EMA/168468/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: pembrolizumab

Procedure No. EMEA/H/C/003820/II/0052

Note

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

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Table of contents

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme Limited submitted to the European Medicines Agency on 1 May 2018 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

Update of sections 4.1, 4.2, 4.4 and 5.1 of the SmPC in order to restrict the indication in the "treatment of adult patients with locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10", based on the review of interim analysis data by the independent data monitoring committee (iDMC) from study KEYNOTE- 361 listed as a PAES in the Annex II; this is a Phase III randomized, active-controlled, parallel-group, open-label trial to determine the efficacy and safety of pembrolizumab with or without chemotherapy versus chemotherapy alone as first line treatment in subjects with advanced or metastatic urothelial carcinoma. The MAH is proposing to distribute a DHPC.

The requested variation proposed amendments to the Summary of Product Characteristics.

Steps taken for assessment:

steps taken for the assessment			
Current step[1]	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	02 May 2018	02 May 2018
☐	CHMP Rapporteur Assessment Report	16 May 2018	17/05/2018
☐	CHMP members comments	22 May 2018	22/05/2018
☐	Updated CHMP Rapporteur Assessment Report	24 May 2018	25/05/2018
☒	Opinion	31 May 2018	31 May 2018

2. Introduction

The Scope of this variation is to revise the existing indication for Keytruda as monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma (UC) in adults who are not eligible for cisplatin-containing chemotherapy.

This variation follows the Keytruda PAM ANX/018 procedure, which was triggered by the MAH's decision on February 2018 to stop the randomization into the pembrolizumab monotherapy arm of subjects whose tumours have a PD-L1 Combined Positive Score (CPS) <10 in the KEYNOTE 361 study, based on external Data Monitoring Committee (eDMC) recommendation.

KEYNOTE-361 (KN-361) is a Phase III randomized, active-controlled, parallel-group, open-label trial to determine the efficacy and safety of pembrolizumab with or without chemotherapy versus chemotherapy alone as first line treatment in subjects with advanced or metastatic urothelial carcinoma; this study is an Annex II condition (PAES) for Keytruda.

The CHMP's conclusions (April 2018) of the PAM ANX/018 procedure were the following:

- revise the wording for Section 4.1 of the SmPC to exclude patients with a PD-L1 expression CPS < 10 from the indication of Keytruda in locally advanced/metastatic urothelial carcinoma adult patients who are not eligible for cisplatin-containing chemotherapy

- amend the current wording of Section 4.4 of the SmPC to provide appropriate information to prescribers on factors to be taken into account when considering pembrolizumab use for patients eligible for a carboplatin-based chemotherapy

- further elaborate on potential factors that could be associated with early risk of death (including hyperprogression?) in 1L cisplatin-ineligible urothelial cancer patients treated with pembrolizumab monotherapy

- comment on the exclusion of patients ineligible to all platinum-containing products (Carboplatin and Cisplatin) in the currently authorised indication.

- propose a communication plan, including a draft DHCP to inform prescribers about the change of product information

3. Clinical Efficacy aspects

3.1. Introduction

Urothelial carcinoma (UC) arises from the urothelial endothelium, which lines the renal pelvis, ureter, urinary bladder, and urethra. More than 90% of urothelial tract tumours pertain to bladder, being the fifth most common cancer in men in Europe. Approximately 70% of patients with bladder cancer are >65 years of age, for a median age at diagnosis of 73 years.

Cisplatin-based combination chemotherapy is the standard first-line treatment for advanced UC, for a median survival of 13-15 months (NCCN Guidelines, ESMO guidelines).

About 50% of patients are unfit for cisplatin-containing chemotherapy due to a poor performance status (PS), impaired renal function and/or comorbidity. First-line treatment options for these patients include carboplatin-based combinations, that are associated with inferior outcomes, (median OS of 8-10 months), or platinum-free treatments or single agent chemotherapy (NCCN Guidelines, ESMO guidelines, De Vos 2010, De Santis 2012, Sonpavde 2014).

In general, long-term survival with combination therapy has been reported only in good-risk patients (i.e. good PS, no visceral or bone disease, normal LDH or ALP levels), while poor risk patients (i.e. poor PS or visceral disease), have shown poor tolerance to multiagent combination and few complete remission. According to the so-called Bajorin risk model, patients are placed into 3 prognostic groups depending on their number of adverse prognostic factors (Bajorin risk groups 0, 1, or 2) which includes poor performances status (Karnofsky performance status < 80% which aligns with ECOG PS ≥2) and visceral disease (Bajorin, JCO 1999). NCCN guidelines underlines that the presence of both visceral (non-nodal) metastatic disease and ECOG PS ≥2 strongly predict poor outcome with chemotherapy, and that patients without these adverse prognostic factors have the greatest benefit from chemotherapy. NCCN guidelines noted also that the impact of these factors in relation to immune-checkpoint inhibitors is not fully defined, but they remain poor prognostic indicators in general (NCCN guidelines, v3.2018).

Haemoglobin level has been considered as a further predictor of overall survival for metastatic urothelial cancer patients treated with cisplatin-based chemotherapy and was included in other published prognostic models (Apolo, JNCI 2013).

There are no clear guidelines to define cisplatin-ineligibility. A proposed definition of unfit patients with metastatic US was elaborated with the goal of establishing uniform eligibility criteria for clinical trials: ECOG PS of 2 or Karnofsky PS of 60%-70%, creatinine clearance (calculated or measured) <60 mL/min, CTCAE v4 grade ≥ 2 audiometric hearing loss, CTCAE v4 grade ≥ 2 peripheral neuropathy, NYHA Class III heart failure (at least one of the above criteria) (Galsky, JCO 2011).

Keytruda clinical development plan in UC is including the following clinical trials:

Table 1: Overview of Ongoing Studies of Pembrolizumab in Urothelial Carcinoma

Study/Status	Design	Study Population	Dosage Regimen	Primary Efficacy Point(s)
KEYNOTE-012/ Ongoing	Multicenter, nonrandomized, multi-cohort trial of MK-3475 in subjects with PD-L1 positive advanced solid tumors	33 subjects enrolled in Cohort C (enrollment complete); all subjects with PD-L1 expressing tumors and recurrent or metastatic urinary tract cancer	Pembrolizumab 10 mg/kg Q2W	Safety; ORR in PD-L1+
KEYNOTE-045/ Ongoing	Randomized, controlled, open label phase 3 study	542 subjects randomized (enrollment complete); all subject with 2L+ urothelial cancer; control is physician's choice chemotherapy (docetaxel, paclitaxel, vinflunine).	Pembrolizumab 200 mg Q3W	PFS and OS in all comers, CPS≥1, CPS≥10
KEYNOTE-052/ Ongoing	Multicenter, open-label, non-randomized, phase 2 study	370 subjects enrolled and treated; all subjects have urothelial cancer and are cisplatin-ineligible	Pembrolizumab 200 mg Q3W	ORR in all comers, CPS≥1, PD-L1 strongly positive
KEYNOTE-057/ Ongoing	Single arm, open label phase 2 study	Up to 260 subjects with high risk NMIBC unresponsive to Bacillus Calmette-Guérin	Pembrolizumab 200 mg Q3W	CR rate and DFS in all comers, CPS≥1
KEYNOTE-361/ Ongoing	Randomized, controlled, open label, phase 3 study	Up to 990 subjects with advanced or metastatic urothelial cancer will be treated; 3 treatment regimens in a first-line setting will be evaluated: (1) pembrolizumab monotherapy; (2) pembrolizumab plus combination chemotherapy; or (3) combination chemotherapy only	**Treatment Arm 1** (Monotherapy): Pembrolizumab 200 mg Q3W **Treatment Arm 2** (Combination): Pembrolizumab + cisplatin/carboplatin +gemcitabine **Treatment Arm 3** (Chemotherapy only): cisplatin/ carboplatin + gemcitabine	PFS and OS in all comers, CPS≥10

KEYNOTE-672/ Ongoing	Randomized, placebo-controlled, multi-site, double-blind	Up to 650 subjects with cisplatin-ineligible advanced/unresectable or metastatic urothelial carcinoma	**Treatment Arm 1** Pembrolizumab 200 mg Q3W + epacadostat 100 mg PO BID continuously **Treatment Arm 2** Pembrolizumab 200 mg IV Q3W + placebo PO BID continuously	PFS and OS in all comers
KEYNOTE-698/ Ongoing	Randomized, placebo-controlled, multi-site, double-blind	Up to 648 subjects with advanced/unresectable or metastatic urothelial carcinoma that has recurred or progressed following one prior line of platinum-containing chemotherapy for advanced/metastatic disease	**Treatment Arm 1** Pembrolizumab 200 mg Q3W + epacadostat 100 mg PO BID continuously **Treatment Arm 2** Pembrolizumab 200 mg IV Q3W + placebo PO BID continuously	PFS and OS in all comers

CPS = combined positive score; CR = complete response; DFS = disease-free survival; NMIBC = non-muscle invasive bladder cancer; ORR = objective response rate; PD-L1 = programmed cell death ligand 1; PFS = progression-free survival; Q2W = every 2 weeks; Q3W = every 3 weeks.

In May 2018, the two clinical studies KEYNOTE-672/ECHO-307 and KEYNOTE-698/ECHO-303 of pembrolizumab in combination with epacadostat (IDO1 inhibitor) vs pembrolizumab alone in cisplatin-ineligible and in platinum-progressed UC patients, respectively, permanently halted screening and enrollment of new patients. The same action was taken for the pembrolizumab/epacadostat combination in other indications (HNSCC, RCC). This was presented by the MAH as a strategic decision based on the negative results of the combination pembrolizumab/epacadostat in melanoma from study KEYNOTE-252/ECHO 301, while it was not related to the finding of KN-361 study in UC.

References:

NCCN Guidelines, Bladder Cancer, Version 3-2018. Bellmunt J et al. Bladder Cancer: ESMO Clinical Practice Guidelines. Ann Oncol. 2014;25(suppl 3):iii40-iii48. De Vos FYFL et al. Choosing chemotherapy in patients with advanced urothelial cell cancer who are unfit to receive cisplatin-based chemotherapy. Ther Adv Med Oncol. 2010 Nov; 2(6): 381–388. Sonpavde G et al. Cisplatin-Ineligible and Chemotherapy-Ineligible Patients Should Be the Focus of New Drug Development in Patients With Advanced Bladder Cancer. Clin Genitourin Cancer. 2014;12(2):71-3. Bajorin DF et al. Long-Term Survival in Metastatic Transitional-Cell Carcinoma and Prognostic Factors Predicting Outcome of Therapy. J Clin Oncol. 1999;17:3173-81. Galsky MD et al. Treatment of patients with metastatic urothelial cancer "unfit" for Cisplatin-based chemotherapy. J Clin Oncol. 2011 Jun 10;29(17):2432-8. Apolo AB et al. Prognostic Model for Predicting Survival of Patients With Metastatic Urothelial Cancer Treated With Cisplatin-Based Chemotherapy. J Natl Cancer Inst. 2013 Apr 3;105(7):499–503. De Santis M et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol. 2012 Jan 10;30(2):191-9.

3.2. KEYNOTE-052

KEYNOTE-052 (KN-052) is a Phase II single arm trial of pembrolizumab in first-line cisplatin-ineligible advanced/unresectable or metastatic urothelial carcinoma. This study has been the basis for the approval of pembrolizumab in UC patients previously untreated and not eligible to cisplatin-containing chemotherapy (Keytruda Variation II/23-G, EC decision on 24/08/2017).

Within this submission, the MAH presented updated efficacy and safety results from KN052 study based on a data cutoff date of 30-NOV-2017 (data available in the previous variation II/23-G had a cutoff date of 09-MAR-2017).

Methods – analysis of data submitted

Patients enrolled in KN-052 study had a diagnosis of advanced/unresectable (inoperable) or metastatic urothelial cancer of the renal pelvis, ureter, bladder, or urethra, with measurable disease. Patients were enrolled regardless their PD-L1 tumor status. No prior systemic chemotherapy for advanced/ metastatic urothelial cancer was allowed (with the exception of adjuvant or neoadjuvant platinum-based treatment with recurrence >12 months since completion of therapy. Patients had ECOG PS 0, 1 or 2. Cisplatin-ineligibility definition was based on at least one of the following criteria:

- ECOG Performance Status of 2 (the proportion of these subjects will be limited to approximately 50% of the total population)

- Creatinine clearance (calculated or measured) <60 mL/min but ≥30 mL/min

- CTCAE v.4, Grade ≥2 audiometric hearing loss (25dB in two consecutive wave ranges)

- CTCAE v.4, Grade ≥2 peripheral neuropathy

- New York Heart Association (NYHA) Class III heart failure

A total of 370 patients were enrolled. All patients received a fixed dosing regimen of pembrolizumab 200 mg Q3W.

The primary efficacy endpoint was ORR based on RECIST 1.1 criteria assessed by independent radiology review that was estimated for all subjects, for subjects with PD-L1 expression (CPS) ≥ 1%, and for subjects with strongly positive CPS expression (CPS) ≥ 10. DOR and PFS per RECIST 1.1 by independent radiology review, and OS were secondary endpoints.

Results - efficacy

At the 30-NOV-2017 data cut-off herein provided, the median duration of follow-up was 11.5 months. The last subject was enrolled 17.3 months (21-JUN-2016) prior to the data cut-off.

Table 2: Subject Characteristics - All Subjects (APT Population)

	Pembrolizumab	
	n	(%)
Subjects in population	370	
Gender		
Male	286	(77.3)
Female	84	(22.7)
Age (Years)		
< 65 Years	68	(18.4)
>= 65 Years	302	(81.6)
Mean	73.0	
SD	9.9	
Median	74.0	
Range	34 to 94	
Race		
American Indian Or Alaska Native	2	(0.5)
Asian	26	(7.0)
Black Or African American	8	(2.2)
Multiple	2	(0.5)
White	328	(88.6)
Missing	4	(1.1)

Age Group 2		
< 65 Years	68	(18.4)
>= 65 to < 75 Years	123	(33.2)
>= 75 to < 85 Years	139	(37.6)
>= 85 Years	40	(10.8)
PD-L1 Status		
PD-L1 CPS < 1	79	(21.4)
PD-L1 CPS >= 1 to < 10	172	(46.5)
PD-L1 CPS >= 10	110	(29.7)
Unknown	9	(2.4)
ECOG†		
[0] Normal Activity	80	(21.6)
[1] Symptoms, but ambulatory	134	(36.2)
[2] Ambulatory but unable to work	155	(41.9)
[3] Limited selfcare	1	(0.3)
Metastatic Staging		
M0	46	(12.4)
M1	324	(87.6)
Chemotherapy Naïve (Y/N)		
No	68	(18.4)
Yes	302	(81.6)
Baseline Hemoglobin		
>=10 g/dL	329	(88.9)
<10 g/dL	41	(11.1)
Liver Metastasis (Y/N)		
No	293	(79.2)
Yes	77	(20.8)
Prior Adjuvant or Neoadjuvant Platinum-based Chemotherapy		
No	333	(90.0)
Yes	37	(10.0)
Prior BCG Therapy		
No	314	(84.9)
Yes	56	(15.1)
Metastases Location		
Lymph Node Only	51	(13.8)
Visceral Disease	315	(85.1)
Not Reported	4	(1.1)
Primary Tumor Location		
Upper Tract	69	(18.6)
Lower Tract	300	(81.1)
Unknown	1	(0.3)
Reason for Cisplatin Ineligibility		
ECOG 2	120	(32.4)
Renal Dysfunction	183	(49.5)
ECOG 2 and Renal Dysfunction	34	(9.2)
Other Reasons‡	33	(8.9)
Bajorin Risk Factor		
0	30	(8.1%)
1	209	(56.5%)
2	131	(35.4%)

† ECOG performance status assessed during screening.

‡ Including Class III Heart Failure, Grade ≥ 2 Peripheral Neuropathy, and Grade ≥ 2 Hearing Loss. Missing: not reported or unknown
Renal dysfunction is defined as a baseline creatinine clearance < 60 mL/min.
Database Cutoff Date: 30NOV2017

Table 3: 1L-urothelial-update: Baseline characteristics of KEYNOTE-052 and KEYNOTE-361

Characteristic	KEYNOTE-052 n (%)	KEYNOTE-361 n (%)		
Total Patients	370	Cis-ineligible 399 (55.6%)	Cis-eligible 318 (44.4%)	All 717
Age				
Median age (range)	74 (34-94)	71(29-89)	66(36-85)	69 (29-89)
≥ 75 to < 85 Year	139 (37.6 %)	122 (30.5%)	48 (15.1%)	170 (23.7%)
≥ 85 years	40 (10.8%)	12 (3.0%)	1(0.3%)	13 (1.8%)
ECOG PS 2	155 (41.9%)	45(11.3%)	10(3.1%)	55 (7.7%)
Renal dysfunction	183 (49.5)	199 (49.9)	4 (1.3%)	203 (28.3%)
ECOG PS 2 plus renal dysfunction	34 (9.2)	14 (3.5%)	0	14 (2.0%)
Visceral Metastatic Disease	315 (85.1%)	253(63.4%)	203(63.8%)	456 (63.6%)
Liver Metastases	77 (20.8%)	64(16.0%)	48(15.1%)	112 (15.6%)
Bajorin Risk Factor				
0	30 (8.1%)	90(22.6%)	70(22%)	160(22.3%)
1	209(56.5%)	230(57.6%)	196(61.6%)	426(59.4%)
2	131(35.4%)	31(7.8%)	8(2.5%)	39(5.4%)
missing		48(12%)	44(13.8%)	92(12.8%)

In the table above, a comparison between baseline characteristics of KEYNOTE-052 and KEYNOTE-361 has been presented. The population enrolled in KN-361 is substantially different from that of study KN-052. In particular, only patients fit to receive a platinum-based chemotherapy (cisplatin or carboplatin) are included in KN-361, due to the presence of a chemotherapy-doublet arm. While patients covering the full spectrum of cisplatin-ineligibility, including also patients unfit to receive any platinum-based combination chemotherapy, not enrolled in KN-361, were enrolled in KN-052. Patients in the KEYNOTE-052 study appeared to be older, more frequently with ECOG-PS 2, with visceral metastases and with 2 Bajorin risk Factors compared to cisplatin-ineligible population of KN-361.

Table 4: Subject Disposition All Subjects (APaT Population)

	Pembrolizumab n (%)
Subjects in population	370
Status for Trial	
Discontinued	252 (68.1)
Adverse Event	25 (6.8)
Death	213 (57.6)
Physician Decision	3 (0.8)
Withdrawal By Subject	11 (3.0)
Ongoing in Trial	118 (31.9)
Status for Study Medication	
Started	370
Completed	14 (3.8)
Discontinued	317 (85.7)
Adverse Event	64 (17.3)
Non-Compliance With Study Drug	1 (0.3)
Other	11 (3.0)
Physician Decision	50 (13.5)
Progressive Disease	174 (47.0)
Withdrawal By Subject	17 (4.6)
Treatment Ongoing	39 (10.5)

Each subject is counted once for Trial Status based on the latest Survival Follow-up record.
Each subject is counted once for Study Medication Status based on the latest corresponding disposition record. Unknown: A disposition record did not exist at the time of reporting.
Database Cutoff Date: 30NOV2017

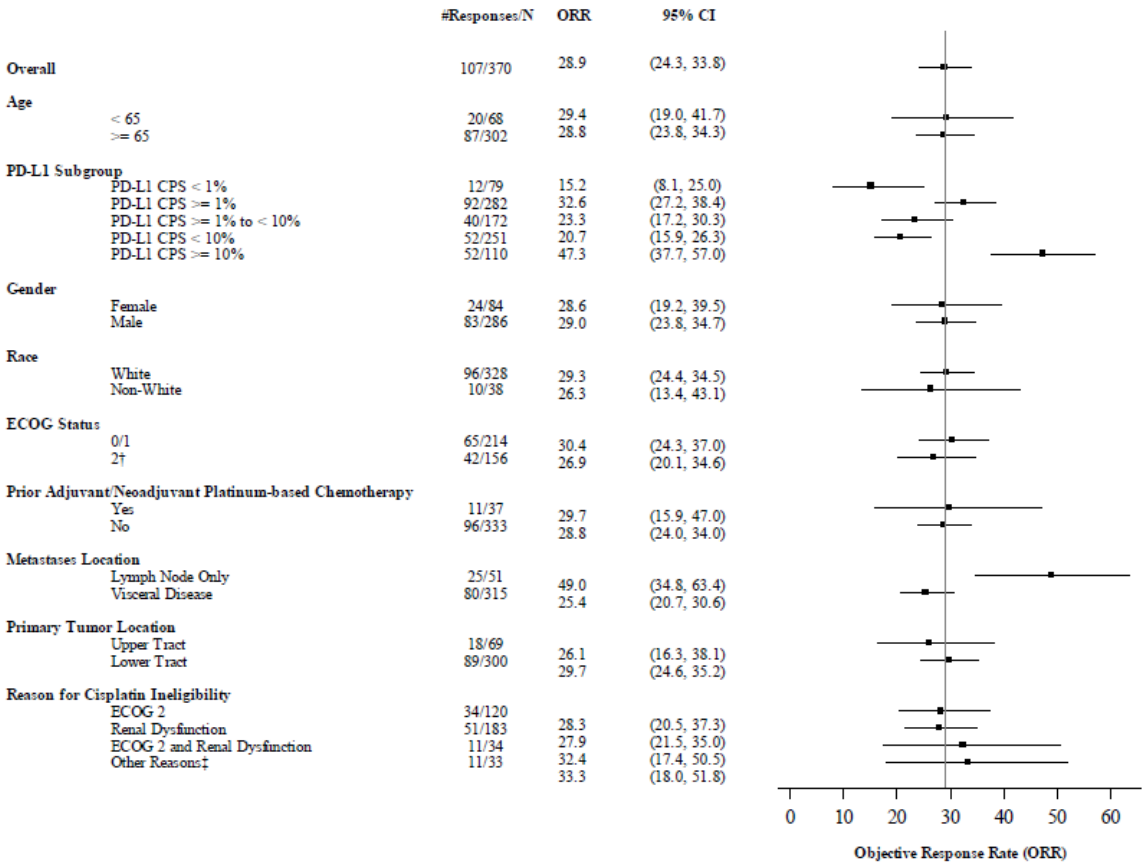
Overall Response Rate

Table 5: Summary of Best Overall Response with Confirmation Based on RECIST 1.1 per Central Radiology Assessment All Subjects (APT Population)

Response Evaluation	Pembrolizumab (N=370)		
	n	%	95% CI†
Complete Response (CR) Partial Response (PR)	30 77	8.1 20.8	(5.5, 11.4) (16.8, 25.3)
Objective Response (CR+PR)	**107**	**28.9**	**(24.3, 33.8)**
Stable Disease (SD)	67	18.1	(14.3, 22.4)
Disease Control (CR+PR+SD)	**174**	**47.0**	**(41.8, 52.3)**
Progressive Disease (PD) Non-evaluable (NE)	156 9	42.2 2.4	(37.1, 47.4) (1.1, 4.6)
No Assessment	31	8.4	(5.8, 11.7)

Confirmed responses are included.
† Based on binomial exact confidence interval method.
Non-evaluable: subject had post-baseline imaging and the BOR was determined to be NE per RECIST 1.1.
No Assessment: subject had no post-baseline imaging
Database Cutoff Date: 30NOV2017

Figure 1: Objective Response Rate with Confirmation Based on RECIST 1.1 per Central Radiology Assessment by Subgroup Factors All Subjects (APT Population)



† Including 1 subject with ECOG = 3
‡ Including Class III Heart Failure, Grade >= 2 Peripheral Neuropathy, and Grade >= 2 Hearing Loss. Renal dysfunction is defined as a baseline creatinine clearance < 60 mL/min. Database Cutoff Date: 30NOV2017

Time to Response and Duration of Response

Table 6: Summary of Time to Response and Response Duration Based on RECIST 1.1 per Central Radiology Assessment in Subjects with Confirmed Response - All Subjects (APT Population)

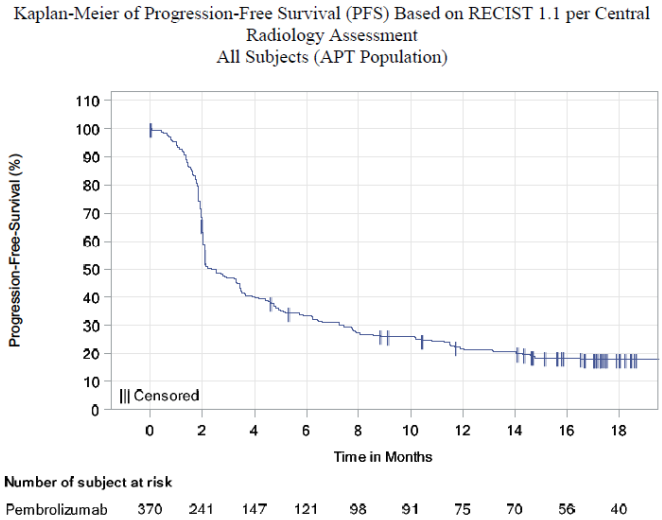
	Pembrolizumab (N=370)
Number of Subjects with Response†	107
Time to Response† (months)	
Mean (SD)	2.4 (1.0)
Median (Range)	2.1 (1.3-9.0)
Response Duration‡ (months)	
Median (Range)	Not reached (1.4+ - 27.9+)
Number of Subjects with Response ≥ 6 Months (%)‡	85 (82)

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

‡ Median and percentage are calculated 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: 30NOV2017

Progression Free Survival

The median PFS among pembrolizumab-treated subjects was 2.3 months (95% CI: 2.1%, 3.4%) with 301 (81.4%) PFS events. PFS rate at 6 months was 33.6% and at 12 months 21.8%.



(Database cutoff date: 30NOV2017)
Source: [P052V01MK3475: analysis-adsl; adtte]

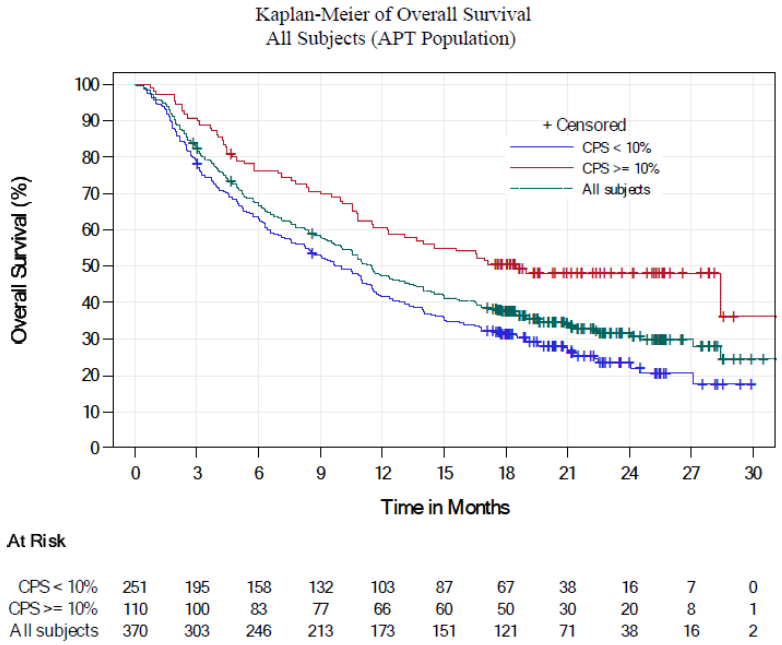
Overall Survival

Table 7: OS results Table made by Assessor based on tables 2.5-1L urothelial update 7,8 and 9

	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS † (Months) (95% CI)	OS Rate at Months 6 in % † (95% CI)	OS Rate at Months 12 in % † (95% CI)
All subjects							
	370	247 (66.8)	4567.1	5.4	11.5 (10.0, 13.3)	67.2 (62.1, 71.7)	47.5 (42.3, 52.5)
CPS ≥ 10							
	110	57 (51.8)	1642.6	3.5	18.5 (12.2, .)	76.3 (67.2, 83.2)	60.7 (50.9, 69.1)
CPS < 10							

	251	186 (74.1)	2799.0	6.6	10.0 (7.8, 11.6)	63.3 (57.0, 68.9)	41.6 (35.4, 47.6)

† From product-limit (Kaplan-Meier) method for censored data. Database Cutoff Date: 30NOV2017



Risk factors analysis of OS in patients with PD-L1 CPS<10

The influence of baseline prognostic factors on the risk of early death (within 3 months after first dose of pembrolizumab) in subjects with PD-L1 CPS <10 was evaluated by univariate and multivariate predictor analysis using Cox regression models. Prognostic factors were tested in separate univariate Cox models and then entered into a multivariate model selection process. Prognostic risk factors tested in the models were age (<75 years vs ≥75 years), ECOG PS (0 or 1 vs 2), liver metastasis (yes vs no), haemoglobin level (<10 g/dL vs ≥10 g/dL), and Bajorin risk group (0/1 vs 2).

In KEYNOTE-052, the Bajorin risk groups were determined on the basis of ECOG PS and visceral metastases; ECOG PS 0 and 1 were transformed into Karnofsky performance status 80% and ECOG PS 2 into Karnofsky performance status less than 80%. When adding presence or absence of visceral metastases, patients were regrouped into 3 prognostic groups depending on their number of adverse prognostic factors (Bajorin risk groups 0, 1, or 2).

Two factors that had significant influence on the risk of early death were identified in the multivariate model, Bajorin risk group 2 HR 2.40 (1.41, 4.08) p = 0.001) and baseline haemoglobin <10 g/dL (HR 3.75 (2.07, 6.82), p <0.001) in KEYNOTE-052 subjects with PD-L1 CPS < 10 (see table below):

Table 8: Prognostic Factors for Early Death Within 3 Months of Treatment Initiation in KN052 Subjects with PD-L1 CPS <10

Variable	N	Number of Events (%)	OS Rate at 3 Months† (%)	Unadjusted HR (95% CI)‡	Unadjusted p-value‡	Adjusted HR (95% CI)#	Adjusted p-value#
Age							
<75	121	26	78.5%				
≥75	130	29	77.7%	1.07 (0.63, 1.81)	0.805	NA	NA
ECOG Status							
0/1	153	25	83.7%				
2/3	98	30	69.4%	2.14 (1.26, 3.64)	0.005	NA	NA
Liver Metastasis							
No	186	33	82.3%				
Yes	65	22	66.2%	2.18 (1.27, 3.74)	0.005	NA	NA
Baseline Haemoglobin							
<10 g/dL	31	15	51.6%	3.61 (1.99, 6.53)	<0.001	3.75 (2.07, 6.82)	<0.001
≥10 g/dL	220	40	81.8%				
Bajorin Risk							
0/1	161	26	83.9%				
2	90	29	67.8%	2.32 (1.36, 3.94)	0.002	2.40 (1.41, 4.08)	0.001
Total	251	55	78.1%				

† From product-limit (Kaplan-Meier) method

‡ From univariate Cox model with term as covariate

From multivariate Cox model with variable selection threshold of 0.05. NA: variable not selected.

Subjects in the PD-L1 CPS <10 subgroup who had at least 1 risk factor (Bajorin risk score 2 or haemoglobin <10 g/dL) experienced worse OS outcome compared to subjects with no risk factors: indeed, median OS values were 6.3 (4.3, 9.7) months for PD-L1 CPS <10 subgroup who had at least 1 risk factor and 11.7 (9.5, 14.6) months for subjects with PD-L1 CPS <10.

For subjects with PD-L1 CPS <10 and at least one poor prognostic feature (Bajorin risk group 2 or haemoglobin <10 g/dL), ORR was 15.9% (95% CI: 9.5%, 24.2%) and 24.3% (95% CI: 17.6, 32.1) for subjects with PD-L1 CPS <10 with no poor prognostic risk factors.

Results – Safety

The MAH presented an overview of the safety data of the KN-052 study at the updated cut-off date of 30-NOV-2017. Safety results were compared with the standard reference safety dataset for pembrolizumab (n=2799 patients, in melanoma KN001, KN002 and KN006 trials and in NSCLC KN001 and KN010 trials).

No new safety signal was identified when safety data from KN-052 data cutoff 30-NOV-2017 were compared to the safety data from cutoff 09-MAR-2017.

In general, the updated safety profile of pembrolizumab in the KN-052 population is consistent with the previously established safety profile for pembrolizumab. A slight increase in the frequencies of Adverse Events is seen compared to the previous dataset, likely related with the additional 8 months of follow-up. The nature and frequency of immune-mediated events in KN-052 were consistent with the reference safety dataset and no new immune-mediated event was identified for pembrolizumab.

KN-052 safety analyses support that, in general, the tolerability of pembrolizumab in the 1L urothelial cancer population is acceptable and consistent with the tolerability observed in the pembrolizumab reference safety dataset. The key discrepancies are likely related to the fact the KN-052 population is

older, and has more than 40% of subjects with ECOG 2 in comparison to the reference safety dataset, or related to the underlying medical condition urothelial cancer.

Exposure: Median exposure was 3.40 months and median number of administrations was 5. A total of 192 (51.9%) subjects received pembrolizumab for ≥3 months, 132 (35.7%) subjects for ≥6 months, and 78 (21.1%) for ≥12 months. Exposure to pembrolizumab was similar compared to the reference safety dataset.

Adverse events: The overall frequency of AEs was similar between the KEYNOTE-052 population and the reference safety dataset. Subjects in KN-052 population, in comparison to the subjects in the reference safety dataset, experienced more Grade 3-5 AEs (62.7% vs 45.5%), drug-related Grade 3-5 AEs (20.3% vs 13.8%), SAEs (50.5% vs 37.2%), AEs leading to discontinuation (17.0% vs 11.9%), and AEs leading to a fatal outcome (6.5% vs 3.9%), but similar or less drug-related AEs (67.6% vs 73.7%), drug-related SAEs (11.1% vs 10.0%), drug-related AEs leading to a fatal outcome (0.3% vs 0.4%).

Table 9: Adverse Event Summary All Subjects (APaT Population)

	Pembrolizumab	
	n	(%)
Subjects in population	370	
with one or more adverse events	361	(97.6)
with no adverse event	9	(2.4)
with drug-related[†] adverse events	250	(67.6)
with toxicity grade 3-5 adverse events	232	(62.7)
with toxicity grade 3-5 drug-related adverse events	75	(20.3)
with serious adverse events	187	(50.5)
with serious drug-related adverse events	41	(11.1)
who died	24	(6.5)
who died due to a drug-related adverse event	1	(0.3)
discontinued[‡] due to an adverse event	63	(17.0)
discontinued due to a drug-related adverse event	36	(9.7)
discontinued due to a serious adverse event	43	(11.6)
discontinued due to a serious drug-related adverse event	18	(4.9)

[†] Determined by the investigator to be related to the drug.
[‡] Study medication withdrawn.
MedDRA V20.1 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.
Grades are based on NCI CTCAE version 4.0. Database Cutoff Date: 30NOV2017

The frequencies of each of the commonly reported **AEs** in KN-052 were, in general, consistent with the frequencies for the same AEs in the reference safety dataset with 3 major exceptions: urinary tract infection (24.3% in KN-052 vs 5.8% in the reference safety dataset), haematuria (16.5% vs 1.4%), blood creatinine increased (14.6% vs 3.9%). Medical review of the available data for those 3 events indicated they were more likely related to the underlying medical condition (urothelial cancer), with its clinical complications or procedures performed due to the underlying medical condition and did not indicate a specific safety issue.

The most commonly reported **Grade 3-5 AEs** in KN-052 were the following (frequencies in KEYNOTE-052 vs reference safety dataset): urinary tract infection (10.8% vs 0.5%), anaemia (7.8% vs 3.2%), and fatigue (5.4% and 2.5%). Urinary tract infection and anaemia events were considered likely related to the underlying medical condition urothelial cancer. The frequencies of drug-related Grade 3-5 AEs reported 1% or higher in KN-052 are consistent with the frequencies of the same events in the reference safety dataset.

Serious adverse events: The frequency of SAEs in KN-052 was 50.5% (vs 37.2% in the reference safety dataset). The most commonly reported SAEs were the following (KN-052 vs reference safety dataset): urinary tract infection (7.0% vs 0.5%), urosepsis (3.5% vs 0.1%), acute kidney injury (3.5% vs 0.8%), and hematuria (3.0% vs 0).

Deaths: Twenty-four (6.5%) subjects experienced a fatal AE in KN-052 (cutoff 30Nov2017), which includes 4 additional fatal events reported since 9-MAR-2017: colonic fistula, death (unknown cause), embolism, and urosepsis. No new drug-related deaths were reported compared to previous cut-off date.

AEs leading to treatment discontinuation: A total of 63 (17.0%) subjects experienced an AE resulting in treatment discontinuation, 9.7% considered drug-related. Pneumonitis (5 events, 1.4%), colitis (3 events, 0.8%), diarrhea (3 events, 0.8%), and tubulo-interstitial nephritis (2 events, 0.5%) were drug-related AEs resulting in treatment discontinuation reported more than once.

Adverse events of special interest: The frequency of subjects in KN-052 who experienced AEOSIs was similar to the frequency observed in the reference safety dataset: 24.6% vs 21.4%. The nature and frequency of AEOSIs in KN-052 were consistent with the nature and frequency of AEOSIs observed in the reference safety dataset.

3.3. KEYNOTE-361

KEYNOTE-361 (KN-361) is an ongoing Phase III randomized, active-controlled, parallel-group, open-label trial to determine the efficacy and safety of pembrolizumab with or without chemotherapy versus chemotherapy alone as first line treatment in subjects with advanced or metastatic urothelial carcinoma.

Following a recommendation from the eDMC in February 2018 taken based on early review of safety data, the MAH decided to stop the randomization into the pembrolizumab monotherapy arm of subjects whose tumors have a PD-L1 Combined Positive Score (CPS) <10. The clinical trial protocol has been amended accordingly.

The study is powered to evaluate the potential benefit of the combination of pembrolizumab + chemotherapy compared to chemotherapy alone for the first line treatment of urothelial carcinoma in all subjects regardless of PD-L1 CPS status, primary endpoints being PFS using RECIST 1.1 assessed by BICR and OS.

As of 8-MAY-2018, the study has enrolled 930 of the targeted 990 subjects.

KEYNOTE-361 data provided to EMA have a data cut-off date of 22-DEC-2017. No additional data analysis has been planned by the MAH other than the Interim Analysis, results of which are expected to be available in September/October 2018.

Methods – analysis of data submitted

To evaluate the baseline characteristics that may predict the risk of early death in the pembrolizumab arm in KN-361, the MAH has been requested by EMA to provide:

1) Descriptive statistics of characteristics at baseline and statistical comparison between the two arms for patients having an OS event.

2) The interaction term and p-values between treatment and each clinical variable by using Cox model and the corresponding HR for each subgroups (including also Bajorin risk factors and haemoglobin), as well as Kaplan Meier curves.

3.4. Discussion – review of interim results of KEYNOTE-361

Keytruda is currently approved in EU for the treatment of locally advanced or metastatic urothelial carcinoma (UC) in adults who are not eligible for cisplatin-containing chemotherapy.

In February 2018, the MAH decided to stop the randomization into the pembrolizumab monotherapy arm of subjects whose tumours have a PD-L1 CPS<10 in the KEYNOTE 361 study, an ongoing phase III trial of pembrolizumab with or without chemotherapy versus chemotherapy alone as first line treatment in subjects with advanced or metastatic UC (Annex II study for Keytruda), following eDMC recommendation.

In order to evaluate the potential impact on the currently authorized Keytruda indication, the CHMP requested and analyzed early data from KEYNOTE-361. The MAH provided also updated results from KEYNOTE-052 study, the single arm study which led to pembrolizumab approval in cisplatin-ineligible patients. Following the assessment of the totality of data (Keytruda PAM-ANX018 procedure), the CHMP concluded that a revision of the current Keytruda indication in cisplatin-ineligible UC patients was warranted, in order to exclude subjects with a PD-L1 expression CPS<10. In addition, an amendment to Section 4.4 of the SmPC and a draft DHPC to inform prescribers about the change of product information were requested, together with further discussion on the exclusion of patients ineligible to all platinum-containing products and on potential factors that could be associated with early risk of death with pembrolizumab.

Wording of the indication

The MAH's proposed revised indication was the following:

"KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥10. Keytruda is also indicated for patients who are ineligible for cisplatin-containing chemotherapy whose tumours express PD-L1 CPS<10 and who are without poor prognostic features (2 Bajorin risk factors and haemoglobin< 10 g/dL), or for patients who are unfit for any chemotherapy (including carboplatin) regardless of PD-L1 status (see section 5.1)."

The proposal to submit a variation to exclude patients with a PD-L1 expression CPS<10 was based on the early findings from KEYNOTE-361 study and the decision not to enrol CPS<10 patients in the pembrolizumab monotherapy arm of the study upon DMC recommendation.

Therefore, the MAH was also requested to clarify if it was possible to identify factors associated to the increased risk of early progression and death.

The MAH should commit to provide KN-361 IA results as well as the requested comprehensive analysis on potential predictive variables when available.

Based on all available data of pembrolizumab in urothelial cancer and on the provided analyses, the MAH's proposal for the restriction of indication is not considered acceptable as not supported by sound evidence.

Following the review of the data provided by the iDMC and the MAH, the CHMP agreed with the changes of section 4.1, 4.2 and 5.1 of the SmPC to restrict the indication as follows:

- **Section 4.1 "Therapeutic indications"**

KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy **and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10 (see section 5.1).**

- **Section 4.2 "Posology and method of administration"**

PD-L1 testing for patients with NSCLC or urothelial carcinoma

Patients with NSCLC or previously untreated urothelial carcinoma should be selected for treatment based on the tumour expression of PD-L1 confirmed by a validated test (see section 5.1).

- **Section 4.4 "Warning and precautions"**

Disease-specific precautions

Use of pembrolizumab in urothelial cancer for patients who are considered ineligible ***for cisplatin-containing chemotherapy and whose tumours express PD-L1 with CPS ≥ 10***

The baseline and prognostic disease characteristics of the study population of KEYNOTE-052 included a proportion of patients eligible for a carboplatin-based combination, for whom the benefit **is being assessed** in a comparative study, **and patients eligible for mono-chemotherapy, for whom no randomized data are available. In addition,** no safety and efficacy data are available in frailer patients (e.g., ECOG performance status 3) considered not eligible for chemotherapy. In the absence of these data, pembrolizumab should be used with caution in this population after careful consideration of the potential risk-benefit on an individual basis.

- **Section 5.1 "Warning and precautions"**

Please refer to the Attachment 1 to see the changes.

In addition, a Direct Healthcare Professional Communication (DHPC) is considered necessary in order to communicate on the restriction of indication after agreement of the translations local specificities of the DHPC with national competent authorities.

The DHPC should be sent by 9 July 2018 to Prescribing Oncologists/Oncology clinics/Oncology departments/Pharmacists as per country-specific distribution channels. The DHPC and the communication plan are provided as attachment II to this report.

3.5. Conclusion

Based on the data provided by the iDMC and the MAH, the CHMP agreed with the SmPC changes to restrict the 1st line indication in urothelial carcinoma in patients not eligible for cisplatin-based chemotherapy based on the preliminary data from on ongoing clinical trial (KEYNOTE-361) which showed reduced survival with Keytruda monotherapy compared to standard chemotherapy when used as first-line treatment for patients with locally advanced or metastatic urothelial carcinoma whose tumour has low expression of PD-L1.

A Direct Healthcare Professional Communication (DHPC) is considered necessary in order to communicate on the revised indication for Keytruda as monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy.

The draft DHPC and the draft communication plan are provided in Attachment 2.

The MAH agreed the translations and local specificities of the DHPC with national competent authorities. The DHPC should be sent by 12th July 2018 to prescribing oncologists, oncology clinics, oncology departments, pharmacists as per country-specific distribution channels.

4. Clinical Safety aspects

The safety of pembrolizumab monotherapy is as expected. The lower OS performance of pembrolizumab compared to chemotherapy observed in KEYNOTE-361 study does not appear to be related to a safety issue.

5. Overall conclusion and impact on the benefit/risk balance

The Scope of this variation is to revise the existing indication for Keytruda as monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma (UC) in adults who are not eligible for cisplatin-containing chemotherapy, following the assessment of early data from the ongoing clinical trial KEYNOTE-361 (phase III randomized open label study of pembrolizumab with/without platinum-based chemotherapy versus chemotherapy alone as first line treatment in advanced or metastatic UC), which was recently amended to stop the randomization into the pembrolizumab monotherapy arm of subjects whose tumours have a PD-L1 Combined Positive Score (CPS) <10, based on external Data Monitoring Committee recommendation.

Thus, a restriction of indication is warranted.

The MAH applied for a variation to update section 4.1, 4.4 and 5.1.

The CHMP agreed with the update of section 4.1, 4.2, 4.4 and 5.1 of the SmPC.

A Direct Healthcare Professional Communication (DHPC) was considered necessary to communicate on the modification of the indication.

The benefit-risk balance of Keytruda, remains positive in the other authorised indications and 2nd line urothelial carcinoma indication. As for the 1st line urothelial indication, the benefit risk remains positive in patients whose tumours have a PDL-1 expression ≥ 10.

The MAH should provide KN-361 IA results as well as the requested comprehensive analysis on potential predictive variables when available.

6. Recommendations

Based on the review of the submitted data, this application regarding 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

Restriction of indication in cisplatin-ineligible urothelial carcinoma patients to exclude patients whose tumours express PD-L1 with a combined positive score (CPS) <10, based on the review of interim analysis data by the independent data monitoring committee (iDMC) from study KEYNOTE- 361 listed as a PAES in the Annex II; this is a Phase III randomised, active-controlled, parallel-group, open-label trial to determine the efficacy and safety of pembrolizumab with or without chemotherapy versus chemotherapy alone as first line treatment in subjects with advanced or metastatic urothelial carcinoma. Sections 4.1, 4.2, 4.4 and 5.1 of the SmPC have been revised accordingly. A DHPC was considered necessary to communicate on the restricted indication.

☒ is recommended for approval by consensus.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex I are recommended.