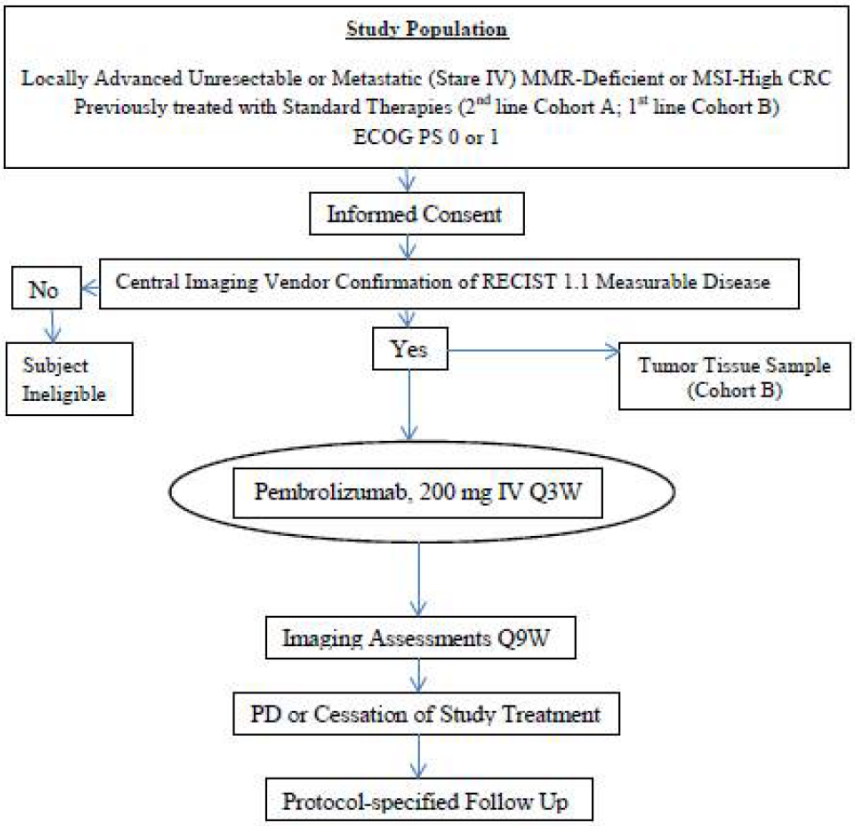
No dose-response studies were submitted as part of this application.

2.4.2. Main study(ies)

KEYNOTE-164

Title of Study: A Phase II Study of Pembrolizumab (MK-3475) as Monotherapy in Subjects with Previously Treated Locally Advanced Unresectable or Metastatic (Stage IV) Mismatched Repair Deficient or Microsatellite Instability-High Colorectal Carcinoma (KEYNOTE-164)

Figure: KEYNOTE-164 study design



Abbreviations: CRC=Colorectal carcinoma; ECOG=Eastern Cooperative Oncology Group; IV=Intravenous; MMR=Mismatch repair; MSI-H=Microsatellite instability-high; PD=Progressive disease; PS=Performance status; Q3W=Every 3 weeks; Q9W=Every 9 weeks; RECIST=Response Evaluation Criteria in Solid Tumours.

KEYNOTE-164 is an open-label, single-arm, multicenter, multicohort, Phase 2 study of pembrolizumab in previously treated participants with locally advanced unresectable or metastatic (Stage IV) MSI-H CRC.

Eligible participants were enrolled into one of 2 cohorts:

• **Cohort A**: Participants with locally advanced unresectable or metastatic dMMR or MSI-H CRC who had been previously treated with at least 2 lines of standard of care therapies, which must have included fluoropyrimidine, oxaliplatin, and irinotecan.

• **Cohort B**: Participants with locally advanced unresectable or metastatic dMMR or MSI-H CRC who had been previously treated with at least 1 line of systemic standard of care therapy (fluoropyrimidine + oxaliplatin or fluoropyrimidine + irinotecan ± antivascular endothelial growth factor [anti-VEGF]/ epidermal growth factor receptor [EGFR] monoclonal antibody [mAb]).

Study participants

Key inclusion criteria:

• Locally confirmed dMMR or MSI-H CRC

• A histologically proven locally advanced unresectable or metastatic (Stage IV) CRC

• Previous treatment with standard of care therapies: at least 2 lines of fluoropyrimidine, oxaliplatin, and irinotecan (Cohort A) and at least 1 line of systemic fluoropyrimidine + oxaliplatin or fluoropyrimidine + irinotecan ± anti-VEGF/EGFR mAb (Cohort B)

• An ECOG PS of 0 or 1

• A life expectancy of greater than 3 months

• At least 1 measurable lesion by RECIST 1.1 as determined by central review for response assessment

• Demonstrated adequate organ function as defined in the study protocol

Key exclusion criteria:

• An active autoimmune disease that had required systemic treatment in the past 2 years (ie, with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs)

• A diagnosis of immunodeficiency or receipt of systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment

• Known active CNS metastases and/or carcinomatous meningitis

• Prior mAb, chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or participant who had not recovered (ie, ≤Grade 1 or at baseline) from AEs due to a previously administered agent

• Received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

Treatments

Patients received Pembrolizumab 200 mg Q3W IV Day 1 of each 3-week cycle for up to a maximum of 35 cycles (approximately 2 years).

Treatment was continued until confirmed radiographic PD (irPD). If radiologic imaging identifies PD, tumour assessment should be repeated ≥4 weeks later in order to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression.

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR (assessed by the site) that have received at least 8 trial treatments (approx. 6 months) of pembrolizumab and had at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects who stop then experience radiographic disease progression may be eligible for up to 17 additional treatments (approx. 1 year) with pembrolizumab in the Second Course Phase at the discretion of the investigator.

Imaging assessment

The first on study imaging assessment should be performed at 9 weeks from the date of allocation. Subsequent tumour imaging should be performed Q9W for the first year, and then Q12W thereafter, or more frequently if clinically indicated until PD.

Objectives and endpoints

Primary Objective(s)	Primary Endpoint(s)
(1) Objective (Cohort A): To evaluate the objective response rate (ORR) per RECIST 1.1 assessed by independent radiologist review (IRC) of the 200 mg Q3W dose of pembrolizumab in participants with locally advanced unresectable or metastatic mismatch repair deficiency (dMMR) or microsatellite instability-high (MSI-H) colorectal carcinoma (CRC) and who have been previously treated with standard of care therapies, which must have included fluoropyrimidine, oxaliplatin, and irinotecan.	ORR is defined as the proportion of participants in the analysis population who have a complete response (CR) or partial response (PR).
(2) Objective (Cohort B): To estimate the ORR per RECIST 1.1 assessed by IRC of the 200 mg Q3W dose of pembrolizumab in participants with locally advanced unresectable or metastatic dMMR or MSI-H CRC and who have been previously treated with at least 1 line of systemic standard of care therapy (fluoropyrimidine + oxaliplatin or fluoropyrimidine + irinotecan ± anti-VEGF/EGFR mAb).	ORR is defined as the proportion of participants in the analysis population who have a CR or PR.
Secondary Objective(s)	**Secondary Endpoint(s)**
In both Cohort A and Cohort B separately:	
(1) Objective: To determine safety and tolerability of pembrolizumab.	Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, vital signs, etc.
(2) Objective: To evaluate duration of response (DOR), disease control rate (DCR), and progression-free survival (PFS) per RECIST 1.1 assessed by IRC and overall survival (OS).	DOR (for participants who demonstrate CR or PR) is defined as time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first. DCR is defined as the percentage of participants who have achieved confirmed CR or PR or have demonstrated stable disease (SD) for at least 24 weeks prior to any evidence of progression. PFS is defined as the time from first day of study treatment to the first documented disease progression or death due to any cause, whichever occurs first. OS is defined as the time from first day of study treatment to death due to any cause.

	Participants without documented death at the time of analysis are censored at the date of the last follow-up.

Sample size

The overall sample size is approximately 120.

Cohort A: With a sample size of 60, the study has 93% power to reject the null hypothesis of ORR=15% with a one-sided type I error rate of 2.5% if the true ORR is 35%. The historical response rate is less than 5% in CORRECT study (regorafenib vs placebo). At alpha level of 2.5% using exact method based on binomial distribution, the boundary to demonstrate statistical success corresponds to an approximate observed ORR ≥26.7% (16/60) at α = 2.5% (one-sided).

Cohort B: The historical response rate is about 20% for subjects with locally advanced unresectable or metastatic MMR deficient or MSI high CRC and have been previously treated with at least one line of systemic standard of care therapy. With a sample size of 60, if there are at least 19 responders observed, the lower bound of the 95% confidence interval for ORR will be above 20%.

Randomisation and blinding (masking)

This is a single arm open-label study.

Statistical methods

Population: The ASaT population was used for analysis of ORR, DOR, PFS and OS, and consists of all subjects who received at least one dose of study treatment.

Efficacy analyses: The primary efficacy endpoint is ORR per RECIST 1.1 assessed by central imaging vendor. In Cohort A, the point estimate, 95% confidence interval, and p-value for testing the response rate is greater than 15% were provided using exact binomial method proposed by Clopper and Pearson (1934).

In Cohort B, the point estimate and 95% confidence interval were provided using exact binomial method proposed by Clopper and Pearson (1934).

Subjects in the primary analysis population (ASaT) without ORR data were counted as non-responder.

For DCR, the point estimate, 95% confidence interval will be provided using exact binomial method proposed by Clopper and Pearson (1934). Subjects in the analysis population (ASaT) with missing DCR are considered as disease not under control.

For DOR, Kaplan-Meier (KM) curves and median estimates from the KM curves were provided as appropriate.

Table 10: analysis strategy for efficacy variables

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoint and Hypothesis			
ORR (Cohort A) • RECIST 1.1, Central assessment Hypotheses: ORR per RECIST 1.1 by central imaging vendor is greater than assumed historical control (15%).	Exact method based on binomial distribution	ASaT in Cohort A	Subjects with missing data are considered non-responders
ORR (Cohort B) • RECIST 1.1, Central assessment		ASaT in Cohort B	
Secondary Endpoints			
DCR • RECIST 1.1, Central assessment	Exact method based on binomial distribution	ASaT in below populations: Cohort A Cohort B	Subjects with missing data are considered as disease not under control
DOR • RECIST 1.1, Central assessment	Summary statistics using Kaplan-Meier method	All responders in below populations: Cohort A Cohort B	Non-responders are excluded from analysis
PFS • RECIST 1.1, Central assessment	Summary statistics using Kaplan-Meier method	ASaT in below populations: Cohort A Cohort B	Censored at last assessment
OS	Summary statistics using Kaplan-Meier method	ASaT in below populations: Cohort A Cohort B	Censored at last known alive date

Censoring rules for DOR:

Table 11: censoring rule for DOR

Situation	Date of Progression or Censoring	Outcome
Neither progression nor death, no new anti-cancer therapy initiated	Last adequate disease assessment	Censor (non-event)
Neither progression nor death, new anti-cancer therapy initiated	Last adequate disease assessment before new anti-cancer therapy initiated	Censor (non-event)
Death or progression after ≥2 consecutive missed adequate disease assessments	Last adequate disease assessment prior to ≥2 missed adequate disease assessments	Censor (non-event)
Death or progression after ≤1 missed adequate disease assessments	PD or death	End of response (Event)
Subjects are considered to have an ongoing response if censored, alive, have not progressed, have not started a new anti-cancer therapy and have not been determined to be lost to follow-up.		

Interim analyses: For Cohort A, an interim analysis for efficacy analysis of ORR was initially planned when the first 40 subjects have been followed up for at least 18 weeks. However, due to the rapid enrollment of the remaining subjects in Cohort A, it was decided to be conducted after all 61 subjects enrolled in Cohort A had been followed up for at least 18 weeks. With this change, the group sequential approach based on the first 40 subjects as originally planned was no longer applicable.

There was no interim analysis planned for Cohort B.

Final analysis: The final analysis was to be performed when all patients have been followed up for at least 6 months. If data is not mature, additional analysis was planned to be performed when all patients have had longer follow-up time or have discontinued study therapy. In that case, the originally planned final analysis was to be considered supportive.

Multiplicity: Cohort A and Cohort B were evaluated independently. No multiplicity adjustment in each cohort.

Subgroup analyses: The estimate of the treatment effect for the primary endpoint was estimated and plotted within each category of the following classification variables:

- Age category (≤65 vs. >65 years)
- Sex (Female vs. Male)
- Race (white vs. non-white)

The consistency of the treatment effect was assessed descriptively via summary statistics by category for the classification variables listed above.

Recruitment

First participant first visit for KEYNOTE-164 was 14-SEP-2015. This study was conducted at 34 sites in 10 countries. The data cut-off date for KEYNOTE-164 in this submission is 09-SEP-2019. As of the data cutoff date, 61 participants were enrolled in Cohort A (participants previously treated with ≥2 lines of prior therapy) and 63 in Cohort B (participants previously treated with ≥1 line of prior therapy). The median follow-up time was 31.4 months (range: 0.2 to 47.8 months) at the time of analysis. Updated data with data cut-off date 19 Feb 2021 were provided during the procedure.

Conduct of the study

Protocol amendments

Main changes in the planned conduct of the KEYNOTE-164 study implemented by protocol amendments are shown in the table 12 below:

Original protocol (21-May-2015)	
General Amendment No.1 (08-Jul-2015)	The indication statement has been updated to reflect clinical practice Allow enrollment flexibility when defining previous treatments.
General Amendment No.2 (19-Oct-2015)	To further clarify prior treatments a subject should have received in order to be eligible for participation in the study. Add clarification that tumour tissue is not mandatory. Interim analysis for futility removed. Updated definition of DOR.
General Amendment No.3 (24-Mar-2016)	Addition of a second cohort (Cohort B) of 60 subjects to evaluate pembrolizumab 200 mg Q3W in subjects with CRC who have undergone 1 line of systemic treatment (fluoropyrimidine + oxaliplatin or

	fluoropyrimidine + irinotecan +/- anti-VEGF/EGFR monoclonal antibody). The first cohort will be designated Cohort A. Added requirement to provide tissue sample in cohort B (optional in cohort A).
General Amendment No.4 (04-Jan-2017)	Since the originally planned final analysis does not provide adequate data maturity, the protocol was amended to allow additional follow-up analysis to be performed. Multiplicity adjustment for Cohort A is removed as no longer applicable as the planned interim analysis was done after the enrolment of all 61 patients and no more after 40 subjects due to fast recruitment.
Country-specific Amendment No.5 (06-Mar-2017)	Alignment with France-specific template requirements
General Amendment No.6 (13-Oct-2017)	The study was updated to recruit additional subjects with MSI-H mCRC to receive pembrolizumab in combination with MK-4280 (anti-LAG-3) in 3 cohorts (C-E) with 30-60 subjects each.
General Amendment No.7 (03-Jan-2018)	Alignment of dose modification language with the most current label and safety information for pembrolizumab. Pharmacokinetic/ADA evaluation and blood collection for these samples were removed.
General Amendment No.8 (13-Nov-2019)	To allow participants access to an extension study.

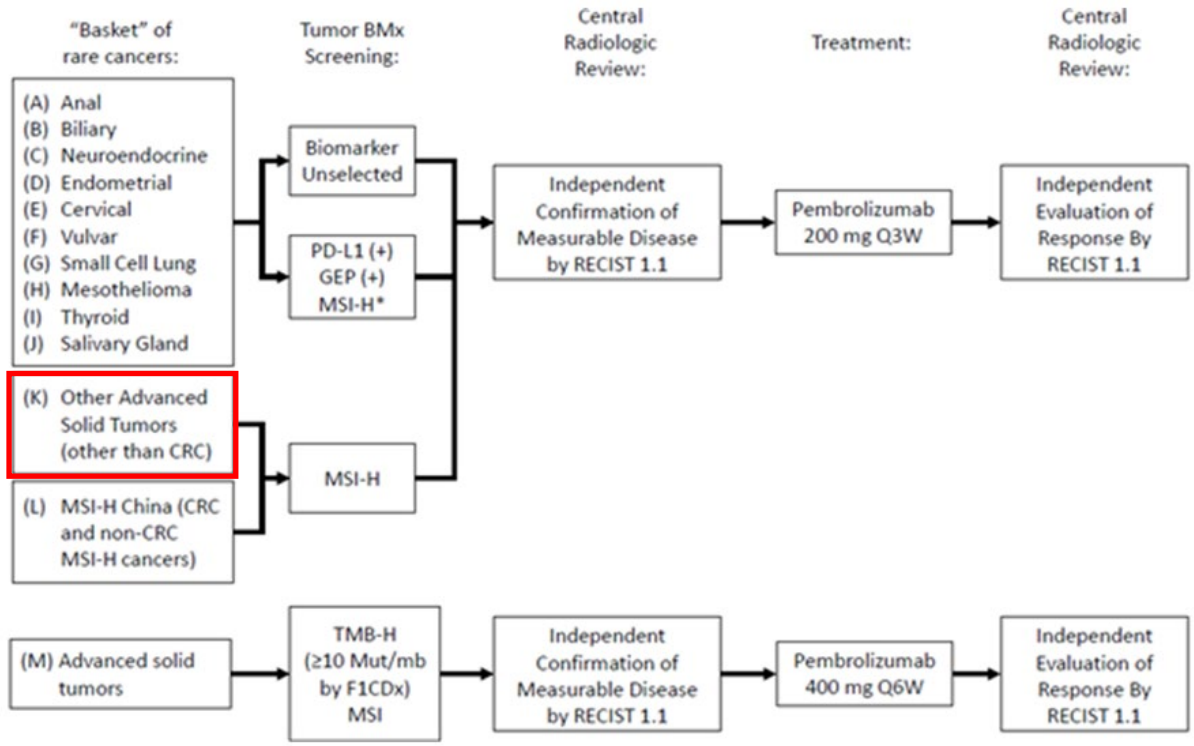
Protocol deviations

Important protocol deviations were reported for 9 (14.8%) participants in Cohort A. Of these, 2 participants had protocol deviations considered to be clinically important: one participant developed study specific discontinuation criteria but was not discontinued from the study, and 1 participant did not have locally confirmed MSI-H or dMMR Stage IV CRC. The other important protocol deviations were related to safety reporting not within the timelines. Important protocol deviations were reported for 5 (7.9%) participants in Cohort B, none was considered to be clinically important.

No participant's data were excluded from analyses due to an important protocol deviation. No important protocol deviations were classified as a serious GCP compliance issue.

KEYNOTE-158 (Cohort K)

Title of Study: A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predictive Biomarkers in Subjects with Advanced Solid Tumours (KEYNOTE-158)



*Selection of BMx(s) for biomarker enrichment may occur after interim analyses. Abbreviations: BMx=Biomarker; CRC=Colorectal carcinoma; GEP=Gene expression profile; MSI-H=Microsatellite instability-high; PD L1=Programmed Cell Death-Ligand 1; Q3W=Every 3 weeks; RECIST=Response Evaluation Criteria in Solid Tumours. For Cohort M, MSI= MSI-H excluded.

KEYNOTE-158 is an open-label, single-arm, multicenter, multicohort, Phase 2 study of pembrolizumab in previously treated participants with advanced solid tumours evaluated for predictive biomarkers. Cohort K enrolled any participant with an advanced solid tumour that was MSI-H (with the exception of CRC, which was being evaluated in KEYNOTE-164).

The MAH informed that the enrollment for Chinese Cohort L was initiated in May 2020 and included 5 patients, so no additional data in MSI-H tumours are expected from this cohort.

Study participants

Key Inclusion criteria:

- ≥18 years of age on the day of signing informed consent.
- Had a histologically or cytologically-documented, advanced (metastatic and/or unresectable) solid tumour that was incurable and for which prior standard first-line treatment had failed.
- Had any advanced solid tumour (except CRC), which was MSI-H (Cohort K). Note: following enrollment of the initial approximately 100 subjects in this cohort, subsequent enrollment will be

limited such that a total of no more than approximately 20 subjects with any single specific tumour type are enrolled in this MSI-H cancer cohort. The IVRS system will be used to determine if subjects with an MSI-H tumour of a particular type may be enrolled.

- Had submitted an evaluable tissue sample for biomarker analysis from a tumour lesion not previously irradiated.
- Had a tumour that was positive for one or more of the pre-specified primary biomarker(s), as assessed by the central laboratory.
- Had radiologically measurable disease based on RECIST 1.1 confirmed by independent central radiologic review.
- Had a performance status of 0 or 1 on the ECOG Performance Scale.
- Life expectancy of at least 3 months.
- Demonstrated adequate organ function.

Key Exclusion criteria:

- Had participated in any other pembrolizumab (MK-3475) trial, or received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, or any other immune-modulating mAb.
- Had a diagnosis of immunodeficiency or was receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
- Had an active autoimmune disease that had required systemic treatment in the past 2 years.
- Had a prior anti-cancer mAb within 4 weeks prior to study Day 1 or had not recovered (ie, ≤ Grade 1 or at baseline) from an AE due to mAbs administered more than 4 weeks earlier.
- Had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or had not recovered (ie, ≤ Grade 1 or at baseline) from an AE due to a previously administered agent.
- Had a known additional malignancy within 2 years prior to enrollment.
- Had known active CNS metastases and/or carcinomatous meningitis.

Treatments

Patients in Cohort K received pembrolizumab 200 mg Q3W IV Day 1 of each 3-week cycle for up to a maximum of 35 cycles (approximately 2 years).

Treatment was continued until radiologic disease progression was confirmed by local site assessment. For subjects who have initial radiological evidence of radiological PD by RECIST 1.1 as determined by the site, the investigator may elect to continue a subject on study treatment until repeat imaging is obtained (irRECIST-based management) if the subject is clinically stable, based on clinical factors including performance status, clinical symptoms, and laboratory data.

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR and have been treated for at least 24 weeks, receiving at least 2 doses of pembrolizumab and at least 80% of the planned dose beyond the date when the initial CR was declared. Subjects who stop trial treatment with SD, PR, or CR, may be eligible for up to 1 year of pembrolizumab if they experience disease progression after stopping pembrolizumab, at discretion of the investigator (Retreatment).

Imaging assessment

The initial tumour imaging was performed after tissue collection and within 28 days prior to the date of Cycle 1 Day 1. The central imaging vendor confirmed presence of measurable disease. Tumour assessment imaging was performed at 9 weeks after Cycle 1 Day 1, and then every 9 weeks thereafter, or more frequently if clinically indicated. After 12 months, imaging frequency was reduced to every 12 weeks. Local site investigator assessments will be used for subject management.

Objectives and endpoints

The table 13 below shows objectives and endpoints for the current protocol analysed in this interim analysis which is focused on Cohort K (MSI-H) only.

Primary Objective(s)	Primary Endpoint(s)
Objective (2): To evaluate the ORR to pembrolizumab, based on RECIST 1.1 as assessed by independent central radiologic review, in biomarker-selected subjects with any one of multiple types of advanced (metastatic and/or unresectable) solid tumours (Groups A through K). The primary biomarkers to be evaluated are (1) tumour expression of PD-L1 by immunohistochemistry (IHC) (Groups A through J), (2) tumour gene expression profile (GEP) by RNA analysis (Groups A through J), and (3) tumour MSI-H (Groups A through K). Note: GEP by RNA analysis was not evaluated in this interim analysis. PD-L1 by IHC was assessed only for participants with MSI-H tumours.	The primary efficacy endpoint ORR is defined as the proportion of subjects in the analysis population (ASaT) who have a confirmed complete response (CR) or partial response (PR). Response for the primary analysis will be determined by independent central radiologic review, with confirmatory assessment as required per RECIST 1.1.
Secondary Objective(s)	**Secondary Endpoint(s)**
Objective (4): To determine the safety and tolerability of pembrolizumab.	Safety assessments included adverse events, serious adverse events, and adverse events of special interest.
Objective (5): To evaluate DOR, (based on RECIST 1.1 as assessed by Institutional Review Committee [IRC]) in subjects receiving pembrolizumab and the relationship between DOR and tumour MSI-H status.	DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause (whichever occurs first).
Objective (6): To evaluate PFS (based on RECIST 1.1 as assessed by IRC) in subjects receiving pembrolizumab and the relationship between PFS and tumour MSI-H status.	PFS is defined as the time from allocation to the first documented disease progression or death due to any cause (whichever occurs first).
Objective (7): To evaluate OS in subjects receiving pembrolizumab and the relationship between tumour MSI-H status.	OS is defined as the time from allocation to death due to any cause.

Sample size

For patients in Group K (MSI-H), the study originally planned to enroll up to approximately 100 subjects with MSI-H advanced solid tumours with the exception of colorectal carcinoma (CRC). The patients enrolled in Group A-J with MSI-H were included in Group K for the purpose of analysis. An initial interim analysis was performed when 19 subjects in Group K had been followed for a minimum of 9 weeks. This interim analysis pooled data from patients with MSI-H across Groups A to K and was performed to support the filing of a supplemental biologics licensing application (sBLA) to FDA for pembrolizumab monotherapy in the treatment of subjects with MSI-H cancer.

To further evaluate efficacy of subjects with MSI-H cancer across a broad range of tumour types, the protocol was amended (Amendment 07) to expand the enrollment in Cohort K to approximately 350 subjects.

Randomisation and blinding (masking)

This is a single arm open label study.

Statistical methods

Population: for KEYNOTE-158, the primary population for the analysis of efficacy was based on the ASaT population consisting of all participants who have received at least one dose of study treatment with a minimum of 6 months follow-up.

Efficacy analyses: ORR includes complete response and partial response which both need to be confirmed. Subjects with Not Evaluable (NE), unknown or missing responses were considered non-responders; i.e. they were included in the denominator when calculating the percentage. The best confirmed overall response is the best confirmed response recorded from the start of treatment until disease progression or start of new anti-cancer therapy, whichever is earlier. It was planned to provide a point estimate and exact 95% Clopper-Pearson confidence interval. No hypothesis and no threshold for the primary endpoint ORR was formulated.

Interim analysis: It was planned to conduct multiple interim analyses based on the primary endpoint with the opportunity to modify the planned sample size. The trial is still ongoing. It was stated in the clinical study report that the report is based on the eleventh interim analysis.

Multiplicity: It was planned, to review the data by the study team on an ongoing basis without multiplicity control.

Table 13': Analysis strategy for key efficacy endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary Objectives			
ORR per RECIST 1.1 by independent central radiologic assessment	Exact test of binomial parameter, 95% CI calculated using the Clopper-Pearson method	ASaT	Subjects with missing data are considered non-responders
Secondary Objectives			
DOR per RECIST 1.1 by independent central radiologic assessment	Summary statistics using the Kaplan-Meier method	All responders	Non-responders are excluded in analysis
PFS per RECIST 1.1 by independent central radiologic assessment	Summary statistics using the Kaplan-Meier method	ASaT	Censored at last assessment
OS	Summary statistics using the Kaplan-Meier method	ASaT	Censored at last assessment

Censoring rules for DOR:

Table 14: censoring rule for DOR

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anti-cancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anti-cancer therapy initiated	Last adequate disease assessment before new anti-cancer therapy initiated	Censor (non-event)
Death or progression after $\geqslant$ 2 missed adequate disease assessments	Last adequate disease assessment prior to the after $\geqslant$ 2 missed adequate disease assessments	Censor (non-event)
Death or progression after $\leqslant$ 1 missed adequate disease assessments	PD or death	End of response (Event)
Patients are considered to have an ongoing response if censored, alive, have not progressed, and have not started a new anti-cancer therapy and have not been lost to follow-up (i.e., Situation 1 in the first row of the table). Patients are considered lost to follow-up if there is no scan within 22 weeks of the data cutoff.		

Patient reported outcome (PRO): PRO were exploratory objectives in KN158, and thus no formal hypotheses were formulated. The PRO instruments used were EORTC QLQ-C30, and EuroQoL EQ-5D. The PRO data were summarized within each cohort, across cohorts (overall, in CR/PR, SD, and PD subgroups). The primary time point of interest for PRO endpoints was Week 9.

Recruitment

First participant first visit for KEYNOTE-158 was on 01-FEB-2016. A total of 351 participants with 26 tumour types were allocated to Cohort K across 54 study sites in 18 countries at CCOD of 05-OCT-2020. Patients affected by one of the 5 tumour type proposed for the indication (i.e. MSI-H endometrial, gastric, small intestine, biliary, or pancreatic cancer) were 179 (50.9%). All received at least 1 dose of study intervention. Updated data with data cut-off date 15 Oct 2021 were provided during the procedure.

Conduct of the study

Protocol amendments

Changes in the planned conduct of the KEYNOTE-158 study implemented by protocol amendments are shown in the table below:

Amendment	Date of Issue	Overall Rationale
MK3475-158-00	11-SEP-2015	Original protocol
MK3475-158-01	05-NOV-2015	FDA recommended changes (when requesting new IND approval for rare tumors)
MK3475-158-02	23-NOV-2015	Clarifications of FDA recommendations from IND review
MK3475-158-03 (UK-specific amendment)	10-DEC-2015	MHRA recommended clarifications
MK3475-158-04 (France-specific amendment)	25-JAN-2016	French Health Authority recommended changes
MK3475-158-05	29-MAR-2016	Additional clarification of tumor tissue collection and inclusion criteria
MK3475-158-06	20-MAY-2016	Clarification to exclude patients with a history of pneumonitis
MK3475-158-07	17-APR-2017	Enrollment increase (per FDA discussions) and clarification to tumor tissue sampling for Cohort K
MK3475-158-08	03-OCT-2017	Adding/updating dose modification and toxicity management guidelines to align with the most current label and safety information for pembrolizumab
MK3475-158-09 (China-specific amendment)	16-AUG-2019	Added a new group, Group L, any advanced solid tumor (including CRC), which is mismatch repair deficient (dMMR)/MSI-H in subjects from mainland China who are of Chinese descent
MK3475-158-10	16-JUL-2020	To add a cohort of subjects with any advanced solid tumor that has failed at least one line of therapy and is TMB-H (≥10 mut/Mb, F1CDx assay), excluding subjects with dMMR/MSI-H tumors. The dosing regimen for this cohort will be 400 mg every 6 weeks (Q6W)

Part of the study was conducted during the COVID-19 pandemic. The Sponsor continued to follow its SOPs for study conduct, monitoring, and oversight, using a risk-based approach, consistent with Health Authority (FDA, EMA) guidance, to assess and mitigate the impact of the pandemic on study conduct in order to 1) ensure the safety of study participants, study staff, and health care providers, 2) maintain compliance with GCP principles, and 3) minimize risks to study data integrity. Contingency measures were implemented as per the Sponsor's SOP. Exceptions and deviations from SOPs were documented.

Protocol deviations

Important protocol deviations (i.e. 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) were reported for 14 participants in this study. Of these, 1 participant had an important protocol deviation that was considered to be clinically important (a participant who develop an adverse event for which the protocol instructs study treatment discontinuation, but were not discontinued). All other important protocol deviations were related to safety reporting outside the timelines outlined in the protocol. Protocol deviations associated with the COVID-19 pandemic were reported for 37 participants and were considered to be not important. No participant's data were excluded from analyses due to protocol deviation.

Results

Participant flow/patient disposition

CRC

KEYNOTE-164 - Cohort A: Of 74 participants screened, **61** were enrolled and received at least 1 dose of study treatment. The 13 participants who were not enrolled were screen failures (did not meet inclusion/exclusion criteria).

KEYNOTE-164 - Cohort B: Of 74 participants screened, **63** were enrolled and received at least 1 dose of study treatment. The 11 participants who were not enrolled were screen failures (did not meet inclusion/exclusion criteria).

Table 15: Disposition of Subjects – CRC – KEYNOTE-164 Cohort A+B (ASaT Population)

.-	MK-3475 200 mg n	(%)
Subjects in population	124	
Trial Disposition		
Discontinued	69	(55.6)
Adverse Event	4	(3.2)
Death	57	(46.0)
Lost To Follow-Up	2	(1.6)
Withdrawal By Subject	6	(4.8)
Ongoing	55	(44.4)
Subject Study Medication Disposition		
Completed	38	(30.6)
Discontinued	85	(68.5)
Adverse Event	10	(8.1)
Non-Compliance With Study Drug	2	(1.6)
Physician Decision	5	(4.0)
Progressive Disease	58	(46.8)
Withdrawal By Subject	10	(8.1)
Treatment Ongoing	1	(0.8)
Each subject is counted once for Trial Disposition, Subject Study Medication Disposition based on the latest corresponding disposition record. (Database Cutoff Date: 09SEP2019).		

non-CRC

The overall population included in KEYNOTE-158 Cohort K was composed by 351 subjects.
At the data cut-off date of 05 Oct 2020, of those, the population relevant for the indication (i.e. including

5 MSI-H cancer types – endometrial, gastric, small intestine, pancreatic, or biliary) consists of **179** participants, corresponding to 50.9% of the overall patients in the cohort. In the overall cohort, 718 patients were not enrolled, 684 due to screen failure, main reason being not submitting tissue from the same single tumour specimen used for prior MSI testing for subsequent retrospective MSI testing.
An updated analysis with data cut-off date 15 Oct 2021 was submitted during the procedure. The population relevant for the indication including the 5 MSI-H cancer types included a total of **205** patients (additional subjects have been included in endometrial, gastric and small intestine cohorts).

Tables 16: Disposition of Subjects by tumour types - KEYNOTE-158 Cohort K (ASaT Population)

Initial submission (cut-off date 05 Oct 2020)

Endometrial

	MK-3475 200 mg Q3W	
	n	(%)
Subjects in population	79	
Status for Study Medication in Trial Segment		
Started	79	
Completed	17	(21.5)
Discontinued	42	(53.2)
Adverse Event	4	(5.1)
Clinical Progression	5	(6.3)
Complete Response	1	(1.3)
Physician Decision	2	(2.5)
Progressive Disease	26	(32.9)
Withdrawal By Subject	4	(5.1)
Treatment Ongoing	20	(25.3)
Status for Trial		
Discontinued	26	(32.9)
Death	23	(29.1)
Withdrawal By Subject	3	(3.8)
Ongoing In Trial	53	(67.1)
(Database Cutoff Date: 05OCT2020).		

Updated data (cut-off date 15 Oct 2021)

	MK-3475 200 mg Q3W	
	n	(%)
Subjects in population	83	
Status for Study Medication in Trial Segment		
Started	83	
Completed	17	(20.5)
Discontinued	56	(67.5)
Adverse Event	6	(7.2)
Clinical Progression	5	(6.0)
Complete Response	2	(2.4)
Physician Decision	1	(1.2)
Progressive Disease	38	(45.8)
Withdrawal By Subject	4	(4.8)
Treatment Ongoing	10	(12.0)
Status for Trial		
Discontinued	35	(42.2)
Death	30	(36.1)
Lost To Follow-Up	1	(1.2)
Withdrawal By Subject	4	(4.8)
Ongoing In Trial	48	(57.8)
(Database Cutoff Date: 15OCT2021).		

Gastric

	MK-3475 200 mg Q3W	
	n	(%)
Subjects in population	51	
Status for Study Medication in Trial Segment		
Started	51	
Completed	8	(15.7)
Discontinued	30	(58.8)
Adverse Event	11	(21.6)
Clinical Progression	2	(3.9)
Progressive Disease	15	(29.4)
Withdrawal By Subject	2	(3.9)
Treatment Ongoing	13	(25.5)
Status for Trial		
Discontinued	27	(52.9)
Death	24	(47.1)
Withdrawal By Subject	3	(5.9)
Ongoing In Trial	24	(47.1)
(Database Cutoff Date: 05OCT2020).		

	MK-3475 200 mg Q3W	
	n	(%)
Subjects in population	51	
Status for Study Medication in Trial Segment		
Started	51	
Completed	10	(19.6)
Discontinued	35	(68.6)
Adverse Event	12	(23.5)
Clinical Progression	2	(3.9)
Progressive Disease	19	(37.3)
Withdrawal By Subject	2	(3.9)
Treatment Ongoing	6	(11.8)
Status for Trial		
Discontinued	29	(56.9)
Death	26	(51.0)
Withdrawal By Subject	3	(5.9)
Ongoing In Trial	22	(43.1)
(Database Cutoff Date: 15OCT2021).		

Pancreatic

	MK-3475 200 mg Q3W	
	n	(%)
Subjects in population	22	
Status for Study Medication in Trial Segment		
Started	22	
Completed	3	(13.6)
Discontinued	19	(86.4)
Adverse Event	5	(22.7)
Clinical Progression	5	(22.7)
Progressive Disease	9	(40.9)
Status for Trial		
Discontinued	18	(81.8)
Death	15	(68.2)
Lost To Follow-Up	1	(4.5)
Withdrawal By Subject	2	(9.1)
Ongoing In Trial	4	(18.2)
(Database Cutoff Date: 05OCT2020).		

	MK-3475 200 mg Q3W	
	n	(%)
Subjects in population	22	
Status for Study Medication in Trial Segment		
Started	22	
Completed	3	(13.6)
Discontinued	19	(86.4)
Adverse Event	4	(18.2)
Clinical Progression	5	(22.7)
Progressive Disease	10	(45.5)
Status for Trial		
Discontinued	18	(81.8)
Death	15	(68.2)
Lost To Follow-Up	1	(4.5)
Withdrawal By Subject	2	(9.1)
Ongoing In Trial	4	(18.2)
(Database Cutoff Date: 15OCT2021).		

Small intestine

	MK-3475 200 mg Q3W	
	n	(%)
Subjects in population	26	
Status for Study Medication in Trial Segment		
Started	26	
Completed	8	(30.8)
Discontinued	12	(46.2)
Adverse Event	4	(15.4)
Clinical Progression	1	(3.8)
Complete Response	1	(3.8)
Progressive Disease	5	(19.2)
Withdrawal By Subject	1	(3.8)
Treatment Ongoing	6	(23.1)
Status for Trial		
Discontinued	9	(34.6)
Death	9	(34.6)
Ongoing In Trial	17	(65.4)
(Database Cutoff Date: 05OCT2020).		

	MK-3475 200 mg Q3W	
	n	(%)
Subjects in population	27	
Status for Study Medication in Trial Segment		
Started	27	
Completed	11	(40.7)
Discontinued	14	(51.9)
Adverse Event	5	(18.5)
Clinical Progression	1	(3.7)
Complete Response	1	(3.7)
Progressive Disease	5	(18.5)
Withdrawal By Subject	2	(7.4)
Treatment Ongoing	2	(7.4)
Status for Trial		
Discontinued	10	(37.0)
Death	10	(37.0)
Ongoing In Trial	17	(63.0)
(Database Cutoff Date: 15OCT2021).		

Biliary/Cholangiocarcinoma

	MK-3475 200 mg Q3W	
	n	(%)
Subjects in population	22	
Status for Study Medication in Trial Segment		
Started	22	
Completed	4	(18.2)
Discontinued	18	(81.8)
Adverse Event	3	(13.6)
Clinical Progression	6	(27.3)
Complete Response	1	(4.5)
Progressive Disease	8	(36.4)
Status for Trial		
Discontinued	15	(68.2)
Death	15	(68.2)
Ongoing In Trial	7	(31.8)
(Database Cutoff Date: 05OCT2020).		

	MK-3475 200 mg Q3W	
	n	(%)
Subjects in population	22	
Status for Study Medication in Trial Segment		
Started	22	
Completed	4	(18.2)
Discontinued	18	(81.8)
Adverse Event	3	(13.6)
Clinical Progression	6	(27.3)
Complete Response	1	(4.5)
Progressive Disease	8	(36.4)
Status for Trial		
Discontinued	16	(72.7)
Death	16	(72.7)
Ongoing In Trial	6	(27.3)
(Database Cutoff Date: 15OCT2021).		

Baseline data

CRC

Table 17: Subject Characteristics – CRC – KEYNOTE-164 Cohort A+B (ASaT Population) UPDATED data cut-off date 19 Feb 2021

	MK-3475 200 mg	
	n	(%)
Subjects in population	124	
Gender		
Male	69	(55.6)
Female	55	(44.4)

Age (Years)		
<=65	83	(66.9)
>65	41	(33.1)
Mean	56.1	
SD	14.9	
Median	55.5	
Range	21 to 84	
Race		
Asian	33	(26.6)
Black Or African American	7	(5.6)
White	84	(67.7)
Ethnicity		
Hispanic Or Latino	4	(3.2)
Not Hispanic Or Latino	119	(96.0)
Not Reported	1	(0.8)
ECOG PS		
0	51	(41.1)
1	73	(58.9)
Cancer Stage		
IV	124	(100.0)
Metastatic Staging		
M0	4	(3.2)
M1	120	(96.8)
History of Brain Metastases		
No	124	(100.0)
MSI-High Status*		
POSITIVE	123	(99.2)
NEGATIVE	1	(0.8)
KRAS		
MUTANT	39	(31.5)
WILD TYPE	74	(59.7)
UNDETERMINED	11	(8.9)
NRAS		
MUTATION DETECTED	7	(5.6)
MUTATION NOT DETECTED	56	(45.2)
UNDETERMINED	61	(49.2)
BRAF		
MUTANT	15	(12.1)
WILD TYPE	61	(49.2)
UNDETERMINED	48	(38.7)
RAS		
MUTANT	44	(35.5)
WILD TYPE	38	(30.6)
UNDETERMINED	42	(33.9)
Prior Adjuvant or Neoadjuvant Therapy		
Yes	38	(30.6)
No	86	(69.4)
Number of Prior Therapy for Recurrent or Metastatic Disease		
1	30	(24.2)
2	48	(38.7)
3	22	(17.7)
4	11	(8.9)

5 OR GREATER	13	(10.5)
Baseline Tumour Size (mm) based on IRC Assessment per RECIST 1.1		
Subjects with data	124	
Mean	98.2	
SD	78.9	
Median	77.0	
Range	10.4 to 407.6	
*MSI status by PCR test or IHC test at local site laboratory. (Database Cutoff Date: 19FEB2021).		

non-CRC

Table 18: Summary of Demographic and Baseline Characteristics by tumour type in KEYNOTE-158 (ASaT Population, regardless follow-up time) – UPDATED data cut-off date 15 Oct 2021

Endometrial

	MK-3475 200 mg Q3W	
	n	(%)
Participants in population	83	
Sex		
Female	83	(100.0)
Age (Years)		
< 65	45	(54.2)
>= 65	38	(45.8)
Mean	64.3	
SD	8.7	
Median	64.0	
Range	42 to 86	
Race		
American Indian Or Alaska Native	1	(1.2)
Asian	5	(6.0)
Black Or African American	3	(3.6)
Multiple	2	(2.4)
White, Asian	2	(2.4)
White	70	(84.3)
Missing	2	(2.4)
Ethnicity		
Hispanic Or Latino	13	(15.7)
Not Hispanic Or Latino	60	(72.3)
Not Reported	10	(12.0)
Geographic Region		
US	16	(19.3)
Non-US	67	(80.7)
ECOG		
[0] Normal Activity	38	(45.8)
[1] Symptoms, but ambulatory	45	(54.2)
Metastatic Staging		
M0	2	(2.4)
M1	81	(97.6)

Gastric

	MK-3475 200 mg Q3W	
	n	(%)
Participants in population	51	
Sex		
Male	33	(64.7)
Female	18	(35.3)
Age (Years)		
< 65	22	(43.1)
>= 65	29	(56.9)
Mean	66.2	
SD	11.9	
Median	67.0	
Range	41 to 89	
Race		
American Indian Or Alaska Native	3	(5.9)
Asian	14	(27.5)
Multiple	2	(3.9)
Black Or African American, White	2	(3.9)
White	32	(62.7)
Ethnicity		
Hispanic Or Latino	6	(11.8)
Not Hispanic Or Latino	40	(78.4)
Not Reported	4	(7.8)
Unknown	1	(2.0)
Geographic Region		
US	4	(7.8)
Non-US	47	(92.2)
ECOG		
[0] Normal Activity	23	(45.1)
[1] Symptoms, but ambulatory	28	(54.9)
Metastatic Staging		
M1	51	(100.0)

Overall Stage		
IIIC	2	(2.4)
IV	67	(80.7)
IVB	14	(16.9)
Brain Metastases Present		
No	83	(100.0)
Number of Prior Lines of Therapy		
1	44	(53.0)
2	20	(24.1)
3	13	(15.7)
4	5	(6.0)
5 or more	1	(1.2)
Sum of Target Lesions Measurable at Baseline (mm)		
Participants with data	83	
Mean	91.9	
SD	70.8	
Median	71.1	
Range	11.8 to 282.8	
Tumor Type		
ENDOMETRIAL	83	(100.0)
Prior Radiation Therapy		
Yes	54	(65.1)
No	29	(34.9)
PD-L1 Status		
Positive	10	(12.0)
Negative	2	(2.4)
Not Evaluable	1	(1.2)
Missing	70	(84.3)
PD-L1 positive was based on CPS >=1. (Database Cutoff Date: 15OCT2021).		

Overall Stage		
IV	47	(92.2)
IVB	4	(7.8)
Brain Metastases Present		
Yes	1	(2.0)
No	50	(98.0)
Number of Prior Lines of Therapy		
1	28	(54.9)
2	11	(21.6)
3	9	(17.6)
4	2	(3.9)
5 or more	1	(2.0)
Sum of Target Lesions Measurable at Baseline (mm)		
Participants with data	51	
Mean	78.9	
SD	60.4	
Median	62.9	
Range	14.4 to 255.9	
Tumor Type		
GASTRIC	51	(100.0)
Prior Radiation Therapy		
Yes	14	(27.5)
No	37	(72.5)
PD-L1 Status		
Positive	6	(11.8)
Negative	5	(9.8)
Missing	40	(78.4)
PD-L1 positive was based on CPS >=1. (Database Cutoff Date: 15OCT2021).		

Small intestine

	MK-3475 200 mg Q3W	
	n	(%)
Participants in population	27	
Sex		
Male	17	(63.0)
Female	10	(37.0)
Age (Years)		
< 65	18	(66.7)
>= 65	9	(33.3)
Mean	57.6	
SD	13.1	
Median	58.0	
Range	21 to 77	
Race		
American Indian Or Alaska Native	2	(7.4)
Asian	3	(11.1)
White	22	(81.5)
Ethnicity		
Hispanic Or Latino	3	(11.1)
Not Hispanic Or Latino	20	(74.1)
Not Reported	4	(14.8)
Geographic Region		
US	7	(25.9)
Non-US	20	(74.1)
ECOG		
[0] Normal Activity	15	(55.6)
[1] Symptoms, but ambulatory	12	(44.4)
Metastatic Staging		
M0	1	(3.7)
M1	26	(96.3)
Overall Stage		
IIIA	1	(3.7)

Pancreatic

	MK-3475 200 mg Q3W	
	n	(%)
Participants in population	22	
Sex		
Male	13	(59.1)
Female	9	(40.9)
Age (Years)		
< 65	15	(68.2)
>= 65	7	(31.8)
Mean	59.0	
SD	9.9	
Median	61.5	
Range	44 to 79	
Race		
American Indian Or Alaska Native	1	(4.5)
Asian	1	(4.5)
Black Or African American	2	(9.1)
White	18	(81.8)
Ethnicity		
Hispanic Or Latino	3	(13.6)
Not Hispanic Or Latino	18	(81.8)
Not Reported	1	(4.5)
Geographic Region		
US	2	(9.1)
Non-US	20	(90.9)
ECOG		
[0] Normal Activity	14	(63.6)
[1] Symptoms, but ambulatory	8	(36.4)
Metastatic Staging		
M1	22	(100.0)
Overall Stage		
IV	22	(100.0)

IV	26	(96.3)
Brain Metastases Present		
No	27	(100.0)
Number of Prior Lines of Therapy		
0	2	(7.4)
1	15	(55.6)
2	6	(22.2)
3	3	(11.1)
4	1	(3.7)
Sum of Target Lesions Measurable at Baseline (mm)		
Participants with data	27	
Mean	63.0	
SD	38.9	
Median	55.3	
Range	14.8 to 165.5	
Tumor Type		
SMALL INTESTINE	27	(100.0)
Prior Radiation Therapy		
Yes	2	(7.4)
No	25	(92.6)
PD-L1 Status		
Positive	2	(7.4)
Negative	5	(18.5)
Missing	20	(74.1)
PD-L1 positive was based on CPS >=1. (Database Cutoff Date: 15OCT2021).		

Brain Metastases Present		
No	22	(100.0)
Number of Prior Lines of Therapy		
1	6	(27.3)
2	7	(31.8)
3	5	(22.7)
4	2	(9.1)
5 or more	2	(9.1)
Sum of Target Lesions Measurable at Baseline (mm)		
Participants with data	22	
Mean	93.3	
SD	57.4	
Median	77.2	
Range	15.1 to 185.9	
Tumor Type		
PANCREATIC	22	(100.0)
Prior Radiation Therapy		
Yes	6	(27.3)
No	16	(72.7)
PD-L1 Status		
Positive	3	(13.6)
Negative	4	(18.2)
Missing	15	(68.2)
PD-L1 positive was based on CPS >=1. (Database Cutoff Date: 15OCT2021).		

Biliary/Cholangiocarcinoma

	MK-3475 200 mg Q3W	
	n	(%)
Participants in population	22	
Sex		
Male	16	(72.7)
Female	6	(27.3)
Age (Years)		
< 65	13	(59.1)
>= 65	9	(40.9)
Mean	59.7	
SD	11.1	
Median	60.5	
Range	40 to 77	
Race		
Asian	2	(9.1)
White	20	(90.9)
Ethnicity		
Hispanic Or Latino	2	(9.1)
Not Hispanic Or Latino	18	(81.8)
Not Reported	2	(9.1)
Geographic Region		
US	2	(9.1)
Non-US	20	(90.9)
ECOG		
[0] Normal Activity	10	(45.5)
[1] Symptoms, but ambulatory	12	(54.5)
Metastatic Staging		
M0	4	(18.2)
M1	18	(81.8)
Overall Stage		
III	1	(4.5)
IIIB	1	(4.5)

IV	14	(63.6)
IVA	1	(4.5)
IVB	5	(22.7)
Brain Metastases Present		
No	22	(100.0)
Number of Prior Lines of Therapy		
0	2	(9.1)
1	11	(50.0)
2	6	(27.3)
3	1	(4.5)
4	2	(9.1)
Sum of Target Lesions Measurable at Baseline (mm)		
Participants with data	22	
Mean	89.9	
SD	61.3	
Median	80.8	
Range	21.3 to 231.1	
Tumor Type		
CHOLANGIOCARCINOMA	22	(100.0)
Prior Radiation Therapy		
Yes	3	(13.6)
No	19	(86.4)
PD-L1 Status		
Positive	3	(13.6)
Negative	2	(9.1)
Missing	17	(77.3)
PD-L1 positive was based on CPS >=1. (Database Cutoff Date: 15OCT2021).		

Small intestine: For the 2 participants with small intestine cancer who had not received prior therapy, 1 had surgery only and was enrolled as, per the investigator, no alternative therapy was available. For the other participant, although the Sponsor declined eligibility, this participant was enrolled, as per the investigator, no alternative therapy was available. These 2 cases were reported as not important protocol deviations. All but one participant had metastatic cancer.

Biliary: Two participants had not received prior lines of therapy. One participant had declined chemotherapy, and one participant was not eligible for cisplatin-based chemotherapy due to prediction of acute renal toxicity; both were reported as not important protocol deviations.

Prior treatments

CRC

Table 19: Number of Prior Lines of Therapy for Recurrent or Metastatic Disease KEYNOTE-164 (ASaT Population)

Number of Prior Lines of Therapy*	Cohort A	Cohort B
1	6 (9.8)	24 (38.1)
2	28 (45.9)	20 (31.7)
>=3	27 (44.3)	19 (30.2)

*Participants with prior adjuvant therapy for advanced disease were counted as having 1 prior line of therapy.
(Database Cutoff Date: 09SEP2019).

Table 20: Subjects With Specific Prior Oncologic Therapies KEYNOTE-164, Cohort A (ASaT Population)

	MK-3475 200 mg	
	n	(%)
Subjects in population	61	
With one or more systemic therapies	61	(100.0)
Chemotherapy	61	(100.0)
Biologics	53	(86.9)
Other	16	(26.2)
Summary of Prior Systemic Oncologic Therapies		
Chemotherapy	**61**	**(100.0)**
Fluoropyrimidine (S1, 5FU or capecitabine)	61	(100.0)
Prior Oxaliplatin	58	(95.1)
Prior irinotecan	58	(95.1)
detoxifying agent for antineoplastic	47	(77.0)
Biologics	**53**	**(86.9)**
Anti-EGFR	31	(50.8)
Cetuximab (or Erbitux)	25	(41.0)
Panitumumab (or Vectibix)	10	(16.4)
Anti-angiogenic	45	(73.8)
Bevacizumab (or Avastin)	45	(73.8)
Ziv-Aflibercept (or Zaltrap)	4	(6.6)
Other	**16**	**(26.2)**
Regorafenib (or Stivaga)	5	(8.2)
Trifluridine/tipirafcil (or Lonsurf)	3	(4.9)
Other including experimental therapies	9	(14.8)

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

(Database Cutoff Date: 09SEP2019).

Source: [P164V04MK3475: analysis-adsl] [P164V04MK3475: tabulations-cmplus]

Table 21: Subjects With Specific Prior Oncologic Therapies KEYNOTE-164, Cohort B (ASaT Population)

	MK-3475 200 mg	
	n	(%)
Subjects in population	63	
With one or more systemic therapies	63	(100.0)
Chemotherapy	63	(100.0)
Biologics	44	(69.8)
Other	11	(17.5)
Summary of Prior Systemic Oncologic Therapies		
Chemotherapy	**63**	**(100.0)**
Fluoropyrimidine (S1, 5FU or capecitabine)	63	(100.0)
Prior Oxaliplatin	61	(96.8)
Prior irinotecan	41	(65.1)
detoxifying agent for antineoplastic	52	(82.5)
Biologics	**44**	**(69.8)**
Anti-EGFR	19	(30.2)
Cetuximab (or Erbitux)	7	(11.1)
Panitumumab (or Vectibix)	13	(20.6)
Anti-angiogenic	34	(54.0)
Bevacizumab (or Avastin)	34	(54.0)
Ziv-Aflibercept (or Zaltrap)	1	(1.6)
Other	**11**	**(17.5)**
Regorafenib (or Stivaga)	5	(7.9)
Trifluridine/tipirafcil (or Lonsurf)	2	(3.2)
Other including experimental therapies	7	(11.1)
Every subject is counted a single time for each applicable row and column. (Database Cutoff Date: 09SEP2019). Source: [P164V04MK3475: analysis-adsl]		

NON-CRC

Table 22: Frequency Table of Prior Line of Systemic Therapy (Baseline MSI-H) (MK3475 200mg Q3W) KEYNOTE-158 (ASaT Population)

	No Line of Prior Therapy		One Line of Prior Therapy		Two or More Lines of Prior Therapy		Total
	n	(%)	n	(%)	n	(%)	n
Tumour Type							
Cholangiocarcinoma	2	(9.1)	11	(50.0)	9	(40.9)	22
Endometrial	0	(0.0)	44	(53.0)	39	(47.0)	83
Gastric	0	(0.0)	28	(54.9)	23	(45.1)	51
Pancreatic	0	(0.0)	6	(27.3)	16	(72.7)	22
Small Intestine	2	(7.4)	15	(55.6)	10	(37.0)	27
(Database Cutoff Date: 15OCT2021). [P158V09MK3475: adam-adsl]							

Table 23: Frequency Table of Prior Oncologic Surgery (Baseline MSI-H) (MK3475 200mg Q3W) (ASaT Population)

	Yes		No		Total
	n	(%)	n	(%)	n
Tumour Type					
Cholangiocarcinoma	9	(40.9)	13	(59.1)	22
Endometrial	71	(85.5)	12	(14.5)	83
Gastric	33	(64.7)	18	(35.3)	51
Pancreatic	11	(50.0)	11	(50.0)	22
Small Intestine	12	(44.4)	15	(55.6)	27
(Database Cutoff Date: 15OCT2021). [P158V09MK3475: adam-adsl]					

Table 24: Frequency Table of Prior Radiation Therapy (Baseline MSI-H) (MK3475 200mg Q3W) (ASaT Population)

	Yes		No		Total
	n	(%)	n	(%)	n
Tumour Type					
Cholangiocarcinoma	3	(13.6)	19	(86.4)	22
Endometrial	54	(65.1)	29	(34.9)	83
Gastric	14	(27.5)	37	(72.5)	51
Pancreatic	6	(27.3)	16	(72.7)	22
Small Intestine	2	(7.4)	25	(92.6)	27
(Database Cutoff Date: 15OCT2021). [P158V09MK3475: adam-adsl]					

Table 25: Frequency Table for Prior Systemic Treatment of Subjects with 5 Tumour Types (Baseline MSI-H) (MK3475 200mg Q3W) (ASaT Population)

Prior Systemic Treatment	Tumour Type n (%)
	Cholangiocarcinoma (N=22)
Gemcitabine and Cisplatin	14 (63.6)
Gemcitabine and Oxaliplatin	5 (22.7)
Gemcitabine and Capecitabine	0
Other chemo	1 (4.5)
Total prior systemic therapy	20 (91%)
	Endometrial (N=83)
Carboplatin	75 (90.4)
Cisplatin	2 (2.4)
Other chemo	6 (7.2)
Total prior systemic therapy	83 (100%)
	Gastric (N=51)
Fluorouracil-containing Regimen	28 (54.9)
Paclitaxel or Carboplatin	9 (17.6)
Capecitabine and Oxaliplatin	9 (17.6)
Other chemo	5 (9.8)
Total prior systemic therapy	51 (100%)
	Pancreatic (N=22)
Gemcitabine	15 (68.2)
FOLFIRINOX or modified FOLFIRINOX	7 (31.8)

Capecitabine	0
Other chemo	0
Total prior systemic therapy	22 (100%)
	Small Intestine (N=27)
Oxaliplatin and Fluorouracil and Leucovorin	16 (59.3)
Irinotecan and Fluorouracil and Leucovorin	1 (3.7)
Other chemo	8 (29.6)
Total prior systemic therapy	25 (93%)
(Database Cutoff Date: 15OCT2021). [P158V09MK3475: adam-adsl]	

Numbers analysed

The study population analysed for efficacy representing the sought indication includes a total of 303 patients, as follows:

- **124 MSI-H/dMMR CRC** patients from KEYNOTE-164, including Cohort A (n=61) + Cohort B (n=63) (ASaT population, i.e. all patients received at least one study treatment)

- **179 MSI-H/dMMR non-CRC** patients from KEYNOTE-158 Cohort K, including 5 tumour types (**endometrial n=68, gastric n=42, small intestine n=25, biliary n=22, pancreas n=22**) (ASaT population for Efficacy Analysis, i.e. all patients received at least one study treatment and have at least 6 months of follow-up at the data cut-off date of 05 Oct 2020).

Table 26: Summary of Follow-up Duration by Tumour Type (KN158 and KN164) (MK3475 200mg Q3W) (ASaT Population for Efficacy Analysis)

Tumour Type	N	Follow-up duration (months)†	
		Median (Range)	Mean (SD)
COLORECTAL	124	36.1 (0.1, 47.8)	27.2 (15.6)
ENDOMETRIAL	68	16.6 (1.5, 51.7)	24.4 (18.4)
GASTRIC	42	9.9 (1.1, 54.5)	19.8 (19.2)
SMALL INTESTINE	25	18.3 (4.2, 55.4)	27.0 (17.5)
CHOLANGIOCARCINOMA	22	19.4 (1.1, 48.5)	21.8 (15.7)
PANCREATIC	22	3.7 (0.4, 55.6)	13.0 (17.7)
† Follow-up duration is defined as the time from first dose to the date of death or the database cutoff date if the subject is still alive. Subjects who received at least one dose of MK-3475 in KN158 with MSI-H tumours in cohort K with 6 months follow-up and KN164 are included. KN164 Database Cutoff Date: 09-SEP-2019 KN158 Database Cutoff Date: 05-OCT-2020			

Outcomes and estimation

Table 27: <u>Summary</u> of Efficacy Results for KEYNOTE-164 (CRC) and KEYNOTE-158 (non-CRC) for tumour types included in the claimed indication (KN164 Database Cutoff Date: 09-SEP-2019; KN158 Database Cutoff Date: 05-OCT-2020)

	CRC (N=124)	**Endometrial (N=68)**	**Gastric (N=42)**	**Small Intestine (N=25)**	**Biliary (N=22)**	**Pancreatic (N=22)**
Primary Outcome: ORR (IRC per RECIST 1.1)						
ORR, % (95% CI)	42 (33.9) (25.6, 42.9)	33 (48.5) (36.2, 61.0)	13 (31.0) (17.6, 47.1)	12 (48.0) (27.8, 68.7)	9 (40.9) (20.7, 63.6)	4 (18.2) (5.2, 40.3)

DCR, % (95% CI)	67 (54.0) (44.9, 63.0)	46 (67.6) (55.2, 78.5)	20 (47.6) (32.0, 63.6)	19 (76.0) (54.9, 90.6)	12 (54.5) (32.2, 75.6)	7 (31.8) (13.9, 54.9)
Secondary Outcome: DOR (Confirmed CR or PR, IRC per RECIST 1.1)						
Number of responders	42	33	13	12	9	4
Median DOR, months (range)	NR (3.9+ -41.2+)	NR (2.9 - 47.1+)	NR (6.3 - 51.1+)	NR (2.1+ - 41.8+)	30.6 (6.2 - 40.5+)	NR (8.1 - 24.3+)
Secondary Outcome: PFS (IRC per RECIST 1.1)						
Median PFS, months (95% CI)	4.0 (2.1, 7.4)	13.1 (4.9, 34.4)	3.2 (2.1, 12.9)	23.4 (4.3, NR)	4.2 (2.1, 24.9)	2.1 (1.9, 3.4)
PFS rate, % at 12 Months	37.5	51.8	37.8	55.3	36.4	15.6
PFS rate, % at 24 Months	33.8	39.6	35.3	49.1	31.8	10.4
Secondary Outcome: OS						
Median OS, months (95% CI)	36.1 (24.0, NR)	NR (32.4, NR)	11.0 (5.8, 31.5)	NR (16.2, NR)	19.4 (6.5, NR)	3.7 (2.1, 9.8)
OS rate, % at 12 Months	74.2	73.6	49.5	79.6	63.6	22.7
OS rate, % at 24 Months	59.1	66.9	47.0	58.7	50.0	22.7

- ***Overall Response Rate (primary endpoint)***

Table 28: Summary of Best Objective Response Based on RECIST1.1 per Central Radiology Assessment by Tumour Type (KN158 and KN164) (MK3475 200mg Q3W) (ASaT Population for Efficacy Analysis)

Tumour Type	N	Objective Response (CR+PR) n (%) 95% CI†	Complete Response (CR) n (%) 95% CI†	Partial Response (PR) n (%) 95% CI†	Stable Disease (SD) n (%) 95% CI†	Disease Control (CR+PR+SD) n (%) 95% CI†	Progressive Disease (PD) n (%) 95% CI†	Non-evaluable (NE) n (%) 95% CI†	No Assessment n (%) 95% CI†
COLORECTAL	124	42 (33.9) (25.6, 42.9)	11 (8.9) (4.5, 15.3)	31 (25.0) (17.7, 33.6)	25 (20.2) (13.5, 28.3)	67 (54.0) (44.9, 63.0)	53 (42.7) (33.9, 51.9)	4 (3.2) (0.9, 8.1)	0 (0.0) (0.0, 2.9)
ENDOMETRIAL	68	33 (48.5) (36.2, 61.0)	10 (14.7) (7.3, 25.4)	23 (33.8) (22.8, 46.3)	13 (19.1) (10.6, 30.5)	46 (67.6) (55.2, 78.5)	19 (27.9) (17.7, 40.1)	1 (1.5) (0.0, 7.9)	2 (2.9) (0.4, 10.2)
GASTRIC	42	13 (31.0) (17.6, 47.1)	4 (9.5) (2.7, 22.6)	9 (21.4) (10.3, 36.8)	7 (16.7) (7.0, 31.4)	20 (47.6) (32.0, 63.6)	15 (35.7) (21.6, 52.0)	1 (2.4) (0.1, 12.6)	6 (14.3) (5.4, 28.5)
SMALL INTESTINE	25	12 (48.0) (27.8, 68.7)	4 (16.0) (4.5, 36.1)	8 (32.0) (14.9, 53.5)	7 (28.0) (12.1, 49.4)	19 (76.0) (54.9, 90.6)	5 (20.0) (6.8, 40.7)	0 (0.0) (0.0, 13.7)	1 (4.0) (0.1, 20.4)
CHOLANGIOCARCINOMA	22	9 (40.9) (20.7, 63.6)	3 (13.6) (2.9, 34.9)	6 (27.3) (10.7, 50.2)	3 (13.6) (2.9, 34.9)	12 (54.5) (32.2, 75.6)	8 (36.4) (17.2, 59.3)	0 (0.0) (0.0, 15.4)	2 (9.1) (1.1, 29.2)
PANCREATIC	22	4 (18.2) (5.2, 40.3)	1 (4.5) (0.1, 22.8)	3 (13.6) (2.9, 34.9)	3 (13.6) (2.9, 34.9)	7 (31.8) (13.9, 54.9)	8 (36.4) (17.2, 59.3)	0 (0.0) (0.0, 15.4)	7 (31.8) (13.9, 54.9)

† Based on binomial exact confidence interval method.

Only confirmed responses are included.

'No Assessment' counts subjects who had a baseline assessment evaluated by the investigator assessment but no post-baseline assessment on the data cutoff date including missing, discontinuing or death before the first post-baseline scan.

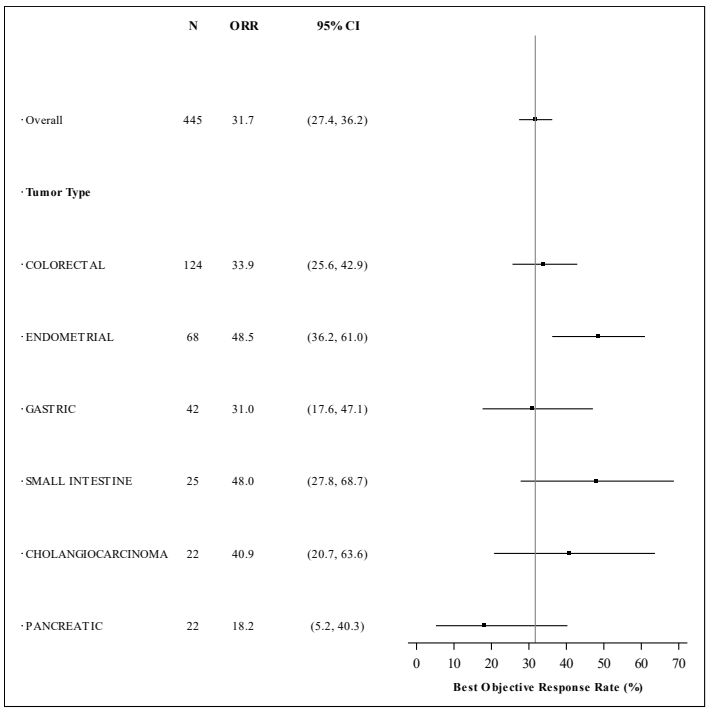
Subjects who received at least one dose of MK-3475 in KN158 with MSI-H tumours in cohort K with 6 months follow-up and KN164 are included.

KN164 Database Cutoff Date: 09-SEP-2019

KN158 Database Cutoff Date: 05-OCT-2020

For CRC in Keynote-164, ORR was similar regardless line of therapy: ORR was 32.8% (95%CI 21.3, 46) in Cohort A, with 20 patients with objective response, of those 3 participants (4.9%) had CR. ORR was 34.9% (95%CI 23.3, 48) in Cohort B with 22 responding patients, of those 8 subjects (12.7%) achieved CR.

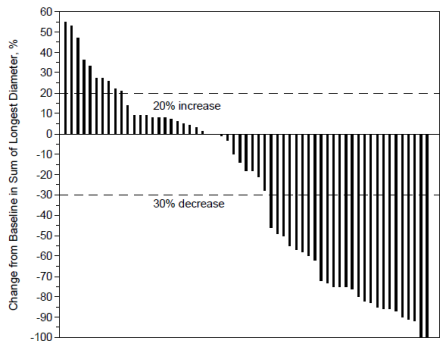
Figure: Forest Plot of Objective Response Rate by Tumour Type Based on RECIST 1.1 per Central Radiology Assessment (KN158 and KN164) (MK3475 200mg Q3W) (ASaT Population for Efficacy Analysis)



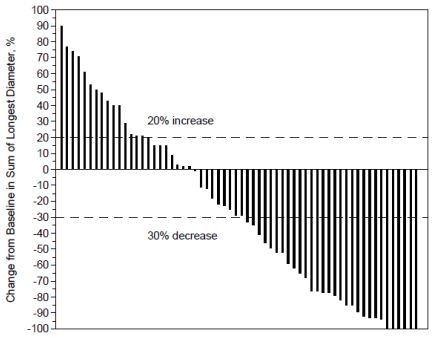
Only confirmed responses are included. KN164 Database Cutoff Date: 09-SEP-2019. KN158 Database Cutoff Date: 05-OCT-2020

Figures: Waterfall Plots of Best Tumour Change from Baseline Based on RECIST 1.1 Per Central Radiology Assessment by tumour types (ASaT Population for Efficacy Analysis)

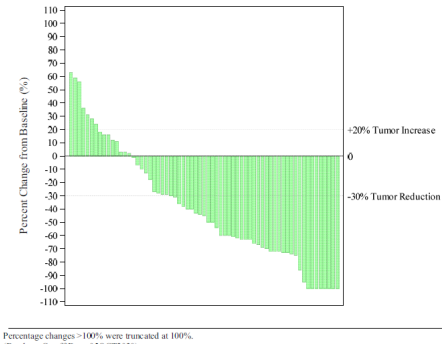
CRC (Keynote-164 Cohort A)

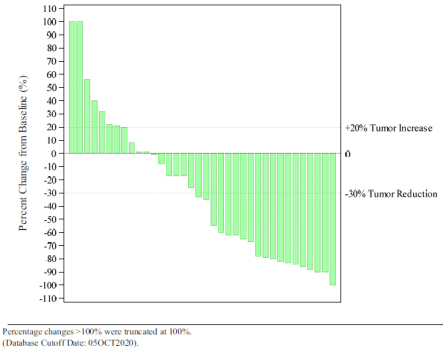


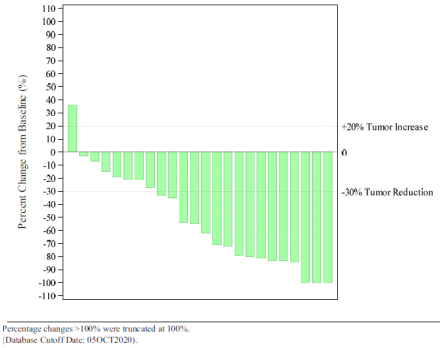
CRC (Keynote-164 Cohort B)



Endometrial (Keynote-158) **Gastric (Keynote-158)** **Small intestine (Keynote-158)**

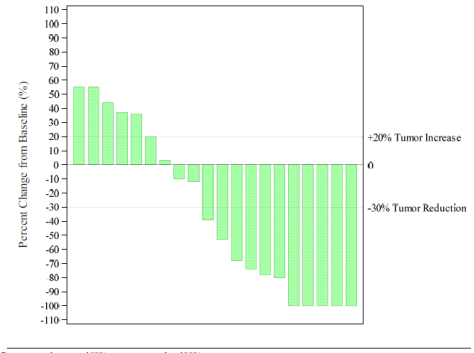


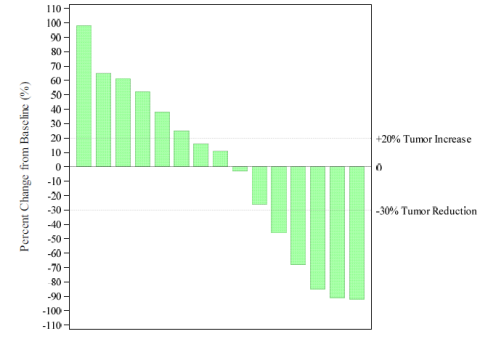




Cholangiocarcinoma (Keynote-158)

Pancreatic (Keynote-158)

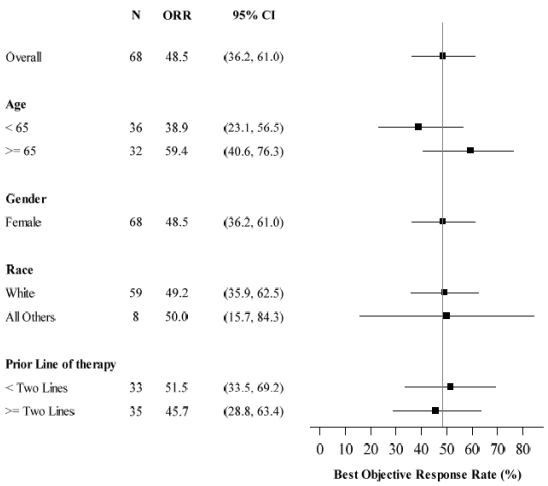




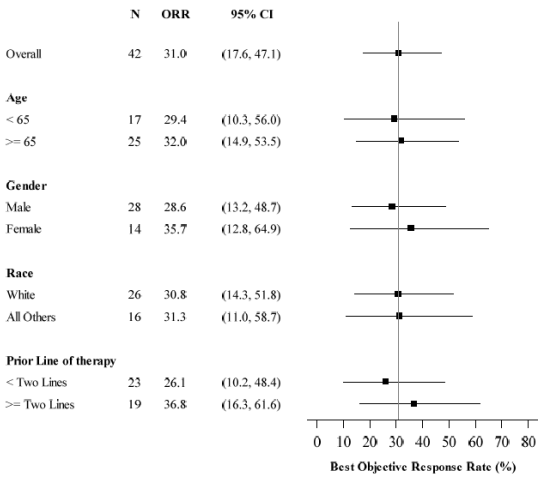
ORR by subgroups

Figures: Forest Plot of Objective Response Rate Based on RECIST 1.1 per Central Radiology Assessment by tumour type (ASaT Population for Efficacy Analysis)

Endometrial (Keynote-158)

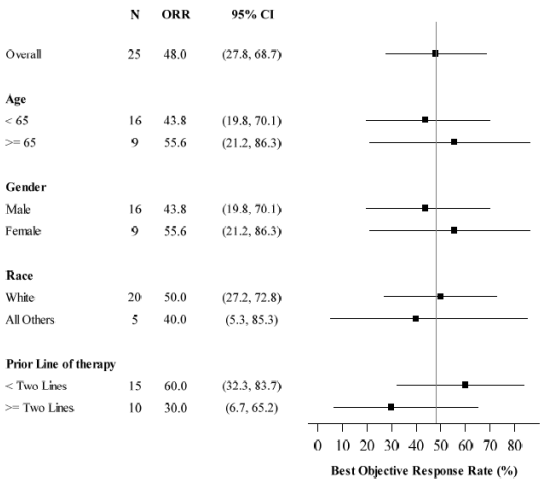


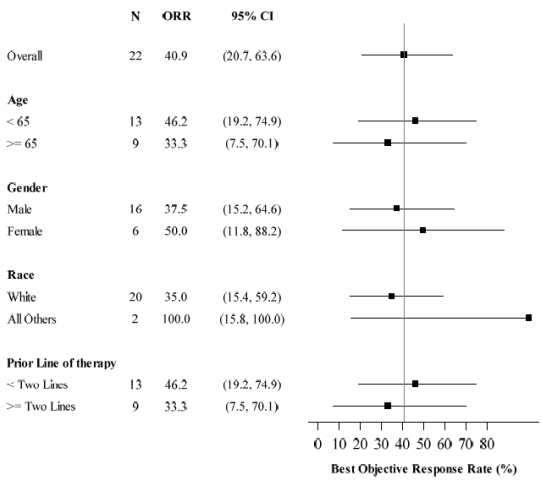
Gastric (Keynote-158)



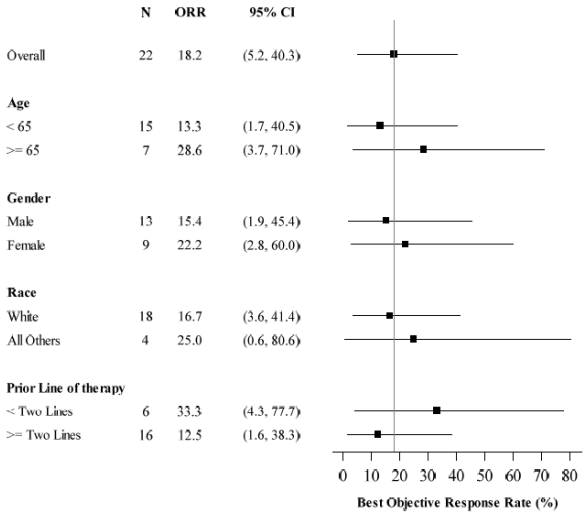
Small intestine (Keynote-158)

Cholangiocarcinoma (Keynote-158)





Pancreatic (Keynote-158)



The MAH has provided ORR by metastatic sites and mutational status for CRC patients enrolled in KEYNOTE-164 study (data not shown). No consistent trend can be observed and definitive conclusions are difficult to be made due to the small sample size within each subgroup.

- ***Duration of Response (secondary endpoint)***

Table 29: Summary of Time to Response and Response Duration Based on RECIST1.1 per Central Radiology Assessment by Tumour Type (KN158 and KN164) (MK3475 200mg Q3W) (Responders)

Tumour Type	N	Number of Subjects with Response†	Time to Response† (Months)		Response Duration‡ (Months)
			Mean (SD)	Median (Range)	Median (Range)
COLORECTAL	124	42	6.2 (6.3)	4.1 (1.8-31.3)	NR (3.9+ - 41.2+)
ENDOMETRIAL	68	33	3.3 (2.2)	2.1 (1.3-10.6)	NR (2.9 - 47.1+)
GASTRIC	42	13	3.1 (1.1)	2.4 (1.9-4.8)	NR (6.3 - 51.1+)
SMALL INTESTINE	25	12	3.4 (3.1)	2.1 (1.9-12.9)	NR (2.1+ - 41.8+)
CHOLANGIOCARCINOMA	22	9	3.0 (1.1)	2.4 (1.9-4.2)	30.6 (6.2 - 40.5+)
PANCREATIC	22	4	2.1 (0.1)	2.1 (1.9-2.1)	NR (8.1 - 24.3+)

† 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.
KN164 Database Cutoff Date: 09-SEP-2019
KN158 Database Cutoff Date: 05-OCT-2020

CRC

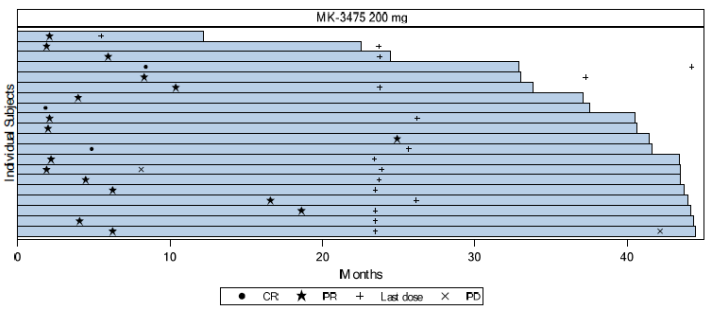
Table 30: Summary of Time to Response and Response Duration in Subjects with Confirmed Response Based on IRC Assessment per RECIST 1.1 (ASaT Population)

Response Evaluation	MK-3475 200 mg
	(N=124)
Number of Subjects with Response†	42
Time to Response† (Months)	
Mean (SD)	6.2 (6.3)
Median (Range)	4.1 (1.8 - 31.3)
Response Duration‡ (Months)	
Median (Range)	Not reached (3.9+ - 41.2+)
Number (%‡) of Subjects with Response	
≥6 Months (%)	39(97.6)
≥12 Months (%)	34(95.0)
≥18 Months (%)	31(95.0)
≥24 Months (%)	25(95.0)
≥36 Months (%)	8(95.0)

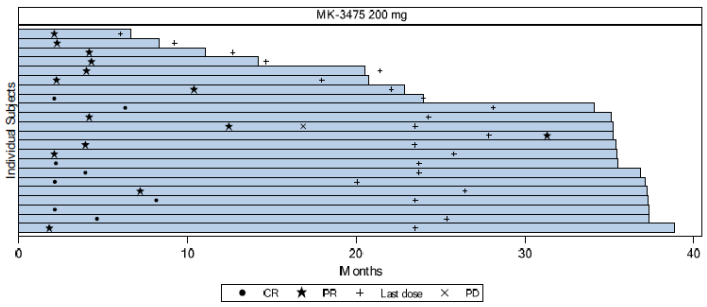
† Analysis on time to response and response duration are based on subjects with a best objective response as confirmed complete response or partial response only.
‡ From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
(Database Cutoff Date: 09SEP2019).

Median DOR was Not reached (range 6.2 - 41.2+) in Cohort A for the 20 patients with confirmed response, with 95% of subjects with response ≥12 months. Median DOR was also Not reached (range 3.9+ - 37.1+) in Cohort B for the 22 patients with confirmed response, with 95.2% of subjects with response ≥12 months.

Swimmer Plot of Subjects With Time to Response (Confirmed) and Time to Progression Based on IRC Assessment per RECIST 1.1
(Cohort A, Responders)



Swimmer Plot of Subjects With Time to Response (Confirmed) and Time to Progression Based on IRC Assessment per RECIST 1.1
(Cohort B, Responders)



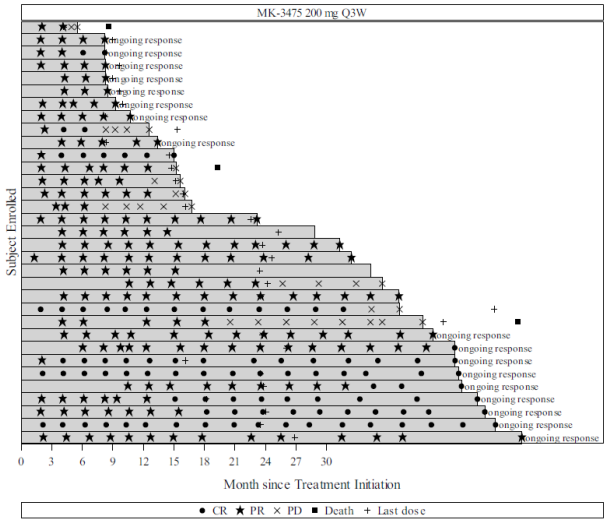
(Database Cutoff Date: 09SEP2019)

non-CRC

Endometrial

	MK-3475 200 mg Q3W (N=68)
Number of subjects with response†	33
Time to Response (months)	
Mean (SD)	3.3 (2.2)
Median (Range)	2.1 (1.3-10.6)
Response Duration‡ (months)	
Median (Range)	NR (2.9 - 47.1+)
Number (%‡) of Subjects with Extended Response Duration:	
≥6 months	29 (90.5)
≥12 months	19 (86.0)
≥18 months	14 (67.1)
≥24 months	13 (67.1)
≥36 months	8 (61.0)

† 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: 05OCT2020).

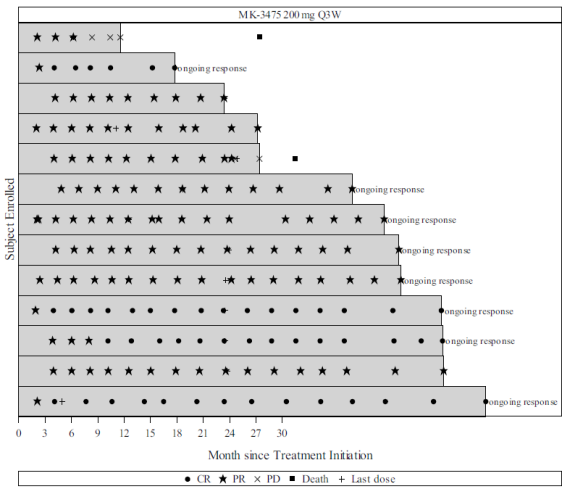


Response is based on single time point visit assessment per RECIST 1.1 (Central Radiology assessed unconfirmed response)
(Database Cutoff Date: 05OCT2020)

Gastric

	MK-3475 200 mg Q3W (N=42)
Number of subjects with response†	13
Time to Response (months)	
Mean (SD)	3.1 (1.1)
Median (Range)	2.4 (1.9-4.8)
Response Duration‡ (months)	
Median (Range)	NR (6.3 - 51.1+)
Number (%‡) of Subjects with Extended Response Duration:	
≥6 months	13 (100.0)
≥12 months	12 (92.3)
≥18 months	11 (92.3)
≥24 months	9 (83.1)
≥36 months	7 (83.1)

† 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: 05OCT2020).

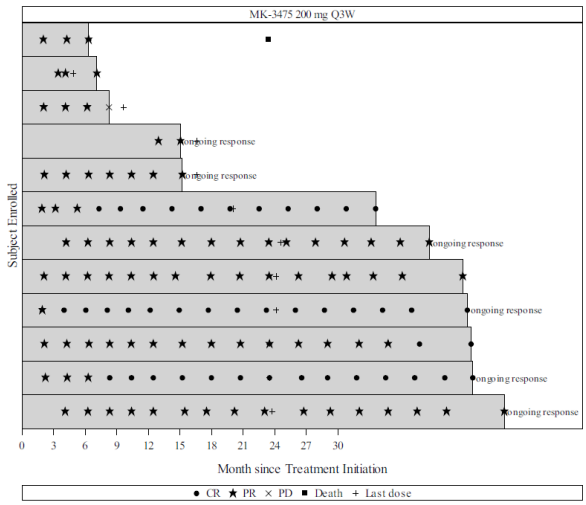


Response is based on single time point visit assessment per RECIST 1.1 (Central Radiology assessed unconfirmed response)
(Database Cutoff Date: 05OCT2020)

Small intestine

	MK-3475 200 mg Q3W (N=25)
Number of subjects with response†	12
Time to Response (months)	
Mean (SD)	3.4 (3.1)
Median (Range)	2.1 (1.9-12.9)
Response Duration‡ (months)	
Median (Range)	NR (2.1+ - 41.8+)
Number (%‡) of Subjects with Extended Response Duration:	
≥6 months	9 (100.0)
≥12 months	8 (88.9)
≥18 months	7 (88.9)
≥24 months	7 (88.9)
≥36 months	5 (88.9)

† 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: 05OCT2020).

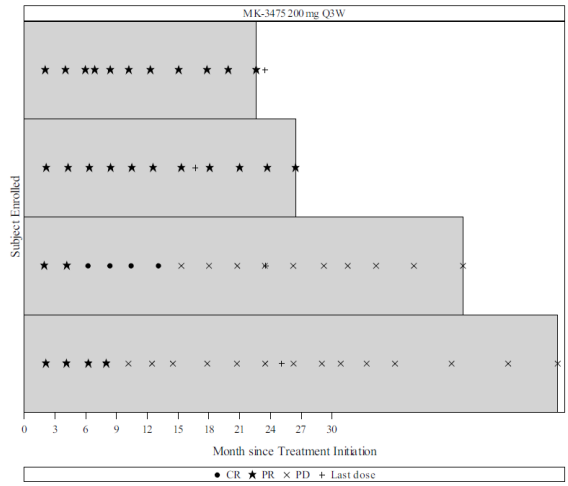


Response is based on single time point visit assessment per RECIST 1.1 (Central Radiology assessed unconfirmed response)
(Database Cutoff Date: 05OCT2020)

Pancreatic

	MK-3475 200 mg Q3W (N=22)
Number of subjects with response†	4
Time to Response (months)	
Mean (SD)	2.0 (0.1)
Median (Range)	2.1 (1.9-2.1)
Response Duration‡ (months)	
Median (Range)	NR (8.1 - 24.3+)
Number (%‡) of Subjects with Extended Response Duration:	
≥6 months	4 (100.0)
≥12 months	3 (75.0)
≥18 months	2 (50.0)
≥24 months	1 (50.0)

† 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: 05OCT2020).

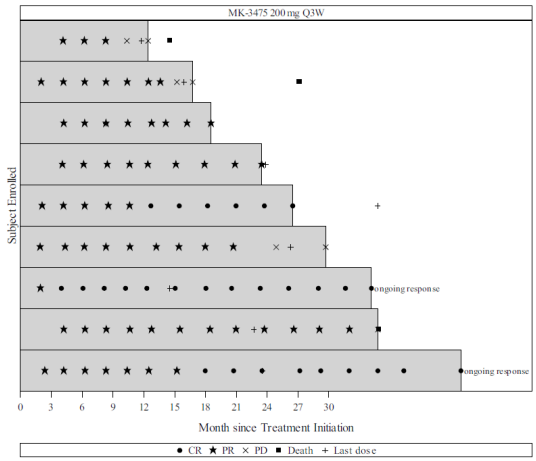


Response is based on single time point visit assessment per RECIST 1.1 (Central Radiology assessed unconfirmed response)
(Database Cutoff Date: 05OCT2020)

Biliary

	MK-3475 200 mg Q3W (N=22)
Number of subjects with response†	9
Time to Response (months)	
Mean (SD)	3.0 (1.1)
Median (Range)	2.4 (1.9-4.2)
Response Duration‡ (months)	
Median (Range)	30.6 (6.2 - 40.5+)
Number (%‡) of Subjects with Extended Response Duration:	
≥6 months	9 (100.0)
≥12 months	8 (88.9)
≥18 months	6 (77.8)
≥24 months	4 (62.2)
≥36 months	1 (41.5)

† 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.
(Database Cutoff Date: 05OCT2020).



Response is based on single time point visit assessment per RECIST 1.1 (Central Radiology assessed unconfirmed response)
(Database Cutoff Date: 05OCT2020)

- ***Progression Free Survival (secondary endpoint)***

Table 31: Summary of Progression-Free Survival (PFS) Based on RECIST 1.1 per Central Radiology Assessment by Tumour Type (KN158 and KN164) (MK3475 200mg Q3W) (ASaT Population for Efficacy Analysis)

	COLORECTAL (N=124)	ENDOMETRIAL (N=68)	GASTRIC (N=42)	CHOLANGIO CARCINOMA (N=22)	PANCREATIC (N=22)	SMALL INTESTINE (N=25)
Number (%) of PFS Events	83 (66.9)	39 (57.4)	29 (69.0)	17 (77.3)	19 (86.4)	12 (48.0)
Person-Months	1644	978	591	269	111	462
Event Rate/100 Person-Months (%)	5.0	4.0	4.9	6.3	17.1	2.6
Median PFS (Months)[§]	4.0	13.1	3.2	4.2	2.1	23.4
95% CI for Median PFS[§]	(2.1,7.4)	(4.9,34.4)	(2.1,12.9)	(2.1,24.9)	(1.9,3.4)	(4.3,NR)
PFS rate at 6 Months in % [§]	45.8	61.8	42.9	45.5	20.8	68.0
PFS rate at 12 Months in % [§]	37.5	51.8	37.8	36.4	15.6	55.3
PFS rate at 18 Months in % [§]	35.7	44.7	35.3	31.8	10.4	55.3
PFS rate at 24 Months in % [§]	33.8	39.6	35.3	31.8	10.4	49.1

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.

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

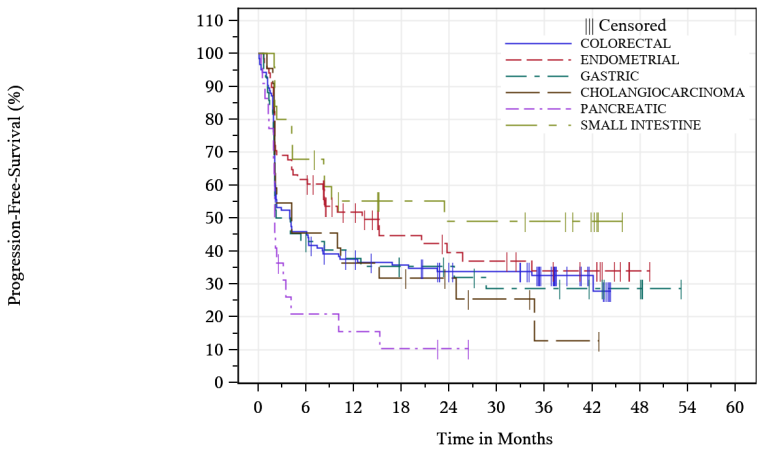
Subjects who received at least one dose of MK-3475 in KN158 with MSI-H tumours in cohort K with 6 months follow-up and KN164 are included.

NR = Not reached.

KN164 Database Cutoff Date: 09-SEP-2019

KN158 Database Cutoff Date: 05-OCT-2020

Figure: Kaplan-Meier Estimates of Progression-Free Survival Based on RECIST 1.1 per Central Radiology Assessment by Tumour Type (KN158 and KN164) (MK3475 200mg Q3W) (ASaT Population for Efficacy Analysis)



n at risk

COLORECTAL	124	64	56	46	43	40	39	36	31	30	30	28	20	11	7	0	0	0	0	0	0
ENDOMETRIAL	68	47	42	29	26	22	18	17	15	14	14	12	11	10	9	4	1	0	0	0	0
GASTRIC	42	21	18	16	15	14	12	12	11	10	8	8	8	7	6	4	4	1	0	0	0
CHOLANGIOCARCINOMA	22	12	10	10	8	8	7	6	5	3	3	3	1	1	1	0	0	0	0	0	0
PANCREATIC	22	7	4	4	3	3	2	2	1	0	0	0	0	0	0	0	0	0	0	0	0
SMALL INTESTINE	25	20	17	14	12	12	9	9	8	8	8	8	7	6	4	1	0	0	0	0	0

- ***Overall Survival (secondary endpoint)***

Table 32: Summary of Overall Survival by Tumour Type (KN158 and KN164) (MK3475 200mg Q3W) (ASaT Population for Efficacy Analysis)

	COLORECTAL (N=124)	ENDOMETRIAL (N=68)	GASTRIC (N=42)	CHOLANGIO CARCINOMA (N=22)	PANCREATIC (N=22)	SMALL INTESTINE (N=25)
Death (%)	63 (50.8)	23 (33.8)	26 (61.9)	15 (68.2)	17 (77.3)	9 (36.0)
Median Survival (Months)[§]	36.1	Not reached	11.0	19.4	3.7	Not reached
95% CI for Median Survival[§]	(24.0,NR)	(32.4,NR)	(5.8,31.5)	(6.5,NR)	(2.1,9.8)	(16.2,NR)
OS rate at 6 Months in % [§]	85.5	85.3	61.9	81.8	36.4	92.0
OS rate at 12 Months in % [§]	74.2	73.6	49.5	63.6	22.7	79.6
OS rate at 18 Months in % [§]	65.8	71.7	47.0	50.0	22.7	70.5
OS rate at 24 Months in % [§]	59.1	66.9	47.0	50.0	22.7	58.7

OS: Overall survival.

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

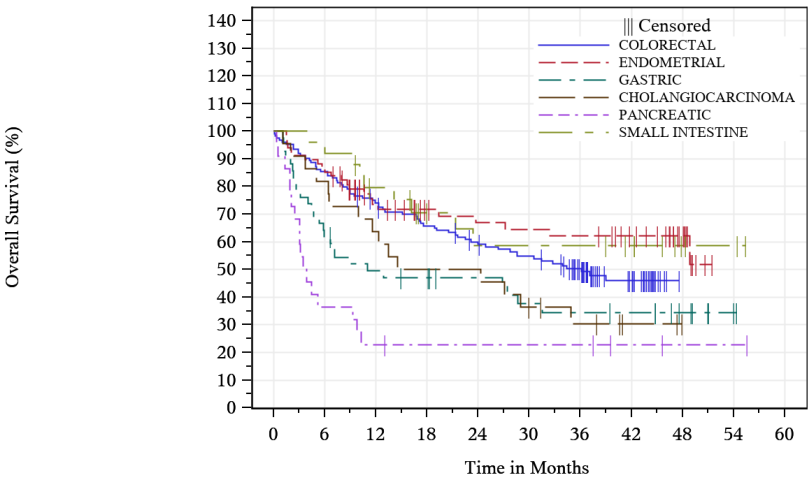
Subjects who received at least one dose of MK-3475 in KN158 with MSI-H tumours in cohort K with 6 months follow-up and KN164 are included.

NR = Not reached.

KN164 Database Cutoff Date: 09-SEP-2019

KN158 Database Cutoff Date: 05-OCT-2020

Figure: Kaplan-Meier Estimates of Overall Survival by Tumour Type (KN158 and KN164) (MK3475 200mg Q3W) (ASaT Population for Efficacy Analysis)



n at risk

COLORECTAL	124	114	106	97	90	85	79	76	69	66	63	59	47	26	23	5	0	0	0	0	0
ENDOMETRIAL	68	62	58	50	39	36	31	29	28	28	27	26	26	25	21	19	11	1	0	0	0
GASTRIC	42	33	26	21	20	18	18	15	15	14	12	11	11	11	10	8	6	3	1	0	0
CHOLANGIOCARCINOMA	22	20	18	16	14	11	11	11	11	10	7	6	5	4	2	2	0	0	0	0	0
PANCREATIC	22	15	8	8	5	4	4	4	4	4	4	4	4	3	2	2	1	1	1	0	0
SMALL INTESTINE	25	25	23	23	18	17	12	12	10	10	10	10	10	9	8	6	3	2	2	0	0

An exploratory analysis of median TTP on the last prior therapy versus median PFS on pembrolizumab therapy was conducted. TTP on the last prior therapy was defined as the time from the start of last prior therapy to the progression/recurrence. If there was no progression/ recurrence reported prior to initiation of pembrolizumab, the participant's data was censored at the start of experimental pembrolizumab therapy.

Table: TTP on Prior Therapy vs PFS on Pembrolizumab Therapy (KEYNOTE-158)

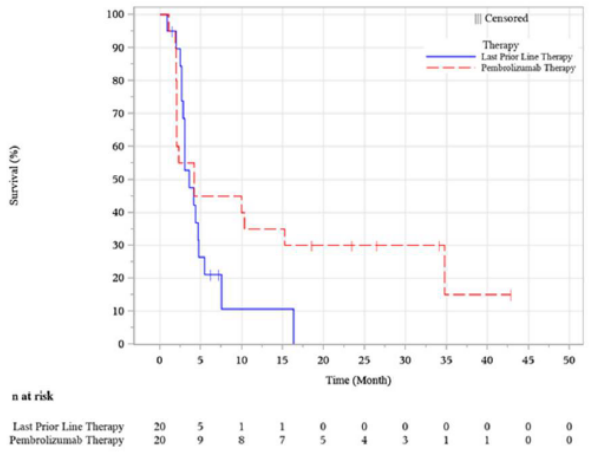
Tumor Type	TTP vs PFS				
	N	Prior Therapy		Pembrolizumab Therapy	
		KM Median (month)	95% CI (month)	KM Median (month)	95% CI (month)
CHOLANGIOCARCINOMA	20	3.6	(2.7, 4.8)	4.2	(2.1, 34.8)
ENDOMETRIAL	77	6.1	(4.9, 8.3)	13.1	(4.9, 25.7)
GASTRIC	50	4	(3.4, 5.5)	2.2	(2.0, 11.0)
PANCREATIC	22	4.1	(2.0, 5.2)	2.1	(1.9, 3.4)
SMALL INTESTINE	24	5.9	(3.1, 8.3)	23.4	(4.2, NR)
Overall*	193	4.7	(4.1, 5.5)	6.1	(4.1, 10.2)

(Database Cutoff Date: 05OCT2020)

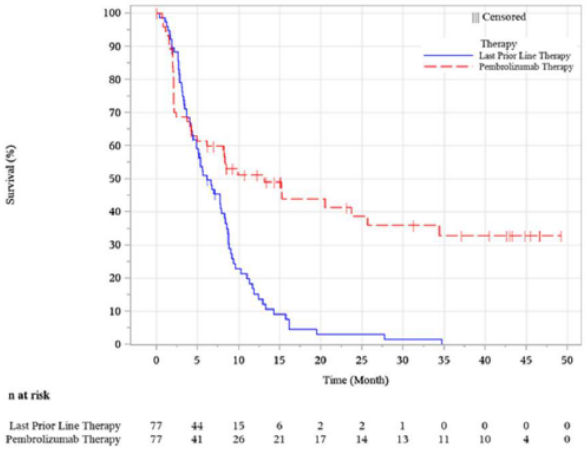
Figure: Kaplan-Meier Plots of TTP on Prior Therapy and PFS on Pembrolizumab Therapy

(KEYNOTE-158)

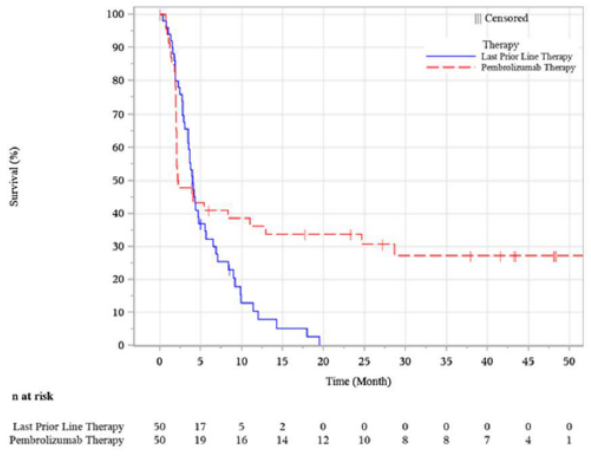
Tumor Type=CHOLANGIOCARCINOMA



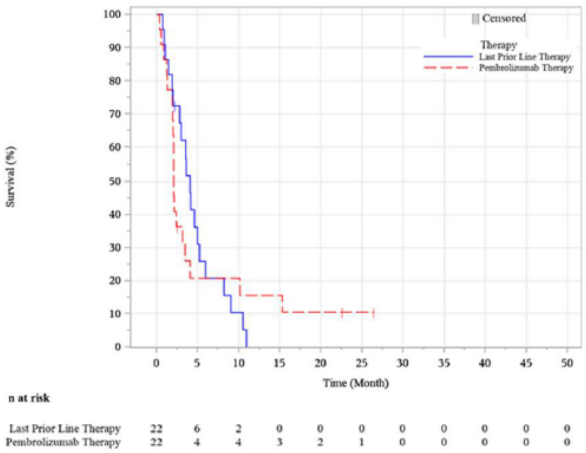
Tumor Type=ENDOMETRIAL

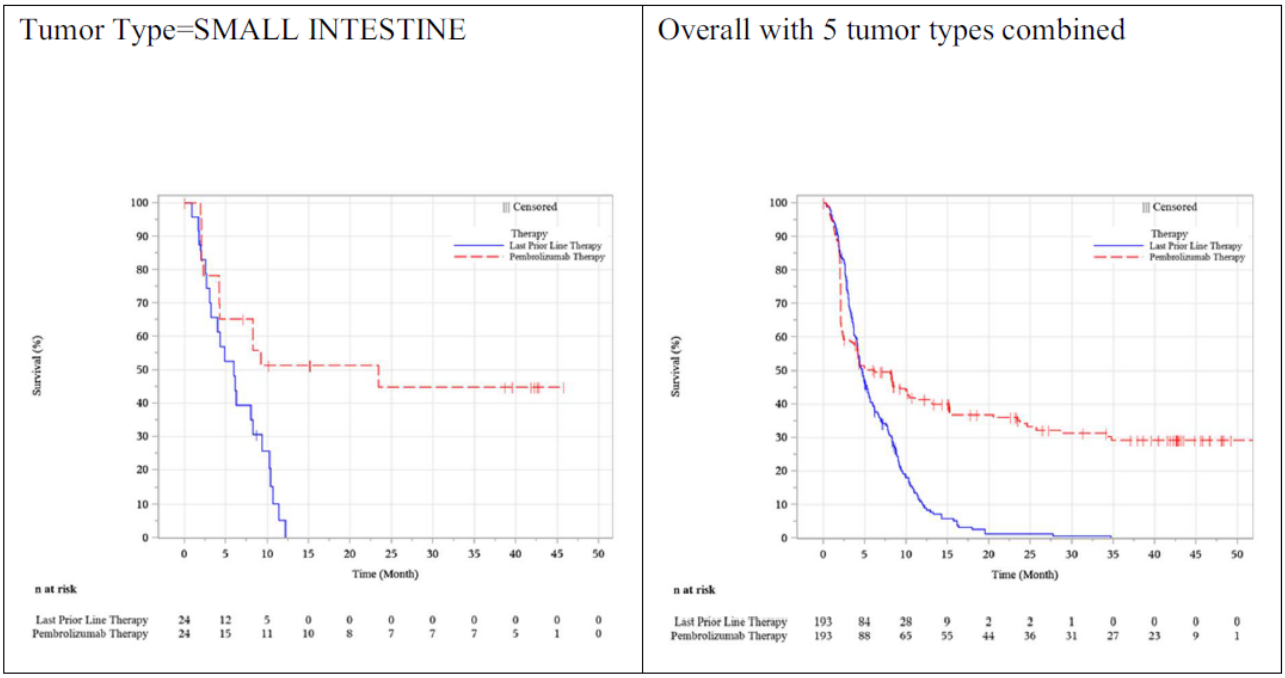


Tumor Type=GASTRIC



Tumor Type=PANCREATIC





(Database Cutoff Date: 05OCT2020)

UPDATED RESULTS

CRC

No new patients have been presented for **MSI-H/dMMR CRC** but an updated analysis with longer follow-up at the data cut-off date 19 Feb 2021 has been provided.

For CRC, follow-up durations at the updated data cut-off date (19 Feb 2021) were 31.4 and 52.7 months for Cohort A (3L+) and Cohort B (2L+), respectively.

Table 33: Summary of Best Overall Response (Confirmed) Based on IRC Assessment per RECIST 1.1 (KEYNOTE-164, ASaT Population)

Response Evaluation	MK-3475 200 mg					
	COHORT A (3L+) (N=61)			**COHORT B (2L+) (N=63)**		
	n	(%)	95% CI†	n	(%)	95% CI†
Subjects in population	61			63		
Complete Response (CR)	3	4.9	(1.0, 13.7)	9	14.3	(6.7, 25.4)
Partial Response (PR)	17	27.9	(17.1, 40.8)	13	20.6	(11.5, 32.7)
Objective Response (CR+PR)	**20**	**32.8**	**(21.3, 46.0)**	**22**	**34.9**	**(23.3, 48.0)**
Stable Disease (SD)	11	18.0	(9.4, 30.0)	13	20.6	(11.5, 32.7)
Disease Control (CR+PR+SD)	**31**	**50.8**	**(37.7, 63.9)**	**35**	**55.6**	**(42.5, 68.1)**
Progressive Disease (PD)	28	45.9	(33.1, 59.2)	25	39.7	(27.6, 52.8)
Non-evaluable (NE)	2	3.3	(0.4, 11.3)	3	4.8	(1.0, 13.3)

† Based on binomial exact confidence interval method.
(Database Cutoff Date: 19FEB2021).

Table 34: Summary of Best Overall Response (Confirmed) Based on IRC Assessment per RECIST 1.1 (KEYNOTE-164 Cohort A + Cohort B, ASaT Population)

Response Evaluation	MK-3475 200 mg (N=124)		
	n	(%)	95% CI[†]
Subjects in population	124		
Complete Response (CR)	12	9.7	(5.1, 16.3)
Partial Response (PR)	30	24.2	(17.0, 32.7)
Objective Response (CR+PR)	**42**	**33.9**	**(25.6, 42.9)**
Stable Disease (SD)	24	19.4	(12.8, 27.4)
Disease Control (CR+PR+SD)	**66**	**53.2**	**(44.1, 62.2)**
Progressive Disease (PD)	53	42.7	(33.9, 51.9)
Non-evaluable (NE)	5	4.0	(1.3, 9.2)

[†] Based on binomial exact confidence interval method.
(Database Cutoff Date: 19FEB2021).

Table 35: Summary of Time to Response and Response Duration in Subjects with Confirmed Response Based on IRC Assessment per RECIST 1.1 (KEYNOTE-164, ASaT Population)

Response Evaluation	MK-3475 200 mg	MK-3475 200 mg
	COHORT A (3L+) (N=61)	**COHORT B (2L+) (N=63)**
Number of Subjects with Response[†]	20	22
Time to Response[†] (Months)		
Mean (SD)	6.9 (6.4)	5.6 (6.4)
Median (Range)	4.7 (1.8 - 24.9)	4.0 (1.8 - 31.3)
Response Duration[‡] (Months)		
Median (Range)	Not reached (6.2 - 58.5+)	Not reached (4.4 - 52.4+)
Number (%[‡]) of Subjects with Response		
≥6 Months (%)	20(100.0)	20(95.5)
≥12 Months (%)	18(95.0)	16(95.5)
≥18 Months (%)	16(89.7)	14(95.5)
≥24 Months (%)	13(89.7)	12(95.5)
≥36 Months (%)	9(89.7)	12(95.5)

[†] Analysis on time to response and response duration are based on subjects with a best objective response as confirmed complete response or partial response only.
[‡] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
(Database Cutoff Date: 19FEB2021).

Table 36: Summary of Time to Response and Response Duration in Subjects with Confirmed Response Based on IRC Assessment per RECIST 1.1 (KEYNOTE-164 Cohort A + Cohort B, ASaT Population)

Response Evaluation	MK-3475 200 mg
	(N=124)
Number of Subjects with Response[†]	42
Time to Response[†] (Months)	
Mean (SD)	6.2 (6.3)

Median (Range)	4.1 (1.8 - 31.3)
Response Duration‡ (Months) Median (Range)	Not reached (4.4 - 58.5+)
Number (%‡) of Subjects with Response	
≥6 Months (%)	40(97.6)
≥12 Months (%)	34(95.1)
≥18 Months (%)	30(92.2)
≥24 Months (%)	25(92.2)
≥36 Months (%)	21(92.2)

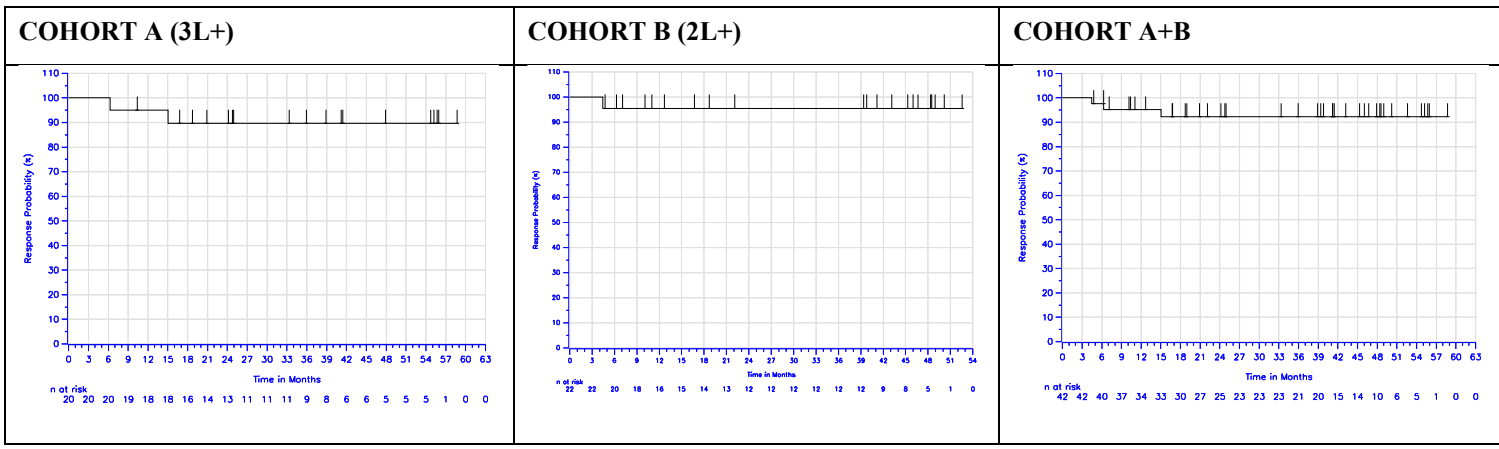
† Analysis on time to response and response duration are based on subjects with a best objective response as confirmed complete response or partial response only.

‡ From product-limit (Kaplan-Meier) method for censored data.

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

(Database Cutoff Date: 19FEB2021).

Figure: Kaplan-Meier Estimates of Objective Response (Confirmed) Duration Based on IRC Assessment per RECIST 1.1 (KEYNOTE-164, ASaT Population)



(Database Cutoff Date: 19FEB2021).

Table 37: Summary of Progression-Free Survival (PFS) Based on IRC Assessment per RECIST 1.1 (KEYNOTE-164, ASaT Population)

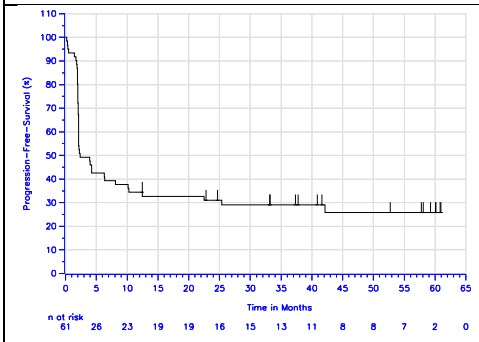
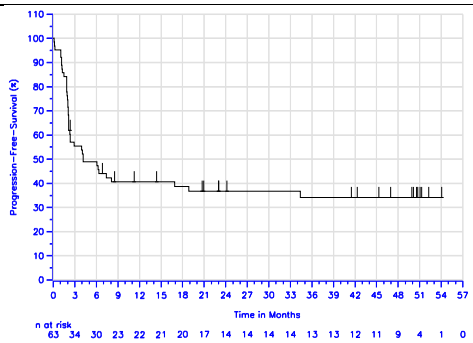
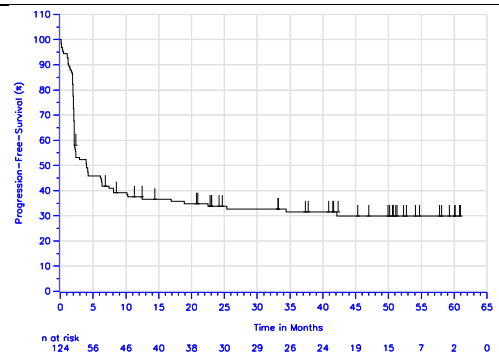
	MK-3475 200 mg	MK-3475 200 mg
Subjects in population	**COHORT A (3L+) (N=61)**	**COHORT B (2L+) (N=63)**
Number (%) of PFS Events	44 (72.1)	40 (63.5)
Person-Months	966	958
Event Rate/100 Person-Months (%)	4.6	4.2
Median PFS (Months)§	2.3	4.1
95% CI for Median PFS§	(2.1,8.1)	(2.1,18.9)
PFS rate at 6 Months in % §	42.6	48.9
PFS rate at 12 Months in % §	34.4	40.6
PFS rate at 24 Months in % §	31.0	36.7
PFS rate at 36 Months in % §	29.0	34.1

Progression-free survival is defined as time from first day of study treatment to disease progression, or death, whichever occurs first.

§ From product-limit (Kaplan-Meier) method for censored data.

(Database Cutoff Date: 19FEB2021).

Figure: Kaplan-Meier Estimates of Progression-Free Survival Based on IRC Assessment per RECIST 1.1 (KEYNOTE-164, ASaT Population)

COHORT A (3L+)	COHORT B (2L+)	COHORT A+B
		

Database Cutoff Date: 19FEB2021

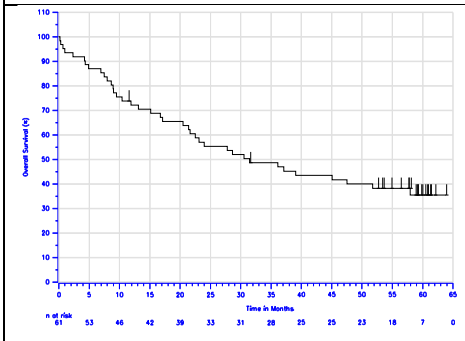
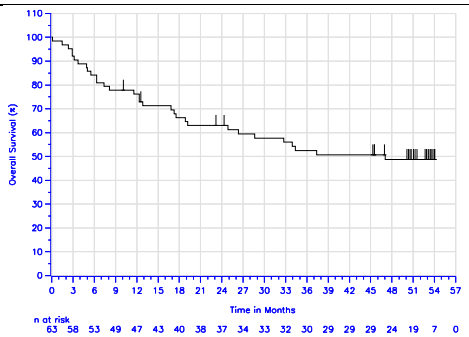
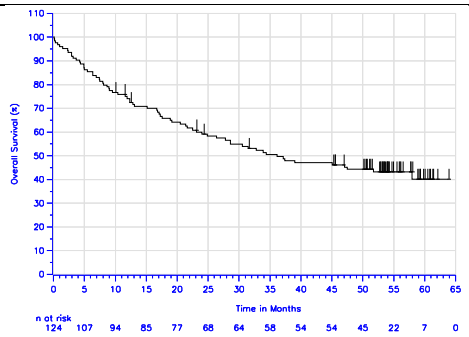
Table 38: Summary of Overall Survival (KEYNOTE-164, ASaT Population)

	MK-3475 200 mg	MK-3475 200 mg
Subjects in population	**COHORT A (3L+) (N=61)**	**COHORT B (2L+) (N=63)**
Number (%) of Events	38 (62.3)	31 (49.2)
Person-Months	1998	1987
Event Rate/100 Person-Months (%)	1.9	1.6
Median OS (Months)[§]	31.4	47.0
95% CI for Median OS[§]	(21.4,58.0)	(19.2,.)
OS rate at 6 Months in % [§]	86.9	84.1
OS rate at 12 Months in % [§]	72.1	76.2
OS rate at 24 Months in % [§]	55.3	63.0
OS rate at 36 Months in % [§]	48.6	52.5
OS: Overall survival [§] From product-limit (Kaplan-Meier) method for censored data. (Database Cutoff Date: 19FEB2021).		

Table 39: Summary of Overall Survival (KEYNOTE-164 Cohort A + Cohort B, ASaT Population)

	MK-3475 200 mg
Subjects in population	124
Number (%) of Events	69 (55.6)
Person-Months	3985
Event Rate/100 Person-Months (%)	1.7
Median OS (Months)[§]	36.1
95% CI for Median OS[§]	(24.0, NR)
OS rate at 12 Months in % [§]	74.2
OS rate at 24 Months in % [§]	59.1
OS rate at 36 Months in % [§]	50.5
OS rate at 48 Months in % [§]	44.3
OS: Overall survival; NR: Not reached. [§] From product-limit (Kaplan-Meier) method for censored data. (Database Cutoff Date: 19FEB2021).	

Figure: Kaplan-Meier Estimates of Overall Survival (KEYNOTE-164, ASaT Population)

COHORT A (3L+)	COHORT B (2L+)	COHORT A+B
		

(Database Cutoff Date: 19FEB2021)

Non-CRC

An **updated** dataset including **205 MSI-H/dMMR non-CRC** patients was provided during the procedure at CHMP request (data cut-off date 15 Oct 2021) including **endometrial n=83, gastric n=51, small intestine n=27, biliary n=22, pancreas n=22** patients (additional patients have been presented in the endometrial, gastric and small intestine cohort). All patients have been followed for at least 6 months.

Table 40: summary of Efficacy Results in KEYNOTE-158 With an Additional 1-Year of Follow-up

	Database Cutoff Date (05-OCT-2020)	Database Cutoff Date (15-OCT-2021)
Endometrial	**n=68**	**n=83**
ORR, % (95% CI)	48.5 (36.2, 61.0)	50.6 (39.4, 61.8)
Median DOR, months (range)	NR (2.9 – 47.1+)	NR (2.9 - 60.4+)
Extended DOR, % at ≥24 months	67.1	65.4
Median PFS, months (95% CI)	13.1 (4.9, 34.4)	13.1 (4.9, 25.7)
PFS rate, % at 24 Months	39.6	39.0
Median OS, months (95% CI)	NR (32.4, NR)	NR (48.0, NR)
OS rate, % at 24 Months	66.9	67.2
Gastric	**n=42**	**n=51**
ORR, % (95% CI)	31.0 (17.6, 47.1)	37.3 (24.1, 51.9)
Median DOR, months (range)	NR (6.3 - 51.1+)	NR (6.2 – 63.0 +)
Extended DOR, % at ≥24 months	83.1	81.3
Median PFS, months (95% CI)	3.2 (2.1, 12.9)	4.1 (2.1, 24.6)
PFS rate, % at 24 Months	35.3	38.5
Median OS, months (95% CI)	11.0 (5.8, 31.5)	26.9 (6.6, NR)
OS rate, % at 24 Months	47.0	50.0
Small Intestine	**n=25**	**n=27**
ORR, % (95% CI)	48.0 (27.8, 68.7)	55 (35.3, 74.5)
Median DOR, months (range)	NR (2.1+ - 41.8+)	NR (3.7+ - 57.3+)
Extended DOR, % at ≥24 months	88.9	73.1
Median PFS, months (95% CI)	23.4 (4.3, NR)	23.4 (4.3, NR)
PFS rate, % at 24 Months	49.1	49.8
Median OS, months (95% CI)	NR (16.2, NR)	NR (16.2, NR)
OS rate, % at 24 Months	58.7	62.7
Biliary Cancer	**n=22**	**n=22**
ORR, % (95% CI)	40.9 (20.7, 63.6)	40.9 (20.7, 63.6)
Median DOR, months (range)	30.6 (6.2 - 40.5+)	30.6 (6.2 - 46.0+)
Extended DOR, % at ≥24 months	62.2	62.2
Median PFS, months (95% CI)	4.2 (2.1, 24.9)	4.2 (2.1, 24.9)
PFS rate, % at 24 Months	31.8	31.8
Median OS, months (95% CI)	19.4 (6.5, NR)	19.4 (6.5, 44.8)
OS rate, % at 24 Months	50.0	50.0
Pancreatic Cancer	**n=22**	**n=22**
ORR, % (95% CI)	18.2 (5.2, 40.3)	18.2 (5.2, 40.3)
Median DOR, months (range)	NR (8.1 - 24.3+)	NR (8.1 - 24.3+)
Extended DOR, % at ≥24 months	50.0	50.0
Median PFS, months (95% CI)	2.1 (1.9, 3.4)	2.1 (1.9, 3.4)
PFS rate, % at 24 Months	10.4	10.4
Median OS, months (95% CI)	3.7 (2.1, 9.8)	3.7 (2.1, 9.8)
OS rate, % at 24 Months	22.7	22.7

Table 41: Summary of Follow-up Duration by Tumour Type (Baseline MSI-H) (MK3475 200mg Q3W) (ASaT Population for Efficacy Analysis) – UPDATED cut-off date 15 Oct 2021

Tumor Type	N	Follow-up duration (months)[a]	
		Median (Range)	Mean (SD)
ENDOMETRIAL	83	21.9 (1.5, 64.0)	28.3 (21.1)
GASTRIC	51	13.9 (1.1, 66.9)	22.2 (22.4)
SMALL INTESTINE	27	29.1 (4.2, 67.7)	34.9 (22.1)
CHOLANGIOCARCINOMA	22	19.4 (1.1, 60.8)	25.3 (20.2)
PANCREATIC	22	3.7 (0.4, 67.9)	15.8 (22.9)

[a] Follow-up duration is defined as the time from first dose to the date of death or the database cutoff date if the subject is still alive.

Subjects who received at least one dose of MK-3475 in KN158 with MSI-H tumors in cohort K with 6 months follow-up are included.

(Database Cutoff Date: 15OCT2021).

Table 42: Summary of Best Objective Response Based on RECIST1.1 per Central Radiology Assessment by Tumour Type (Baseline MSI-H) (MK3475 200mg Q3W) (ASaT Population for Efficacy Analysis)

Tumour Type	N	Objective Response (CR+PR)	Complete Response (CR)	Partial Response (PR)	Stable Disease (SD)	Disease Control (CR+PR+SD)	Progressive Disease (PD)	Non-evaluable (NE)	No Assessment
		n (%) 95% CI[a]	n (%) 95% CI[a]	n (%) 95% CI[a]	n (%) 95% CI[a]	n (%) 95% CI[a]	n (%) 95% CI[a]	n (%) 95% CI[a]	n (%) 95% CI[a]
ENDOMETRIAL	83	42 (50.6) (39.4, 61.8)	13 (15.7) (8.6, 25.3)	29 (34.9) (24.8, 46.2)	16 (19.3) (11.4, 29.4)	58 (69.9) (58.8, 79.5)	22 (26.5) (17.4, 37.3)	1 (1.2) (0.0, 6.5)	2 (2.4) (0.3, 8.4)
GASTRIC	51	19 (37.3) (24.1, 51.9)	7 (13.7) (5.7, 26.3)	12 (23.5) (12.8, 37.5)	7 (13.7) (5.7, 26.3)	26 (51.0) (36.6, 65.2)	18 (35.3) (22.4, 49.9)	1 (2.0) (0.0, 10.4)	6 (11.8) (4.4, 23.9)
SMALL INTESTINE	27	15 (55.6) (35.3, 74.5)	4 (14.8) (4.2, 33.7)	11 (40.7) (22.4, 61.2)	6 (22.2) (8.6, 42.3)	21 (77.8) (57.7, 91.4)	5 (18.5) (6.3, 38.1)	0 (0.0) (0.0, 12.8)	1 (3.7) (0.1, 19.0)
CHOLANGIOCARCINOMA	22	9 (40.9) (20.7, 63.6)	3 (13.6) (2.9, 34.9)	6 (27.3) (10.7, 50.2)	3 (13.6) (2.9, 34.9)	12 (54.5) (32.2, 75.6)	8 (36.4) (17.2, 59.3)	0 (0.0) (0.0, 15.4)	2 (9.1) (1.1, 29.2)
PANCREATIC	22	4 (18.2) (5.2, 40.3)	1 (4.5) (0.1, 22.8)	3 (13.6) (2.9, 34.9)	3 (13.6) (2.9, 34.9)	7 (31.8) (13.9, 54.9)	8 (36.4) (17.2, 59.3)	0 (0.0) (0.0, 15.4)	7 (31.8) (13.9, 54.9)

[a] Based on binomial exact confidence interval method.

Only confirmed responses are included.

'No Assessment' (NA) counts subjects who had a baseline assessment evaluated by the central radiology assessment but no post-baseline assessment on the data cutoff date including missing, discontinuing or death before the first post-baseline scan.

(Database Cutoff Date: 15OCT2021).

Table 43: Summary of Time to Response and Duration of Response Based on RECIST 1.1 per Central Radiology Assessment by Tumour Type in Subjects with Confirmed Response (Baseline MSI-H) (MK3475 200mg Q3W) (Responders)

	ENDOMETRIAL (N=83)	GASTRIC (N=51)	CHOLANGIO CARCINOMA (N=22)	PANCREATIC (N=22)	SMALL INTESTINE (N=27)
Number of subjects with response[a]	42	19	9	4	15
Time to Response (months)					
Mean (SD)	3.5 (2.6)	3.5 (1.5)	3.0 (1.1)	2.0 (0.1)	4.2 (4.7)
Median (Range)	2.1 (1.3-12.7)	3.8 (1.9-6.5)	2.4 (1.9-4.2)	2.1 (1.9-2.1)	2.1 (1.9-17.9)
Response Duration[b] (months)					

Median (Range)	NR (2.9 - 60.4+)	NR (6.2 - 63.0+)	30.6 (6.2 - 46.0+)	NR (8.1 - 24.3+)	NR (3.7+ - 57.3+)
Number (%[b]) of Subjects with Extended Response Duration:					
≥6 months	38 (90.4)	19 (100.0)	9 (100.0)	4 (100.0)	12 (92.9)
≥12 months	29 (84.9)	13 (89.5)	8 (88.9)	3 (75.0)	10 (92.9)
≥18 months	16 (65.4)	12 (89.5)	6 (77.8)	2 (50.0)	9 (83.6)
≥24 months	13 (65.4)	10 (81.3)	4 (62.2)	1 (50.0)	7 (73.1)
≥36 months	11 (59.9)	8 (81.3)	2 (41.5)	0 (NR)	7 (73.1)

[a] Includes subjects with confirmed complete response or partial response.

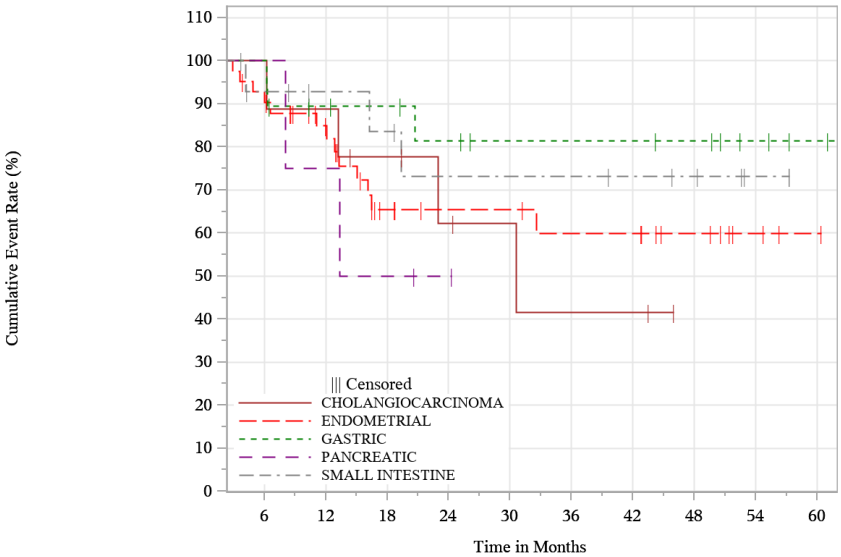
[b] From product-limit (Kaplan-Meier) method for censored data.

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

NR = Not Reached.

(Database Cutoff Date: 15OCT2021).

Figure: Kaplan-Meier Estimates of Objective Response Duration Based on RECIST 1.1 per Central Radiology Assessment in Subjects with Confirmed Response (Baseline MSI-H) (MK3475 200mg Q3W) (Responders)



n at risk

CHOLANGIOCARCINOMA	9	8	6	4	3	2	2	0	0	0
ENDOMETRIAL	38	29	16	13	13	11	11	7	3	1
GASTRIC	19	13	12	10	8	8	8	7	4	2
PANCREATIC	4	3	2	1	0	0	0	0	0	0
SMALL INTESTINE	12	10	9	7	7	7	6	5	2	0

(Database Cutoff Date: 15OCT2021).

Table 44: Summary of Progression-Free Survival Based on RECIST1.1 per Central Radiology Assessment by Tumour Type (Baseline MSI-H) (MK3475 200mg Q3W) (ASaT Population for Efficacy Analysis)

	ENDOMETRIAL (N=83)	GASTRIC (N=51)	CHOLANGIO-CARCINOMA (N=22)	PANCREATIC (N=22)	SMALL INTESTINE (N=27)
Number (%) of PFS Events	51 (61.4)	33 (64.7)	18 (81.8)	19 (86.4)	14 (51.9)
Person-Months	1352	795	304	111	632
Event Rate/100 Person-Months (%)	3.8	4.2	5.9	17.1	2.2
Median PFS (Months)[a]	13.1	4.1	4.2	2.1	23.4
95% CI for Median PFS[a]	(4.9, 25.7)	(2.1, 24.6)	(2.1, 24.9)	(1.9, 3.4)	(4.3, NR)
PFS rate at 6 Months in % [a]	60.0	47.1	45.5	20.8	70.4
PFS rate at 12 Months in % [a]	50.9	41.1	36.4	15.6	58.8
PFS rate at 18 Months in % [a]	44.8	38.5	31.8	10.4	58.8
PFS rate at 24 Months in % [a]	39.0	38.5	31.8	10.4	49.8

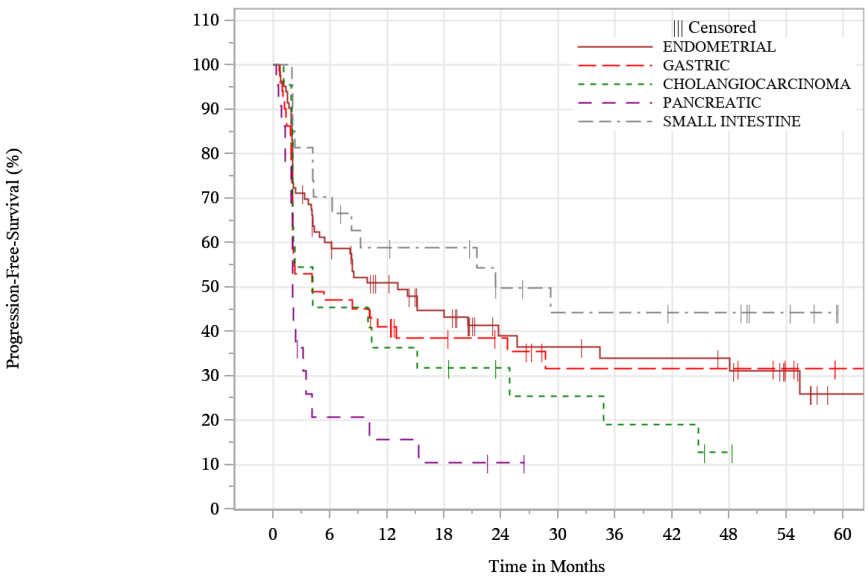
Progression-free survival is defined as time from date of first dose to disease progression, or death, whichever occurs first; NR = Not reached

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

Subjects who received at least one dose of MK-3475 in KN158 with MSI-H tumours in cohort K with 6 months follow-up are included.

(Database Cutoff Date: 15OCT2021).

Figure: Kaplan-Meier Estimates of Progression-Free Survival Based on RECIST1.1 per Central Radiology Assessment by Tumour Type (Baseline MSI-H) (MK3475 200mg Q3W) (ASaT Population for Efficacy Analysis)



n at risk

ENDOMETRIAL	83	48	36	28	16	15	13	13	12	7	1
GASTRIC	51	24	20	15	13	8	8	8	8	5	2
CHOLANGIOCARCINOMA	22	10	8	7	5	4	3	3	1	0	0
PANCREATIC	22	4	3	2	1	0	0	0	0	0	0
SMALL INTESTINE	27	19	15	14	10	8	8	7	7	4	0

(Database Cutoff Date: 15OCT2021).

Table 45: Summary of Overall Survival by Tumour Type (Baseline MSI-H) (ASaT Population for Efficacy Analysis)

	ENDOMETRIAL (N=83)	GASTRIC (N=51)	CHOLANGIO-CARCINOMA (N=22)	PANCREATIC (N=22)	SMALL INTESTINE (N=27)
Death (%)	32 (38.6)	29 (56.9)	16 (72.7)	17 (77.3)	10 (37.0)
Median Survival (Months)[a]	Not reached	26.9	19.4	3.7	Not reached
95% CI for Median Survival[a]	(48.0,NR)	(6.6,NR)	(6.5,44.8)	(2.1,9.8)	(16.2,NR)
OS rate at 6 Months in % [a]	85.5	66.7	81.8	36.4	92.6
OS rate at 12 Months in % [a]	73.3	54.8	63.6	22.7	77.8
OS rate at 18 Months in % [a]	70.6	52.8	50.0	22.7	70.4
OS rate at 24 Months in % [a]	67.2	50.0	50.0	22.7	62.7

OS: Overall survival.

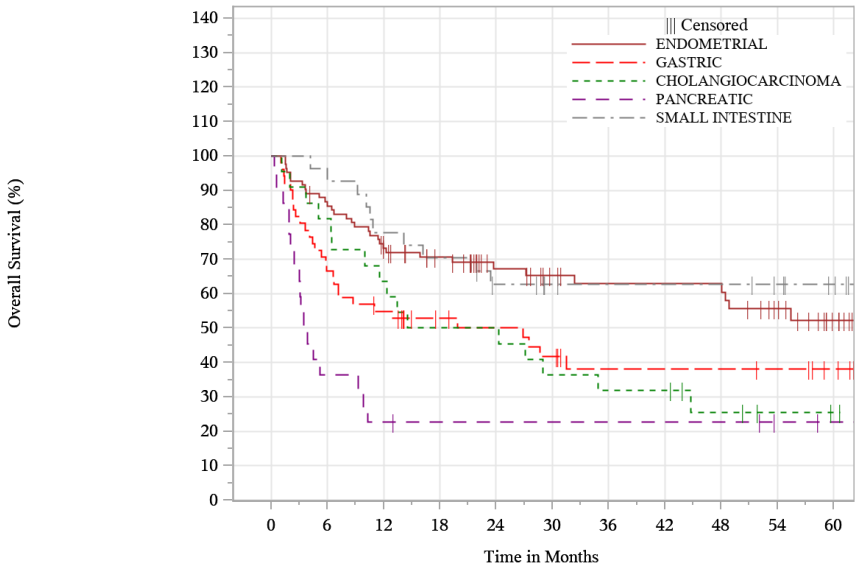
[a] From product-limit (Kaplan-Meier) method for censored data.

Subjects who received at least one dose of MK-3475 in KN158 with MSI-H tumours in cohort K with 6 months follow-up are included.

NR = Not reached.

(Database Cutoff Date: 15OCT2021).

Figure: Kaplan-Meier Estimates of Overall Survival Based on RECIST1.1 per Central Radiology Assessment by Tumour Type (Baseline MSI-H) (MK3475 200mg Q3W) (ASaT Population for Efficacy Analysis)



(Database Cutoff Date: 15OCT2021).

Ancillary analyses

MSI-H/dMMR tumour types <u>not</u> included in the indication:

A summary of all cancer types MSI-H/dMMR included in the two pivotal studies KEYNOTE-164 and KEYNOTE-158 Cohort K is presented in the table below. MSI-H/dMMR CRC are included in KEYNOTE-164

(n=124). A total of 351 participants with 26 MSI-H/dMMR non-CRC tumour types were allocated to Cohort K of KEYNOTE-158.

Table 46: Summary of Cancer Types Pooled Studies (KN158 and KN164) (MK3475 200mg Q3W) (ASaT Population for Efficacy Analysis) (tumour types included in the sought indication ***in Italics***)

	KN158 n (%)	KN164 n (%)	Total n (%)
Subjects in population	321	124	445
ADRENOCORTICAL	7 (2.2)	0 (0.0)	7 (1.6)
ANAL	1 (0.3)	0 (0.0)	1 (0.2)
BRAIN	17 (5.3)	0 (0.0)	17 (3.8)
BREAST	11 (3.4)	0 (0.0)	11 (2.5)
CERVICAL	8 (2.5)	0 (0.0)	8 (1.8)
CHOLANGIOCARCINOMA	***22 (6.9)***	***0 (0.0)***	***22 (4.9)***
COLORECTAL	***0 (0.0)***	***124 (100.0)***	***124 (27.9)***
ENDOMETRIAL	***68 (21.2)***	***0 (0.0)***	***68 (15.3)***
GASTRIC	***42 (13.1)***	***0 (0.0)***	***42 (9.4)***
HNSCC	1 (0.3)	0 (0.0)	1 (0.2)
MESOTHELIOMA	6 (1.9)	0 (0.0)	6 (1.3)
NASOPHARYNGEAL	1 (0.3)	0 (0.0)	1 (0.2)
NEUROENDOCRINE	12 (3.7)	0 (0.0)	12 (2.7)
OVARIAN	24 (7.5)	0 (0.0)	24 (5.4)
Other	3 (0.9)	0 (0.0)	3 (0.7)
PANCREATIC	***22 (6.9)***	***0 (0.0)***	***22 (4.9)***
PROSTATE	8 (2.5)	0 (0.0)	8 (1.8)
RENAL	4 (1.2)	0 (0.0)	4 (0.9)
RETROPERITONEAL	1 (0.3)	0 (0.0)	1 (0.2)
SALIVARY	4 (1.2)	0 (0.0)	4 (0.9)
SARCOMA	14 (4.4)	0 (0.0)	14 (3.1)
SCLC	6 (1.9)	0 (0.0)	6 (1.3)
SMALL INTESTINE	***25 (7.8)***	***0 (0.0)***	***25 (5.6)***
TESTICULAR	1 (0.3)	0 (0.0)	1 (0.2)
THYROID	6 (1.9)	0 (0.0)	6 (1.3)
UROTHELIAL	6 (1.9)	0 (0.0)	6 (1.3)
VAGINAL	1 (0.3)	0 (0.0)	1 (0.2)

Subjects who received at least one dose of MK-3475 in KN158 with MSI-H tumours in cohort K with 6 months follow-up and KN164 are included.

The 'Other' tumour type includes 1 each of appendiceal adenocarcinoma, hepatocellular carcinoma, and carcinoma of unknown origin.

KN164 Database Cutoff Date: 09-SEP-2019

KN158 Database Cutoff Date: 05-OCT-2020

A total of 321 participants of KEYNOTE-158 Cohort K were included in the ASaT population for efficacy analysis, i.e. received at least 1 treatment dose and had a follow-up of at least 6 months at the data cut-off. For this population, ORR and DOR results by tumour type are shown in the tables below.

Summary of Best Objective Response Based on RECIST1.1 Per Central Radiology Assessment by Tumor Type
(Baseline MSI-H)
(MK3475 200mg Q3W)
(ASaT Population for Efficacy Analysis)

Tumor Type	N	Objective Response (CR+PR) n (%) 95% CI†	Complete Response (CR) n (%) 95% CI†	Partial Response (PR) n (%) 95% CI†	Stable Disease (SD) n (%) 95% CI†	Disease Control (CR+PR+SD) n (%) 95% CI†	Progressive Disease (PD) n (%) 95% CI†	Non-evaluable (NE) n (%) 95% CI†	No Assessment n (%) 95% CI†
ENDOMETRIAL	68	33 (48.5) (36.2, 61.0)	10 (14.7) (7.3, 25.4)	23 (33.8) (22.8, 46.3)	13 (19.1) (10.6, 30.5)	46 (67.6) (55.2, 78.5)	19 (27.9) (17.7, 40.1)	1 (1.5) (0.0, 7.9)	2 (2.9) (0.4, 10.2)
GASTRIC	42	13 (31.0) (17.6, 47.1)	4 (9.5) (2.7, 22.6)	9 (21.4) (10.3, 36.8)	7 (16.7) (7.0, 31.4)	20 (47.6) (32.0, 63.6)	15 (35.7) (21.6, 52.0)	1 (2.4) (0.1, 12.6)	6 (14.3) (5.4, 28.5)
SMALL INTESTINE	25	12 (48.0) (27.8, 68.7)	4 (16.0) (4.5, 36.1)	8 (32.0) (14.9, 53.5)	7 (28.0) (12.1, 49.4)	19 (76.0) (54.9, 90.6)	5 (20.0) (6.8, 40.7)	0 (0.0) (0.0, 13.7)	1 (4.0) (0.1, 20.4)
OVARIAN	24	8 (33.3) (15.6, 55.3)	3 (12.5) (2.7, 32.4)	5 (20.8) (7.1, 42.2)	2 (8.3) (1.0, 27.0)	10 (41.7) (22.1, 63.4)	12 (50.0) (29.1, 70.9)	0 (0.0) (0.0, 14.2)	2 (8.3) (1.0, 27.0)
CHOLANGIOCARCINOMA	22	9 (40.9) (20.7, 63.6)	3 (13.6) (2.9, 34.9)	6 (27.3) (10.7, 50.2)	3 (13.6) (2.9, 34.9)	12 (54.5) (32.2, 75.6)	8 (36.4) (17.2, 59.3)	0 (0.0) (0.0, 15.4)	2 (9.1) (1.1, 29.2)
PANCREATIC	22	4 (18.2) (5.2, 40.3)	1 (4.5) (0.1, 22.8)	3 (13.6) (2.9, 34.9)	3 (13.6) (2.9, 34.9)	7 (31.8) (13.9, 54.9)	8 (36.4) (17.2, 59.3)	0 (0.0) (0.0, 15.4)	7 (31.8) (13.9, 54.9)
BRAIN	17	1 (5.9) (0.1, 28.7)	0 (0.0) (0.0, 19.5)	1 (5.9) (0.1, 28.7)	2 (11.8) (1.5, 36.4)	3 (17.6) (3.8, 43.4)	13 (76.5) (50.1, 93.2)	0 (0.0) (0.0, 19.5)	1 (5.9) (0.1, 28.7)
SARCOMA	14	3 (21.4) (4.7, 50.8)	0 (0.0) (0.0, 23.2)	3 (21.4) (4.7, 50.8)	4 (28.6) (8.4, 58.1)	7 (50.0) (23.0, 77.0)	6 (42.9) (17.7, 71.1)	0 (0.0) (0.0, 23.2)	1 (7.1) (0.2, 33.9)
NEUROENDOCRINE	12	2 (16.7) (2.1, 48.4)	0 (0.0) (0.0, 26.5)	2 (16.7) (2.1, 48.4)	5 (41.7) (15.2, 72.3)	7 (58.3) (27.7, 84.8)	5 (41.7) (15.2, 72.3)	0 (0.0) (0.0, 26.5)	0 (0.0) (0.0, 26.5)
BREAST	11	1 (9.1) (0.2, 41.3)	0 (0.0) (0.0, 28.5)	1 (9.1) (0.2, 41.3)	1 (9.1) (0.2, 41.3)	2 (18.2) (2.3, 51.8)	7 (63.6) (30.8, 89.1)	0 (0.0) (0.0, 28.5)	2 (18.2) (2.3, 51.8)
CERVICAL	8	0 (0.0) (0.0, 36.9)	0 (0.0) (0.0, 36.9)	0 (0.0) (0.0, 36.9)	1 (12.5) (0.3, 52.7)	1 (12.5) (0.3, 52.7)	6 (75.0) (34.9, 96.8)	0 (0.0) (0.0, 36.9)	1 (12.5) (0.3, 52.7)
PROSTATE	8	1 (12.5) (0.3, 52.7)	0 (0.0) (0.0, 36.9)	1 (12.5) (0.3, 52.7)	2 (25.0) (3.2, 65.1)	3 (37.5) (8.5, 75.5)	5 (62.5) (24.5, 91.5)	0 (0.0) (0.0, 36.9)	0 (0.0) (0.0, 36.9)
ADRENOCORTICAL	7	1 (14.3) (0.4, 57.9)	0 (0.0) (0.0, 41.0)	1 (14.3) (0.4, 57.9)	1 (14.3) (0.4, 57.9)	2 (28.6) (3.7, 71.0)	4 (57.1) (18.4, 90.1)	0 (0.0) (0.0, 41.0)	1 (14.3) (0.4, 57.9)
MESOTHELIOMA	6	0 (0.0) (0.0, 45.9)	0 (0.0) (0.0, 45.9)	0 (0.0) (0.0, 45.9)	3 (50.0) (11.8, 88.2)	3 (50.0) (11.8, 88.2)	2 (33.3) (4.3, 77.7)	0 (0.0) (0.0, 45.9)	1 (16.7) (0.4, 64.1)
SCLC	6	2 (33.3) (4.3, 77.7)	1 (16.7) (0.4, 64.1)	1 (16.7) (0.4, 64.1)	2 (33.3) (4.3, 77.7)	4 (66.7) (22.3, 95.7)	2 (33.3) (4.3, 77.7)	0 (0.0) (0.0, 45.9)	0 (0.0) (0.0, 45.9)
THYROID	6	0 (0.0) (0.0, 45.9)	0 (0.0) (0.0, 45.9)	0 (0.0) (0.0, 45.9)	2 (33.3) (4.3, 77.7)	2 (33.3) (4.3, 77.7)	3 (50.0) (11.8, 88.2)	1 (16.7) (0.4, 64.1)	0 (0.0) (0.0, 45.9)
UROTHELIAL	6	3 (50.0) (11.8, 88.2)	0 (0.0) (0.0, 45.9)	3 (50.0) (11.8, 88.2)	0 (0.0) (0.0, 45.9)	3 (50.0) (11.8, 88.2)	3 (50.0) (11.8, 88.2)	0 (0.0) (0.0, 45.9)	0 (0.0) (0.0, 45.9)
RENAL	4	1 (25.0) (0.6, 80.6)	0 (0.0) (0.0, 60.2)	1 (25.0) (0.6, 80.6)	1 (25.0) (0.6, 80.6)	2 (50.0) (6.8, 93.2)	2 (50.0) (6.8, 93.2)	0 (0.0) (0.0, 60.2)	0 (0.0) (0.0, 60.2)
SALIVARY	4	1 (25.0) (0.6, 80.6)	0 (0.0) (0.0, 60.2)	1 (25.0) (0.6, 80.6)	1 (25.0) (0.6, 80.6)	2 (50.0) (6.8, 93.2)	2 (50.0) (6.8, 93.2)	0 (0.0) (0.0, 60.2)	0 (0.0) (0.0, 60.2)
Other	3	2 (66.7) (9.4, 99.2)	0 (0.0) (0.0, 70.8)	2 (66.7) (9.4, 99.2)	0 (0.0) (0.0, 70.8)	2 (66.7) (9.4, 99.2)	1 (33.3) (0.8, 90.6)	0 (0.0) (0.0, 70.8)	0 (0.0) (0.0, 70.8)
ANAL	1	0 (0.0) (0.0, 97.5)	0 (0.0) (0.0, 97.5)	0 (0.0) (0.0, 97.5)	0 (0.0) (0.0, 97.5)	0 (0.0) (0.0, 97.5)	1 (100.0) (2.5, 100.0)	0 (0.0) (0.0, 97.5)	0 (0.0) (0.0, 97.5)
HNSCC	1	0 (0.0) (0.0, 97.5)	0 (0.0) (0.0, 97.5)	0 (0.0) (0.0, 97.5)	1 (100.0) (2.5, 100.0)	1 (100.0) (2.5, 100.0)	0 (0.0) (0.0, 97.5)	0 (0.0) (0.0, 97.5)	0 (0.0) (0.0, 97.5)
NASOPHARYNGEAL	1	0 (0.0) (0.0, 97.5)	0 (0.0) (0.0, 97.5)	0 (0.0) (0.0, 97.5)	0 (0.0) (0.0, 97.5)	0 (0.0) (0.0, 97.5)	1 (100.0) (2.5, 100.0)	0 (0.0) (0.0, 97.5)	0 (0.0) (0.0, 97.5)
RETROPERITONEAL	1	1 (100.0) (2.5, 100.0)	0 (0.0) (0.0, 97.5)	1 (100.0) (2.5, 100.0)	0 (0.0) (0.0, 97.5)	1 (100.0) (2.5, 100.0)	0 (0.0) (0.0, 97.5)	0 (0.0) (0.0, 97.5)	0 (0.0) (0.0, 97.5)
TESTICULAR	1	0 (0.0) (0.0, 97.5)	0 (0.0) (0.0, 97.5)	0 (0.0) (0.0, 97.5)	0 (0.0) (0.0, 97.5)	0 (0.0) (0.0, 97.5)	1 (100.0) (2.5, 100.0)	0 (0.0) (0.0, 97.5)	0 (0.0) (0.0, 97.5)
VAGINAL	1	1 (100.0) (2.5, 100.0)	1 (100.0) (2.5, 100.0)	0 (0.0) (0.0, 97.5)	0 (0.0) (0.0, 97.5)	1 (100.0) (2.5, 100.0)	0 (0.0) (0.0, 97.5)	0 (0.0) (0.0, 97.5)	0 (0.0) (0.0, 97.5)

† Based on binomial exact confidence interval method.
Only confirmed responses are included.
The 'Other' tumor type includes 1 each of appendiceal adenocarcinoma, hepatocellular carcinoma, and carcinoma of unknown origin.
'No Assessment' (NA) counts subjects who had a baseline assessment evaluated by the central radiology assessment but no post-baseline assessment on the data cutoff date including missing, discontinuing or death before the first post-baseline scan.
(Database Cutoff Date: 05OCT2020).

Summary of Time to Response and Duration of Response
Based on RECIST 1.1 per Central Radiology Assessment by Tumor Type in Subjects With Confirmed Response
(Baseline MSI-H)
(MK-3475 200mg Q3W)
(Responders)

Tumor Type	N	Number of Subjects with Response†	Time to Response† (Months)		Response Duration‡ (Months)
			Mean (SD)	Median (Range)	Median (Range)
ENDOMETRIAL	68	33	3.3 (2.2)	2.1 (1.3-10.6)	NR (2.9 - 47.1+)
GASTRIC	42	13	3.1 (1.1)	2.4 (1.9-4.8)	NR (6.3 - 51.1+)
SMALL INTESTINE	25	12	3.4 (3.1)	2.1 (1.9-12.9)	NR (2.1+ - 41.8+)
OVARIAN	24	8	2.3 (0.8)	2.0 (1.8-4.2)	NR (4.2 - 43.5+)
CHOLANGIOCARCINOMA	22	9	3.0 (1.1)	2.4 (1.9-4.2)	30.6 (6.2 - 40.5+)
PANCREATIC	22	4	2.0 (0.1)	2.1 (1.9-2.1)	NR (8.1 - 24.3+)
BRAIN	17	1	10.3 (.)	10.3 (10.3-10.3)	6.5 (6.5 - 6.5)
SARCOMA	14	3	2.7 (1.1)	2.1 (2.0-3.9)	NR (32.7+ - 43.6+)
NEUROENDOCRINE	12	2	1.9 (0.0)	1.9 (1.9-1.9)	13.3 (10.4+ - 13.3)
BREAST	11	1	2.0 (.)	2.0 (2.0-2.0)	NR (8.7+ - 8.7+)
CERVICAL	8	0	-	-	-
PROSTATE	8	1	1.7 (.)	1.7 (1.7-1.7)	NR (16.2+ - 16.2+)
ADRENOCORTICAL	7	1	8.1 (.)	8.1 (8.1-8.1)	4.2 (4.2 - 4.2)
MESOTHELIOMA	6	0	-	-	-
SCLC	6	2	2.0 (0.1)	2.0 (1.9-2.1)	33.8 (20.0 - 47.5)
THYROID	6	0	-	-	-
UROTHELIAL	6	3	2.0 (0.2)	2.0 (1.8-2.1)	NR (21.7+ - 49.0+)
RENAL	4	1	2.1 (.)	2.1 (2.1-2.1)	NR (15.9+ - 15.9+)
SALIVARY	4	1	2.0 (.)	2.0 (2.0-2.0)	NR (44.3+ - 44.3+)
Other	3	2	4.2 (2.9)	4.2 (2.1-6.2)	NR (12.0+ - 15.9+)
ANAL	1	0	-	-	-
HNSCC	1	0	-	-	-
NASOPHARYNGEAL	1	0	-	-	-
RETROPERITONEAL	1	1	2.1 (.)	2.1 (2.1-2.1)	NR (6.2+ - 6.2+)
TESTICULAR	1	0	-	-	-
VAGINAL	1	1	1.9 (.)	1.9 (1.9-1.9)	NR (26.9+ - 26.9+)

† 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.
The 'Other' tumor type includes 1 each of appendiceal adenocarcinoma, hepatocellular carcinoma, and carcinoma of unknown origin.
(Database Cutoff Date: 05OCT2020).

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 47: Summary of Efficacy for trials KEYNOTE-164 and KEYNOTE-158 – CRC, gastric, small intestine, endometrial, biliary and pancreatic MSI-H/dMMR population

Title: Integrated efficacy analysis of unresectable or metastatic MSI-H/dMMR solid tumours treated with pembrolizumab monotherapy			
Study identifier	P164V04MK3475 (IND: 123482, EudraCT: 2015-001852-32) P158V09MK3475 (IND: 127548, EudraCT: 2015-002067-41)		
Design	KEYNOTE-164: open-label, single-arm, multicenter, multicohort, Phase 2 study of pembrolizumab in previously treated participants with locally advanced unresectable or metastatic (Stage IV) MSI-H CRC. KEYNOTE-158: open-label, single-arm, multicenter, multicohort, Phase 2 study of pembrolizumab in previously treated participants with advanced solid tumours evaluated for predictive biomarkers. Cohort K was initiated to enroll any participant with an advanced solid tumour that was MSI-H (except CRC)		
	Duration of main phase:		Up to 2 years
	Duration of Run-in phase:		NA
	Duration of Extension phase:		NA
Hypothesis	Exploratory: single arm trials KEYNOTE-164 (Cohort A): ORR based on RECIST 1.1 assessed by IRC in participants with locally advanced unresectable or metastatic dMMR or MSI-H CRC is >15; no hypothesis for Cohort B KEYNOTE-158: No hypothesis		
Treatments groups	Pembrolizumab		200 mg IV Q3W up to 35 cycles N=445 subjects treated KEYNOTE-164: n=124 KEYNOTE-158 (Cohort K): n=351
Endpoints and definitions	Primary endpoint	ORR	ORR per RECIST 1.1 as assessed by IRC is defined as the proportion of participants in the analysis population who have a CR or PR.
	Secondary Endpoints	DOR	DOR per RECIST 1.1 as assessed by IRC is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause (whichever occurs first).
		PFS	PFS per RECIST 1.1 as assessed by IRC is defined as the time from the first day of study treatment to the first documented disease progression or death due to any cause (whichever occurs first).
		OS	OS is defined as the time from the first day of study treatment to death due to any cause.
Database lock	Updated data cut-off date: 15-OCT-2021 for KN158 and 19-FEB-2021 for KN164		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	For KEYNOTE-164, the ASaT population served as the primary population for the analysis. For KEYNOTE-158, the primary population for the analysis of efficacy was based on the ASaT population consisting of all participants with a minimum of 6 months follow-up, which also served as the analysis population for the MSI-H cancer pooled dataset.	
Descriptive statistics and estimate variability	Number of subjects with **CRC (cohort A+B)**	124
	Primary	
	ORR %	42 (33.9)
	(95% CI)	(25.6, 42.9)
	Secondary	
	DOR (number of responders)	42
	Median, months (range)	Not reached (4.4 - 58.5+)
	PFS median, months	4.0
	(95% CI)	(2.1, 7.4)
	PFS rate, % at 12 Months	37.5
	PFS rate, % at 24 Months	33.8
	OS median, months	36.1
	(95% CI)	(24.0, NR)
	OS rate, % at 12 Months	74.2
	OS rate, % at 24 Months	59.1
Descriptive statistics and estimate variability	Number of subjects with **endometrial cancer**	83
	Primary	
	ORR %	42 (50.6)
	(95% CI)	(39.4, 61.8)
	Secondary	
	DOR (number of responders)	42
	Median, months (range)	NR (2.9 - 60.4+)
	PFS median, months	13.1 (4.9, 25.7)
	(95% CI)	
	PFS rate, % at 24 Months	39
	OS median, months	NR (48.0, NR)
	(95% CI)	
	OS rate, % at 24 Months	67.2
Descriptive statistics and estimate variability	Number of subjects with **gastric cancer**	51
	Primary	
	ORR %	19 (37.3)
	(95% CI)	(24.1, 51.9)
	Secondary	
	DOR (number of responders)	19

	Median, months (range)	NR (6.2 – 63.0 +)
	PFS median, months (95% CI)	4.1 (2.1, 24.6)
	PFS rate, % at 24 Months	38.5
	OS median, months (95% CI)	26.9 (6.6, NR)
	OS rate, % at 24 Months	50.0
Descriptive statistics and estimate variability	Number of subjects with **small intestine cancer**	27
	Primary	
	ORR % (95% CI)	15 (55.6) (35.3, 74.5)
	Secondary	
	DOR (number of responders)	15
	Median, months (range)	NR (3.7+ - 57.3+)
	PFS median, months (95% CI)	23.4 (4.3, NR)
	PFS rate, % at 24 Months	49.8
	OS median, months (95% CI)	NR (16.2, NR)
	OS rate, % at 24 Months	62.7
Descriptive statistics and estimate variability	Number of subjects with **biliary cancer**	22
	Primary	
	ORR % (95% CI)	9 (40.9) (20.7, 63.6)
	Secondary	
	DOR (number of responders)	9
	Median, months (range)	30.6 (6.2 - 46.0+)
	PFS median, months (95% CI)	4.2 (2.1, 24.9)
	PFS rate, % at 24 Months	31.8
	OS median, months (95% CI)	19.4 (6.5, 44.8)
	OS rate, % at 24 Months	50.0
Descriptive statistics and estimate variability	Number of subjects with **pancreatic cancer**	22
	Primary	
	ORR % (95% CI)	4 (18.2) (5.2, 40.3)
	Secondary	
	DOR (number of responders)	4

	Median, months (range)	NR (8.1 - 24.3+)
	PFS median, months (95% CI)	2.1 (1.9, 3.4)
	PFS rate, % at 24 Months	10.4
	OS median, months (95% CI)	3.7 (2.1, 9.8)
	OS rate, % at 24 Months	22.7

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

MSI-H/dMMR pooled data:

In the below table, data for the overall population with all MSI-H/dMMR tumour types (i.e. not limited to the tumour types included in the sought indication) analysed in clinical trials are presented. Data are shown for two populations:

- MSI-H data pooled (n=445): Subjects who received at least one dose of pembrolizumab in KEYNOTE-158 with MSI-H tumours (non-CRC) in Cohort K with 6 months follow-up (n=321), and KEYNOTE-164 (CRC, n=124).
- KEYNOTE-158 Cohort K (n=321): Subjects who received at least one dose of pembrolizumab in KEYNOTE-158 with MSI-H tumours (non-CRC) in Cohort K with 6 months follow-up.

	MSI-H Pooled Dataset (N=445)	**KEYNOTE-158 Cohort K (n=321)**
ORR, % (95% CI)	141 (31.7) (27.4, 36.2)	99 (30.8) (25.8, 36.2)
CR % (95% CI)	38 (8.5) (6.1, 11.5)	27 (8.4%) (5.6, 12)
DCR, % (95% CI)	227 (51.0) (46.3, 55.7)	N/A
Number of responders	141	99
Median DOR, months (range)	NR (2.1+ - 51.1+)	47.5 (2.1+ - 51.1+)
Median PFS, months (95% CI)	3.7 (2.3, 4.2)	3.5 (2.3, 4.2)
PFS rate, % at 12 Months	34.9	33.9
PFS rate, % at 24 Months	29.3	27.4
Median OS, months (95% CI)	23.8 (19.4, 31.4)	20.1 (14.1, 27.1)
OS rate, % at 12 Months	63.0	58.6
OS rate, % at 24 Months	49.5	45.7

N/A: not available

Clinical studies in special populations

No clinical trials in special populations have been performed.

The MAH presented efficacy results by age categories for pooled studies (KEYNOTE-158 and KEYNOTE-164) which are showed below:

Endpoint	Age Category	N (Pembrolizumab)	Number of Objective Responses (ORR) or Number of Events (OS and PFS) for Pembrolizumab (%)	ORR (%) (95% CI)† (ORR) or Median (Month) (95% CI)‡ (OS and PFS) for Pembrolizumab
ORR	<65 years	285	84 (29.5)	29.5 (24.24, 35.14)
	65-74 years	103	38 (36.9)	36.9 (27.59, 46.97)
	75-84 years	54	17 (31.5)	31.5 (19.52, 45.55)
	>=85 years	3	2 (66.7)	66.7 (9.43, 99.16)
PFS	<65 years	285	203 (71.2)	3.4 (2.23, 4.17)
	65-74 years	103	69 (67.0)	4.1 (2.10, 13.11)
	75-84 years	54	41 (75.9)	4.8 (2.10, 9.92)
	>=85 years	3	1 (33.3)	(3.06)
OS	<65 years	285	155 (54.4)	24.0 (19.15, 31.94)
	65-74 years	103	52 (50.5)	31.5 (16.82)
	75-84 years	54	35 (64.8)	12.8 (9.69, 27.47)
	>=85 years	3	1 (33.3)	(5.26)

Subjects who received at least one dose of MK-3475 in KN158 with MSI-H tumours in cohort K with 6 months follow-up and KN164 are included.

† Based on binomial exact confidence interval method.

‡ From product-limit (Kaplan-Meier) method for censored data.

KN164 Database Cutoff Date: 09-SEP-2019

KN158 Database Cutoff Date: 05-OCT-2020

Supportive study(ies)

None presented

2.4.3. Discussion on clinical efficacy

The MAH applied for an extension of indication for Keytruda as monotherapy for the treatment of unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR) CRC, endometrial, gastric, small intestine, biliary, or pancreatic cancer in adults who have received prior therapy.

The MAH explained that the six tumour types with MSI-H/dMMR included in the sought indication have been chosen based on a combination of factors including:

1) unmet need
2) MSI-H prevalence
3) enrolled participant numbers
4) antitumour activity observed with anti-PD-1 immunotherapy

Design and conduct of clinical studies

The pivotal trials supporting the indication are two single arm studies:

- KEYNOTE-164: including 124 participants with previously-treated locally advanced unresectable or metastatic MSI-H/dMMR colorectal cancer (CRC) treated in 2L (cohort B, n=63) or 3L+ (cohort A, n=61);
- KEYNOTE-158 (cohort K): including a total of 351 patients with 26 MSI-H/dMMR non-CRC tumour types that was incurable and for which prior standard first-line treatment had failed; of those, tumour types included in the indication are endometrial (n=68), gastric (n=42), small intestine (n= 25), biliary (n=22), and pancreas (n=22).

To be eligible for the above studies, patients should have been ⩾18 years of age, ECOG PS 0-1, and with radiologically measurable disease by RECIST 1.1. Patients with known active CNS metastases and/or carcinomatous meningitis were excluded.

Enrolment in both studies was based on MSI-H/dMMR testing performed locally. Most patients were tested by IHC (71%), followed by PCR (33.3%) and other testing, e.g. NGS (5.6%). 30 out of 124 patients with CRC were tested by both IHC and PCR methods locally, there were 4 discordant results (87% of concordance), which the MAH attribute to the different biology assessed by the two methods and the test taking place locally. The responses of those 4 subjects were not provided. It is understood that 144 tumour samples were retested centrally with an IHC assay (VENTANA MMR RxDx panel). For 95 participants (out of a total of 283) the positive percent agreement (78/95) was 82.1% (95% CI: 73.2, 88.5). Of 17 patients found to be negative by central testing, 3/17 responded (18%). It is difficult to interpret those data due to small number of subjects.

Of note, PD-L1 testing was not required, as a result for each tumour types only 20-30% of tumours have known PD-L1 status, thus preventing any meaningful analysis on the relation between PD-L1 expression and pembrolizumab activity in MSI-H tumours.

Per inclusion criteria, all patients should have received prior treatment in the advanced setting: in KEYNOTE-158 patients should have been affected by incurable tumour for which prior standard first-line treatment had failed. For KEYNOTE-164, previous treatment with at least 2 lines of fluoropyrimidine, oxaliplatin, and irinotecan in Cohort A, and at least 1 line of systemic fluoropyrimidine + oxaliplatin or fluoropyrimidine + irinotecan ± anti-VEGF/EGFR mAb in Cohort B were required.

All patients received pembrolizumab 200 mg Q3W IV for up to a maximum of 35 cycles (approximately 2 years) until radiologic disease progression or any discontinuation criteria were met. Retreatment after PD was possible in specific situations. Overall, 9 patients with CRC and 4 patients with endometrial cancer were retreated, with 2 subjects with CRC experienced PR, 9 SD and 2 PD (one for CRC and one for endometrial). The available data are too limited for inclusion of information in the SmPC. Radiological assessment occurred every 9 weeks for the first year, then every 12 weeks in both studies.

Both studies had Overall Response Rate (ORR) as primary endpoint, according to independent radiology review per RECIST 1.1. Duration of Response (DOR) was one of the secondary endpoint. ORR is acceptable to evaluate activity of a drug in the context of single arm studies, in addition to DOR. PFS and OS were also among secondary endpoints, although the single arm design in general hampers the assessment of time-related endpoints, given also the low number of patients in several tumour type cohort.

KEYNOTE-164 Cohort A (CRC 3L+) was the only cohort with prespecified statistical hypotheses: indeed, with a sample size of 60 subjects, the study had 93% power to show an ORR>15% with a one-sided type I error rate of 2.5%. This was based on an historical response rate <5% in the CORRECT study (regorafenib vs placebo). On the contrary, there were no hypotheses for Cohort B, as well as no multiplicity adjustment for multiple cohorts (Cohort A and Cohort B), which further underlines the explorative nature of this trial.

There was also no pre-specified hypothesis for study KEYNOTE-158. As discussed in the Scientific Advice in 2015 (EMEA/H/SAH/039/3/2015/II), KEYNOTE-158 study used an adaptive approach which was not rejected in principle. It was however noted that *"it poses some challenges with regard to the registration strategy. Whilst the exploratory nature of the trial at inception is well understood, it is likely to be necessary, at some point, to more closely define the hypothesis that is subject to 'confirmatory 'test', i.e. that at some point before full recruitment a decision to draw inferences based on histology-selected / histology-unselected / biomarker-selected / biomarker-unselected populations should be taken and 'confirmed' prospectively as the study continues"*. The increased sample size of Cohort K from 100 to 350 patients is understood as a request from FDA after accelerated approval of pembrolizumab in MSI-H/dMMR tumours, with subsequent enrolment capped at approximately 20 subjects with any single specific tumour type. Multiple interim looks paired with no preplanned fixed sample size might have led to bias in estimates and might have affected the coverage probability of interval estimates. In addition, the study was not adjusted for the analysis of multiple cohorts as well as for the analysis of the different subgroups defined by histology within Cohort K. There was no hypothesis prespecified as well as no formal sample size calculation performed. As a result, KEYNOTE-158 appears mainly as an exploratory study, with no confirmation of results in an independent prospectively analysed data set differently to what advised by CHMP at the time of the SA. Furthermore, the lack of multiplicity adjustment due to multiple interim looks (according to the CSR eleven for Cohort K), multiple cohorts (Cohort A-L) as well as multiple subgroups within Cohort K defined by the five tumour types underline the exploratory nature of the trial. The data driven post-hoc choice of the five tumour types has the high potential to lead to bias. Moreover, capping of recruitment appears to be based on the need to have sufficient diversity of tissue of origin to assess homogeneity of response (in relation to the histology-independent approval in US), rather than on the relative frequency of the target molecular entity across histologies.

The ASaT population, i.e. all patients receiving at least one dose of treatment, served as the primary population for the analysis of the two trials. All patients have been observed for a minimum of 6 months follow-up.

Progressive disease was the main reason for pembrolizumab discontinuation in all tumour types analysed. Discontinuation due to adverse events ranges from 5.1% in endometrial cancer to 22.7% in pancreatic cancer. At the data cut-off date for KEYNOTE-158 (5-Oct-2020), treatment was still ongoing in about 25% of subjects with endometrial, gastric and small intestine cancer. Only one CRC patient was still on treatment at the data cut-off date for KEYNOTE-164 (9-Sep-2019).

No concern is raised regarding the impact of protocol deviations on study results.

Efficacy data and additional analyses

Efficacy results are summarized by tumour type for which indication is sought.

CRC

Of the total **124 patients** with CRC, the majority of participants in the pooled KEYNOTE-164 group were male (55.6%), white (67.7%), with a median age of 55.5 years. Patients were younger than in KEYNOTE-177 (median age 63 years), the study leading to approval of pembrolizumab monotherapy in MSI-H CRC in 1st line, which is not clearly explicable. Most participants had an ECOG PS of 1 (58.9%) and received at least 1 (24.2%), 2 (38.7%) or 3 (17.7%) lines of prior treatment for recurrent or metastatic disease. Approximately 12% were BRAF mutant, and 37% KRAS/NRAS mutant.

Median FU was 36.1 months (range: 0.1 to 47.8 months).

ORR was 33.9% (95% CI: 25.6, 42.9), with 11 CR (8.9%). ORR was similar in both Cohorts A and B regardless number of prior lines of therapy. Median DOR was not reached (range: 3.9+ to 41.2+

months), with 95% of subjects with response ≥12 months. Based on the data provided, patients achieving confirmed tumour response are usually long responders, and responses can last several months after the administration of the last dose of pembrolizumab as shown in the swimmer plots. Median TTR was 4.1 months.

Median PFS was 4.0 months (95% CI: 2.1, 7.4), and median OS was 36.1 months (95% CI: 24.0, NR).

The MAH has provided updated efficacy data for CRC. As compared to the initial dataset, there are no additional patients, but 2 more years of follow-up have been provided. Updated results confirmed sustained and durable responses in responding patients, with median DOR still not reached in either cohort. Within the limits of time-related endpoints assessment in single arm trial, a plateau in PFS and OS curves seem evident.

Based on literature data, patients with MSI-H/dMMR mCRC have a poorer prognosis and a trend toward worse survival outcome compared to microsatellite stable mCRC was seen according to most literature data (see introduction). To contextualize the results for pembrolizumab in MSI-H mCRC, the MAH has provided a systematic literature review/meta-analysis including a total of 22 randomized clinical trials of ⩾2L chemotherapy- and targeted therapies, although the data are available only for an unselected population regardless MSI status. The ORR point estimates of chemotherapy/targeted therapies analysed ranged from 0.9% to 47.7%. By indirect comparison of KEYNOTE-164 results with SLR/meta-analysis results provided by the MAH (table 23), an encouraging ORR for pembrolizumab is seen, which appear overall consistent with the ORR results of other immunotherapies in the same setting. While median PFS does appear shorter than with chemotherapy, a relevant median OS and in particular OS rate at 24 months are observed. Median DOR for pembrolizumab is still not reached, as compared to median DOR ranging from 4.8 months to 15.2 months in the subset of clinical trials for which such information was available. When interpreting the data, the limits related to the meta-analysis, the indirect comparison and the single arm trial data for pembrolizumab should be considered. The MAH mentioned the results of study KEYNOTE-177 comparing pembrolizumab to combination chemotherapy in 1L for MSI-H mCRC, leading to approval in the EU of pembrolizumab in the 1L setting (EPAR Keytruda II-91). To date, the results of KEYNOTE-177 study are the only available controlled data for immunotherapy specifically in the MSI-H subset of mCRC. The demonstration of benefit for pembrolizumab over chemotherapy shown in a randomized controlled setting in 1L (and an indication already granted to pembrolizumab in 1L) are considered supportive for the use of pembrolizumab in MSI-H mCRC also in later line. Based on the overall evidence provided, an indication can be granted for pembrolizumab for 2L+ treatment of MSI-H mCRC patients.

Endometrial cancer

The MAH presented the results of **68 patients** with advanced endometrial MSI-H/dMMR cancer who received pembrolizumab in KEYNOTE-158 study and had at least 6 months of follow-up. Median age was 64 years. At the time of study entry, all participants had metastatic or unresectable disease, more than 50% had a baseline ECOG Performance Status of 1, and the majority have received at least 2 prior lines of therapy.

Median FU was 16.6 months (range: 1.5 to 51.7 months).

ORR was 48.5% (95% CI: 36.2, 61.0), with 10 CRs (14.7%). Among the 6 tumour types selected for the indication, ORR was the highest in endometrial cancer. Median DOR was not reached (range: 2.9 to 47.1+ months), with 17/33 patients with ongoing response at the data cut-off date, and 86% of subjects with response ≥12 months. Median TTR was 2.1 months.

Median PFS was 13.1 months (95% CI: 4.9, 34.4), while median OS was not reached at the data cut-off date (95% CI: 32.4, NR).

In the updated dataset, the MAH has provided data for a total of **83** MSI-H endometrial cancer patients all followed for at least 6 months. The results of the updated analyses were consistent with the initial data, showing an ORR of 50.6% (95%CI 39.4, 61.8), including 15.7% of complete responses. Median DOR was not reached (range, 2.9 to 60.4+ months).

There is no definitive evidence of a significant association between MMR status and detrimental survival in advanced endometrial cancer.

To better contextualize the results, the MAH has conducted a SLR/meta-analysis identifying 23 clinical trials which included an unselected endometrial cancer population treated with ≥2L chemotherapy. ORR estimates ranged from 0% to 57.1%. DOR was available from few studies only (from 2.7 months of pegylated liposomal doxorubicin to 10.9 months for oxaliplatin). Within the limits of SLR/meta-analysis and of an indirect comparison, a trend toward better outcome for pembrolizumab in an MSI-H population as compared to chemotherapy in a population regardless of MSI-H status is suggested.

The outcome of standard treatment in endometrial cancer was discussed in the same setting for a dMMR population in the context of the recent approval of pembrolizumab+lenvatinib in (EPAR Keytruda II/105). The results of the chemotherapy control treatment in the dMMR subgroup lies within the range of results shown in the meta-analysis, providing additional support. Results of clinical trials and observational studies of ⩾2L immunotherapy (monotherapy) in MSI H/dMMR endometrial cancer overall showing ORR consistent with pembrolizumab results (see introduction). To conclude, an indication for pembrolizumab in MSI-H/dMMR previously treated endometrial cancer is considered acceptable.

Within the procedure II/105 leading to the approval of pembrolizumab+lenvatinib in pretreated endometrial cancer, the CHMP concluded that, within all the limits of indirect comparison and data from SAT, "both the point estimates and the confidence intervals of all efficacy endpoints do not suggest any relevant difference in activity of the combination (pembrolizumab + lenvatinib) as compared to pembrolizumab alone in dMMR pretreated EC." Given that both options (pembrolizumab monotherapy and the combination pembrolizumab + lenvatinib) are approved in the EU for dMMR EC, physicians should consider the benefit/risk balance of the available treatment options (pembrolizumab monotherapy or pembrolizumab in combination with lenvatinib) before initiating treatment in patients with advanced or recurrent MSI-H or dMMR endometrial carcinoma (see section 4.4 of the SmPC).

Gastric cancer

Efficacy data in MSI-H/dMMR gastric cancer are coming from **42 subjects** enrolled in KEYNOTE-158, with a median age of 67 years and ECOG performance status 1 in 57% of subjects. About 30% of patients were from Asia, which is understood based on the epidemiology of this disease. 55% of subjects were treated with 1 line of prior therapy.

Median FU was 9.9 months (range: 1.1 to 54.5 months).

ORR was 31.0% (95% CI: 17.6, 47.1), with 9 patients achieving CR (21.4%). Median DOR was not reached (range: 6.3 to 51.1+ months).

Median PFS was 3.2 months (95% CI: 2.1, 12.9), and median OS was 11.0 months (95% CI: 5.8, 31.5).

In the updated dataset from KEYNOTE-158, the MAH has provided additional 9 patients in the gastric cancer cohort (from 42 to 51). Updated ORR is 37.3% (95%CI 24.1, 51.9) with 19/51 patients responding (7 CR, i.e. 13.7%), which is consistent with data previously provided.

The MAH underlined that gastric cancer is neither a rare cancer, nor is microsatellite instability a rare subset. The evidence supporting the prognostic value of MSI status in the advanced gastric cancer setting are limited to date (see introduction).

A SLR/meta-analysis was provided, in which a total of 42 clinical studies (50 arms) were included of ≥2L chemo- and targeted therapies in an unselected population. ORR estimated ranged from 0% to 51.4%. with the exception of 3 arms showing an ORR>40%, most of the arms have an ORR estimate <30%. Overall short PFS and OS was observed, with median OS <1 year.

During the procedure, the MAH presented additional 23 patients with MSI-H/dMMR gastric cancer after prior treatment retrieved across pembrolizumab clinical programme (KEYNOTE-016, n=5 patients, ORR 60%, DOR not reported; KEYNOTE-059, n=7 patients, ORR 57.1%, DOR NR; KEYNOTE-061, n=11 patients, ORR 54.5%, vs 20% in 10 patients receiving paclitaxel). The small number of patients extracted from different studies is a limit of the data.

The ORR obtained with pembrolizumab in gastric cancer does not appear outstanding, although seems to compare favourably with most of the chemotherapy options included in the meta-analysis. As observed repeatedly, the benefit of pembrolizumab mostly lies on durability of response (median DOR NR, tails in the OS and PFS curves). The MAH will submit additional data on gastric cancer post-approval as an Annex II condition.

Small intestine

The MAH presented efficacy data for **26 subjects** with MSI-H small intestine cancer. Most were male with median age 59 years and 58% ECOG PS 0. All patients had adenocarcinoma. 54% of patients received one prior line of therapy, and 23% two lines, although two participants did not receive prior therapy.

Median FU was 18.3 months (range: 4.2 to 55.4 months).

ORR was 48% (95% CI: 27.8, 68.7), with 4 patients achieving CR (16%). Median DOR was not reached (range: 2.1+ to 41.8+ months). ORR achieved with pembrolizumab in the small intestine cohort is one of the highest reported among the 6 tumour types selected, and responses appear durable, although the large confidence interval for ORR should be noted.

Median PFS was 23.4 months (95% CI: 4.3, NR), and median OS was not reached as per data cutoff date (95% CI: 16.2, NR).

As compared to the initial submission, additional 2 evaluable patients were included in the updated MSI-H small intestine cancer cohort treated with pembrolizumab (**n=27**). In the updated dataset, two additional patients had an objective response and one patient who previously had SD also achieved PR, for an updated ORR of 55.6%, 95%CI 35.3, 74.5 (15/27 patients with CR or PR). Median DOR is still not reached with 7 out of 12 responding patients still with ongoing response after 36 months. The MAH retrieved **n=5** additional patients from KEYNOTE-016 study, where an ORR of 80% was observed, but DOR was not available.

Almost all available literature evidence about the prognostic value of MSI-H status in small bowel cancer (all about adenocarcinoma) refers to resected disease, while very few cases of MSI-H metastatic disease are reported. Based on the available evidence, no conclusion can therefore be drawn on the prognostic value of MSI status in small intestine cancer in an advanced setting. It is acknowledged that historical data and existing treatments are limited in this disease.

In an apparently very rare disease setting, within the limits of the data provided and the lack of reliable prognostic information, an indication for pembrolizumab in MSI-H small intestine cancer is considered justified based on the results in the updated cohort and the comparison with historical data and intrapatient comparison. The MAH will submit additional data on small intestine cancer post-approval as an Annex II condition.

Biliary

Overall, efficacy data on **22 patients** with biliary cancer have been presented. Most patients were male, with median age of 60.5 years, half had ECOG PS 1. Four patients had no distant metastases. Half of the patients received 1 prior line of treatment, and 27% a second line. Two participants did not receive prior systemic treatment.

Median FU was 19.4 months (range: 1.1 to 48.5 months).

ORR was 40.9% (95% CI: 20.7, 63.6), with 3 CR (13.6%). Median TTR was 2.4 months (range: 1.9 to 4.2 months) and median DOR was 30.6 months (range: 6.2 to 40.5+ months). Median PFS was 4.2 months (95% CI: 2.1, 24.9) and median OS was 19.4 months (95% CI: 6.5, NR).

No additional MSI-H patients have been provided with the updated data. ORR and DOR were unchanged after one additional year of observation, with one additional patient experienced a PFS and OS event.

The MAH retrieved **4** additional patients from KEYNOTE-016 study. Of those 4 patients, 1 responded (ORR 25%).

Regarding the prognostic value of MSI-H in biliary cancer, it is agreed that there is limited evidence in literature to conclude on the prognostic role of MSI status in this disease. For contextualization, the result of the SLR/meta-analysis performed by the MAH reported ORR to chemotherapy treatment in an unselected biliary cancer population 2L+ ranging from 0 to 30%. Historical DOR is not comparable as only one study did report it. Survival estimates are low for historical control, for a median OS around 6 months.

The most relevant limitation of pembrolizumab data in MSI biliary tract cancer is the small sample size (n=22). The ORR achieved seems however acceptable as compared to historical data, and in particular the durability of response that can be achieved, leading to a tail in PFS and OS curves. The exploratory intrapatient comparison TTP/PFS did not show relevant differences in median TTP/PFS but seem to support some long-term benefit. The MAH will submit additional data on biliary cancer post-approval as an Annex II condition.

The Annex II condition is submitted according to the Commission delegated (EU) No 357/2014, c (uncertainties with respect to the efficacy of a medicinal product in certain sub-populations that could not be resolved prior to marketing authorisation and require further clinical evidence).

Pancreatic

A total of **22 subjects** with pancreatic MSI-H/dMMR have been presented. Patients were mostly male (59%) with a median age of 61.5 years, and about 60% had ECOG PS 0. Approximately 30% of patients have received 1 and 2 prior lines of treatment, and 23% 3 prior lines.

Median FU was 3.7 months (range: 0.4 to 55.6 months).

ORR was 18.2% (95% CI: 5.2, 40.3). Of the 4 responding patients, 1 achieved CR (4.5%). In the ORR analysis there were 7 not evaluable patients out of 22 patients, and at least 5 progressed before the first assessment at 9 weeks, which further raise doubts on the potential for pembrolizumab to control the disease. The large confidence interval of ORR is noted, and the lower bound of the CI (5.1%) is rather disappointing. Median TTR was 2.1 months (range: 1.9 to 2.1 months). Median DOR was not reached (range: 8.1 to 24.3+ months), however only 4 patients were evaluated for DOR, and it is difficult to draw conclusion. A more conservative DOR analysis reported a median DOR of 18 months. Median duration of treatment in the pancreatic cohort was 1.58 months, with only a median of 3 pembrolizumab administrations.

Median PFS was 2.1 months (95% CI: 1.9, 3.4), and median OS was 3.7 months (95% CI: 2.1, 9.8), which appears overall disappointing.

No additional patients have been provided with the updated dataset.

The MAH subsequently retrieved additional **8** patients with MSI-H/dMMR pancreatic cancer from an older phase II study KEYNOTE-016. All patients received at least one prior therapy and had evidence of progressive disease prior to enrolment. For those 8 subjects, the MAH reported an ORR of 62% (5 of 8 patients responded, 2CRs and 3 PRs). They were treated with one of the highest dose used in the pembrolizumab clinical programme of 10 mg/kg Q2W, while patients in KN158 received the currently approved dosage of 200 mg Q3W. The MAH noted that, combining KEYNOTE-016 (n=8) and KEYNOTE-158 (n=22) participants with pancreatic cancer, an "overall" ORR of 28.3% (95% CI 12.6, 46.7) is achieved. There were no pre-defined hypotheses for the pancreatic cancer subset of KN016, and pooling a limited number of studies with differing response rates is associated with many caveats. However, the data from KN016 appear very different from the "pivotal" KEYNOTE-158 delineating the weakness of the overall evidence from very few patients coming from a subgroup of a SAT.

With regard to the prognostic value of MSI-H in pancreatic cancer, a more favourable prognosis was seen in pancreatic MSI-H cancer after surgical resection while evidence is too limited to date to conclude on the prognostic value of MSI-H status in the advanced setting which is the one discussed in this procedure (see introduction).

The MAH has provided a systematic literature review and meta-analysis including 1775 patients with pancreatic cancer regardless of MSI status treated with chemotherapy as 2L+ from 18 clinical trials (controlled and single arm trials). Based on this analysis, pembrolizumab did not appear to provide any relevant advantage over chemotherapy in PFS and OS. The possibility to achieve durable responses in this disease with IO were supported by the MAH with reference to some case reports and retrospective or observational studies in literature.

An intrapatient comparison of TTP on prior therapy vs PFS on pembrolizumab therapy (median 4.1 vs 2.1 months) did not provide support for the indication.

In conclusion, it is acknowledged that the activity of chemotherapy in this setting appears very limited, and that MSI-H/dMMR pancreatic cancer is a quite uncommon condition where an unmet need post prior therapy is agreed. However, while the possibility to have long responses is recognised, the likelihood of achieving a response with pembrolizumab in MSI-H disease appears very low and not predictable. It remains that the ORR estimate for pembrolizumab in pancreatic cancer (18.2%, 95%CI 5.2, 40.3) is lower than what is generally considered by the CHMP to indicate clinically relevant activity and it is based on a very limited number of patients (n=22). The data from KN016 are surprising and highlight the limitation of making conclusion from such a low number of subjects in an uncontrolled setting, with no confirmation planned. An indication in MSI-H pancreatic cancer is not agreed. The MAH therefore removed pancreatic cancer from the applied indication.

Data in other tumour types/pooled data

The MAH also presented all results for all the tumour histologies enrolled in KEYNOTE-158 Cohort K study but not included in the sought indication, as well as a pooled analysis of the overall population treated within both pivotal trials (n=445).

In cohort K of KEYNOTE-158 study, 25 tumour types were included. Endometrial cancer is the most represented (n=79), followed by gastric (n=51), small intestine (n=26), ovarian (n=25), pancreas and cholangiocarcinoma (n=22 each). All other tumour types represented included less than 20 patients each, some of them with only one patient, which limits the interpretation of the results. Pembrolizumab generally did not show outstanding activity in terms of ORR in any of the tumours not selected for the

indication. Overall, there appears to be substantial heterogeneity of response depending on tumour type (including types for which an indication is not sought). However, duration of response is relevant, as median DOR was not reached in most of the cases. Median DOR was also not reached in the pooled analysis (range 2.1+ - 51.1+), underlying the long response in patients achieving an objective response, however a modest pooled ORR of 31.7% (95%CI 27.4, 36.2) was observed.

2.4.4. Conclusions on the clinical efficacy

The MAH applied for an indication in 6 selected tumour types (CRC, endometrial, gastric, small intestine, biliary, pancreatic) with MSI-H/dMMR after prior treatment, based on the results of the single arm trials KEYNOTE-164 and KEYNOTE-158 Cohort K. Several limitations and uncertainties have been found in the dossier related to the overall exploratory nature of the data provided, with data coming from single arm trials and post-hoc selected subset of single arm trial, limited number of patients, no prespecified hypotheses, lack of multiplicity control and no confirmatory data sets. A major drawback of this application is that this is based on a hybrid strategy, where approval is sought for a selected subset of cancer types justified based on a histology-independent approach. However, the number of patients in some of the selected tumours are so few, that transfer of information between tumour types would seem to be required for regulatory conclusions. MSI-H is not a driver mutation, which complicates this conception. Furthermore, there appears to be substantial heterogeneity of response depending on tumour type (including types for which an indication is not sought). Thus, the MAH's position that MSI-H can be viewed as a marker of pembrolizumab efficacy independent of the tissue of origin of the tumour, can be challenged. As a result of the uncertainty about the predictive value of MSI-H across tumour types, the B/R has been assessed separately by tumour type. The overall conclusion is that

- an indication can be granted for pembrolizumab in MSI-H colon and endometrial cancer, for which larger evidence available, supported also by external data.

- for gastric, small intestine and biliary MSI-H cancer, an indication can be acceptable for pembrolizumab based on the overall data provided in each tumour type, but due to the limited available evidence, the MAH has accepted to provide additional data post-approval (e.g. extended enrollment in single arm trial) to confirm the results in those 3 tumour types.

- in pancreatic cancer, efficacy has not been established and an indication cannot be granted. The MAH therefore removed pancreatic cancer from the applied indication.

The following measures are considered necessary to address issues related to efficacy:
Annex II: "Post authorisation efficacy study (PAES): in order to further characterise the efficacy of Keytruda in patients with MSI-H/dMMR gastric, biliary and small intestine cancers, the MAH should submit the results including ORR data from Cohort K and L of study KEYNOTE-158, a Phase II study investigating pembrolizumab (MK-3475) in previously treated patients with advanced solid tumours."

2.5. Clinical safety

Introduction

The safety profile of pembrolizumab (KEYTRUDA®, MK-3475) in the context of its intended use as monotherapy for the treatment of unresectable or metastatic MSI-H or dMMR solid tumours (CRC, endometrial, gastric, small intestine, biliary, or pancreatic cancer) in adults who have received prior therapy.

The safety results for pembrolizumab are presented for the following 3 datasets:

• MSI-H Safety Dataset (N=475): comprised participants with MSI-H cancer who participated in KEYNOTE-158 Cohort K (351 participants, MSI-H population) and KEYNOTE 164 (124 participants [Cohort A: 61 participants; Cohort B: 63 participants] with MSI-H CRC).

• Pembrolizumab Monotherapy Reference Safety Dataset (N=5884): The RSD contains safety data from participants who received pembrolizumab monotherapy 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-010, KEYNOTE-024 and KEYNOTE-042; HNSCC (n=909) in KEYNOTE- 012 (Cohorts B and B2), KEYNOTE-040, KEYNOTE-048 and KEYNOTE-055; HL (n=241) in KEYNOTE-013 (Cohort 3) and KEYNOTE-087; Bladder (n=636) in KEYNOTE-045 and KEYNOTE-052.This dataset represents the established safety profile for pembrolizumab.

• Cumulative Running Pembrolizumab Monotherapy Safety Dataset (N=9090): comprised participants from the RSD and participants treated with pembrolizumab in KEYNOTE- 012 (Cohorts C and D), KEYNOTE-013 (Cohort 4A), KEYNOTE-017, KEYNOTE-028 (Cohorts A4, B4, and C1), KEYNOTE-057, KEYNOTE-059 (Cohorts 1 and 3), KEYNOTE-061, KEYNOTE-062, KEYNOTE-158 (Cohorts E, G, K, and TMB-H in cohorts A through J), KEYNOTE-164 (Cohorts A and B), KEYNOTE-170, KEYNOTE- 177, KEYNOTE-180, KEYNOTE-181, KEYNOTE 204, KEYNOTE-224, KEYNOTE- 427, and KEYNOTE-629.

Table: Safety datasets

KEYNOTE-158 and KEYNOTE-164 (MSI-H Safety Dataset) (N = 475)	Pembrolizumab Monotherapy Reference Safety Dataset (N = 5884)	Cumulative Running Safety Dataset for Pembrolizumab Monotherapy (N = 9090)
Pooled data from participants with locally advanced unresectable or metastatic (Stage IV) MSI-H CRC (KEYNOTE-164) and advanced MSI-H, non-CRC solid tumors (KEYNOTE-158, Cohort K) who received pembrolizumab monotherapy.	Represents the established safety profile of pembrolizumab monotherapy and is used as a comparison of the new safety data from the MSI-H Safety Dataset to the established safety profile of pembrolizumab.	Provided to demonstrate that no clinically significant changes from the RSD have occurred, supporting the consistency of the safety data of pembrolizumab across indications; this dataset is not used as a comparison with the MSI-H Safety Dataset.

Source: [Sec. 2.7.4-msi-hcancer4: 1.1.1]

Patient exposure

KEYNOTE-164 is completed. As of the data cutoff on 09-SEP-2019, 61 and 63 participants had received at least 1 dose of pembrolizumab in Cohorts A and B, respectively. No participants were still receiving pembrolizumab in Cohort A (41.0% of participants were ongoing in the study), and 1 participant (1.6%) was still receiving pembrolizumab in Cohort B (47.6% of participants were ongoing in the study).

KEYNOTE-158 is ongoing. As of the data cutoff on 05-OCT-2020, 351 participants in the MSI-H population had received at least 1 dose of pembrolizumab, and 16.0% of participants were still receiving pembrolizumab (46.2% of participants were ongoing in the study).

Table 48: summary of drug exposure

	KN158 Cohort K + KN164 Cohorts A and B MSI-H Data for Pembrolizumab‡‡ (N=475)	Reference Safety Dataset for Pembrolizumab†† (N=5884)	Cumulative Running Safety Dataset for Pembrolizumab§§ (N=9090)
Duration On Therapy (month)			
Mean	9.7	7.3	7.2
Median	5.49	4.86	4.17
SD	9.30	6.79	7.15
Range	0.03 to 38.01	0.03 to 32.46	0.03 to 40.05
Number of Administrations			
Mean	14.3	11.6	11.3
Median	8.00	8.00	7.00
SD	12.83	10.17	10.49
Range	1.00 to 35.00	1.00 to 59.00	1.00 to 59.00

Each subject is counted once on each applicable duration category row.
Duration of Exposure is calculated as last dose date - first dose date + 1.
‡‡ Includes all subjects who received at least one dose of pembrolizumab in KN158 cohort K: MSI-H, and KN164 cohorts A and B.
†† 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, KN013 cohort 3, 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 ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN158 Cohorts E, G, K and TMB-H in Cohorts A-J, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN427 and KN629.
Database cutoff date for Melanoma (KN001:18APR2014, KN002:28FEB2015, KN006:03MAR2015, KN054:02OCT2017)
Database cutoff date for Lung (KN001:23JAN2015, KN010:30SEP2015, KN024:10JUL2017, KN028:31JUL2018, KN042:04SEP2018, KN158:27JUN2019)
Database cutoff date for Gastric (KN012:26APR2016, KN059:08AUG2018, KN061:26OCT2017, KN062:26MAR2019)
Database cutoff date for cHL (KN013:28SEP2018, KN087: 21MAR2019, KN204:16JAN2020)
Database cutoff date for Bladder (KN012:01SEP2015, KN045:26OCT2017, KN052:26SEP2018)
Database cutoff date for PMBCL (KN013:04AUG2017, KN170: 07MAY2020)
Database cutoff date for Cervical (KN028:20FEB2017, KN158: 27JUN2019)
Database cutoff date for HNSCC (KN012:26APR2016, KN040:15MAY2017, KN048:25FEB2019, KN055:22APR2016)
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 NMIBC (KN057 24MAY2019)
Database cutoff date for TMB-H (KN158:27JUN2019)
Database cutoff date for CRC MSI-H or dMMMR (KN177:19FEB2020)
Database cutoff date for cSCC (KN629:08APR2019)
Database cutoff date for MSI-H (KN158:05OCT2020)
Database cutoff date for Colorectal (KN164:09SEP2019)

Source: [ISS: adam-adsl; adexsum]

Table 49: drug exposure by duration (ASaT population)

	KN158 Cohort K + KN164 Cohorts A and B MSI-H Data for Pembrolizumab‡‡ (N=475)			Reference Safety Dataset for Pembrolizumab†† (N=5884)			Cumulative Running Safety Dataset for Pembrolizumab§§ (N=9090)		
	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years
Duration of exposure									
>0 m	475	(100.0)	(384.2)	5,884	(100.0)	(3,555.4)	9,090	(100.0)	(5,420.7)
>=1 m	405	(85.3)	(382.3)	5,033	(85.5)	(3,527.2)	7,621	(83.8)	(5,369.8)
>=3 m	305	(64.2)	(365.5)	3,620	(61.5)	(3,291.9)	5,343	(58.8)	(4,994.0)
>=6 m	227	(47.8)	(337.9)	2,612	(44.4)	(2,926.0)	3,757	(41.3)	(4,422.2)
>=12 m	161	(33.9)	(290.9)	1,281	(21.8)	(1,915.3)	1,979	(21.8)	(3,090.4)

Each subject is counted once on each applicable duration category row.
Duration of Exposure is calculated as last dose date - first dose date + 1.
‡‡ Includes all subjects who received at least one dose of pembrolizumab in KN158 cohort K: MSI-H, and KN164 cohorts A and B.
†† 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, KN013 cohort 3, 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 ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN158 Cohorts E, G, K and TMB-H in Cohorts A-J, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN427 and KN629.
Database cutoff date for Melanoma (KN001:18APR2014, KN002:28FEB2015, KN006:03MAR2015, KN054:02OCT2017)
Database cutoff date for Lung (KN001:23JAN2015, KN010:30SEP2015, KN024:10JUL2017, KN028:31JUL2018, KN042:04SEP2018, KN158:27JUN2019)
Database cutoff date for Gastric (KN012:26APR2016, KN059:08AUG2018, KN061:26OCT2017, KN062:26MAR2019)
Database cutoff date for cHL (KN013:28SEP2018, KN087: 21MAR2019, KN204:16JAN2020)
Database cutoff date for Bladder (KN012:01SEP2015, KN045:26OCT2017, KN052:26SEP2018)
Database cutoff date for PMBCL (KN013:04AUG2017, KN170: 07MAY2020)
Database cutoff date for Cervical (KN028:20FEB2017, KN158: 27JUN2019)
Database cutoff date for HNSCC (KN012:26APR2016, KN040:15MAY2017, KN048:25FEB2019, KN055:22APR2016)
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 NMIBC (KN057 24MAY2019)
Database cutoff date for TMB-H (KN158:27JUN2019)
Database cutoff date for CRC MSI-H or dMMMR (KN177:19FEB2020)
Database cutoff date for cSCC (KN629:08APR2019)
Database cutoff date for MSI-H (KN158:05OCT2020)
Database cutoff date for Colorectal (KN164:09SEP2019)

Source: [ISS: adam-adsl; adexsum]

Demographic and Other Characteristics of Study Population

Table 50: subjects characteristics (ASaT population)

	KN158 Cohort K + KN164 Cohorts A and B MSI-H Data for Pembrolizumab‡‡		Reference Safety Dataset for Pembrolizumab††		Cumulative Running Safety Dataset for Pembrolizumab§§	
	n	(%)	n	(%)	n	(%)
Subjects in population	475		5,884		9,090	
Gender						
Male	213	(44.8)	3,887	(66.1)	5,964	(65.6)
Female	262	(55.2)	1,997	(33.9)	3,126	(34.4)
Age (Years)						
<65	305	(64.2)	3,385	(57.5)	5,202	(57.2)
>=65	170	(35.8)	2,499	(42.5)	3,888	(42.8)
Mean	58.3		60.6		60.5	
SD	13.8		13.2		13.5	
Median	60.0		62.0		62.0	
Range	20 to 89		15 to 94		15 to 95	
Race						
American Indian Or Alaska Native	18	(3.8)	29	(0.5)	67	(0.7)
Asian	64	(13.5)	658	(11.2)	1,385	(15.2)
Black Or African American	16	(3.4)	108	(1.8)	167	(1.8)
Multiracial	7	(1.5)	66	(1.1)	95	(1.0)
Native Hawaiian Or Other Pacific Islander	0	(0.0)	4	(0.1)	10	(0.1)
Unknown	0	(0.0)	0	(0.0)	4	(0.0)
White	368	(77.5)	4,444	(75.5)	6,678	(73.5)
Missing	2	(0.4)	575	(9.8)	684	(7.5)
Ethnicity						
Hispanic Or Latino	59	(12.4)	389	(6.6)	643	(7.1)
Not Hispanic Or Latino	378	(79.6)	4,690	(79.7)	7,392	(81.3)
Not Reported	37	(7.8)	181	(3.1)	354	(3.9)
Unknown	1	(0.2)	110	(1.9)	172	(1.9)
Missing	0	(0.0)	514	(8.7)	529	(5.8)
Geographic Region						
EU	205	(43.2)	2,092	(35.6)	3,223	(35.5)
Ex-EU	270	(56.8)	3,792	(64.4)	5,867	(64.5)
ECOG Performance Scale						
[0] Normal Activity	208	(43.8)	2,761	(46.9)	4,154	(45.7)
[1] Symptoms, but ambulatory	267	(56.2)	2,931	(49.8)	4,625	(50.9)
Other/Missing	0	(0.0)	192	(3.3)	311	(3.4)

‡‡ Includes all subjects who received at least one dose of pembrolizumab in KN158 cohort K: MSI-H, and KN164 cohorts A and B.

†† 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, KN013 cohort 3, 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 ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN158 Cohorts E, G, K and TMB-H in Cohorts A-J, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN427 and KN629.

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

Database cutoff date for Lung (KN001:23JAN2015, KN010:30SEP2015, KN024:10JUL2017, KN028:31JUL2018, KN042:04SEP2018, KN158:27JUN2019)

Database cutoff date for Gastric (KN012:26APR2016, KN059:08AUG2018, KN061:26OCT2017, KN062:26MAR2019)

Database cutoff date for cHL (KN013:28SEP2018, KN087: 21MAR2019, KN204:16JAN2020)

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

Database cutoff date for PMBCL (KN013:04AUG2017, KN170: 07MAY2020)

Database cutoff date for Cervical (KN028:20FEB2017, KN158: 27JUN2019)

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

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 NMIBC (KN057 24MAY2019)

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

Database cutoff date for CRC MSI-H or dMMMR (KN177:19FEB2020)

Database cutoff date for cSCC (KN629:08APR2019)

Database cutoff date for MSI-H (KN158:05OCT2020)

Database cutoff date for Colorectal (KN164:09SEP2019)

Source: [ISS: adam-adsl]

Adverse events

AEs were coded using MedDRA version 23.1 and reported according to NCI CTCAE Version 4.0.

Table 51: Adverse event summary (ASaT population)

	KN158 Cohort K + KN164 Cohorts A and B MSI-H Data for Pembrolizumab‡‡		Reference Safety Dataset for Pembrolizumab††		Cumulative Running Safety Dataset for Pembrolizumab§§	
	n	(%)	n	(%)	n	(%)
Participants in population	475		5,884		9,090	
with one or more adverse events	455	(95.8)	5,690	(96.7)	8,766	(96.4)
with no adverse event	20	(4.2)	194	(3.3)	324	(3.6)
with drug-relateda adverse events	310	(65.3)	4,132	(70.2)	6,226	(68.5)
with toxicity grade 3-5 adverse events	237	(49.9)	2,829	(48.1)	4,451	(49.0)
with toxicity grade 3-5 drug-related adverse events	60	(12.6)	913	(15.5)	1,436	(15.8)
with serious adverse events	169	(35.6)	2,266	(38.5)	3,462	(38.1)
with serious drug-related adverse events	34	(7.2)	656	(11.1)	1,012	(11.1)
with dose modificationb due to an adverse event	195	(41.1)	2,040	(34.7)	3,154	(34.7)
who died	22	(4.6)	312	(5.3)	496	(5.5)
who died due to a drug-related adverse event	3	(0.6)	39	(0.7)	68	(0.7)
discontinued drug due to an adverse event	47	(9.9)	790	(13.4)	1,141	(12.6)
discontinued drug due to a drug-related adverse event	27	(5.7)	410	(7.0)	607	(6.7)
discontinued drug due to a serious adverse event	30	(6.3)	572	(9.7)	822	(9.0)
discontinued drug due to a serious drug-related adverse event	12	(2.5)	245	(4.2)	360	(4.0)

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

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

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.

‡‡ Includes all subjects who received at least one dose of pembrolizumab in KN158 cohort K: MSI-H, and KN164 cohorts A and B.

†† 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, KN013 cohort 3, 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 ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN158 Cohorts E, G, K and TMB-H in Cohorts A-J, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN427 and KN629.

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

Database cutoff date for Lung (KN001:23JAN2015, KN010:30SEP2015, KN024:10JUL2017, KN028:31JUL2018, KN042:04SEP2018, KN158:27JUN2019)

Database cutoff date for Gastric (KN012:26APR2016, KN059:08AUG2018, KN061:26OCT2017, KN062:26MAR2019)

Database cutoff date for cHL (KN013:28SEP2018, KN087: 21MAR2019, KN204:16JAN2020)

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

Database cutoff date for PMBCL (KN013:04AUG2017, KN170: 07MAY2020)

Database cutoff date for Cervical (KN028:20FEB2017, KN158: 27JUN2019)

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

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 NMIBC (KN057 24MAY2019)

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

Database cutoff date for CRC MSI-H or dMMMR (KN177:19FEB2020)

Database cutoff date for cSCC (KN629:08APR2019)

Database cutoff date for MSI-H (KN158:05OCT2020)

Database cutoff date for Colorectal (KN164:09SEP2019)

Source: [ISS: adam-adsl; adae]

Table 52: Adverse event summary including multiple occurrences of events (ASaT population)

	Event Count and Rate (Events/100 person-years)†		
	KN158 Cohort K + KN164 Cohorts A and B MSI-H Data for Pembrolizumab‡‡	Reference Safety Dataset for Pembrolizumab††	Cumulative Running Safety Dataset for Pembrolizumab§§
Number of subjects exposed	475	5884	9090
Total exposure‡ in person-years	420.16	3990.32	6105.72
Total events (rate)			
adverse events	4827 (1148.84)	61600 (1543.74)	91105 (1492.13)
drug-related§ adverse events	1221 (290.60)	19283 (483.24)	27026 (442.63)
toxicity grade 3-5 adverse events	552 (131.38)	6162 (154.42)	9940 (162.80)
toxicity grade 3-5 drug-related adverse events	87 (20.71)	1374 (34.43)	2163 (35.43)
serious adverse events	300 (71.40)	4094 (102.60)	6151 (100.74)
serious drug-related adverse events	38 (9.04)	916 (22.96)	1381 (22.62)
adverse events leading to death	22 (5.24)	319 (7.99)	505 (8.27)
drug-related adverse events leading to death	3 (0.71)	39 (0.98)	68 (1.11)
adverse events resulting in drug discontinuation	49 (11.66)	863 (21.63)	1227 (20.10)
drug-related adverse events resulting in drug discontinuation	29 (6.90)	448 (11.23)	652 (10.68)
serious adverse events resulting in drug discontinuation	31 (7.38)	609 (15.26)	864 (14.15)

serious drug-related adverse events resulting in drug discontinuation	13 (3.09)	259 (6.49)	378 (6.19)

† Event rate per 100 person-years of exposure=event count *100/person-years of exposure.
‡ Drug exposure is defined as the interval between the first dose date + 1 day and the earlier of the last dose date + 30 during the first course treatment phase 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.
‡‡ Includes all subjects who received at least one dose of pembrolizumab in KN158 cohort K: MSI-H, and KN164 cohorts A and B.
†† 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, KN013 cohort 3, 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 ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN158 Cohorts E, G, K and TMB-H in Cohorts A-J, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN427 and KN629.
Database cutoff date for Melanoma (KN001:18APR2014, KN002:28FEB2015, KN006:03MAR2015, KN054:02OCT2017)
Database cutoff date for Lung (KN001:23JAN2015, KN010:30SEP2015, KN024:10JUL2017, KN028:31JUL2018, KN042:04SEP2018, KN158:27JUN2019)
Database cutoff date for Gastric (KN012:26APR2016, KN059:08AUG2018, KN061:26OCT2017, KN062:26MAR2019)
Database cutoff date for cHL (KN013:28SEP2018, KN087: 21MAR2019, KN204:16JAN2020)
Database cutoff date for Bladder (KN012:01SEP2015, KN045:26OCT2017, KN052:26SEP2018)
Database cutoff date for PMBCL (KN013:04AUG2017, KN170: 07MAY2020)
Database cutoff date for Cervical (KN028:20FEB2017, KN158: 27JUN2019)
Database cutoff date for HNSCC (KN012:26APR2016, KN040:15MAY2017, KN048:25FEB2019, KN055:22APR2016)
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 NMIBC (KN057 24MAY2019)
Database cutoff date for TMB-H (KN158:27JUN2019)
Database cutoff date for CRC MSI-H or dMMMR (KN177:19FEB2020)
Database cutoff date for cSCC (KN629:08APR2019)
Database cutoff date for MSI-H (KN158:05OCT2020)
Database cutoff date for Colorectal (KN164:09SEP2019)

Source: [ISS: adam-adsl; adae]

All common AEs

Table 53: subjects with Adverse event (incidence >=10% in one or more treatment groups) by decreasing frequency of preferred term (ASaT population)

	KN158 Cohort K + KN164 Cohorts A and B MSI-H Data for Pembrolizumab‡‡		Reference Safety Dataset for Pembrolizumab††		Cumulative Running Safety Dataset for Pembrolizumab§§	
	n	(%)	n	(%)	n	(%)
Subjects in population	475		5,884		9,090	
with one or more adverse events	455	(95.8)	5,690	(96.7)	8,766	(96.4)
with no adverse events	20	(4.2)	194	(3.3)	324	(3.6)
Diarrhoea	122	(25.7)	1,200	(20.4)	1,838	(20.2)
Fatigue	116	(24.4)	1,884	(32.0)	2,728	(30.0)
Nausea	106	(22.3)	1,213	(20.6)	1,863	(20.5)
Arthralgia	90	(18.9)	1,104	(18.8)	1,553	(17.1)
Vomiting	89	(18.7)	732	(12.4)	1,201	(13.2)
Asthenia	84	(17.7)	666	(11.3)	1,062	(11.7)
Pruritus	82	(17.3)	1,060	(18.0)	1,539	(16.9)
Abdominal pain	79	(16.6)	480	(8.2)	929	(10.2)
Anaemia	74	(15.6)	836	(14.2)	1,382	(15.2)
Constipation	72	(15.2)	995	(16.9)	1,553	(17.1)
Pyrexia	70	(14.7)	746	(12.7)	1,158	(12.7)
Decreased appetite	69	(14.5)	1,136	(19.3)	1,767	(19.4)
Back pain	63	(13.3)	662	(11.3)	1,030	(11.3)
Cough	59	(12.4)	1,148	(19.5)	1,603	(17.6)
Dyspnoea	57	(12.0)	989	(16.8)	1,338	(14.7)
Alanine aminotransferase increased	53	(11.2)	393	(6.7)	657	(7.2)
Hypothyroidism	53	(11.2)	651	(11.1)	976	(10.7)
Rash	52	(10.9)	904	(15.4)	1,231	(13.5)
Headache	49	(10.3)	711	(12.1)	951	(10.5)

Urinary tract infection	48	(10.1)	384	(6.5)	595	(6.5)

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

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

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.

‡‡ Includes all subjects who received at least one dose of pembrolizumab in KN158 cohort K: MSI-H, and KN164 cohorts A and B.

†† 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, KN013 cohort 3, 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 ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN158 Cohorts E, G, K and TMB-H in Cohorts A-J, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN427 and KN629.

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

Database cutoff date for Lung (KN001:23JAN2015, KN010:30SEP2015, KN024:10JUL2017, KN028:31JUL2018, KN042:04SEP2018, KN158:27JUN2019)

Database cutoff date for Gastric (KN012:26APR2016, KN059:08AUG2018, KN061:26OCT2017, KN062:26MAR2019)

Database cutoff date for cHL (KN013:28SEP2018, KN087: 21MAR2019, KN204:16JAN2020)

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

Database cutoff date for PMBCL (KN013:04AUG2017, KN170: 07MAY2020)

Database cutoff date for Cervical (KN028:20FEB2017, KN158: 27JUN2019)

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

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 NMIBC (KN057 24MAY2019)

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

Database cutoff date for CRC MSI-H or dMMMR (KN177:19FEB2020)

Database cutoff date for cSCC (KN629:08APR2019)

Database cutoff date for MSI-H (KN158:05OCT2020)

Database cutoff date for Colorectal (KN164:09SEP2019)

Source: [ISS: adam-adsl; adae]

Drug-related AEs

Table 54: subjects with drug-related adverse events (incidence >=5% in one or more treatment groups) by decreasing frequency of preferred term (ASaT population)

	KN158 Cohort K + KN164 Cohorts A and B MSI-H Data for Pembrolizumab‡‡		Reference Safety Dataset for Pembrolizumab††		Cumulative Running Safety Dataset for Pembrolizumab§§	
	n	(%)	n	(%)	n	(%)
Subjects in population	475		5,884		9,090	
with one or more adverse events	310	(65.3)	4,132	(70.2)	6,226	(68.5)
with no adverse events	165	(34.7)	1,752	(29.8)	2,864	(31.5)
Pruritus	64	(13.5)	836	(14.2)	1,184	(13.0)
Fatigue	60	(12.6)	1,170	(19.9)	1,631	(17.9)
Diarrhoea	56	(11.8)	630	(10.7)	924	(10.2)
Arthralgia	51	(10.7)	464	(7.9)	665	(7.3)
Hypothyroidism	45	(9.5)	565	(9.6)	848	(9.3)
Asthenia	42	(8.8)	363	(6.2)	547	(6.0)
Nausea	37	(7.8)	535	(9.1)	737	(8.1)
Rash	33	(6.9)	676	(11.5)	906	(10.0)

Decreased appetite	15	(3.2)	461	(7.8)	654	(7.2)

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

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

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

[#] Includes all subjects who received at least one dose of pembrolizumab in KN158 cohort K: MSI-H, and KN164 cohorts A and B.

[††] 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, KN013 cohort 3, 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 ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN158 Cohorts E, G, K and TMB-H in Cohorts A-J, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN427 and KN629.

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

Database cutoff date for Lung (KN001:23JAN2015, KN010:30SEP2015, KN024:10JUL2017, KN028:31JUL2018, KN042:04SEP2018, KN158:27JUN2019)

Database cutoff date for Gastric (KN012:26APR2016, KN059:08AUG2018, KN061:26OCT2017, KN062:26MAR2019)

Database cutoff date for cHL (KN013:28SEP2018, KN087: 21MAR2019, KN204:16JAN2020)

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

Database cutoff date for PMBCL (KN013:04AUG2017, KN170: 07MAY2020)

Database cutoff date for Cervical (KN028:20FEB2017, KN158: 27JUN2019)

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

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 NMIBC (KN057 24MAY2019)

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

Database cutoff date for CRC MSI-H or dMMMR (KN177:19FEB2020)

Database cutoff date for cSCC (KN629:08APR2019)

Database cutoff date for MSI-H (KN158:05OCT2020)

Database cutoff date for Colorectal (KN164:09SEP2019)

Source: [ISS: adam-adsl; adae]

Grade 3 to 5 Adverse Events

Table 55: subjects with grade 3-5 adverse events (incidence >=1% in one or more treatment groups) by decreasing frequency of preferred term (ASaT population)

	KN158 Cohort K + KN164 Cohorts A and B MSI-H Data for Pembrolizumab[‡‡]		Reference Safety Dataset for Pembrolizumab[††]		Cumulative Running Safety Dataset for Pembrolizumab[§§]	
	n	(%)	n	(%)	n	(%)
Subjects in population	475		5,884		9,090	
with one or more adverse events	237	(49.9)	2,829	(48.1)	4,451	(49.0)
with no adverse events	238	(50.1)	3,055	(51.9)	4,639	(51.0)
Anaemia	27	(5.7)	233	(4.0)	448	(4.9)
Alanine aminotransferase increased	14	(2.9)	61	(1.0)	121	(1.3)
Aspartate aminotransferase increased	14	(2.9)	65	(1.1)	145	(1.6)
Abdominal pain	12	(2.5)	42	(0.7)	112	(1.2)
Blood alkaline phosphatase increased	11	(2.3)	48	(0.8)	103	(1.1)
Dyspnoea	11	(2.3)	131	(2.2)	186	(2.0)
Sepsis	10	(2.1)	45	(0.8)	83	(0.9)
Fatigue	9	(1.9)	144	(2.4)	225	(2.5)
Gamma-glutamyltransferase increased	9	(1.9)	35	(0.6)	80	(0.9)
Urinary tract infection	9	(1.9)	73	(1.2)	108	(1.2)
Asthenia	7	(1.5)	58	(1.0)	112	(1.2)
Hyperglycaemia	7	(1.5)	64	(1.1)	110	(1.2)
Pneumonia	7	(1.5)	242	(4.1)	348	(3.8)
Diarrhoea	6	(1.3)	79	(1.3)	126	(1.4)
Hypertension	6	(1.3)	102	(1.7)	143	(1.6)
Hyponatraemia	6	(1.3)	153	(2.6)	233	(2.6)
Intestinal obstruction	6	(1.3)	12	(0.2)	32	(0.4)
Lipase increased	6	(1.3)	16	(0.3)	24	(0.3)
Small intestinal obstruction	6	(1.3)	9	(0.2)	25	(0.3)
Transaminases increased	6	(1.3)	9	(0.2)	22	(0.2)
Ascites	5	(1.1)	16	(0.3)	50	(0.6)
Death	5	(1.1)	42	(0.7)	70	(0.8)
Hypokalaemia	5	(1.1)	58	(1.0)	91	(1.0)
Hypophosphataemia	5	(1.1)	41	(0.7)	69	(0.8)
Pneumonitis	5	(1.1)	83	(1.4)	111	(1.2)
Back pain	4	(0.8)	64	(1.1)	98	(1.1)
Dehydration	4	(0.8)	62	(1.1)	103	(1.1)
Pulmonary embolism	4	(0.8)	91	(1.5)	130	(1.4)
Vomiting	3	(0.6)	42	(0.7)	89	(1.0)
Arthralgia	2	(0.4)	58	(1.0)	74	(0.8)
Pleural effusion	2	(0.4)	68	(1.2)	100	(1.1)
Colitis	0	(0.0)	60	(1.0)	87	(1.0)

Decreased appetite	0	(0.0)	74	(1.3)	119	(1.3)

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.

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.

‡‡ Includes all subjects who received at least one dose of pembrolizumab in KN158 cohort K: MSI-H, and KN164 cohorts A and B.

†† 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, KN013 cohort 3, 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 ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN158 Cohorts E, G, K and TMB-H in Cohorts A-J, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN427 and KN629.

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

Database cutoff date for Lung (KN001:23JAN2015, KN010:30SEP2015, KN024:10JUL2017, KN028:31JUL2018, KN042:04SEP2018, KN158:27JUN2019)

Database cutoff date for Gastric (KN012:26APR2016, KN059:08AUG2018, KN061:26OCT2017, KN062:26MAR2019)

Database cutoff date for cHL (KN013:28SEP2018, KN087: 21MAR2019, KN204:16JAN2020)

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

Database cutoff date for PMBCL (KN013:04AUG2017, KN170: 07MAY2020)

Database cutoff date for Cervical (KN028:20FEB2017, KN158: 27JUN2019)

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

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 NMIBC (KN057 24MAY2019)

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

Database cutoff date for CRC MSI-H or dMMMR (KN177:19FEB2020)

Database cutoff date for cSCC (KN629:08APR2019)

Database cutoff date for MSI-H (KN158:05OCT2020)

Database cutoff date for Colorectal (KN164:09SEP2019)

Source: [ISS: adam-adsl; adae]

Grade 3 to 5 Drug-related Adverse Events

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)

	KN158 Cohort K + KN164 Cohorts A and B MSI-H Data for Pembrolizumab‡‡		Reference Safety Dataset for Pembrolizumab††		Cumulative Running Safety Dataset for Pembrolizumab§§	
	n	(%)	n	(%)	n	(%)
Subjects in population	475		5,884		9,090	
with one or more adverse events	60	(12.6)	913	(15.5)	1,436	(15.8)
with no adverse events	415	(87.4)	4,971	(84.5)	7,654	(84.2)
Alanine aminotransferase increased	5	(1.1)	35	(0.6)	63	(0.7)
Fatigue	4	(0.8)	63	(1.1)	97	(1.1)
Pneumonitis	4	(0.8)	78	(1.3)	104	(1.1)

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.

Serious adverse event/deaths/other significant events

All Serious Adverse Events

Table 56: 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)

	KN158 Cohort K + KN164 Cohorts A and B MSI-H Data for Pembrolizumab[‡‡]		Reference Safety Dataset for Pembrolizumab[††]		Cumulative Running Safety Dataset for Pembrolizumab[§§]	
	n	(%)	n	(%)	n	(%)
Subjects in population	475		5,884		9,090	
with one or more adverse events	169	(35.6)	2,266	(38.5)	3,462	(38.1)
with no adverse events	306	(64.4)	3,618	(61.5)	5,628	(61.9)
Sepsis	10	(2.1)	42	(0.7)	75	(0.8)
Dyspnoea	8	(1.7)	81	(1.4)	104	(1.1)
Abdominal pain	7	(1.5)	27	(0.5)	64	(0.7)
Pneumonia	7	(1.5)	246	(4.2)	347	(3.8)
Small intestinal obstruction	7	(1.5)	10	(0.2)	27	(0.3)
Urinary tract infection	7	(1.5)	59	(1.0)	86	(0.9)
Pneumonitis	6	(1.3)	117	(2.0)	159	(1.7)
Death	5	(1.1)	42	(0.7)	70	(0.8)
Intestinal obstruction	5	(1.1)	12	(0.2)	31	(0.3)
Anaemia	4	(0.8)	59	(1.0)	105	(1.2)
Diarrhoea	4	(0.8)	59	(1.0)	87	(1.0)
Pulmonary embolism	4	(0.8)	71	(1.2)	99	(1.1)
Pyrexia	4	(0.8)	67	(1.1)	104	(1.1)
Pleural effusion	3	(0.6)	83	(1.4)	114	(1.3)
Acute kidney injury	2	(0.4)	50	(0.8)	91	(1.0)
Colitis	0	(0.0)	59	(1.0)	81	(0.9)

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

A system organ class or specific adverse event appears on this report only if its incidence 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.

[‡‡] Includes all subjects who received at least one dose of pembrolizumab in KN158 cohort K: MSI-H, and KN164 cohorts A and B.

[††] 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, KN013 cohort 3, 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 ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN158 Cohorts E, G, K and TMB-H in Cohorts A-J, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN427 and KN629.

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

Database cutoff date for Lung (KN001:23JAN2015, KN010:30SEP2015, KN024:10JUL2017, KN028:31JUL2018, KN042:04SEP2018, KN158:27JUN2019)

Database cutoff date for Gastric (KN012:26APR2016, KN059:08AUG2018, KN061:26OCT2017, KN062:26MAR2019)

Database cutoff date for cHL (KN013:28SEP2018, KN087: 21MAR2019, KN204:16JAN2020)

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

Database cutoff date for PMBCL (KN013:04AUG2017, KN170: 07MAY2020)

Database cutoff date for Cervical (KN028:20FEB2017, KN158: 27JUN2019)

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

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)

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Database cutoff date for NMIBC (KN057 24MAY2019)

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

Database cutoff date for CRC MSI-H or dMMMR (KN177:19FEB2020)

Database cutoff date for cSCC (KN629:08APR2019)

Database cutoff date for MSI-H (KN158:05OCT2020)

Database cutoff date for Colorectal (KN164:09SEP2019)

Source: [ISS: adam-adsl; adae]

Drug-related Serious Adverse Events

Table 57: 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)

	KN158 Cohort K + KN164 Cohorts A and B MSI-H Data for Pembrolizumab‡‡		Reference Safety Dataset for Pembrolizumab††		Cumulative Running Safety Dataset for Pembrolizumab§§	
	n	(%)	n	(%)	n	(%)
Subjects in population	475		5,884		9,090	
with one or more adverse events	34	(7.2)	656	(11.1)	1,012	(11.1)
with no adverse events	441	(92.8)	5,228	(88.9)	8,078	(88.9)
Pneumonitis	5	(1.1)	111	(1.9)	151	(1.7)

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.

‡‡ Includes all subjects who received at least one dose of pembrolizumab in KN158 cohort K: MSI-H, and KN164 cohorts A and B.

†† 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, KN013 cohort 3, 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 ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN158 Cohorts E, G, K and TMB-H in Cohorts A-J, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN427 and KN629.

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

Database cutoff date for Lung (KN001:23JAN2015, KN010:30SEP2015, KN024:10JUL2017, KN028:31JUL2018, KN042:04SEP2018, KN158:27JUN2019)

Database cutoff date for Gastric (KN012:26APR2016, KN059:08AUG2018, KN061:26OCT2017, KN062:26MAR2019)

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Database cutoff date for MSI-H (KN158:05OCT2020)

Database cutoff date for Colorectal (KN164:09SEP2019)

Source: [ISS: adam-adsl; adae]

Deaths Due to Adverse Events

The proportion of participants in the MSI-H Safety Dataset who experienced an AE leading to death was consistent with the RSD (4.6% vs 5.3%, respectively) [Table 2.7.4-msihcancer4:10].

The 22 AEs that led to death in the MSI-H Safety Dataset were:

• Cardiac failure, pneumonia, and sepsis (2 participants for each AE)

• Acute myeloid leukemia, aspiration, cardiopulmonary failure, euthanasia, gastric haemorrhage, general physical health deterioration, Guillain-Barre syndrome, malabsorption, myocarditis, respiratory tract infection, and septic shock (1 participant for each AE). Of those, myocarditis, pneumonia, and Guillain-Barre syndrome were considered drug-related deaths by investigator.

• Five participants died of an unknown cause (preferred term=death).

Laboratory findings

The following laboratory parameters (all grades) occurred at an increased frequency (≥10% point difference) in the MSI-H Safety Dataset compared with the RSD: activated partial thromboplastin time increased (25.4% vs 13.4%), alkaline phosphatase increased (37.5% vs 27.2%), calcium decreased (35.2% vs 22.8%), calcium increased (28.7% vs 11.5%), glucose decreased (41.2% vs 10.0%), hemoglobin increased (31.2% vs 0.0%), potassium decreased (29.2% vs 12.7%) and sodium increased (24.5% vs 5.4%) [Table 5.3.5.3.3-msi-hcancer4:149]. Most lab abnormalities were Grade 1 or Grade 2.

One participant met the predetermined protocol-specified laboratory criteria for potential DILI (aminotransaminase [alanine aminotransferase and aspartate aminotransferase] ≥3 × ULN, bilirubin ≥2 × ULN, and alkaline phosphatase <2 × ULN) [Ref. 5.3.5.2: P158V09MK3475: Table 12-7]. Although laboratory criteria consistent with potential DILI were met, the participant had primary gastric cancer with extensive liver metastases and progressive disease was noted on imaging at the time these abnormal laboratory values were obtained. The site did not code the event as DILI and no association to study treatment was noted. The participant died 1 day after these assessments.

Adverse Events of Special Interest

AEOSI are immune-related events and infusion-related reactions known to be associated with pembrolizumab.

Table 58: adverse event summary AEOSI (ASaT population)

	KN158 Cohort K + KN164 Cohorts A and B MSI-H Data for Pembrolizumab‡‡		Reference Safety Dataset for Pembrolizumab††		Cumulative Running Safety Dataset for Pembrolizumab§§	
	n	(%)	n	(%)	n	(%)
Participants in population	475		5,884		9,090	
with one or more adverse events	108	(22.7)	1,475	(25.1)	2,207	(24.3)
with no adverse event	367	(77.3)	4,409	(74.9)	6,883	(75.7)
with drug-relateda adverse events	92	(19.4)	1,282	(21.8)	1,923	(21.2)
with toxicity grade 3-5 adverse events	24	(5.1)	381	(6.5)	572	(6.3)
with toxicity grade 3-5 drug-related adverse events	19	(4.0)	331	(5.6)	498	(5.5)
with serious adverse events	21	(4.4)	381	(6.5)	555	(6.1)
with serious drug-related adverse events	17	(3.6)	337	(5.7)	493	(5.4)
who died	2	(0.4)	11	(0.2)	21	(0.2)
who died due to a drug-related adverse event	2	(0.4)	11	(0.2)	21	(0.2)
discontinued drug due to an adverse event	13	(2.7)	232	(3.9)	339	(3.7)
discontinued drug due to a drug-related adverse event	13	(2.7)	228	(3.9)	335	(3.7)
discontinued drug due to a serious adverse event	7	(1.5)	156	(2.7)	219	(2.4)
discontinued drug due to a serious drug-related adverse event	7	(1.5)	154	(2.6)	217	(2.4)

[a] 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.

‡‡ Includes all subjects who received at least one dose of pembrolizumab in KN158 cohort K: MSI-H, and KN164 cohorts A and B.

†† 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, KN013 cohort 3, 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 ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN158 Cohorts E, G, K and TMB-H in Cohorts A-J, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN427 and KN629.

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

Database cutoff date for Lung (KN001:23JAN2015, KN010:30SEP2015, KN024:10JUL2017, KN028:31JUL2018, KN042:04SEP2018, KN158:27JUN2019)

Database cutoff date for Gastric (KN012:26APR2016, KN059:08AUG2018, KN061:26OCT2017, KN062:26MAR2019)

Database cutoff date for cHL (KN013:28SEP2018, KN087: 21MAR2019, KN204:16JAN2020)

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

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Database cutoff date for Cervical (KN028:20FEB2017, KN158: 27JUN2019)

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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)

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Database cutoff date for NMIBC (KN057 24MAY2019)

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Database cutoff date for cSCC (KN629:08APR2019)

Database cutoff date for MSI-H (KN158:05OCT2020)

Database cutoff date for Colorectal (KN164:09SEP2019)

Source: [ISS: adam-adsl; adae]

Table 59: subjects with adverse events of special interest (AEOSI) (ASaT population)

	KN158 Cohort K + KN164 Cohorts A and B MSI-H Data for Pembrolizumab‡‡		Reference Safety Dataset for Pembrolizumab††		Cumulative Running Safety Dataset for Pembrolizumab§§	
	n	(%)	n	(%)	n	(%)
Subjects in population	475		5,884		9,090	
with one or more adverse events	108	(22.7)	1,475	(25.1)	2,207	(24.3)
with no adverse events	367	(77.3)	4,409	(74.9)	6,883	(75.7)
Adrenal Insufficiency	**0**	**(0.0)**	**47**	**(0.8)**	**72**	**(0.8)**
Addison's disease	0	(0.0)	2	(0.0)	4	(0.0)
Adrenal insufficiency	0	(0.0)	42	(0.7)	61	(0.7)
Adrenocortical insufficiency acute	0	(0.0)	2	(0.0)	3	(0.0)
Primary adrenal insufficiency	0	(0.0)	0	(0.0)	2	(0.0)
Secondary adrenocortical insufficiency	0	(0.0)	1	(0.0)	3	(0.0)
Colitis	**10**	**(2.1)**	**110**	**(1.9)**	**177**	**(1.9)**
Colitis	8	(1.7)	95	(1.6)	151	(1.7)
Enterocolitis	2	(0.4)	8	(0.1)	16	(0.2)
Autoimmune colitis	0	(0.0)	3	(0.1)	6	(0.1)
Colitis microscopic	0	(0.0)	4	(0.1)	4	(0.0)
Immune-mediated enterocolitis	0	(0.0)	3	(0.1)	3	(0.0)
Encephalitis	**0**	**(0.0)**	**3**	**(0.1)**	**6**	**(0.1)**
Encephalitis	0	(0.0)	3	(0.1)	5	(0.1)
Encephalitis autoimmune	0	(0.0)	0	(0.0)	1	(0.0)
Guillain-Barre Syndrome	**2**	**(0.4)**	**4**	**(0.1)**	**8**	**(0.1)**
Guillain-Barre syndrome	2	(0.4)	2	(0.0)	6	(0.1)
Axonal neuropathy	0	(0.0)	1	(0.0)	1	(0.0)
Demyelinating polyneuropathy	0	(0.0)	1	(0.0)	1	(0.0)
Hepatitis	**4**	**(0.8)**	**56**	**(1.0)**	**92**	**(1.0)**
Hepatitis	3	(0.6)	24	(0.4)	39	(0.4)
Autoimmune hepatitis	1	(0.2)	25	(0.4)	40	(0.4)
Drug-induced liver injury	0	(0.0)	6	(0.1)	9	(0.1)
Hepatitis acute	0	(0.0)	1	(0.0)	1	(0.0)
Immune-mediated hepatitis	0	(0.0)	1	(0.0)	4	(0.0)
Hyperthyroidism	**25**	**(5.3)**	**247**	**(4.2)**	**397**	**(4.4)**
Hyperthyroidism	25	(5.3)	247	(4.2)	397	(4.4)
Hypophysitis	**0**	**(0.0)**	**36**	**(0.6)**	**50**	**(0.6)**
Hypophysitis	0	(0.0)	22	(0.4)	30	(0.3)
Hypopituitarism	0	(0.0)	14	(0.2)	19	(0.2)

Hypophysitis	**0**	**(0.0)**	**36**	**(0.6)**	**50**	**(0.6)**
Lymphocytic hypophysitis	0	(0.0)	0	(0.0)	1	(0.0)
Hypothyroidism	**53**	**(11.2)**	**652**	**(11.1)**	**980**	**(10.8)**
Hypothyroidism	53	(11.2)	651	(11.1)	976	(10.7)
Autoimmune hypothyroidism	0	(0.0)	0	(0.0)	2	(0.0)
Myxoedema	0	(0.0)	1	(0.0)	2	(0.0)
Primary hypothyroidism	0	(0.0)	1	(0.0)	1	(0.0)
Infusion Reactions	**6**	**(1.3)**	**138**	**(2.3)**	**188**	**(2.1)**
Infusion related reaction	5	(1.1)	56	(1.0)	90	(1.0)
Drug hypersensitivity	1	(0.2)	18	(0.3)	22	(0.2)
Anaphylactic reaction	0	(0.0)	10	(0.2)	12	(0.1)
Anaphylactoid reaction	0	(0.0)	1	(0.0)	1	(0.0)
Cytokine release syndrome	0	(0.0)	8	(0.1)	9	(0.1)
Hypersensitivity	0	(0.0)	47	(0.8)	57	(0.6)
Myasthenic Syndrome	**0**	**(0.0)**	**3**	**(0.1)**	**4**	**(0.0)**
Myasthenia gravis	0	(0.0)	1	(0.0)	1	(0.0)
Myasthenic syndrome	0	(0.0)	2	(0.0)	3	(0.0)
Myelitis	**0**	**(0.0)**	**2**	**(0.0)**	**2**	**(0.0)**
Myelitis	0	(0.0)	1	(0.0)	1	(0.0)
Myelitis transverse	0	(0.0)	1	(0.0)	1	(0.0)
Myocarditis	**1**	**(0.2)**	**5**	**(0.1)**	**10**	**(0.1)**
Myocarditis	1	(0.2)	5	(0.1)	10	(0.1)
Myositis	**5**	**(1.1)**	**19**	**(0.3)**	**38**	**(0.4)**
Myopathy	2	(0.4)	4	(0.1)	6	(0.1)
Myositis	2	(0.4)	13	(0.2)	26	(0.3)
Rhabdomyolysis	1	(0.2)	1	(0.0)	5	(0.1)
Necrotising myositis	0	(0.0)	1	(0.0)	1	(0.0)
Polymyositis	0	(0.0)	0	(0.0)	1	(0.0)
Nephritis	**2**	**(0.4)**	**23**	**(0.4)**	**39**	**(0.4)**
Nephritis	1	(0.2)	3	(0.1)	12	(0.1)
Tubulointerstitial nephritis	1	(0.2)	11	(0.2)	14	(0.2)
Acute kidney injury	0	(0.0)	2	(0.0)	2	(0.0)
Autoimmune nephritis	0	(0.0)	3	(0.1)	5	(0.1)

Nephritis	**2**	**(0.4)**	**23**	**(0.4)**	**39**	**(0.4)**
Glomerulonephritis	0	(0.0)	0	(0.0)	1	(0.0)
Glomerulonephritis membranous	0	(0.0)	1	(0.0)	1	(0.0)
Nephrotic syndrome	0	(0.0)	1	(0.0)	2	(0.0)
Renal failure	0	(0.0)	2	(0.0)	2	(0.0)
Pancreatitis	**5**	**(1.1)**	**18**	**(0.3)**	**35**	**(0.4)**
Pancreatitis	5	(1.1)	14	(0.2)	30	(0.3)
Autoimmune pancreatitis	0	(0.0)	1	(0.0)	1	(0.0)
Pancreatitis acute	0	(0.0)	4	(0.1)	5	(0.1)
Pneumonitis	**15**	**(3.2)**	**264**	**(4.5)**	**377**	**(4.1)**
Pneumonitis	12	(2.5)	242	(4.1)	336	(3.7)
Interstitial lung disease	3	(0.6)	22	(0.4)	41	(0.5)
Organising pneumonia	0	(0.0)	3	(0.1)	3	(0.0)
Sarcoidosis	**1**	**(0.2)**	**10**	**(0.2)**	**12**	**(0.1)**
Sarcoidosis	1	(0.2)	10	(0.2)	12	(0.1)
Severe Skin Reactions	**6**	**(1.3)**	**97**	**(1.6)**	**142**	**(1.6)**
Erythema multiforme	2	(0.4)	5	(0.1)	8	(0.1)
Rash	2	(0.4)	30	(0.5)	44	(0.5)
Rash maculo-papular	2	(0.4)	16	(0.3)	26	(0.3)
Dermatitis bullous	0	(0.0)	8	(0.1)	9	(0.1)
Dermatitis exfoliative	0	(0.0)	5	(0.1)	5	(0.1)
Dermatitis exfoliative generalised	0	(0.0)	2	(0.0)	3	(0.0)
Exfoliative rash	0	(0.0)	2	(0.0)	6	(0.1)
Lichen planus	0	(0.0)	5	(0.1)	6	(0.1)
Oral lichen planus	0	(0.0)	1	(0.0)	2	(0.0)
Pemphigoid	0	(0.0)	3	(0.1)	6	(0.1)
Pemphigus	0	(0.0)	2	(0.0)	2	(0.0)
Pruritus	0	(0.0)	12	(0.2)	15	(0.2)
Pruritus genital	0	(0.0)	1	(0.0)	2	(0.0)
Rash erythematous	0	(0.0)	1	(0.0)	1	(0.0)
Rash pruritic	0	(0.0)	2	(0.0)	3	(0.0)
Rash pustular	0	(0.0)	1	(0.0)	2	(0.0)
Skin necrosis	0	(0.0)	2	(0.0)	2	(0.0)
Stevens-Johnson syndrome	0	(0.0)	3	(0.1)	3	(0.0)
Toxic skin eruption	0	(0.0)	2	(0.0)	4	(0.0)

	n	(%)	n	(%)	n	(%)
Thyroiditis	**0**	**(0.0)**	**58**	**(1.0)**	**78**	**(0.9)**
Autoimmune thyroiditis	0	(0.0)	14	(0.2)	18	(0.2)
Thyroid disorder	0	(0.0)	5	(0.1)	6	(0.1)
Thyroiditis	0	(0.0)	41	(0.7)	56	(0.6)
Type 1 Diabetes Mellitus	**2**	**(0.4)**	**20**	**(0.3)**	**32**	**(0.4)**
Diabetic ketoacidosis	1	(0.2)	9	(0.2)	13	(0.1)
Type 1 diabetes mellitus	1	(0.2)	16	(0.3)	25	(0.3)
Fulminant type 1 diabetes mellitus	0	(0.0)	0	(0.0)	1	(0.0)
Uveitis	**1**	**(0.2)**	**21**	**(0.4)**	**29**	**(0.3)**
Uveitis	1	(0.2)	13	(0.2)	20	(0.2)
Chorioretinitis	0	(0.0)	1	(0.0)	1	(0.0)
Iridocyclitis	0	(0.0)	4	(0.1)	4	(0.0)
Iritis	0	(0.0)	3	(0.1)	4	(0.0)
Vasculitis	**1**	**(0.2)**	**2**	**(0.0)**	**3**	**(0.0)**
Vasculitis	1	(0.2)	2	(0.0)	3	(0.0)

Every subject is counted a single time for each applicable row and column.
A bolded term or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
[#] Includes all subjects who received at least one dose of pembrolizumab in KN158 cohort K: MSI-H, and KN164 cohorts A and B.
[††] 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, KN013 cohort 3, 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 ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN158 Cohorts E, G, K and TMB-H in Cohorts A-J, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN427 and KN629.
Database cutoff date for Melanoma (KN001:18APR2014, KN002:28FEB2015, KN006:03MAR2015, KN054:02OCT2017)
Database cutoff date for Lung (KN001:23JAN2015, KN010:30SEP2015, KN024:10JUL2017, KN028:31JUL2018, KN042:04SEP2018, KN158:27JUN2019)
Database cutoff date for Gastric (KN012:26APR2016, KN059:08AUG2018, KN061:26OCT2017, KN062:26MAR2019)
Database cutoff date for cHL (KN013:28SEP2018, KN087: 21MAR2019, KN204:16JAN2020)
Database cutoff date for Bladder (KN012:01SEP2015, KN045:26OCT2017, KN052:26SEP2018)
Database cutoff date for PMBCL (KN013:04AUG2017, KN170: 07MAY2020)
Database cutoff date for Cervical (KN028:20FEB2017, KN158: 27JUN2019)
Database cutoff date for HNSCC (KN012:26APR2016, KN040:15MAY2017, KN048:25FEB2019, KN055:22APR2016)
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 NMIBC (KN057 24MAY2019)
Database cutoff date for TMB-H (KN158:27JUN2019)
Database cutoff date for CRC MSI-H or dMMMR (KN177:19FEB2020)
Database cutoff date for cSCC (KN629:08APR2019)
Database cutoff date for MSI-H (KN158:05OCT2020)
Database cutoff date for Colorectal (KN164:09SEP2019)

Source: [ISS: adam-adsl; adae]

Safety in special populations

Intrinsic Factors

Age

Table 60: Adverse event summary by age category (<65, >=65 years)

	KN158 Cohort K + KN164 Cohorts A and B MSI-H Data for Pembrolizumab[#]				Reference Safety Dataset for Pembrolizumab[††]				Cumulative Running Safety Dataset for Pembrolizumab[§§]			
	<65		>=65		<65		>=65		<65		>=65	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	305		170		3,385		2,499		5,202		3,888	
with one or more adverse events	289	(94.8)	166	(97.6)	3,268	(96.5)	2,422	(96.9)	5,011	(96.3)	3,755	(96.6)
with no adverse event	16	(5.2)	4	(2.4)	117	(3.5)	77	(3.1)	191	(3.7)	133	(3.4)
with drug-related[†] adverse events	188	(61.6)	122	(71.8)	2,366	(69.9)	1,766	(70.7)	3,503	(67.3)	2,723	(70.0)
with toxicity grade 3-5 adverse events	149	(48.9)	88	(51.8)	1,505	(44.5)	1,324	(53.0)	2,424	(46.6)	2,027	(52.1)
with toxicity grade 3-5 drug-related adverse events	34	(11.1)	26	(15.3)	456	(13.5)	457	(18.3)	728	(14.0)	708	(18.2)
with serious adverse events	107	(35.1)	62	(36.5)	1,182	(34.9)	1,084	(43.4)	1,832	(35.2)	1,630	(41.9)
with serious drug-related adverse events	20	(6.6)	14	(8.2)	346	(10.2)	310	(12.4)	525	(10.1)	487	(12.5)
with dose modification[‡] due to an adverse event	122	(40.0)	73	(42.9)	1,073	(31.7)	967	(38.7)	1,654	(31.8)	1,500	(38.6)
who died	9	(3.0)	13	(7.6)	144	(4.3)	168	(6.7)	220	(4.2)	276	(7.1)
who died due to a drug-related adverse event	0	(0.0)	3	(1.8)	21	(0.6)	18	(0.7)	29	(0.6)	39	(1.0)
discontinued drug due to an adverse event	25	(8.2)	22	(12.9)	399	(11.8)	391	(15.6)	566	(10.9)	575	(14.8)
discontinued drug due to a drug-related adverse event	13	(4.3)	14	(8.2)	207	(6.1)	203	(8.1)	298	(5.7)	309	(7.9)
discontinued drug due to a serious adverse event	16	(5.2)	14	(8.2)	287	(8.5)	285	(11.4)	409	(7.9)	413	(10.6)

discontinued drug due to a serious drug-related adverse event	5	(1.6)	7	(4.1)	123	(3.6)	122	(4.9)	177	(3.4)	183	(4.7)

† Determined by the investigator to be related to the drug.
‡ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Non-serious adverse events up to 30 days 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.
‡‡Includes all subjects who received at least one dose of pembrolizumab in KN158 cohort K: MSI-H, and KN164 cohorts A and B.
†† 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, KN013 cohort 3, 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 ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN158 Cohorts E, G, K and TMB-H in Cohorts A-J, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN427 and KN629.
Database cutoff date for Melanoma (KN001:18APR2014, KN002:28FEB2015, KN006:03MAR2015, KN054:02OCT2017)
Database cutoff date for Lung (KN001:23JAN2015, KN010:30SEP2015, KN024:10JUL2017, KN028:31JUL2018, KN042:04SEP2018, KN158:27JUN2019)
Database cutoff date for Gastric (KN012:26APR2016, KN059:08AUG2018, KN061:26OCT2017, KN062:26MAR2019)
Database cutoff date for cHL (KN013:28SEP2018, KN087: 21MAR2019, KN204:16JAN2020)
Database cutoff date for Bladder (KN012:01SEP2015, KN045:26OCT2017, KN052:26SEP2018)
Database cutoff date for PMBCL (KN013:04AUG2017, KN170: 07MAY2020)
Database cutoff date for Cervical (KN028:20FEB2017, KN158: 27JUN2019)
Database cutoff date for HNSCC (KN012:26APR2016, KN040:15MAY2017, KN048:25FEB2019, KN055:22APR2016)
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 NMIBC (KN057 24MAY2019)
Database cutoff date for TMB-H (KN158:27JUN2019)
Database cutoff date for CRC MSI-H or dMMMR (KN177:19FEB2020)
Database cutoff date for cSCC (KN629:08APR2019)
Database cutoff date for MSI-H (KN158:05OCT2020)
Database cutoff date for Colorectal (KN164:09SEP2019)

Source: [ISS: adam-adsl; adae]

Table 61: Adverse event summary by age category (<65, 65-74, 75-84 >=85 years)

	KN158 Cohort K + KN164 Cohorts A and B MSI-H Data for Pembrolizumab‡‡								Reference 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	305		107		60		3		3,385		1,737		663		99	
with one or more adverse events	289	(94.8)	104	(97.2)	59	(98.3)	3	(100.0)	3,268	(96.5)	1,678	(96.6)	646	(97.4)	98	(99.0)
with no adverse event	16	(5.2)	3	(2.8)	1	(1.7)	0	(0.0)	117	(3.5)	59	(3.4)	17	(2.6)	1	(1.0)
with drug-related† adverse events	188	(61.6)	73	(68.2)	46	(76.7)	3	(100.0)	2,366	(69.9)	1,224	(70.5)	467	(70.4)	75	(75.8)
with toxicity grade 3-5 adverse events	149	(48.9)	54	(50.5)	33	(55.0)	1	(33.3)	1,505	(44.5)	891	(51.3)	373	(56.3)	60	(60.6)
with toxicity grade 3-5 drug-related adverse events	34	(11.1)	16	(15.0)	9	(15.0)	1	(33.3)	456	(13.5)	311	(17.9)	128	(19.3)	18	(18.2)
with serious adverse events	107	(35.1)	33	(30.8)	27	(45.0)	2	(66.7)	1,182	(34.9)	719	(41.4)	315	(47.5)	50	(50.5)
with serious drug-related adverse events	20	(6.6)	9	(8.4)	3	(5.0)	2	(66.7)	346	(10.2)	213	(12.3)	85	(12.8)	12	(12.1)
with dose modification‡ due to an adverse event	122	(40.0)	40	(37.4)	32	(53.3)	1	(33.3)	1,073	(31.7)	648	(37.3)	284	(42.8)	35	(35.4)
who died	9	(3.0)	6	(5.6)	7	(11.7)	0	(0.0)	144	(4.3)	103	(5.9)	54	(8.1)	11	(11.1)
who died due to a drug-related adverse event	0	(0.0)	1	(0.9)	2	(3.3)	0	(0.0)	21	(0.6)	12	(0.7)	5	(0.8)	1	(1.0)
discontinued drug due to an adverse event	25	(8.2)	13	(12.1)	8	(13.3)	1	(33.3)	399	(11.8)	246	(14.2)	131	(19.8)	14	(14.1)
discontinued drug due to a drug-related adverse event	13	(4.3)	9	(8.4)	4	(6.7)	1	(33.3)	207	(6.1)	135	(7.8)	62	(9.4)	6	(6.1)
discontinued drug due to a serious adverse event	16	(5.2)	7	(6.5)	6	(10.0)	1	(33.3)	287	(8.5)	174	(10.0)	100	(15.1)	11	(11.1)
discontinued drug due to a serious drug-related adverse event	5	(1.6)	4	(3.7)	2	(3.3)	1	(33.3)	123	(3.6)	81	(4.7)	38	(5.7)	3	(3.0)

† Determined by the investigator to be related to the drug.
‡ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Non-serious adverse events up to 30 days 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.
‡‡Includes all subjects who received at least one dose of pembrolizumab in KN158 cohort K: MSI-H, and KN164 cohorts A and B.
†† 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, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.
Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
Database Cutoff Date for Lung (KN001- NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018))
Database Cutoff Date for Hodgkin's Lymphoma (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019)
Database Cutoff Date for HNSCC (KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database Cutoff Date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Source: [ISS: adam-adsl; adae]

Table 62: Adverse event summary with specific AEs by age category (<65, 65-74, 75-84 >=85 years)

	KN158 Cohort K + KN 164 Cohorts A and B MSI-H Data for Pembrolizumab‡‡								Reference 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	305	(100.0)	107	(100.0)	60	(100.0)	3	(100.0)	3385	(100.0)	1737	(100.0)	663	(100.0)	99	(100.0)
with one or more adverse events	289	(94.8)	104	(97.2)	59	(98.3)	3	(100.0)	3268	(96.5)	1678	(96.6)	646	(97.4)	98	(99.0)
who died	9	(3.0)	6	(5.6)	7	(11.7)	0	(0.0)	144	(4.3)	103	(5.9)	54	(8.1)	11	(11.1)
with serious adverse events	107	(35.1)	33	(30.8)	27	(45.0)	2	(66.7)	1182	(34.9)	719	(41.4)	315	(47.5)	50	(50.5)
discontinued due to an adverse event	25	(8.2)	13	(12.1)	8	(13.3)	1	(33.3)	399	(11.8)	246	(14.2)	131	(19.8)	14	(14.1)
CNS (confusion/extrapyramidal)	22	(7.2)	12	(11.2)	5	(8.3)	0	(0.0)	251	(7.4)	157	(9.0)	46	(6.9)	16	(16.2)
AE related to falling	19	(6.2)	13	(12.1)	4	(6.7)	1	(33.3)	229	(6.8)	152	(8.8)	70	(10.6)	20	(20.2)
CV events	48	(15.7)	25	(23.4)	11	(18.3)	0	(0.0)	653	(19.3)	396	(22.8)	160	(24.1)	25	(25.3)
Cerebrovascular events	4	(1.3)	3	(2.8)	1	(1.7)	0	(0.0)	61	(1.8)	40	(2.3)	20	(3.0)	3	(3.0)
Infections	134	(43.9)	56	(52.3)	21	(35.0)	2	(66.7)	1453	(42.9)	773	(44.5)	308	(46.5)	44	(44.4)

MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Non-serious AEs were followed 30 days after last dose of study treatment; SAEs were followed 90 days after last dose of study treatment.
‡‡ Includes all subjects who received at least one dose of pembrolizumab in KN158 cohort K: MSI-H, and KN164 cohorts A and B.
†† 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, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.
Pembrolizumab Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
Pembrolizumab Database Cutoff Date for Lung (KN001- NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)
Pembrolizumab Database Cutoff Date for Hodgkin's Lymphoma (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019)
Pembrolizumab Database Cutoff Date for HNSCC (KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Pembrolizumab Database Cutoff Date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Source: [ISS: adam-adsl; adae]

Sex

Table 63: Adverse event summary by gender category

	KN158 Cohort K + KN164 Cohorts A and B MSI-H Data for Pembrolizumab‡‡				Reference Safety Dataset for Pembrolizumab††				Cumulative Running Safety Dataset for Pembrolizumab‡‡			
	M		F		M		F		M		F	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	213		262		3,887		1,997		5,964		3,126	
with one or more adverse events	203	(95.3)	252	(96.2)	3,756	(96.6)	1,934	(96.8)	5,735	(96.2)	3,031	(97.0)
with no adverse event	10	(4.7)	10	(3.8)	131	(3.4)	63	(3.2)	229	(3.8)	95	(3.0)
with drug-related† adverse events	129	(60.6)	181	(69.1)	2,710	(69.7)	1,422	(71.2)	4,029	(67.6)	2,197	(70.3)
with toxicity grade 3-5 adverse events	102	(47.9)	135	(51.5)	1,894	(48.7)	935	(46.8)	2,931	(49.1)	1,520	(48.6)
with toxicity grade 3-5 drug-related adverse events	29	(13.6)	31	(11.8)	630	(16.2)	283	(14.2)	985	(16.5)	451	(14.4)
with serious adverse events	79	(37.1)	90	(34.4)	1,534	(39.5)	732	(36.7)	2,309	(38.7)	1,153	(36.9)
with serious drug-related adverse events	18	(8.5)	16	(6.1)	448	(11.5)	208	(10.4)	698	(11.7)	314	(10.0)
with dose modification‡ due to an adverse event	88	(41.3)	107	(40.8)	1,350	(34.7)	690	(34.6)	2,062	(34.6)	1,092	(34.9)
who died	14	(6.6)	8	(3.1)	221	(5.7)	91	(4.6)	358	(6.0)	138	(4.4)
who died due to a drug-related adverse event	3	(1.4)	0	(0.0)	25	(0.6)	14	(0.7)	45	(0.8)	23	(0.7)
discontinued drug due to an adverse event	25	(11.7)	22	(8.4)	529	(13.6)	261	(13.1)	765	(12.8)	376	(12.0)
discontinued drug due to a drug-related adverse event	12	(5.6)	15	(5.7)	278	(7.2)	132	(6.6)	404	(6.8)	203	(6.5)
discontinued drug due to a serious adverse event	17	(8.0)	13	(5.0)	386	(9.9)	186	(9.3)	559	(9.4)	263	(8.4)
discontinued drug due to a serious drug-related adverse event	6	(2.8)	6	(2.3)	167	(4.3)	78	(3.9)	245	(4.1)	115	(3.7)

† Determined by the investigator to be related to the drug.
‡ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Non-serious adverse events up to 30 days 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.
‡‡ Includes all subjects who received at least one dose of pembrolizumab in KN158 cohort K: MSI-H, and KN164 cohorts A and B.
†† 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, KN013 cohort 3, 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 ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN158 Cohorts E, G, K and TMB-H in Cohorts A-J, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN427 and KN629.
Database cutoff date for Melanoma (KN001:18APR2014, KN002:28FEB2015, KN006:03MAR2015, KN054:02OCT2017)
Database cutoff date for Lung (KN001:23JAN2015, KN010:30SEP2015, KN024:10JUL2017, KN028:31JUL2018, KN042:04SEP2018, KN158:27JUN2019)
Database cutoff date for Gastric (KN012:26APR2016, KN059:08AUG2018, KN061:26OCT2017, KN062:26MAR2019)
Database cutoff date for cHL (KN013:28SEP2018, KN087: 21MAR2019, KN204:16JAN2020)
Database cutoff date for Bladder (KN012:01SEP2015, KN045:26OCT2017, KN052:26SEP2018)
Database cutoff date for PMBCL (KN013:04AUG2017, KN170: 07MAY2020)
Database cutoff date for Cervical (KN028:20FEB2017, KN158: 27JUN2019)
Database cutoff date for HNSCC (KN012:26APR2016, KN040:15MAY2017, KN048:25FEB2019, KN055:22APR2016)
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 NMIBC (KN057 24MAY2019)
Database cutoff date for TMB-H (KN158:27JUN2019)
Database cutoff date for CRC MSI-H or dMMMR (KN177:19FEB2020)
Database cutoff date for cSCC (KN629:08APR2019)
Database cutoff date for MSI-H (KN158:05OCT2020)
Database cutoff date for Colorectal (KN164:09SEP2019)

Source: [ISS: adam-adsl; adae]

ECOG Status

Table 64: Adverse event summary by ECOG status

	KN158 Cohort K + KN164 Cohorts A and B MSI-H Data for Pembrolizumab‡‡				Reference Safety Dataset for Pembrolizumab††				Cumulative Running Safety Dataset for Pembrolizumab§§			
	[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	208		267		2,761		2,931		4,154		4,625	
with one or more adverse events	199	(95.7)	256	(95.9)	2,671	(96.7)	2,835	(96.7)	4,000	(96.3)	4,467	(96.6)
with no adverse event	9	(4.3)	11	(4.1)	90	(3.3)	96	(3.3)	154	(3.7)	158	(3.4)
with drug-related† adverse events	149	(71.6)	161	(60.3)	2,085	(75.5)	1,940	(66.2)	3,041	(73.2)	2,983	(64.5)
with toxicity grade 3-5 adverse events	88	(42.3)	149	(55.8)	1,112	(40.3)	1,605	(54.8)	1,711	(41.2)	2,573	(55.6)
with toxicity grade 3-5 drug-related adverse events	25	(12.0)	35	(13.1)	410	(14.8)	471	(16.1)	623	(15.0)	748	(16.2)
with serious adverse events	56	(26.9)	113	(42.3)	872	(31.6)	1,294	(44.1)	1,308	(31.5)	2,007	(43.4)
with serious drug-related adverse events	12	(5.8)	22	(8.2)	311	(11.3)	325	(11.1)	456	(11.0)	514	(11.1)
with dose modification‡ due to an adverse event	84	(40.4)	111	(41.6)	844	(30.6)	1,122	(38.3)	1,308	(31.5)	1,714	(37.1)
who died	8	(3.8)	14	(5.2)	79	(2.9)	217	(7.4)	140	(3.4)	337	(7.3)
who died due to a drug-related adverse event	0	(0.0)	3	(1.1)	14	(0.5)	25	(0.9)	23	(0.6)	44	(1.0)
discontinued drug due to an adverse event	18	(8.7)	29	(10.9)	304	(11.0)	452	(15.4)	446	(10.7)	640	(13.8)
discontinued drug due to a drug-related adverse event	12	(5.8)	15	(5.6)	193	(7.0)	200	(6.8)	284	(6.8)	290	(6.3)
discontinued drug due to a serious adverse event	8	(3.8)	22	(8.2)	198	(7.2)	350	(11.9)	285	(6.9)	502	(10.9)
discontinued drug due to a serious drug-related adverse event	3	(1.4)	9	(3.4)	106	(3.8)	130	(4.4)	151	(3.6)	193	(4.2)

† Determined by the investigator to be related to the drug.
‡ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Non-serious adverse events up to 30 days 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.
‡‡ Includes all subjects who received at least one dose of pembrolizumab in KN158 cohort K: MSI-H, and KN164 cohorts A and B.
†† 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, KN013 cohort 3, 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 ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN158 Cohorts E, G, K and TMB-H in Cohorts A-J, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN427 and KN629.
Database cutoff date for Melanoma (KN001:18APR2014, KN002:28FEB2015, KN006:03MAR2015, KN054:02OCT2017)
Database cutoff date for Lung (KN001:23JAN2015, KN010:30SEP2015, KN024:10JUL2017, KN028:31JUL2018, KN042:04SEP2018, KN158:27JUN2019)
Database cutoff date for Gastric (KN012:26APR2016, KN059:08AUG2018, KN061:26OCT2017, KN062:26MAR2019)
Database cutoff date for cHL (KN013:28SEP2018, KN087: 21MAR2019, KN204:16JAN2020)
Database cutoff date for Bladder (KN012:01SEP2015, KN045:26OCT2017, KN052:26SEP2018)
Database cutoff date for PMBCL (KN013:04AUG2017, KN170: 07MAY2020)
Database cutoff date for Cervical (KN028:20FEB2017, KN158: 27JUN2019)
Database cutoff date for HNSCC (KN012:26APR2016, KN040:15MAY2017, KN048:25FEB2019, KN055:22APR2016)
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 NMIBC (KN057 24MAY2019)
Database cutoff date for TMB-H (KN158:27JUN2019)
Database cutoff date for CRC MSI-H or dMMMR (KN177:19FEB2020)
Database cutoff date for cSCC (KN629:08APR2019)
Database cutoff date for MSI-H (KN158:05OCT2020)
Database cutoff date for Colorectal (KN164:09SEP2019)

Source: [ISS: adam-adsl; adae]

Extrinsic Factors

Region

Table 65: Adverse event summary by region (EU, ex-EU)

	KN158 Cohort K + KN164 Cohorts A and B MSI-H Data for Pembrolizumab‡‡				Reference Safety Dataset for Pembrolizumab††				Cumulative Running Safety Dataset for Pembrolizumab§§			
	EU		Ex-EU		EU		Ex-EU		EU		Ex-EU	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	205		270		2,092		3,792		3,223		5,867	
with one or more adverse events	195	(95.1)	260	(96.3)	2,014	(96.3)	3,676	(96.9)	3,094	(96.0)	5,672	(96.7)
with no adverse event	10	(4.9)	10	(3.7)	78	(3.7)	116	(3.1)	129	(4.0)	195	(3.3)
with drug-related† adverse events	135	(65.9)	175	(64.8)	1,430	(68.4)	2,702	(71.3)	2,152	(66.8)	4,074	(69.4)
with toxicity grade 3-5 adverse events	105	(51.2)	132	(48.9)	960	(45.9)	1,869	(49.3)	1,550	(48.1)	2,901	(49.4)
with toxicity grade 3-5 drug-related adverse events	31	(15.1)	29	(10.7)	317	(15.2)	596	(15.7)	498	(15.5)	938	(16.0)
with serious adverse events	77	(37.6)	92	(34.1)	796	(38.0)	1,470	(38.8)	1,260	(39.1)	2,202	(37.5)
with serious drug-related adverse events	17	(8.3)	17	(6.3)	241	(11.5)	415	(10.9)	362	(11.2)	650	(11.1)
with dose modification‡ due to an adverse event	88	(42.9)	107	(39.6)	701	(33.5)	1,339	(35.3)	1,117	(34.7)	2,037	(34.7)
who died	12	(5.9)	10	(3.7)	109	(5.2)	203	(5.4)	181	(5.6)	315	(5.4)
who died due to a drug-related adverse event	2	(1.0)	1	(0.4)	12	(0.6)	27	(0.7)	22	(0.7)	46	(0.8)
discontinued drug due to an adverse event	19	(9.3)	28	(10.4)	267	(12.8)	523	(13.8)	400	(12.4)	741	(12.6)
discontinued drug due to a drug-related adverse event	10	(4.9)	17	(6.3)	151	(7.2)	259	(6.8)	217	(6.7)	390	(6.6)
discontinued drug due to a serious adverse event	12	(5.9)	18	(6.7)	193	(9.2)	379	(10.0)	286	(8.9)	536	(9.1)

discontinued drug due to a serious drug-related adverse event	4	(2.0)	8	(3.0)	89	(4.3)	156	(4.1)	124	(3.8)	236	(4.0)

† Determined by the investigator to be related to the drug.
‡ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Non-serious adverse events up to 30 days 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.
‡‡ Includes all subjects who received at least one dose of pembrolizumab in KN158 cohort K: MSI-H, and KN164 cohorts A and B.
†† 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, KN013 cohort 3, 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 ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN158 Cohorts E, G, K and TMB-H in Cohorts A-J, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN427 and KN629.
Database cutoff date for Melanoma (KN001:18APR2014, KN002:28FEB2015, KN006:03MAR2015, KN054:02OCT2017)
Database cutoff date for Lung (KN001:23JAN2015, KN010:30SEP2015, KN024:10JUL2017, KN028:31JUL2018, KN042:04SEP2018, KN158:27JUN2019)
Database cutoff date for Gastric (KN012:26APR2016, KN059:08AUG2018, KN061:26OCT2017, KN062:26MAR2019)
Database cutoff date for cHL (KN013:28SEP2018, KN087: 21MAR2019, KN204:16JAN2020)
Database cutoff date for Bladder (KN012:01SEP2015, KN045:26OCT2017, KN052:26SEP2018)
Database cutoff date for PMBCL (KN013:04AUG2017, KN170: 07MAY2020)
Database cutoff date for Cervical (KN028:20FEB2017, KN158: 27JUN2019)
Database cutoff date for HNSCC (KN012:26APR2016, KN040:15MAY2017, KN048:25FEB2019, KN055:22APR2016)
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 NMIBC (KN057 24MAY2019)
Database cutoff date for TMB-H (KN158:27JUN2019)
Database cutoff date for CRC MSI-H or dMMMR (KN177:19FEB2020)
Database cutoff date for cSCC (KN629:08APR2019)
Database cutoff date for MSI-H (KN158:05OCT2020)
Database cutoff date for Colorectal (KN164:09SEP2019)

Source: [ISS: adam-adsl; adae]

Safety related to drug-drug interactions and other interactions

No safety data on interaction have been submitted.

Discontinuation due to adverse events

Adverse Events Leading to Treatment Discontinuation

The proportion of participants who experienced AEs leading to pembrolizumab discontinuation in the MSI-H Safety Dataset was consistent with the RSD (9.9% vs 13.4%, respectively).

The most frequently reported (incidence ≥1%) AE leading to treatment discontinuation in the MSI-H Safety Dataset, pneumonitis, occurred in 5 participants (1.1%), which occurred with a similar frequency in the RSD (1.6%). Alanine aminotransferase increased and aspartate aminotransferase increased occurred in 3 participants (0.6%) each; Guillain-Barre syndrome, hepatitis, sepsis, and transaminases increased occurred in 2 participants each (0.4%); all other AEs leading to discontinuation occurred in 1 participant.

Drug-related Adverse Events Leading to Treatment Discontinuation

The proportion of participants who experienced drug-related AEs leading to discontinuation of pembrolizumab in the MSI-H Safety Dataset was consistent with the RSD (5.7% vs 7.0%, respectively). The most frequently reported (incidence ≥1%) drug-related AE leading to discontinuation of pembrolizumab in the MSI-H Safety Dataset was pneumonitis (5 participants, 1.1%), which occurred with a similar frequency in the RSD (1.6%). Alanine aminotransferase increased and aspartate aminotransferase increased occurred in 3 participants (0.6%) each; Guillain-Barre syndrome, hepatitis, and transaminases increased occurred in 2 participants each (0.4%); all other drug-related AEs leading to discontinuation occurred in 1 participant.

Adverse Events Leading to Treatment Interruption

The proportion of participants who experienced AEs leading to treatment interruption in the MSI-H Safety Dataset was higher than the RSD (35.4% vs 25.4%, respectively). The most frequently reported (incidence ≥2%) AEs leading to interruption of pembrolizumab in the MSI-H Safety Dataset, compared with the RSD, were diarrhea (3.6% vs 1.9%), alanine aminotransferase increased (3.2% vs 1.2%), and aspartate aminotransferase increased (2.7% vs 1.1%).

Drug-related Adverse Events Leading to Treatment Interruption

The proportion of participants who experienced drug-related AEs leading to the interruption of pembrolizumab in the MSI-H Safety Dataset was generally consistent with the RSD (14.5% vs 14.2%, respectively). The most frequently reported (incidence ≥1%) drug-related AEs leading to interruption of pembrolizumab in the MSI-H Safety Dataset, compared with the RSD, were diarrhea (1.7% vs 1.4%) and alanine aminotransferase increased (1.5% vs 0.8%).

Post marketing experience

The safety profile of pembrolizumab was summarized in the Periodic Safety Update Report covering the period 04-SEP-2019 through 03-SEP-2020, specifically Appendix 20.3 (Numbers of Adverse Drug Reactions by Preferred Term from Post-authorization Sources).

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

Safety evaluation of pembrolizumab monotherapy for second or later line of treatment of adult patients with unresectable or metastatic MSI-H cancer or dMMR (CRC, endometrial, gastric, small intestine, biliary, or pancreatic cancer) is based on pooled safety data (MSI-H Safety Dataset; N=475) from KEYNOTE-164 study and KEYNOTE-158. Both studies evaluated pembrolizumab 200 mg Q3W when used either in participants with locally advanced unresectable or metastatic dMMR or MSI-H CRC (KN-164) or in participants with advanced solid tumours who had at least 1 prior line of therapy (KN-158). For comparative evaluation with the established pembrolizumab monotherapy safety profile, the Pembrolizumab Monotherapy Reference Safety Dataset (N=5884) including studies on pembrolizumab monotherapy for treatment of melanoma, NCSLC, HNSCC, and bladder cancer was submitted. In addition, safety data from the Cumulative Running Pembrolizumab Monotherapy Safety Dataset (N=9090) is shown in the side-by-side columns of the tables.

The MSI-H Safety dataset showed higher median months on treatment and mean number of administrations (5.49, SD±9.3 and 14.3, SD±12.83, respectively) when compared to the pembrolizumab RDS (4.86, SD±6.79 and 11.6, SD±10.17) or the Cumulative Running Safety DS (4.17, SD±7.15 and 11.3, SD±10.49). In particular, proportion of subjects with extended exposure was higher for KN164+KN158 participants (≥6 and ≥12 months: 47.8% and 33.9%, respectively) in respect to the other two datasets (RSD≥6 and ≥12 months: 44.4% and 21.8%, Cumulative Running Safety Dataset ≥6 and ≥12 months: 41.3% and 21.8%, respectively).

When compared to RSD and the Cumulative Running Safety Dataset, the higher proportion of females (55.2% vs 33.9% and 34.4%) and subjects aged <65 years (64.2% vs 57.5% and 57.2%) are likely to be attributable to the contribution of endometrial cancer to the MSI-H Safety Dataset. In the MSI-H Safety Dataset, participants were generally more symptomatic than in the other Safety Datasets (ECOG=1: 56.2% vs 49.8% in the RSD and 50.9% in the Cumulative Running Dataset). Across datasets, a similar proportion of subjects were White (~75%) and overall more than half were enrolled outside the EU (56.8%-64.5%).

Safety profile

In the MSI-H Safety Dataset, the summary of AEs showed an overall pembrolizumab monotherapy safety profile that was comparable to that of the RSD, with however slightly lower proportions in MSI-H subjects for almost all safety items: drug-related AEs 65.3% vs 70.2%, grade 3-5 drug-related AEs 12.6% vs

15.5%, SAEs 35.6% vs 38.5%, drug-related SAEs 7.2% vs 11.1%, deaths 4.6% vs 5.3%, discontinuation due to a drug-related AE 9.9% vs 13.4%, respectively. Only proportion of participants with dose modifications due to an AE was higher in the MSI-H Dataset compared to the RSD (41.1% vs 34.7%, respectively).

Exposure-adjusted incidence rates confirmed the better safety profile of pembrolizumab monotherapy in MSI-H participants in respect to the RSD showing lower event rates per 100 person-years of exposure for all safety items: AEs 1148 vs 1543, drug-related AEs 290 vs 483, Grade 3-5 AEs 131 vs 154, drug-related Grade 3-5 AEs 20.71 vs 34.43, SAEs 71.40 vs 102.60, drug-related SAEs 9.04 vs 22.96, AEs leading to death 5.24 vs 7.99, drug-related AEs leading to death 0.71 vs 0.98, discontinuation due to AE 11.66 vs 21.63, drug-related AEs resulting in drug discontinuation 6.90 vs 11.23, SAE resulting in drug discontinuation 7.38 vs 15.26, drug-related SAE resulting in drug discontinuation 3.09 vs 6.49.

Similar to findings in the RSD, the most common AEs (occurring in >20% of subjects) in the MSI-H subjects were: diarrhoea (25.7%), fatigue (24.4%), nausea (22.3%). Higher frequencies in the MSI-H Safety Dataset compared to the RSD are found for vomiting (18.9% vs 12.4%), abdominal pain (16.6% vs 8.2%), back pain (13.3% vs 11.3%), ALT increased (11.2% vs 6.7%) and UTI (10.1% vs 6.5%). Contribution of the type of cancers included in the group of interest to this finding cannot be excluded. The most frequent drug-related AEs (incidence >5% of subjects) in the MSI-H Safety Dataset were pruritus (13.5%), fatigue (12.6%), diarrhoea (11.8%), arthralgia (10.7%), hypothyroidism (9.5%), asthenia (8.8%), nausea (7.8%), rash (6.9%). Except for arthralgia (10.7% in MSI-H and 7.9% in RSD), all PTs showed proportions that were similar or lower than those found in the RSD.

In MSI-H participants, Grade 3-5 AEs were reported in 49.9% of subjects receiving pembrolizumab monotherapy, which is comparable to what was expected based on the RSD (48.1%). Most often found Grade 3-5 AEs generally scored slightly higher than in the RSD and were anaemia (5.7% vs 4.0%, respectively), ALT increased (2.9% vs 1.0%), AST increased (2.9% vs 1.1%), abdominal pain (2.5% vs 0.7%), blood alkaline phosphatase increased (2.3% vs 0.8%), dyspnoea (2.3% and 2.2%), sepsis (2.1% vs 0.8%). Drug-related Grade 3-5 AEs were less frequently found in MSI-H subjects in respect to RSD (12.6 vs 15.5%). The only PT with incidence >1% was ALT increased (1.1%).

SAEs were reported in a similar proportion of subjects in the MSI-H Safety Dataset (35.6%) and of the RSD (38.5%). The most recorded SAE (>2% incidence) was sepsis, occurring in 2.1% of subjects. Drug-related SAEs in pembrolizumab-treated subjects with MSI-H were found in 7.2%, when compared to 11.1% of those participating to the RSD. Pneumonitis, occurring in 5 subjects, was the only PT with frequency >1%.

Death due to AEs was recorded in 4.6% of subjects participating to the MSI-H Safety Database and in 5.3% of those in the RSD. Causes of death in the 22 cases were: cardiac failure, pneumonia, and sepsis (2 participants for each AE); acute myeloid leukemia, aspiration, cardiopulmonary failure, euthanasia, gastric hemorrhage, general physical health deterioration, Guillain-Barre syndrome, malabsorption, myocarditis, respiratory tract infection, and septic shock (1 participant for each AE); and unknown cause (5 participants). Of those, myocarditis, pneumonia, and Guillain-Barre syndrome were considered drug-related deaths by investigator. Those are known ADR for Keytruda.

Laboratory safety AEs observed with higher frequency in the MSI-H group when compared to the RSD were the following: activated partial thromboplastin time increased (25.4% vs 13.4%), alkaline phosphatase increased (37.5% vs 27.2%), calcium decreased (35.2% vs 22.8%), calcium increased (28.7% vs 11.5%), glucose decreased (41.2% vs 10.0%), hemoglobin increased (31.2% vs 0.0%), potassium decreased (29.2% vs 12.7%) and sodium increased (24.5% vs 5.4%). One participant of the MSI-H Safety Dataset with extensive liver disease met the criteria for potential DILI, however clinical site did not classify the event as such.

In the MSI-H Safety Dataset, proportions of overall AEOSIs (22.7% vs 25.1%) and specific safety AEOSIs were lower than in the RSD (drug-related AEOSIs 19.4% vs 21.8%, drug-related Grade 3-5 AEOSIs 4.0% vs 5.6%, drug-related serious AEOSIs 3.6% vs 5.7%, discontinuation due to drug-related AEOSIs 1.5% vs 2.7%. As expected, specific AEOSI PTs had similar frequency across safety datasets.

Safety profile by intrinsic and extrinsic factors

Regarding age categories, like what is known for the RSD also in the MSI-H Safety Database a slightly worse safety profile of pembrolizumab monotherapy is found in the elderly (≥65 years of age) as compared to the younger participants. Notably, also in the older age categories a slightly more favourable safety pattern is found for MSI-H subjects if compared to those contributing to the RSD. Not surprisingly, higher proportions of SAEs and drug-related SAEs were found in symptomatic patients (ECOG=1) compared to asymptomatic patients (ECOG=0). No significant safety differences are noted with regards to gender and enrolment region in the MSI-H Safety Dataset.

No significant differences are noted between frequencies and incidence rates of AEs in the pembrolizumab monotherapy RSD and the Cumulative Reference Safety Dataset.

2.5.2. Conclusions on clinical safety

In conclusion, the safety profile of pembrolizumab monotherapy for treatment of adult patients with unresectable or metastatic MSI-H cancer or dMMR solid tumours was comparable to the well-known Keytruda safety profile. No new safety concerns were identified. Notably, when considering exposure-adjusted safety analysis incidence rates of overall and specific AEs were lower than expected based on the Running Safety Database for pembrolizumab monotherapy.

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 35 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 35 with the following content:

Safety concerns

Table SVIII.1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Immune-related adverse reactions (including immune related pneumonitis, colitis, hepatitis, nephritis, and endocrinopathies)

Table SVIII.1: Summary of Safety Concerns

Summary of safety concerns	
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

Pharmacovigilance plan

There are no ongoing or planned additional pharmacovigilance studies that are required for pembrolizumab.

Risk minimisation measures

Table V.3.1: 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
Important Potential Risks		

Table V.3.1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
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

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 in sections 1 and 4.

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 a bridged 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

Final approved indication: KEYTRUDA as monotherapy is indicated for the treatment of the following MSI-H or dMMR tumours in adults with:

-unresectable or metastatic colorectal cancer after previous fluoropyrimidine-based combination therapy;

-advanced or recurrent endometrial carcinoma, who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation;

-unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy.

3.1.1. Available therapies and unmet medical need

The prevalence of MSI-H across different tumours varied widely by tumour type and by disease stage. Endometrial, colorectal and gastric cancer have the highest MSI-H prevalence (>10%), being <5% for most other tumours. The prognostic effect of MSI-H/dMMR status also varies by tumour type and by stage, indicating generally a better prognosis in the early/resectable stages while no impact or worse prognosis is shown in the advanced/metastatic setting, although in the advanced stages, data are too limited, especially in some tumour types, to make definitive conclusion. To date, drugs specifically approved in EU for MSI-H/dMMR disease are the anti-PD1 agent dostarlimab in recurrent or advanced MSI-H/dMMR endometrial cancer after prior platinum-based treatment, pembrolizumab as first-line treatment of metastatic MSI-H/dMMR colorectal cancer, and the combination nivolumab with ipilimumab in metastatic MSI-H/dMMR colorectal cancer after prior fluoropyrimidine-based combination chemotherapy. Where no specific treatments are available, patients with MSI-H cancer are managed with the standard of care treatments used regardless of the molecular alteration.

3.1.2. Main clinical studies

This application is based on 2 single arm studies:

- **KEYNOTE-164**: including 124 participants with previously-treated locally advanced unresectable or metastatic MSI-H/dMMR colorectal cancer (CRC) treated in 2L (cohort B, n=63) or 3L+ (cohort A, n=61);
- **KEYNOTE-158 (cohort K)**: including a total of 351 patients with 26 MSI-H/dMMR non-CRC tumour types that was incurable and for which prior standard first-line treatment had failed. The updated dataset includes endometrial (n=83), gastric (n=51), small intestine (n= 27), biliary (n=22), and pancreas (n=22).

3.2. Favourable effects

- **CRC**: in 124 patients, ORR was 33.9% (95% CI: 25.6, 42.9), with 11 CR (8.9%). Median DOR was not reached (range: 3.9+ to 41.2+ months), based on median 3 years of follow-up. An encouraging ORR for pembrolizumab is seen as compared to historical data in an unselected population with longer duration of response. The data in pre-treated patients is considered supported by a randomized controlled study in 1L (KN-177) based on which an indication has been already granted for pembrolizumab in EU.
- **EC**: in 83 patients, ORR of 50.6% (95%CI 39.4, 61.8), including 15.7% of complete responses. Median DOR was not reached (range, 2.9 to 60.4+ months), after a median follow up of about 22 months. A trend toward better outcome for pembrolizumab in an MSI-H EC population as compared to chemotherapy in a population regardless of MSI-H status is suggested based on indirect comparison. The data in pre-treated patients is considered supported by indirect comparison with the randomized controlled Study 309–KEYNOTE-775 in 2L. Of note, another anti-PD1 agent (dostarlimab) has been already granted EU approval for dMMR/MSI-H endometrial cancer following prior treatment.
- **Gastric, small intestine and biliary cancer**: in 52 patients with MSI-H/dMMR **gastric cancer**, ORR is 37.3% (95%CI 24.1, 51.9) with 13.7% CR, and median DOR is not reached after a median follow up of about 14 months. A consistent trend is noted in additional patients found across Keytruda clinical trial programmes. The results appear to compare favourably with most of the historical chemotherapy options regardless MSI status.
  In 27 patients with MSI-H **small intestine cancer**, ORR was 55.6% (95%CI 35.3, 74.5) with median DOR not reached after a median follow-up of 29 months. Results are considered relevant based on updated cohort and an indirect comparison with historical data and intrapatient comparison, although the number of patients is limited in this very rare disease setting.
  In 22 patients **with biliary cancer**, ORR was 40.9% (95% CI: 20.7, 63.6), with 3 CR (13.6%). Median DOR was 30.6 months (range: 6.2 to 40.5+ months) after a median follow up of approximately 20 months. The ORR seems relevant as compared to historical data and TTP/PFS comparison.

3.3. Uncertainties and limitations about favourable effects

- Results submitted are based on single arm trial data, and/or subgroups from single arm trial which were selected post-hoc, lacking multiplicity control and independent prospectively analysed confirmatory datasets, with limited number of patients included in some tumour types. Tissue of origin remains a not fully understood effect modifier of pembrolizumab in MSI-H tumours. Because of the limited available evidence, further characterization of the efficacy of Keytruda is requested by the CHMP post-approval for biliary, gastric and small intestine cancers (Annex II condition).

3.4. Unfavourable effects

Safety evaluation is based on pooled safety data (MSI-H Safety Dataset; N=475) from the KEYNOTE-164 and KEYNOTE-158 evaluating pembrolizumab 200 mg Q3W.

Higher median months on treatment and mean number of administrations when compared to the pembrolizumab RSD.

The summary of AEs showed an overall pembrolizumab monotherapy safety profile that was comparable to that of the RSD, with however slightly lower proportions in MSI-H subjects for almost all safety items, except for dose modifications due to an AE, confirmed by exposure-adjusted incidence rates.

Similar to the RSD, the most common AEs (>20%) in the MSI-H subjects were: diarrhoea (25.7%), fatigue (24.4%), nausea (22.3%). The most frequent drug-related AEs (>5%) were pruritus (13.5%), fatigue (12.6%), diarrhoea (11.8%), arthralgia (10.7%), hypothyroidism (9.5%), asthenia (8.8%), nausea (7.8%), rash (6.9%).

The only PT with incidence >1% was ALT increased (1.1%) with regard to Drug-related Grade 3-5 AEs.

The most recorded SAE (>2%) was sepsis (2.1%). Pneumonitis, occurring in 5 subjects, was the only PT among Drug-related SAEs with frequency >1%.

Death due to AEs was recorded in 4.6% of subjects. Of the 22 deaths due to AEs, 3 of those were considered drug related myocarditis, pneumonia, and Guillain-Barre syndrome, which are known ADR for Keytruda.

In the MSI-H Safety Dataset, proportions of overall AEOSIs (22.7% vs 25.1%) and specific safety AEOSIs were lower than in the RSD. Specific AEOSI PTs had similar frequency across safety datasets.

Slightly worse safety profile of pembrolizumab monotherapy is found in the elderly (≥65 years of age) as compared to the younger participants, but better than in the RSD.

3.5. Uncertainties and limitations about unfavourable effects

None

3.6. Effects Table

Table 65. Effects Table for Keytruda as monotherapy in the treatment of unresectable or metastatic MSI-H or dMMR colorectal, endometrial, gastric, small intestine, biliary cancer in adults who have received prior therapy (data cut-off: 19-FEB-2021 for KEYNOTE-158 Cohort K and 15-OCT-2021 for KEYNOTE-164).

Effect	Short description	Unit	Treatment	Uncertainties / Strength of evidence	References
Favourable Effects					
ORR	Overall response rate (CR+PR) by IRC per RECIST 1.1	% (95%CI)	Pembrolizumab 200 mg Q3W	Long duration of response/ not outstanding ORR, single arm trials, small number of patients, post-hoc selection of tumour types subgroups	
DOR	Duration of response for pts with CR and PR	Median months (range)			
	CRC (n=124)	ORR DOR	33.9% (25.6,42.9) NR (4.4 - 58.5+)		KN164*
	Endometrial (n=83)	ORR DOR	50.6 (39.4, 61.8) NR (2.9 - 60.4+)		KN158*
	Gastric cancer (n=51)	ORR DOR	37.3 (24.1, 51.9) NR (6.2 – 63.0 +)		
	Small intestine cancer	ORR DOR	55.6 (35.3, 74.5) NR (3.7+ - 57.3+)		

Effect	Short description	Unit	Treatment	Uncertainties / Strength of evidence	References
	(n=27)				
	Biliary cancer (n=22)	ORR DOR	40.9% (20.7,63.6) 30.6 (6.2 – 46.0+)		
Unfavourable Effects					
	Drug-related AEs	65.3%		Toxicity as expected possibly slightly better than reference safety dataset.	KN164 CSR
	G3-5 drug-related AEs	12.6%			
	Drug-related SAE	7.2%			KN158 CSR
	Drug-related death	0.6%			
	Discontinuation due to drug-related AEs	5.7%			
	AEOSI	22.7%			
	G3-5 AEOSI	4%			

* Efficacy data results from Updated data cut-off date: 15-OCT-2021 for KN158 and 19-FEB-2021 for KN164

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The MAH applied for an indication in selected MSI-H/dMMR tumour types after prior treatment, based on the results of the single arm trials KEYNOTE-164 and KEYNOTE-158 Cohort K. MSI-H is not a driver mutation. However, considering scientific literature data, it can be acknowledged that MSI-H status has generally shown to be predictive of increased activity relative to non MSI-H tumours of the same origin, for the treatment with checkpoint inhibitors/Keytruda.

Clinically relevant impact of pembrolizumab targeting agents on time-dependent endpoints in MSI-H has been demonstrated in RCT in colorectal carcinoma and can be inferred based on an indirect comparison with RCT in endometrial carcinoma. Therefore, efficacy is considered established for later-line use of pembrolizumab in MSI-H colon-rectal and endometrial cancer.

In gastric, small intestine and biliary MSI-H cancers, pembrolizumab efficacy is considered relevant based on the overall data provided in each tumour type and intrapatient comparison between response to prior treatment and response to subsequent pembrolizumab. This is further supported by a comparison with historical data; this however provides context rather than unequivocal evidence of efficacy. The target disease in each of these adenocarcinomas is very rare. Moreover, there are no truly satisfactory treatment options after progression on first line therapy.

While the datasets are smaller than generally accepted, the CHMP notes the unmet medical need for these conditions. In this light, the provided evidence indicating that MSI-status status has a positive predictive value in the sought indications, is considered supportive of the conclusion of a positive B/R in the proposed indications, notwithstanding the limited size of the datasets. Because of the limited available evidence, however, further characterization of the efficacy of Keytruda is requested by the CHMP post-approval. The MAH has agreed to submit data from Cohort K and L of study KN158 of additional patients with gastric, small intestine and biliary MSI-H cancer as Annex II condition.

While evidence is borrowed across adenocarcinomas to support approval in the rarer, less studied indications listed above, it remains evident that tissue of origin remains an important effect modifier for MSI-H tumours treated with pembrolizumab. In summary, while MSI-H status allows for the inference of efficacy in niches where small samples indicate high activity and alternative treatment options have limited utility, a fully tissue agnostic approach is not considered warranted.

Toxicity was as expected for pembrolizumab and comparable with the known safety profile of pembrolizumab monotherapy reference safety dataset. No new safety signals were identified.

3.7.2. Balance of benefits and risks

Of the 6 MSI-H/dMMR tumour types for which the MAH is seeking an indication, the CHMP considered the B/R positive in 5 of them (CRC, endometrial, small intestine, biliary, gastric).

No new safety signals were identified.

3.7.3. Additional considerations on the benefit-risk balance

In order to further characterise the efficacy of pembrolizumab in patients with MSI-H/dMMR small intestine, gastric, and biliary cancers, the MAH will re-open Cohort K in KEYNOTE-158 to prospectively collect data post-approval. In addition to Cohort K in KEYNOTE-158, the MAH will submit data from Cohort L enrolling Chinese participants in CRC and non-CRC MSI-H cancers.

*Table 66**: Summary of Current and Projected Enrolment for Participants with Gastric, Small Intestine, and Biliary Tumours in KEYNOTE-158***

Tumour Type	Cohort K Enrolment (as of 15-OCT-2021 data cutoff)	Projected Cohort K Enrolment	Current Cohort L Enrolment (as of 16-MAR-2022)	Total Participants for Post-Authorization Measures
Gastric	51	~15	8	~23
Small Intestine	26	~7-10	-	~7-10
Biliary	22	~7-10	1	~8-11

This proposal has been deemed acceptable by the CHMP, and it has been included as an Annex II condition (PAES).

3.8. Conclusions

The B/R of pembrolizumab in unresectable or metastatic MSI-H/dMMR colorectal cancer after previous fluoropyrimidine-based combination therapy is positive.

The B/R of pembrolizumab in advanced or recurrent MSI-H/dMMR endometrial carcinoma who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation is positive.

The B/R of pembrolizumab in unresectable or metastatic MSI-H/dMMR gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy is positive.

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

Annex II: "Post authorisation efficacy study (PAES): in order to further characterise the efficacy of

Keytruda in patients with MSI-H/dMMR gastric, biliary and small intestine cancers, the MAH should submit the results including ORR data from Cohort K and L of study KEYNOTE-158, a Phase II study investigating pembrolizumab (MK-3475) in previously treated patients with advanced solid tumours."

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by a majority of 29 out of 31 votes, the variation to the terms of the Marketing Authorisation, concerning the following change:

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

Extension of indication for KEYTRUDA as monotherapy for the treatment of the following MSI-H or dMMR tumours in adults with: -unresectable or metastatic colorectal cancer after previous fluoropyrimidine-based combination therapy; -advanced or recurrent endometrial carcinoma, who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation; -unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy.

The proposed indication is based on the results from the KEYNOTE-164 (KN164) and KEYNOTE-158 (KN158) trials. 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. An updated version of the RMP (Version 35) has been submitted.

Amendments to the marketing authorisation

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

This recommendation is subject to the following new condition:

D. Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-authorisation efficacy study (PAES): in order to further characterise the efficacy of Keytruda in patients with MSI-H/dMMR gastric, biliary and small intestine cancers, the MAH should submit the results including ORR data from Cohort K and L	1Q 2025

of study KEYNOTE-158, a Phase II study investigating pembrolizumab (MK-3475) in previously treated patients with advanced solid tumours.	

Similarity with authorised orphan medicinal products

The CHMP is of the opinion that Keytruda is not similar to Pemazyre within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Divergent position(s) to the majority recommendation are appended to this report.

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-0109'

Appendix: Divergent position, dated 24 March 2022

Keytruda EMEA/H/C/003820/0000

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending to extend the indications for Keytruda as follows:

KEYTRUDA as monotherapy is indicated for the treatment of the following MSI-H or dMMR tumours in adults with:

-unresectable or metastatic colorectal cancer after previous fluoropyrimidine-based combination therapy;

-advanced or recurrent endometrial carcinoma, who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation;

-unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy.

The reason for divergent opinion was the following:

The key issue in this extension of indication application for Keytruda is that MSI-H status ought to be considered a driver for oncogenesis and/or predictive of a high response rate across tumour types to support of a histology-independent assessment approach. In our view there is insufficient evidence to support this.

Therefore, in our opinion an indication for MSI-H gastric, small intestine, and biliary cancer cannot be approved, as the data for each indication separately is too limited to conclude on a positive B/R. The required substantial transfer of information between cohorts is not agreed in the absence of adequate support for a histology-independent approach.

Johannes Lodewijk Hillege

Outi Maki-Ikola