EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 July 2017
EMA/512404/2017
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Keytruda

International non-proprietary name: pembrolizumab

Procedure No. EMEA/H/C/003820/II/0023/G

## 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

| | |
|---|---|
| AE | Adverse Event |
| AEOSI | Adverse Event of Special Interest |
| ALB | Albumin |
| ADA | Anti-drug antibody |
| APT | All Patients Treated |
| ASaT/APat | All Subject as Treated/ All Patient as Treated |
| AUC | Area under the concentration-time curve |
| AUCss | Area under the concentration-time curve at steady state |
| CI | Confidence interval |
| CV | Coefficient of variation |
| CL | Clearance |
| CMAX | Peak serum concentration |
| Cmin | Trough serum concentration |
| CONC | Concentration |
| CR | Complete Response |
| CWRES | Conditional weighted residuals |
| ECI | Event of Clinical Interest |
| ECOG | Eastern Cooperative Oncology Group |
| eDMC | external Data Monitoring Committee |
| DOR | Duration of Response |
| eGFR | Estimated glomerular filtration rate |
| ePROs | electronically collected Patient-Reported Outcomes |
| FAS | Full Analysis Set |
| FWER | family-wise type I error rate |
| HR | Hazard Ratio |
| HL | Hodgkin lymphoma |
| HNSCC | Head and neck squamous cell carcinoma |
| IA2 | Second Interim Analysis |
| IPRED | Individual predicted concentration |
| irAE | Immune-related Adverse Event |
| ITT | Intention To Treat |
| IIV | Interindividual variability |
| IV | Intravenous |
| IWRES | Individual weighted residual |
| LS | least squares |
| mAb | Monoclonal antibody |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MSI-H | microsatellite instability-high |
| Nab | Neutralizing antibody |
| NONMEM | Nonlinear mixed-effects modeling software |
| NSCLC | Non Small Cell Lung Cancer |
| OFV | Objective function value |
| ORR | Objective Response Rate |
| OS | Overall Survival |
| PFS | Progression Free Survival |

| | |
|---|---|
| PK | Pharmacokinetic |
| Pop PK | Population Pharmacokinetic |
| PRED | Population predicted concentration |
| PS | Performance Status |
| PR | Partial Response |
| PRO | Patien-Reported Outcome |
| Q | Inter-compartmental flow rate |
| Q3W | every 3 weeks |
| QoL | Quality of Life |
| RECIST 1.1 | Response Evaluation Criteria on Solid Tumors Version 1.1 |
| mRECIST | modified Response Evaluation Criteria on Solid Tumors Version |
| RSE | Percent relative standard error = [standard error/population mean estimate] x 100 |
| SAE | Serious Adverse Event |
| SD | Standard Deviation |
| SOC | Standard of Care |
| t1/2 | Terminal elimination half-life |
| ULN | Upper limit of normal |
| WRES | Weighted residuals |
| WT | Body weight |

# 1. Background information on the procedure

## *1.1. Type II group of variations*

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme Limited submitted to the European Medicines Agency on 1 February 2017 an application for a group of variations.

The following variations were requested in the group:

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

Extension of Indication to add treatment of urothelial carcinoma in patients previously treated with chemotherapy based on the results from study KEYNOTE-045; a phase 3, randomized, active-controlled, multi-site, open-label trial evaluating pembrolizumab administered at 200 mg Q3W versus investigators' choice of paclitaxel, docetaxel, or vinflunine in patients previously treated with chemotherapy.

Extension of Indication to add treatment of urothelial carcinoma in patients ineligible for cisplatin (not previously treated) based on the results from study KEYNOTE-52; a phase 2, single-arm, multisite, open-label trial of pembrolizumab at 200 mg Q3W in the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy.

As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated and the Package Leaflet has been updated accordingly.

Further, the MAH is proposing a change to section 4.3 of the SmPC to add that only patients with severe hypersensitivity should be excluded from therapy, and a change to section 4.4 of the SmPC adding possible hypersensitivity and anaphylaxis as part of infusion reactions.

The application included an updated RMP version 7.0.

The group of variations proposed amendments to the Summary of Product Characteristics and Package Leaflet and the Risk Management Plan.

## *Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0059/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0059/2014 was not yet completed as some measures were deferred.

### *Information relating to orphan market exclusivity*

#### Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

### *Scientific advice*

The applicant did not seek Scientific Advice at the CHMP.

## *1.2. Steps taken for the assessment of the product*

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

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

| Timetable | Actual dates |
|---|---|
| Submission date | 1 February 2017 |
| Start of procedure | 18 February 2017 |
| CHMP Rapporteur Assessment Report | 17 April 2017 |
| CHMP Co-Rapporteur Assessment Report | 12 April 2017 |
| PRAC Rapporteur Assessment Report | 19 April 2017 |
| PRAC members comments | n/a |
| PRAC Outcome | 5 May 2017 |
| CHMP members comments | 11 May 2017 |
| Updated CHMP Rapporteur(s) (Joint) Assessment Report | 12 May 2017 |
| Request for supplementary information (RSI) | 18 May 2017 |
| CHMP Rapporteur joint response Assessment Report | 4 July 2017 |
| CHMP members comments | 12 July 2017 |
| Updated CHMP Rapporteur joint response Assessment Report | 14 July 2017 |
| Opinion | 20 July 2017 |

# 2. Scientific discussion

## *2.1. Introduction*

Keytruda (pembrolizumab, MK-3475) is a humanised monoclonal antibody acting as immune checkpoint inhibitor through the block of the interaction between the programmed death-1 (PD-1) receptor and its ligands PD-L1 and PDL2, with a consequent impediment of inhibitory signal in T cells.

Urothelial cancer (UC) is an aggressive malignancy associated with a 5 years survival of about 5% in the metastatic setting. More than 90% of urothelial tract tumours pertain to bladder, 8% originate in the renal pelvis and the remaining 2% arise from ureter and urethra. In the large majority of cases, the histological subtype is transitional cell carcinoma. The other types, including lymphoepithelioma-like or sarcomatoid carcinoma, micropapillary or nested variants and primary squamous cell carcinoma and adenocarcinoma, are relatively uncommon.

Approximately 4% of patients have metastatic disease at the time of diagnosis. Cisplatin-containing combination chemotherapy has been the standard of care in the treatment of advanced or metastatic urothelial cancer since the late 1980s. A median OS of about 14 months has been observed with the combination of cisplatin/gemcitabine or MVAC (methotrexate, vinblastine, adriamycin and cisplatin) in advanced surgically unresectable and metastatic urothelial cancer patients (von der Maase H, J Clin Oncol 2005). No improvement in survival has been achieved with newer triplets, novel four-drug regimens or dose-dense chemotherapy (Bellmunt J, J Clin Oncol 2012; Milowsky MI, J Clin Oncol 2009).

More than 50% of patients are unfit for cisplatin due to poor performance status, impaired renal function, or specific comorbidities. For these patients, NCCN Guidelines (version 2.2017) and ESMO Practice Guideline (Bellmunt J, Annals of Oncology 2014) recommend carboplatin-based regimens or single agent taxane or gemcitabine. A median OS of 9 months has been reported with the carboplatin/gemcitabine combination (De Santis M, J Clin Oncol 2012). In case of patients with PS ≥2 and poor renal function, the participation in clinical trials or BSC is recommended by ESMO guidelines.

Failing first-line platinum-based chemotherapy, the prognosis is compromised with a median OS reduced to 5 to 7 months (Bellmunt J, J Clin Oncol 2009). In this setting there is no globally recognised standard of care, and vinflunine is the only drug approved in EU for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen.

The role of immunotherapy in UC was first established in the 1970s with the use of BCG for non-muscle invasive bladder cancer. Urothelial carcinoma appears to be immunogenic, with high expression level of PD-L1 (Boorjian SA, Clin Cancer Res 2008; Faraj SF, Urology 2015).

In EU, Keytruda received a MA on 17 July 2015 as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults, and was approved as monotherapy on 29 July 2016 for the treatment of previously treated PD-L1 TPS ≥1% locally advanced or metastatic NSCLC patients and on 27 January 2017 for the first-line treatment of metastatic PD-L1 TPS ≥50% NSCLC.

The current application is a type II variation to extend the indication in treatment of locally advanced or metastatic urothelial carcinoma both in patients previously treated with chemotherapy, based on results from the study KEYNOTE-045 ("*A Phase III Randomized Clinical Trial of Pembrolizumab versus Paclitaxel, Docetaxel or Vinflunine in Subjects with Recurrent or Progressive Metastatic Urothelial Cancer*"), and in those not eligible for cisplatin-containing chemotherapy, based on results from the study KEYNOTE-052 ("*A Phase II Clinical Trial of Pembrolizumab in Subjects with Advanced/Unresectable or Metastatic Urothelial Cancer*").

The MAH applied for the following change of indication:

*KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior chemotherapy.*

*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.*

An overview of the current pembrolizumab development plan in urothelial carcinoma is reported in the following Table:

**Table: Ongoing and planned pembrolizumab studies in Urothelial Carcinoma**

| Study/Status | Design | Study Population | Dosage Regimen | Primary Efficacy Point(s) |
|---|---|---|---|---|
| KEYNOTE-012 Ongoing | Multicenter, nonrandomized, multicohort 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 IV Q2W OR Pembrolizumab 200 mg IV Q3W | Safety; ORR in PD-L1+ |
| KEYNOTE-045 Ongoing | Randomized, controlled, open label Phase 3 study | 542 subjects randomized (enrollment complete); all subjects with 2L+ urothelial cancer; control is physician's choice chemotherapy (docetaxel, paclitaxel, vinflunine) | Pembrolizumab 200 mg IV Q3W | PFS and OS in all comers, CPS ≥1%, CPS ≥10% |
| KEYNOTE-052 Ongoing | Multicenter, open label, nonrandomized, Phase 2 study | 374 subjects enrolled; all subjects have urothelial cancer and are cisplatin-ineligible; 100 subjects constituted a training set for the CPS strongly positive cut point determination | Pembrolizumab 200 mg IV Q3W | ORR in all comers, CPS ≥1%, CPS 10% |
| KEYNOTE-057 Ongoing | Single arm, open label Phase 2 study | Up to 260 subjects with high risk non-muscle-invasive bladder cancer (NMIBC) unresponsive to Bacillus Calmette Guerin | Pembrolizumab 200 mg IV Q3W | Anti-tumor activity of pembrolizumab, with regards to absence of high risk NMIBC or progressive disease |
| 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 | **Regimen (1)** (Monotherapy): Pembrolizumab 200 mg IV Q3W **Regimen (2)** (Combination): Pembrolizumab+ cisplatin/carboplatin+gemcitabine **Regimen (3)** (Chemotherapy only): cisplatin/ carboplatin + gemcitabine | PFS and OS in all comers, CPS ≥1% |

## *2.2. Non-clinical aspects*

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

### 2.2.1. Ecotoxicity / environmental risk assessment

The rationale for not submitting an environmental risk assessment was provided.

According to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00), pembrolizumab is exempt from preparation of an Environmental Risk Assessment as the product and excipients do not pose a significant risk to the environment.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

### GCP

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

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

- Tabular overview of clinical studies

| Trial ID | Phase | Country | Trial Title | Trial design | Dosing regimen | Trial population | Subject exposure |
|---|---|---|---|---|---|---|---|
| *MK-3475-012V02*<br>*[Ref. 5.3.5.2 : P012V02]* | *Ib* | *Worldwide*<br>*Israel*<br>*USA* | *A Phase Ib Multi-Cohort Study of MK-3475 in Subjects with Advanced Tumors* | *Multi-center nonrandomized open label*<br>*24 months* | *10 mg/kg of MK-3475 IV every 2 weeks (Cohort C)* | *Males/females*<br>*Age: ≥18*<br>*Urinary tract cancer patients (Cohort C)* | *10 mg/kg Q2W: 33 subjects (Cohort C)* |

| Trial ID | Phase | Country | Trial Title | Trial design | Dosing regimen | Trial population | Subject exposure |
|---|---|---|---|---|---|---|---|
| *3475-052*<br>*[Ref. 5.3.5.2: P052 V01MK3475]* | *2* | *Australia*<br>*Canada*<br>*Denmark*<br>*Guatemala*<br>*Hungary*<br>*Ireland*<br>*Israel*<br>*Italy*<br>*Republic of Korea*<br>*Malaysia*<br>*Netherlands*<br>*Puerto Rico*<br>*Singapore*<br>*Spain*<br>*Taiwan*<br>*United Kingdom*<br>*United States* | *A Phase II Clinical Trial of Pembrolizumab (MK-3475) in Subjects with Advanced/Unresectable or Metastatic Urothelial Cancer* | *Non-randomized, open-label, multi-site trial* | *Pembrolizumab 200 mg Q3W* | *Males/females*<br>*Age: ≥18 years with advanced/unresectacble (inoperable) or metastatic urothelial cancer who have not received prior systemic chemotherapy and who are not eligible to receive cisplatin* | *Pembrolizumab 200 mg Q3W: 370* |

| Trial ID | Phase | Country | Trial Title | Trial design | Dosing regimen | Trial population | Subject exposure |
|---|---|---|---|---|---|---|---|
| *3475-045*<br>*[Ref. 5.3.5.1 : P045V01]* | *III* | *US, Australia, Austria, Belgium, Canada, Chile, Denmark, France, Germany, Hungary , Ireland, Israel, Italy, Japan, Netherlands , New Zealand, Norway, Peru, Poland, Portugal, Puerto Rico, Romania, Singapore, South Korea, Spain, Sweden, Taiwan, Turkey, UK* | *A Phase III Randomized Clinical Trial of Pembrolizumab (MK-3475) versus Paclitaxel,Docetaxel or Vinflunine in Subjects with Recurrent or Progressive Metastatic Urothelial Cancer* | *Randomized, open-label, active-controlled trial* | *Pembrolizumab 200 mg IV Q3W*<br>*Or, investigator's choice of: Paclitaxel 175 mg/m$^2$ every 3 weeks; Docetaxel 75 mg/m$^2$ every 3 weeks OR Vinflunine 320 mg/m$^2$ every 3 weeks* | *Male and female subjects ≥18 years of age on the day of consent with metastatic or locally advanced/unresectable urothelial cancer that has recurred or progressed following platinum-based chemotherapy* | *521subjects treated ( pembrolizumab: 266; paclitaxel: 84; docetaxiel: 84; vinflunine: 87)* |

## 2.3.2. Pharmacokinetics

Clinical pharmacology data related to Urothelial Carcinoma (UC) indication are available from two clinical studies KEYNOTE-052 and KEYNOTE-045 and are further informed by results obtained in other indications previously approved with pembrolizumab. In addition, results from KEYNOTE-012 C are included as supportive information.

The updated clinical pharmacology results in this submission include:

- Pharmacokinetic (PK) data from **KEYNOTE-052** at 200 mg every three weeks (Q3W) in patients with locally advanced or metastatic urothelial carcinoma (UC) who are not eligible for cisplatin-containing chemotherapy.
- Pharmacokinetic (PK) data from **KEYNOTE-045** at 200 mg every three weeks (Q3W) in patients with locally advanced or metastatic urothelial carcinoma (UC) who have disease progression on or after platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
- Pharmacokinetic (PK) data from **KEYNOTE-012 cohort C** at 10 mg/Kg every two weeks (Q2W) in subjects with UC as supportive information.
- The available data supporting the appropriateness of the 200 mg Q3W dose of pembrolizumab for UC.
- An updated program-wide evaluation of incidence of immunogenicity including data from KEYNOTE-052, KEYNOTE-045 and KEYNOTE-012 in UC.

**Pharmacokinetics using human biomaterials**

*PD-L1 assessment in Merck Urothelial cancer Trials of Pembrolizumab*
A cut-off point for the PD-L1 biomarker using the Combined Positive Score (CPS) of 1% and 10% was established for the urothelial carcinoma program and was used in evaluation of samples from KN052 and KN045. The CPS 1% cut-point was developed based on data from KN012 and studies in indications outside of the urothelial carcinoma program, and the CPS 10% was developed based on a 100 patient training set of KN052 (biomarker discovery population). The CPS 10% cut-off point was validated in the remaining population for KN052 (approximately 250 subjects - validation population).

Formaline-fixed paraffin-embedded (FFPE) samples from the Merck urothelial cancer clinical studies will be assessed for PD-L1 expression using the CPS method, following staining using the PD-L1 IHC 22C3 pharmDx assay.
**CPS** is defined as the percentage of tumour cells and mononuclear inflammatory cells (MIC) within the tumour nests and the adjacent supporting stroma expressing PD-L1 at any intensity. The denominator (all tumour cells) includes count of all tumour cells within the section determined using adjacent haematoxylin/eosin staining, independent of PD-L1 staining. The maximum of Combined Positive Score is defined as 100% and is represented by the equation below.

$$\text{Combined Positive Score} = \frac{\textit{Positive tumor cells} + \textit{Positive MIC's}}{\textit{All Tumor Cells}} \times 100\%$$

Samples were considered PD-L1 positive if CPS ≥ 1% and strongly positive if CPS ≥ 10%). Samples were considered PD-L1 negative if CPS <1% (or <10)%.

Details of the PD-L1 IHC 22C3 pharmDx assay have also been submitted for NSCLC.

Analytical validation related to analytical sensitivity and precision around the CPS ≥ 1% cut-off in urothelial carcinoma specimens was conducted at Quintiles Laboratories (PD-L1 testing lab for the urothelial carcinoma clinical studies) and the report was submitted as well as analytical validation related to precision around the CPS ≥ 10% cut-off in urothelial carcinoma specimens.

**Pharmacokinetic data in UC subjects**

Sparse samples for pharmacokinetic analysis were collected in KEYNOTE-012 cohort C (10 mg/kg Q2W), KEYNOTE-052 (200 mg Q3W) and KEYNOTE-045 (200 mg Q3W).
PK sample schedule in **KN012**: Pre-dose pembrolizumab serum concentrations (Ctrough) were obtained within 24 hours prior to dosing at Cycles 1, 2, 5, 9 and every 4 cycles (8 weeks) thereafter up to Cycle 37. Post-dose serum concentrations (Cmax) were drawn within approximately 30 minutes after the end of the infusion in Cycle 1 and Cycle 2. One additional PK sample is drawn between 24 and 96 hours (1-4 days) after Cycle 1 dosing.

Summary statistics of the observed pembrolizumab trough (pre-dose) and post-dose concentrations in UC subjects from KN012 are presented in the table below:

**Summary Statistics of Pembrolizumab Predose ($C_{trough}$), Postdose ($C_{max}$), Post Cycle 1 Serum Concentration Values Following Administration of Multiple 10 mg/kg I.V. Doses with a 2 Week Dosing Interval in KN012 Urothelial Cancer Cohort**

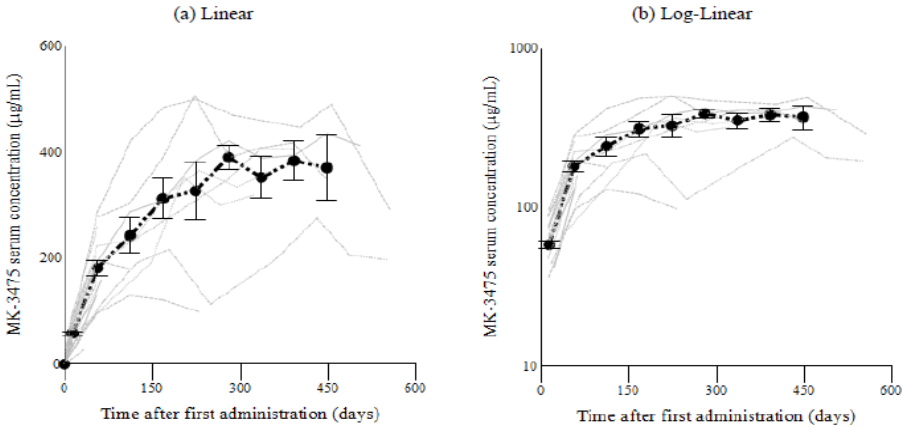
| Cycle | NOMTAFD day | N | GM (%CV) | AM (SD) (µg/mL) | Min | Median | Max |
|---|---|---|---|---|---|---|---|
| **Predose ($C_{trough}$)** | | | | | | | |
| Cycle 2 (Week 2) | 14 | 28 | 55.5 (33) | 58.2 (18) | 28.2 | 57.7 | 96.8 |
| Cycle 5 (Week 8) | 56 | 16 | 172 (34) | 181 (59) | 96.1 | 180 | 286 |
| Cycle 9 (Week 16) | 112 | 8 | 228 (38) | 242 (93) | 129 | 213 | 423 |
| Cycle 13 (Week 24) | 168 | 8 | 292 (44) | 313 (109) | 121 | 314 | 485 |
| Cycle 17 (Week 32) | 224 | 8 | 283 (71) | 327 (154) | 98.2 | 358 | 507 |
| Cycle 21 (Week 40) | 280 | 6 | 387 (15) | 391 (56) | 319 | 399 | 470 |
| Cycle 25 (Week 48) | 336 | 5 | 341 (32) | 353 (88) | 198 | 389 | 408 |
| Cycle 29 (Week 56) | 392 | 4 | 378 (22) | 384 (75) | 276 | 406 | 447 |
| Cycle 33 (Week 64) | 448 | 4 | 353 (40) | 371 (124) | 206 | 393 | 491 |
| **Postdose ($C_{max}$) (within 30 min post end of infusion)** | | | | | | | |
| Cycle 1 (Week 0) | 0 | 29 | 236 (20) | 240 (50) | 168 | 228 | 349 |
| Cycle 2 (Week 2) | 14 | 29 | 271 (23) | 278 (67) | 179 | 267 | 482 |
| **Post Cycle 1 (24-96 hours post cycle 1)** | | | | | | | |
| Cycle 1 (Week 0) | 2 | 31 | 147 (32) | 153 (42) | 64.7 | 157 | 229 |

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

Data Source: [04JQV8: p012pkdmbld04]

The individual and arithmetic mean observed pembrolizumab trough concentrations from these same subjects are presented in the figure below:

**Individual and Arithmetic Mean (SE) Pembrolizumab $C_{trough}$ -Time Profiles Following Multiple I.V. Doses of 10 mg/kg Q2W in Study KN012 Urothelial Cancer Cohort; (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: [04JQV8: p012pkdmbld04]

**PK comparison across indication (Study KN012 cohort C)**

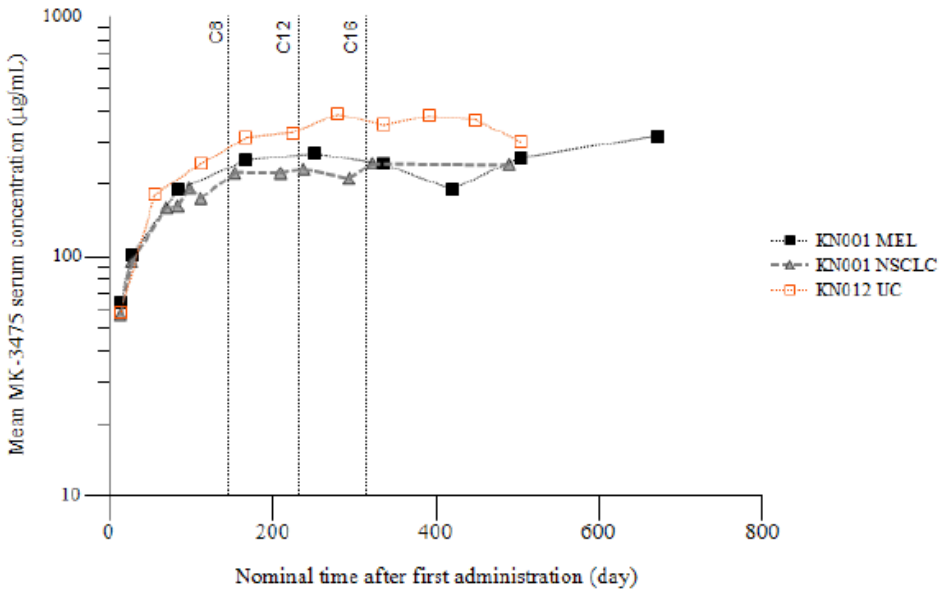
Comparison of PK parameters among KN001 Melanoma, KN001 NSCLC, and KN012 urothelial cancer (UC) subjects were presented in the following table and figure:

**Geometric Mean (GMCV %) Serum Concentration Values of Pembrolizumab Following Administration of Multiple I.V. 10 mg/kg Q2W in KN012 Urothelial Cancer Cohort and Multiple 10 mg/kg Q2W I.V. Doses Q2W in KN001 Melanoma and NSCLC**

| NOMTAFD (day) | Cycle | Relative Time | N | KN001 Melanoma GM(CV%) (µg/mL) | N | KN001 NSCLC GM(CV%) (µg/mL) | N | KN012 UC GM(CV%) (µg/mL) |
|---|---|---|---|---|---|---|---|---|
| 0.02 | Cycle 1 (Week 0) | Postdose | 168 | 223 (25) | 197 | 227 (27) | 29 | 236 (20) |
| 2 | | 24-72HRS postdose | - | - | 169 | 155 (29) | 31 | 147 (32) |
| 14 | Cycle 2 (Week 2) | Predose | 5 | 63.7 (14) | 188 | 54.6 (33) | 28 | 55.5 (33) |
| 14.02 | | Postdose | 3 | 304 (8) | - | - | 29 | 271 (23) |
| 28 | Cycle 3 (Week 4) | Predose | 150 | 94.0 (47) | 173 | 89.3 (39) | - | - |
| 28.02 | | Postdose | 147 | 316 (30) | - | - | - | - |
| 56 | Cycle 5 (Week 8) | Predose | - | - | - | - | 16 | 172 (34) |
| 70 | Cycle 6 (Week 10) | Predose | - | - | 116 | 148 (42) | - | - |
| 70.02 | | Postdose | - | - | 107 | 385 (34) | - | - |
| 84 | Cycle 7 (Week 12) | Predose | 111 | 174 (50) | 5 | 159 (19) | - | - |
| 98 | Cycle 8 (Week 14) | Predose | - | - | 91 | 179 (42) | - | - |
| 112 | Cycle 9 (Week 16) | Predose | - | - | 11 | 157 (52) | 8 | 228 (38) |
| 112.02 | | Postdose | - | - | 10 | 339 (25) | - | - |
| 154 | Cycle 12 (Week 22) | Predose | - | - | 75 | 206 (43) | - | - |
| 168 | Cycle 13 (Week 24) | Predose | 87 | 233 (44) | - | - | 8 | 292 (44) |
| 210 | Cycle 16 (Week 30) | Predose | - | - | 33 | 205 (46) | - | - |
| 224 | Cycle 17 (Week 32) | Predose | - | - | - | - | 8 | 283 (71) |
| 238 | Cycle 18 (Week 34) | Predose | - | - | 28 | 218 (37) | - | - |
| 252 | Cycle 19 (Week 36) | Predose | 60 | 254 (38) | - | - | - | - |
| 280 | Cycle 21 (Week 40) | Predose | - | - | - | - | 6 | 387 (15) |
| 294 | Cycle 22 (Week 42) | Predose | - | - | 3 | 209 (18) | - | - |
| 322 | Cycle 24 (Week 46) | Predose | - | - | 36 | 229 (38) | - | - |
| 336 | Cycle 25 (Week 48) | Predose | 17 | 234 (27) | - | - | 5 | 341 (32) |
| 392 | Cycle 29 (Week 56) | Predose | - | - | - | - | 4 | 378 (22) |
| 420 | Cycle 31 (Week 60) | Predose | 4 | 184 (29) | - | - | - | - |
| 448 | Cycle 33 (Week 64) | Predose | - | - | - | - | 4 | 353 (40) |
| 490 | Cycle 36 (Week 70) | Predose | - | - | 9 | 229 (35) | - | - |
| 504 | Cycle 37 (Week 72) | Predose | 14 | 242 (40) | - | - | 3 | 287 (38) |
| 672 | Cycle 49 (Week 96) | Predose | 10 | 289 (53) | - | - | - | - |

NOMTAFD = Nominal time after first pembrolizumab administration
GM = Geometric Mean;
CV%: Geometric Coefficient of Variation;
Postdose samples are drawn within 30 min after infusion;

**Arithmetic Mean Ctrough-Time Profiles of Pembrolizumab Following Administration of Multiple I.V. 10 mg/kg Q2W in KN012 Urothelial Cancer Cohort and Multiple 10 mg/kg I.V. Doses Q2W in KN001 Melanoma and NSCLC (Log-Linear scale)**




Data Source: [04JQV8: p1p12bldpoolpk10q2w01]

PK sample schedule in **KN052**: Pre-dose pembrolizumab serum concentrations (Ctrough) were obtained within 24 hours prior to dosing at Cycles 1, 2, 4, 8 and every 4 cycles (12 weeks) thereafter. Post-dose serum concentrations (Cmax) were drawn within approximately 30 minutes after the end of the infusion in Cycle 1 and Cycle 8. Additional PK samples are drawn between 72 and 168 hours (3-7 days) and Day 15 after Cycle 1 dosing.

Summary statistics of the observed pembrolizumab trough (pre-dose) and post-dose concentrations in UC subjects from KN052 are presented in the table below:

**Summary Statistics of Pembrolizumab Predose ($C_{trough}$), Postdose ($C_{max}$), Post Cycle 1 Serum Concentration Values Following Administration of Multiple 200 mg I.V. Doses with a 3 Week Dosing Interval in KN052**

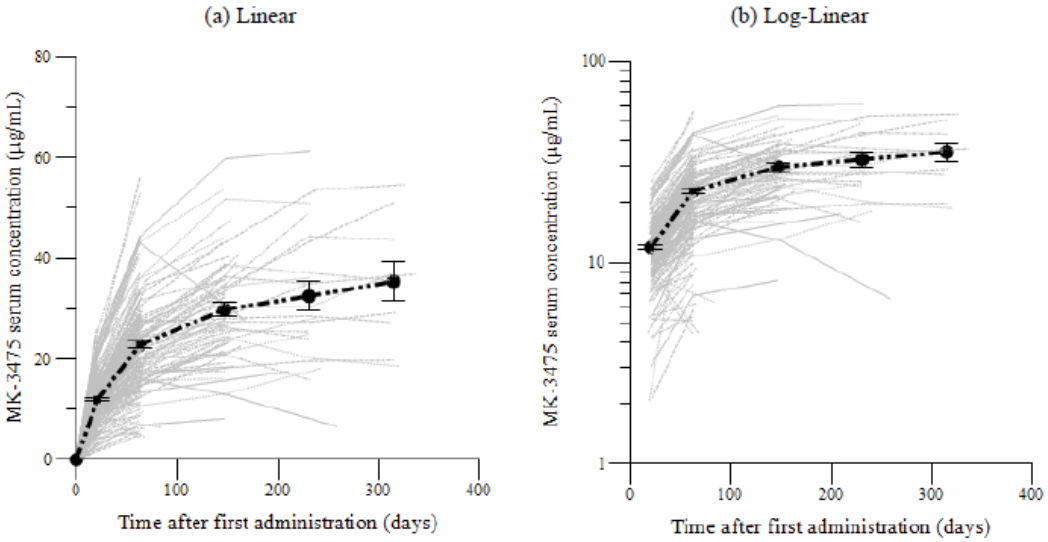
| Cycle | NOMTAFD (day) | N | GM (%CV) (µg/mL) | AM (SD) (µg/mL) | Min (µg/mL) | Median (µg/mL) | Max (µg/mL) |
|---|---|---|---|---|---|---|---|
| **Predose ($C_{trough}$)** | | | | | | | |
| Cycle 2 (Week 3) | 21 | 286 | 11.1 (42) | 11.9 (4) | 2.07 | 11.5 | 26.2 |
| Cycle 4 (Week 9) | 63 | 170 | 20.6 (51) | 22.8 (9) | 4.41 | 22.4 | 56.1 |
| Cycle 8 (Week 21) | 147 | 59 | 28.0 (38) | 29.9 (10) | 8.15 | 27.9 | 59.8 |
| Cycle 12 (Week 33) | 231 | 22 | 29.4 (53) | 32.5 (14) | 6.60 | 29.5 | 61.4 |
| Cycle 16 (Week 45) | 315 | 10 | 33.4 (38) | 35.4 (12) | 18.6 | 36.2 | 54.7 |
| **Postdose (within 30 min post end of infusion)** | | | | | | | |
| Cycle 1 (Week 0) | 0 | 298 | 58.0 (28) | 60.2 (17) | 22.8 | 57.4 | 148 |
| Cycle 8 (Week 21) | 147 | 53 | 83.1 (29) | 86.4 (24) | 37.2 | 81.1 | 149 |
| **Post C1 (additional samples drawn after Cycle 1 dosing )** | | | | | | | |
| Cycle 1 (72-168 hr) | 5 | 299 | 23.4 (31) | 24.5 (8) | 8.52 | 23.5 | 61.3 |
| Cycle 1 (336 hr) | 14 | 287 | 14.4 (36) | 15.2 (5) | 4.39 | 14.7 | 35.5 |

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

Data Source: [04JR0J: p052pkdm05]

The individual and arithmetic mean observed pembrolizumab trough concentrations from these same subjects are presented in the figure below:

**Individual and Arithmetic Mean (SE) Pembrolizumab $C_{trough}$ -Time Profiles Following Multiple I.V. Doses of 200 mg Q3W in Study KN052 (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: [04JR0J: p052pkdm05]

**PK comparison across indication (study KN052)**

Comparison of PK parameters among KN001 Melanoma, KN001 NSCLC, and KN052 urothelial cancer (UC) subjects were presented in the following table and boxplots:

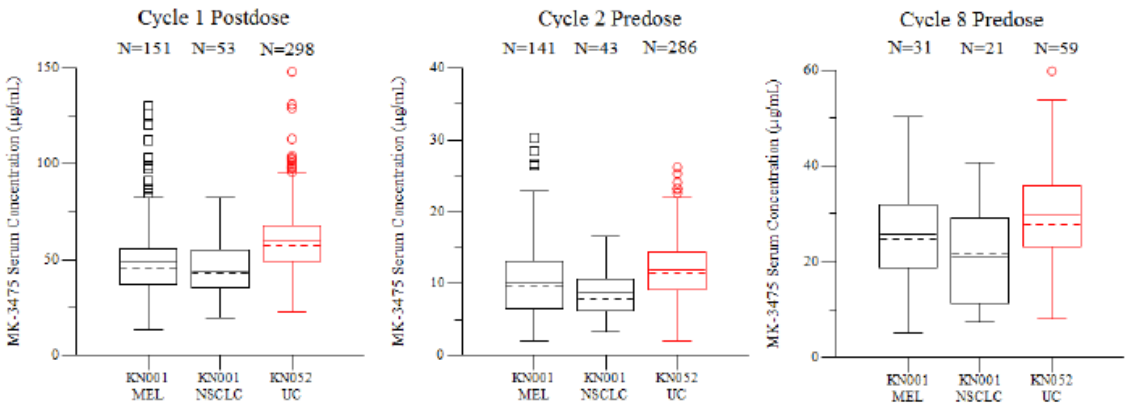
**Geometric Mean (GMCV %) Serum Concentration Values of Pembrolizumab Following Administration of Multiple I.V. 200 mg Q3W Fixed Doses in KN052 UC and Multiple 2 mg/kg Q3W I.V. Doses in KN001 Melanoma and NSCLC**

| | | | KN001 MEL 2mg/kg | | KN001 NSCLC 2mg/kg | | KN052 UC 200 mg | |
|---|---|---|---|---|---|---|---|---|
| NOMTAFD (day) | Cycle | Relative time | N | GM(CV%) (µg/mL) | N | GM(CV%) (µg/mL) | N | GM(CV%) (µg/mL) |
| 0.02 | Cycle 1 (Week 0) | Postdose | 151 | 46.0 (37) | 53 | 42.4 (32) | 298 | 58.0 (28) |
| 21 | Cycle 2 (Week 3) | Predose | 141 | 9.12 (51) | 43 | 8.09 (39) | 286 | 11.1 (42) |
| 21.02 | | Postdose | 89 | 52.6 (49) | - | - | - | - |
| 42 | Cycle 3 (Week 6) | Predose | 47 | 16.6 (57) | 38 | 11.5 (63) | - | - |
| 63 | Cycle 4 (Week 9) | Predose | - | - | - | - | 170 | 20.6 (51) |
| 84 | Cycle 5 (Week 12) | Predose | 62 | 19.6 (57) | - | - | - | -- |
| 105 | Cycle 6 (Week 15) | Predose | 32 | 24.6 (34) | 27 | 18.7 (42) | - | - |
| 105.02 | | Postdose | 30 | 65.6 (24) | 26 | 58.9 (43) | - | - |
| 147 | Cycle 8 (Week 21) | Predose | 31 | 23.5 (50) | 21 | 18.9 (55) | 59 | 28.0 (38) |
| 147.02 | | Postdose | - | - | - | - | 53 | 83.1 (29) |
| 168 | Cycle 9 (Week 24) | Predose | 46 | 25.3 (59) | - | - | - | - |
| 231 | Cycle 12 (Week 33) | Predose | 23 | 29.6 (35) | 7 | 22.3 (64) | 22 | 29.4 (53) |
| 252 | Cycle 13 (Week 36) | Predose | 47 | 27.1 (50) | - | - | - | - |
| 315 | Cycle 16 (Week 45) | Predose | 18 | 33.8 (67) | - | - | 10 | 33.4 (38) |
| 336 | Cycle 17 (Week 48) | Predose | 39 | 32.2 (45) | - | - | - | - |
| 483 | Cycle 24 (Week 69) | Predose | 8 | 30.3 (40) | - | - | - | - |
| 504 | Cycle 25 (Week 72) | Predose | 11 | 28.1 (37) | - | - | - | - |

NOMTAFD = Nominal time after first pembrolizumab administration;
GM = Geometric Mean;
%CV = Geometric Coefficient of Variation;
Postdose samples are drawn within 30 min after infusion;
Results for time points with N > 3.

Data Source: [04JR0J: p1p52poolpk2q3w200f01]

**Boxplots with Serum Pembrolizumab Concentration Values from KN052 UC 200 mg Q3W Regimen Compared with KN001 Melanoma and NSCLC 2 mg/kg Q3W Regimen**




Data Source: [04JR0J: p1p52poolpk2q3w200f01]

PK sample schedule in **KN045**: Pre-dose pembrolizumab serum concentrations (Ctrough) were obtained within 24 hours prior to dosing at Cycles 1, 2, 4, 8 and every 4 cycles (12 weeks) thereafter. Post-dose serum concentrations (Cmax) were drawn within approximately 30 minutes after the end of the infusion in Cycle 1 and Cycle 8. One additional PK sample is drawn between 72 and 168 hours (3-7 days) after Cycle 1 dosing.

Summary statistics of the observed pembrolizumab trough (pre-dose) and post-dose concentrations in UC subjects from KN045 are presented in the table below:

**Summary Statistics of Pembrolizumab Predose ($C_{trough}$), Postdose ($C_{max}$), Post Cycle 1 Serum Concentration Values Following Administration of Multiple 200 mg I.V. Doses with a 3 Week Dosing Interval in KN045**

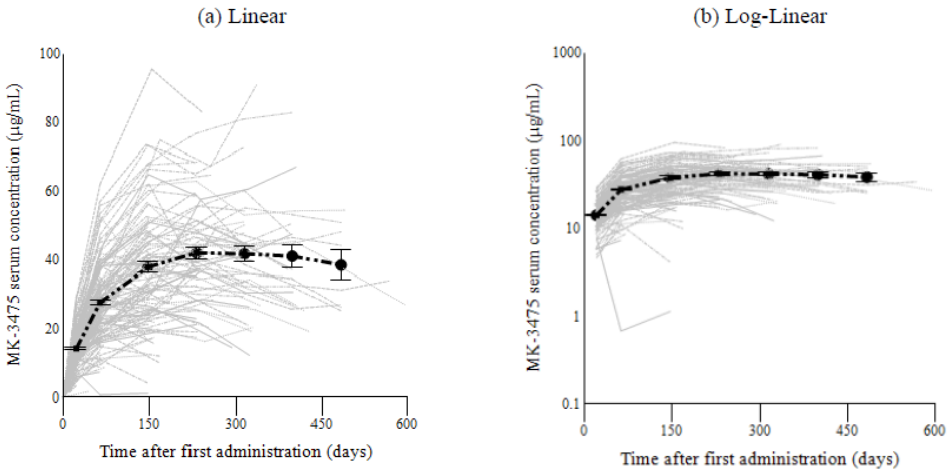
| Cycle | NOMTAFD | N | GM (%CV) | AM (SD) | Min | Median | Max |
|---|---|---|---|---|---|---|---|
| | day | | (µg/mL) | | | | |
| **Predose ($C_{trough}$)** | | | | | | | |
| Cycle 2 (Week 3) | 21 | 233 | 13.1 (47) | 14.2 (5) | 0.475 | 13.9 | 29.3 |
| Cycle 4 (Week 9) | 63 | 169 | 25.3 (52) | 27.7 (11) | 0.677 | 26.6 | 62.1 |
| Cycle 8 (Week 21) | 147 | 104 | 33.4 (64) | 37.8 (17) | 1.13 | 37.5 | 95.6 |
| Cycle 12 (Week 33) | 231 | 73 | 39.2 (40) | 42.0 (15) | 14.5 | 39.4 | 83.1 |
| Cycle 16 (Week 45) | 315 | 44 | 39.0 (39) | 41.7 (15) | 12.2 | 42.2 | 90.9 |
| Cycle 20 (Week 57) | 399 | 22 | 38.7 (36) | 41.0 (15) | 19.3 | 37.3 | 82.8 |
| Cycle 24 (Week 69) | 483 | 8 | 36.7 (33) | 38.5 (12) | 25.3 | 37.8 | 54.5 |
| **Postdose ($C_{max}$) (within 30 min post end of infusion)** | | | | | | | |
| Cycle 1 (Week 0) | 0 | 247 | 65.7 (26) | 67.9 (18) | 33.9 | 65.9 | 144 |
| Cycle 8 (Week 21) | 147 | 97 | 103 (31) | 107 (32) | 44.8 | 103 | 219 |
| **Post Cycle 1 (72-168 hours post cycle 1)** | | | | | | | |
| Cycle 1 (Week 0) | 5 | 245 | 29.0 (29) | 30.2 (9) | 15.2 | 29.2 | 57.5 |

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

Data Source: [04JT5G: p045pkdm09]

The individual and arithmetic mean observed pembrolizumab trough concentrations from these same subjects are presented in the figure below:

**Individual and Arithmetic Mean (SE) Pembrolizumab $C_{trough}$ -Time Profiles Following Multiple I.V. Doses of 200 mg Q3W in Study KN045 (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: [04JT5G: p045pkdm09]

**PK comparison across indication (study KN045)**

Comparison of PK parameters among KN001 Melanoma, KN001 NSCLC, and KN045 urothelial cancer (UC) subjects were presented in the following table and boxplots:

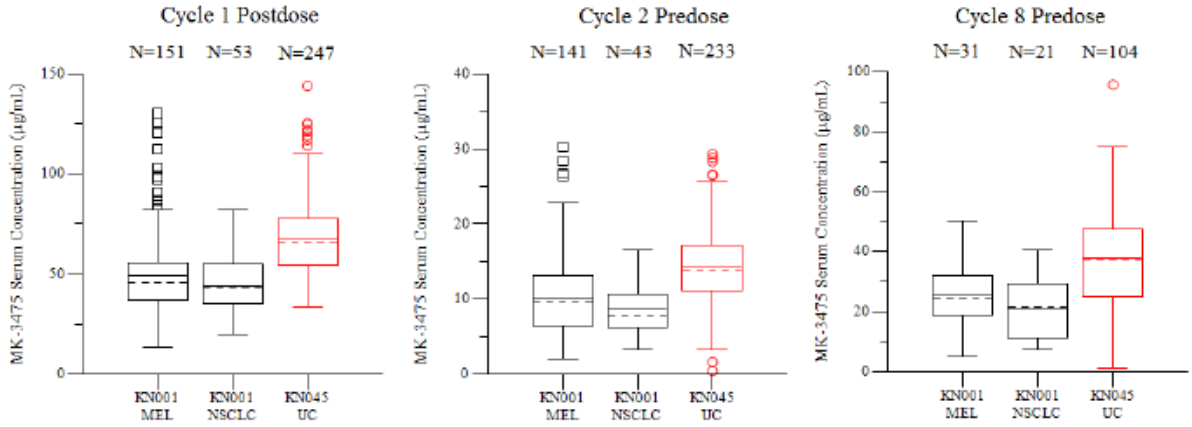
**Geometric Mean (GMCV %) Serum Concentration Values of Pembrolizumab Following Administration of Multiple I.V. 200 mg Q3W in KN045 UC and Multiple 2 mg/kg I.V. Doses Q3W in KN001 Melanoma and NSCLC**

| Cycle | NOMTAFD (day) | Relative Time | N | KN001 Melanoma GM(CV%) (µg/mL) | N | KN001 NSCLC GM(CV%) (µg/mL) | N | KN045 UC GM(CV%) (µg/mL) |
|---|---|---|---|---|---|---|---|---|
| Cycle 1 (Week 0) | 0 | Postdose | 151 | 46.0 (37) | 53 | 42.4 (32) | 247 | 65.7 (26) |
| Cycle 2 (Week 3) | 21 | Predose | 141 | 9.12 (51) | 43 | 8.09 (39) | 233 | 13.1 (47) |
| Cycle 2 (Week 3) | 21 | Postdose | 89 | 52.6 (49) | - | - | - | - |
| Cycle 3 (Week 6) | 42 | Predose | 47 | 16.6 (57) | 38 | 11.5 (63) | - | - |
| Cycle 4 (Week 9) | 63 | Predose | - | - | - | - | 169 | 25.3 (52) |
| Cycle 5 (Week 12) | 84 | Predose | 62 | 19.6 (57) | - | - | - | - |
| Cycle 6 (Week 15) | 105 | Predose | 32 | 24.6 (34) | 27 | 18.7 (42) | - | - |
| Cycle 6 (Week 15) | 105 | Postdose | 30 | 65.6 (24) | 26 | 58.9 (43) | - | - |
| Cycle 8 (Week 21) | 147 | Predose | 31 | 23.5 (50) | 21 | 18.9 (55) | 104 | 33.4 (64) |
| Cycle 8 (Week 21) | 147 | Postdose | - | - | - | - | 97 | 103 (31) |
| Cycle 9 (Week 24) | 168 | Predose | 46 | 25.3 (59) | - | - | - | - |
| Cycle 12 (Week 33) | 231 | Predose | 23 | 29.6 (35) | 7 | 22.3 (64) | 73 | 39.2 (40) |
| Cycle 13 (Week 36) | 252 | Predose | 47 | 27.1 (50) | - | - | - | - |
| Cycle 16 (Week 45) | 315 | Predose | 18 | 33.8 (67) | - | - | 44 | 39.0 (39) |
| Cycle 17 (Week 48) | 336 | Predose | 39 | 32.2 (45) | - | - | - | - |
| Cycle 20 (Week 57) | 399 | Predose | - | - | - | - | 22 | 38.7 (36) |
| Cycle 24 (Week 69) | 483 | Predose | 8 | 30.3 (40) | - | - | 8 | 36.7 (33) |
| Cycle 25 (Week 72) | 504 | Predose | 11 | 28.1 (37) | - | - | - | - |
| Cycle 33 (Week 96) | 672 | Predose | 3 | 38.7 (15) | - | - | - | - |

NOMTAFD = Nominal time after first pembrolizumab administration;
GM = Geometric Mean;
CV%: Geometric Coefficient of Variation;
Postdose samples are drawn within 30 min after infusion.

Data Source: [04JT5G: p1p45poolpk2q3w200f01]

**Boxplots with Serum Pembrolizumab Concentration Values from KN045 UC 200 mg Q3W Regimen Compared with KN001 Melanoma and NSCLC 2 mg/kg Q3W Regimen**




Data Source: [04JT5G: p1p45poolpk2q3w200f01]

## *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 (~7.5 L; CV: 20%). As expected for an antibody, pembrolizumab does not bind to plasma proteins in a specific manner.

## *Elimination*

The systemic clearance of pembrolizumab is ~0.2 L/day (CV: 37%) and the terminal half-life (t½) is ~25 days (CV: 38%).

## *Special populations*

The effects of various covariates on the pharmacokinetics of pembrolizumab were assessed in population pharmacokinetic analyses. The following factors had no clinically important effect on the clearance of pembrolizumab: age (range 15-94 years), gender, race, mild or moderate renal impairment, mild hepatic impairment and tumour burden. The relationship between body weight and clearance supports the use of either fixed dose or body weight-based dosing to provide adequate and similar control of exposure.

Renal impairment

The effect of renal impairment on the clearance of pembrolizumab was evaluated by population pharmacokinetic analyses in patients with mild or moderate renal impairment compared to patients with normal renal function. No clinically important differences in the clearance of pembrolizumab were found between patients with mild or moderate renal impairment and patients with normal renal function. Pembrolizumab has not been studied in patients with severe renal impairment.

Hepatic impairment

The effect of hepatic impairment on the clearance of pembrolizumab was evaluated by population pharmacokinetic analyses in patients with mild hepatic impairment (as defined using the US National Cancer Institute criteria of hepatic dysfunction) compared to patients with normal hepatic function. No clinically important differences in the clearance of pembrolizumab were found between patients with mild hepatic impairment and normal hepatic function. Pembrolizumab has not been studied in patients with moderate or severe hepatic impairment (see section 4.2 of the SmPC).

## 2.3.3. Pharmacodynamics

### *Mechanism of action*

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

### *Primary and secondary pharmacology*

**Immunogenicity**

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

Only Tier 2 confirmed ADA positive samples were moved to Tier 3 and reported with a titer value and a NAb result.

The initial neutralising assay, as used at Intertek, was a validated ligand binding ECL assay and consisted of two tiers: a screening tier and a confirmatory tier.

The first tier used a cut point aiming for 5% false positives while in the second, confirmatory, tier the cut point allowed for 1% false positives. In the confirmatory tier, Protein G depletion was used to confirm the presence of pembrolizumab neutralising antibodies. The neutralising assay was subsequently redesigned at a second CRO (PPD). The assay was a validated ligand binding ECL assay in which the approach was adjusted to a single tier approach. The assay cut point was aiming for 1% false positives instead of 5%, supporting the elimination of a second tier.

An integrated immunogenicity evaluation has been performed using data across studies keynote-001, -002, -006, -012, -013, -024, -045, -052, -055, -087 and -164. A total of 3727 subjects were included in the immunogenicity assessment across indications (1535 melanoma, 1238 NSCLC, 101 HNSCC, 45 MSI-H, 220 HL and 579 UC) and across doses (at 2 mg/kg Q3W, 10 mg/kg Q3W/Q2W and 200 mg Q3W).

Out of the 3727 subjects included in the immunogenicity assessment, 2034 subjects were evaluable.

The observed incidence of treatment emergent ADA in evaluable subjects based on the pooled analysis is 1.8% (36 out of 2034). Of the 36 treatment emergent positive subjects, 9 (1 melanoma, 5 NSCLC, 1 HL

and 2 UC) tested positive in the neutralizing assay. The 9 subjects positive in the neutralising assay accounted for a total incidence rate of treatment neutralizing positive subjects of 0.4% (9 out of 2034) in the overall population.

A summary of subject immunogenicity results is reported below:

**Summary of Subject Immunogenicity Results (pooled analysis)**

| **Stratified by treatment** | | | | |
|---|---|---|---|---|
| Immunogenicity status | **All treatments** | **Treatment** | | |
| | | **2 mg/kg** | **10 mg/kg** | **200 mg** |
| Assessable subjects[a] | 3727 | 706 | 2038 | 983 |
| Inconclusive subjects[b] | 1693 | 136 | 1489 | 68 |
| Evaluable subjects[c] | **2034** | **570** | **549** | **915** |
| Negative[d] | 1977 (97.2%) | 555 (97.4%) | 533 (97.1%) | 889 (97.2%) |
| Non-Treatment emergent positive[d] | 21 (1.0%)[e] | 7 (1.2%) | 4 (0.7%) | 10 (1.1%)[e] |
| Neutralizing negative | 19 (0.9%)[e] | 5 (%) | 4 (0.7%) | 10 (1.1%)[e] |
| Neutralizing positive | 2 (0.1%) | 2 (%) | 0 | 0 |
| Treatment emergent positive[d] | 36 (1.8%)[f, g] | 8 (1.4%) | 12 (2.2%)[g] | 16 (1.7%)[f] |
| Neutralizing negative | 27 (1.3%)[f, g] | 6 (1.1%) | 11 (2.0%)[g] | 10 (1.1%)[f] |
| Neutralizing positive | 9 (0.4%) | 2 (0.4%) | 1 (0.2%) | 6 (0.7%) |

| **Stratified by Indication** | | | | | | |
|---|---|---|---|---|---|---|
| Immunogenicity status | **Melanoma** | **NSCLC** | **HNSCC** | **MSI-H** | **HL** | **UC** |
| Assessable subjects[a] | 1535 | 1238 | 101 | 54 | 220 | 579 |
| Inconclusive subjects[b] | 1101 | 445 | 39 | 0 | 38 | 70 |
| Evaluable subjects[c] | **434** | **793** | **62** | **54** | **182** | **509** |
| Negative[d] | 427 (98.4%) | 764 (96.3%) | 59 (95.2%) | 51 (94.4%) | 179 (98.4%) | 497 (97.6%) |
| Non-Treatment emergent positive[d] | 4 (0.9%) | 6 (0.7%) | 2 (3.2%) | 2 (3.7%) | 2 (1.1%)[h] | 5 (1.0%)[i] |
| Neutralizing negative | 3 (0.7%) | 5 (0.6%) | 2 (3.2%) | 2 (3.7%) | 2 (1.1%)[h] | 5 (1.0%)[i] |
| Neutralizing positive | 1 (0.2%) | 1 (0.1%) | 0 | 0 | 0 | 0 |
| Treatment emergent Positive[d] | 3 (0.7%) | 23 (2.9%)[f, g] | 1 (1.6%) | 1 (1.9%) | 1 (0.6%) | 7 (1.4%) |
| Neutralizing negative | 2 (0.5%) | 18 (2.3%)[f, g] | 1 (1.6%) | 1 (1.9%) | 0 | 5 (1.0%) |
| Neutralizing positive | 1 (0.2%) | 5 (0.6%) | 0 | 0 | 1 (0.6%) | 2 (0.4%) |

a: Included are subjects with at least one ADA sample available after treatment with pembrolizumab
b: Inconclusive subjects are the number of subjects with no positive ADA samples present and the drug concentration in the last sample above the DTL.
c: Evaluable subjects are the total number of negative and positive subjects (non-treatment emergent and treatment emergent.
d: Denominator was total number of evaluable subjects.
e: Including three subjects with pre and post dose sample ADA positive, and no increase in titer
f: Including one subject with pre and post dose sample ADA positive, and increase in titer
g: Including one subject with post dose sample ADA positive and pre dose sample missing.
h: Including one subject with pre and post dose sample ADA positive, and no increase in titer.
i: Including two subject with pre and post dose sample ADA positive, and no increase in titer.
NSCLC: Non Small Cell Lung Carcinoma; HNSCC: Head and Neck Squamous Cell Carcinoma;
MSI-H: Microsatellite Instability-High; HL: Hodgkin Lymphoma; UC: Urothelial Cancer

Data source [Appendix 9]

Pembrolizumab exposure for these treatment emergent (ADA and neutralizing) subjects was within the same range of exposure observed for other non-positive subjects treated with the same regimen.

*Evaluation of drug tolerance level*

At the recommended dosing regimen of 200 mg, the pembrolizumab concentration in the last post-dose sample was below the drug tolerance level (<DTL) for about 92.9% of the subjects, indicating that the DLT for the ADA assay is adequate for 200 mg.

**Overview of Subjects with Pembrolizumab Concentrations Relative to the Drug Tolerance Level of the ADA Assay in the Last Postdose Sample**

| | Treatment | | | |
|---|---|---|---|---|
| | **All Treatments** | **2 mg/kg** | **10 mg/kg** | **200 mg** |
| Assessable Subjects[a] | 3727 | 706 | 2038 | 983 |
| Last postdose sample: Pembrolizumab conc. ≥ DTL | 1444 (38.8%)[b] | 117 (16.6%)[b] | 1327 (65.1%)[b] | 0 |
| Last postdose sample: Pembrolizumab conc. unknown | 259 (6.9%)[b] | 20 (2.8%)[b] | 169 (8.3%)[b] | 70 (7.1%)[b] |
| **Last postdose sample: Pembrolizumab conc. < DTL** | **2024 (54.3%)[b]** | **569 (80.6%)[b]** | **542 (26.6%)[b]** | **913 (92.9%)[b]** |

DTL: Drug Tolerance Level of the ADA assay.
a: Assessable subjects are subjects treated with pembrolizumab and with at least 1 postdose sample available.
b: Denominator was the number of assessable subjects.

Data source [Appendix 9]

## 2.3.4. PK/PD modelling

Previously, a pooled population PK analysis (report 04DDV3) using KN001, KN002 and KN006 studies was performed to characterise serum concentrations over time based on a dataset including 2188 subjects across the melanoma and NSCLC indications. This analysis is considered the definitive population PK analysis to characterize pembrolizumab PK and inform the label for pembrolizumab.

The structure of the definitive population PK model for pembrolizumab has a two-compartment model structure with a linear clearance from the central compartment, parameterized in terms of clearance (CL), inter-compartmental clearance (Q), central compartment volume of distribution (Vc), and peripheral compartment volume of distribution (Vp). All PK parameters were allometrically scaled based on body weight with separate exponents estimated for the clearance (CL, Q) and volume (Vc, Vp) parameters, as follows:

$$P^* = \theta_x \cdot \left( \frac{WT}{MedianWT} \right)^{\theta_y}$$

where θx is a typical value of a pharmacokinetic parameter P*, and θy is the fixed-effect parameter to be estimated. WT is the individual body weight, and Median

WT is the median body weight across the analysis population.

In addition to body weight, the existing population PK model contained several more covariate relationships, which were established through a stepwise covariate search. The covariate relationships used the following generic form for continuous covariates, similar to the relationships for body weight.

The following function was used to describe the effects of categorical covariates:

$$P^* = \theta_x \cdot (1 + Q \cdot \theta_y)$$

Where θx is a typical value of a pharmacokinetic parameter P*, and θy is the fixed-effect parameter to be estimated, and Cov is the (continuous) covariate value and Q is the indicator variable denoting the category of the (categorical) covariate.

Specifically, the following covariates were included in the model:

| Covariate | Type of covariate | Parameter |
|---|---|---|
| Gender | Categorical | CL and Vc |
| Bilirubin | Continuous | CL |
| eGFR | Continuous | CL |
| Albumin | Continuous | CL and Vc |
| Tumor burden | Continuous | CL |
| ECOG performance status | Categorical | CL |
| Cancer type | Categorical | CL |
| Prior IPI treatment | Categorical | CL and Vc |

In this model, the impact of these covariates on pembrolizumab exposure was limited (generally less than 20%) and therefore was not considered to be of clinical relevance.

Nevertheless, these covariates have been maintained in the model and re-estimated on the extended dataset. Of note, in establishing the final model on the new dataset, the covariate cancer type was reassessed. The covariate cancer type was redefined in the model in order to have a single category represent the existing (melanoma and NSCLC) dataset to allow comparison of the newly added UC indication.

Upon reassessment of the impact of cancer type (categorised as UC or Melanoma+NSCLC+other), a statistically significant effect of the covariate was observed on clearance, representing an increased clearance (by 14.6%) in UC patients relative to the non- UC patients.

Inter-individual variability (IIV) of the PK parameters (CL, Volume of distributions (Vc and Vp) and inter-compartmental clearance Q) was included using a log-normal random effects model.

Residual variability (RV), a composite measure of assay error, dose/sample time collection errors, model misspecification, and any other unexplained variability within a subject, was modelled using a log-transformed additive error model (for the Assessment of the population PK analysis, please refer to the variation II/11 of Keytruda).

No additional model development was performed in the current analysis, and the definitive population PK was used as is. For this updated PK evaluation, the data from UC patients from studies KN012, KN052 and KN045 were added to the dataset. Therefore, the consistency of pembrolizumab PK in patients with UC from studies KN012, KN052 and KN045 with the established definitive population PK analysis was analysed. The model was used to predict pembrolizumab levels in UC patients after 200 mg Q3W and 10 mg/kg Q2W and the predictions were compared with observed levels determined in studies KN012, KN052 and KN045.

The final analysis dataset from studies KN001, KN002, KN006, KN052, KN012 cohort C and KN045 used for the population PK comprised of a total of 14976 pembrolizumab concentrations from 2794 patients, of which 2743 PK observations were from 606 UC patients. The number of subjects and PK observations by dose in the pooled analysis dataset are provided in the following table:

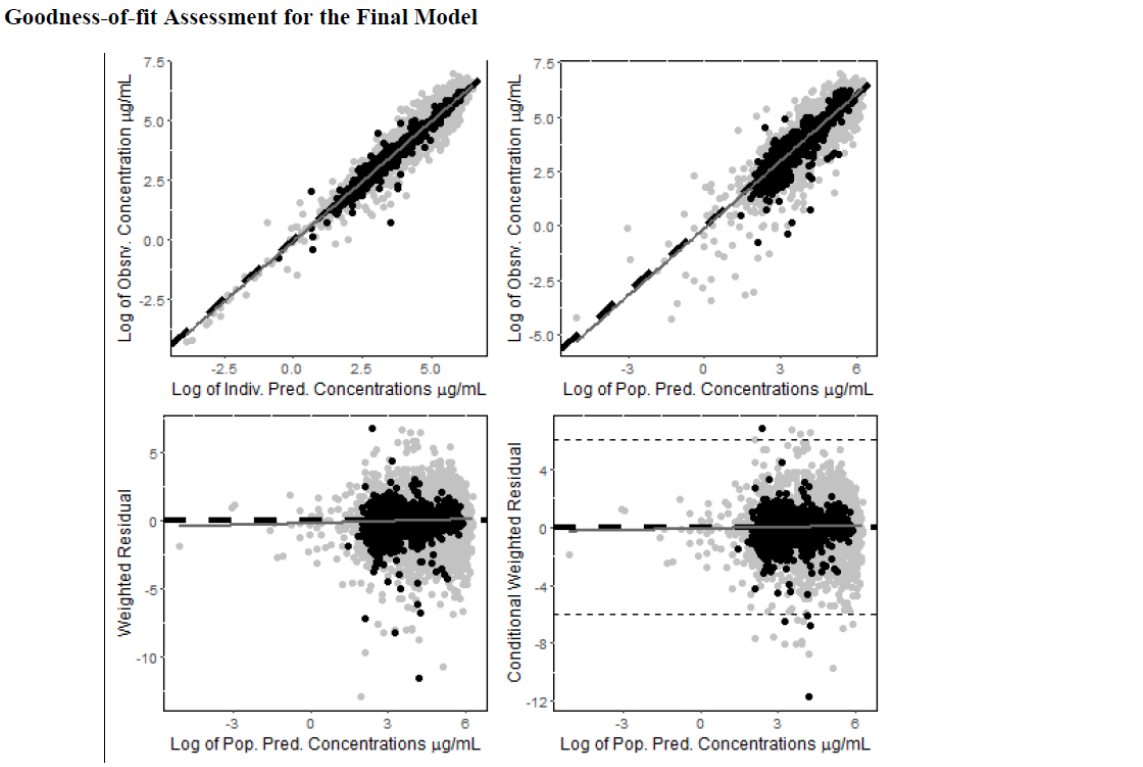
**Numbers of Subjects and Observations by Dose and Dosing Regimen in the Pooled Analysis Dataset (KN001, KN002, KN006, KN012, KN045, KN052)**

| Doses | N of subjects | % of subjects | N of PK observations | % of PK observations |
|---|---|---|---|---|
| 1 mg/kg Q2W (non-UC) | 4 | 0.143 | 43 | 0.287 |
| 1 mg/kg Q3W (non-UC) | 6 | 0.215 | 10 | 0.0668 |
| 2 mg/kg Q3W (non-UC) | 435 | 15.6 | 2114 | 14.1 |
| 3 mg/kg Q2W (non-UC) | 3 | 0.107 | 55 | 0.367 |
| 10 mg/kg Q2W (non-UC) | 660 | 23.6 | 4117 | 27.5 |
| 10 mg/kg Q3W (non-UC) | 1080 | 38.7 | 5894 | 39.4 |
| 10 mg/kg Q2W (UC) | 33 | 1.18 | 169 | 1.13 |
| 200 mg Q3W (UC) | 573 | 20.5 | 2574 | 17.2 |

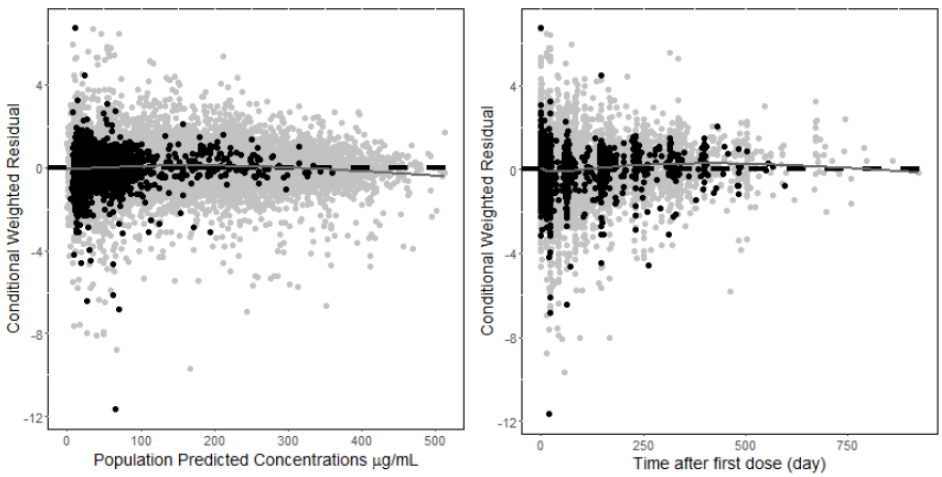
Note: some subjects received more than one dose levels under dose escalation cohorts
Reviewed per SOP-QP2-005

### Goodness of fit plots

Goodness of fit plots of the final model using the integrated dataset, i.e. KN001, KN002, KN006, KN012, KN045 and KN052, are reported below:




Black dots are UC individual data, Grey dots are individual data for other indications, solid lines are smooth lines. In the two plots of the first row, bold dashed lines are lines of identity, whilst in the two plots of the second row dashed lines represent zero line.




Black dots are UC individual data; Grey dots are individual data for other indications; dashes lines are zero line whilst solid lines are the smooth lines.

***Pharmacokinetic in target population***

In support of this specific submission, a focused PK analysis was conducted primarily to show the similarity of observed concentrations in subjects with UC in KN012 (10 mg/kg Q2W), KN052 and KN045 (200 mg Q3W) with the predictions from the definitive population PK analysis.

**Comparison UC vs Other Indications**

The existing population PK model for pembrolizumab was used to re-estimate the PK-parameters for the complete updated dataset (including data from UC patients from studies KN012, KN052 and KN045).

Following finalisation of the population PK model on the pooled dataset, the final model was used to enable comparisons of the pharmacokinetics of pembrolizumab between UC subjects and those from other indications.

Comparison of parameter estimates of the final model using the integrated dataset (i.e. KN001, KN002, KN006, KN012, KN045 and KN052) and the dataset used in previous pop PK model (Pooled Protocol KN001, KN002 and KN006 Dataset) is shown in the table below:

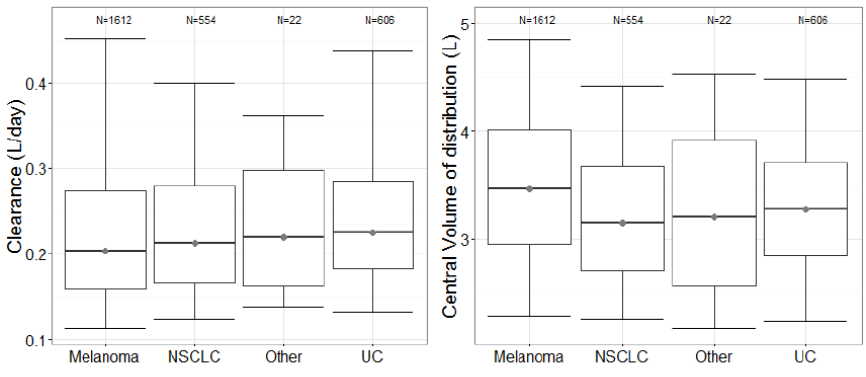
**Comparison of Population Pharmacokinetic Parameters of Pembrolizumab (MK-3475) from the Previous Model with Non-UC vs. Updated Model Including UC Subjects**

| | The Previous Model N=2188 [Ref. 5.3.5.3: 04DDV3] | | | Update Model N=2794 (606 UC out of 2794) | | |
|---|---|---|---|---|---|---|
| **Parts and Studies included in the analysis** | **Melanoma/NSCLC;** A, A1, A2, B1, B2, B3, C, D, F1, F2 and F3 from KN001, KN002, KN006 | | | **Melanoma/NSCLC;** A, A1, A2, B1, B2, B3, C, D and F1, F2, and F3 from KN001, KN002, KN006<br><br>**UC;** KN012, KN045 KN055 | | |
| **Data cut-off date** | KN001V01; 26-July-2013<br>KN001V02; 18-April-2014<br>KN001V04; 23-January-2015<br>KN002V01; 12-May-2014<br>KN006V02; 3-March-2015 | | | KN001V01; 26-July-2013<br>KN001V02; 18-April-2014<br>KN001V04; 23-January-2015<br>KN002V01; 12-May-2014<br>KN006V02; 3-March-2015<br>KN012V02; 01-Sep-2015<br>KN045V01; 07-Sep-2016<br>KN052V01; 01-Sep-2016 | | |
| **Parameter** | **Value** | **%RSE** | **%CV[a]** | **Value** | **%RSE** | **%CV[a]** |
| **CL (L/day)** | 0.22 | 2.14 | 37.9 | 0.235 | 1.65 | 37.8 |
| **Vc (L)** | 3.48 | 0.892 | 20.6 | 3.47 | 0.749 | 20.3 |
| **Q (L/day)** | 0.795 | 4.02 | 37.9 | 0.731 | 2.74 | 37.8 |
| **Vp (L)** | 4.06 | 2.01 | 20.6 | 3.94 | 1.61 | 20.3 |
| **α for CL and Q** | 0.595 | 7.95 | | 0.557 | 7.21 | |
| **α for Vc and Vpc** | 0.489 | 6.06 | | 0.505 | 4.99 | |
| **Albumin on CL** | -0.907 | 8.39 | | -0.671 | 18.7 | |
| **eGFR on CL** | 0.135 | 23.2 | | 0.121 | 21.4 | |
| **GENDER on CL** | -0.152 | 11.7 | | -0.158 | 10.0 | |
| **Cancer Type (NSCLC vs Mel+other) on CL[b]** | 0.145 | 17.1 | | NA | NA | |
| **Cancer Type (UC vs Mel+NSCLC+other) on CL** | NA | NA | | 0.146 | 16.8 | |
| **Baseline ECOG on CL** | -0.0739 | 22.7 | | -0.108 | 14.6 | |
| **Baseline tumor size on CL** | 0.0872 | 12.2 | | 0.100 | 10.4 | |
| **IPI prior treatment status on CL** | 0.139 | 18.4 | | 0.085 | 24.7 | |
| **Albumin on Vc** | -0.208 | 22.7 | | -0.157 | 27.2 | |
| **GENDER Vc** | -0.134 | 9.31 | | -0.134 | 8.35 | |
| **IPI prior treatment status on Vc** | 0.0735 | 23.5 | | 0.0717 | 23.5 | |
| **Residual error** | 0.272 | 1.87 | | 0.259 | 1.86 | |

[a] %CV of residual error is related to estimate of between-subject variability on this parameter
[b] UC not included in update model.
Presented population parameter estimates exclude effects of covariates; therefore apply to a hypothetical typical patient with average characteristics. CL: clearance; Vc: central volume of distribution; Q: intercompartmental clearance; Vp: peripheral volume of distribution; %RSE: relative standard error (%); 95% CI: 95% confidence interval of parameter estimate based on bootstrap results; %CV: coefficient of variation of between-subject distributions of parameters; NA: not applicable.
Reviewed per SOP-QP2-005

Distributions of individual post-hoc parameter estimates for clearance and central volume of distribution by indication UC and non-UC (melanoma, NSCLC, other) is presented below:

**Comparison of CL and Vd Using the Individual Empirical Bayes Parameters by Indication**




Reviewed per SOP-QP2-005

A tabular summary of descriptive statistics for post-hoc estimates and derived parameters for the 200 mg Q3W regimen in the UC population is provided below:

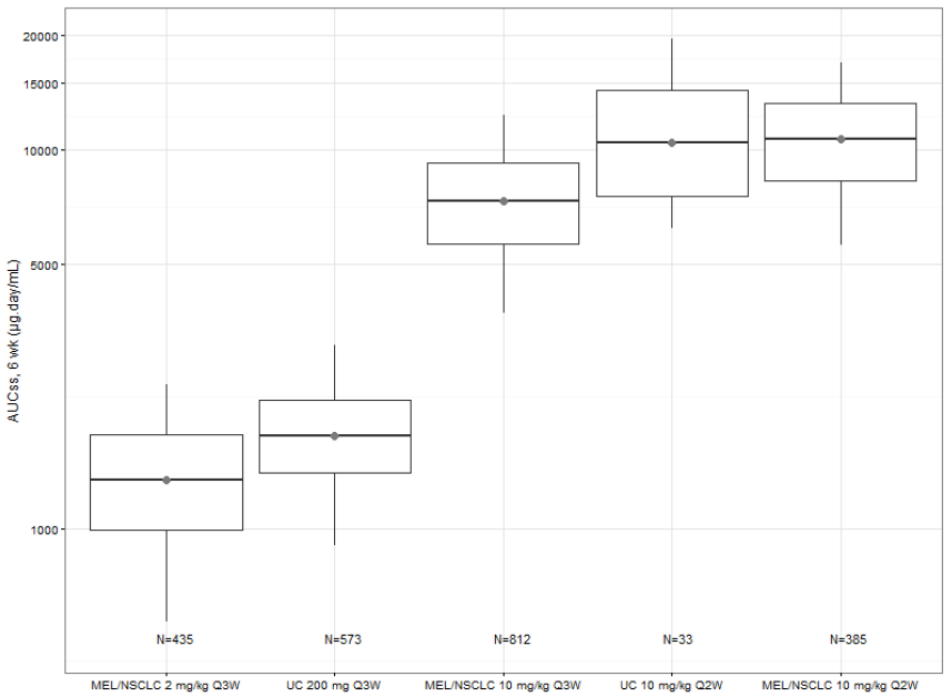
**Descriptive Statistics of Individual PK Parameters (CL, Vc) and Derived Parameters ($C_{max}$, $AUC_{ss}$, t1/2, $C_{min,ss}$) at 200 mg Q3W in UC Patients**

| | N | Mean | Median | Standard deviation |
|---|---|---|---|---|
| CL (L/day) | 573 | 0.249 | 0.227 | 0.113 |
| Vc (L) | 573 | 3.31 | 3.28 | 0.699 |
| $C_{max}$ [a] (µg/mL) | 516 | 62.7 | 60.6 | 13.3 |
| $C_{min}$ [b] (µg/mL) | 150 | 33.5 | 32.4 | 13.2 |
| Half life (days) | 573 | 24.2 | 23.9 | 7.17 |
| $AUC_{ss}$ (µg.d/mL) | 573 | 1850 | 1760 | 707 |
| $Vd_{ss}$ (L) | 573 | 7.16 | 7.07 | 1.4 |
| Time to steady state (days) | 573 | 121 | 119 | 35.9 |

[a] Cmax is concentration at time of peak sample in Cycle 1
[b] Cmin is trough concentration Cycle 8 through 12
Reviewed per SOP-QP2-005

Additionally, the observed exposures for UC subjects receiving the 200 mg Q3W regimen were compared to prior data at 2 mg/kg Q3W and 10 mg/kg Q2W in melanoma and NSCLC subjects:

**Pembrolizumab (MK-3475) Exposure across Indications at Clinically Tested Dose Regimens (Log Scale)**



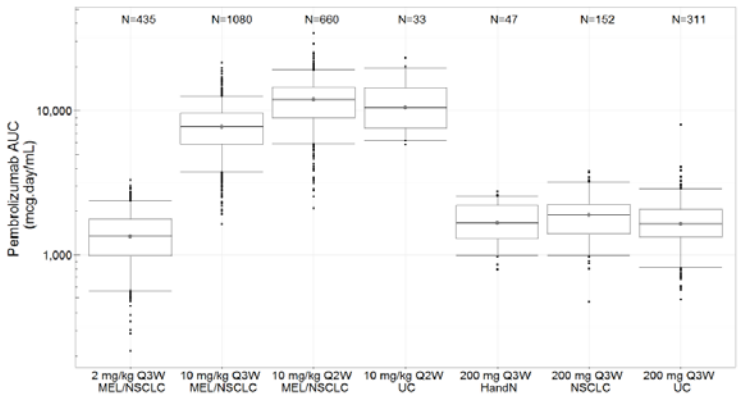

Reviewed per SOP-QP2-005

When assessed specifically for line of therapy (first line / second line) the exposures at 200 mg Q3W in UC subjects are similar to those from other indications at the same regimen.

The following figure shows a comparison of exposure (AUC) across indications at clinically tested doses (log Scale) for the first- and second line UC patients, separately.

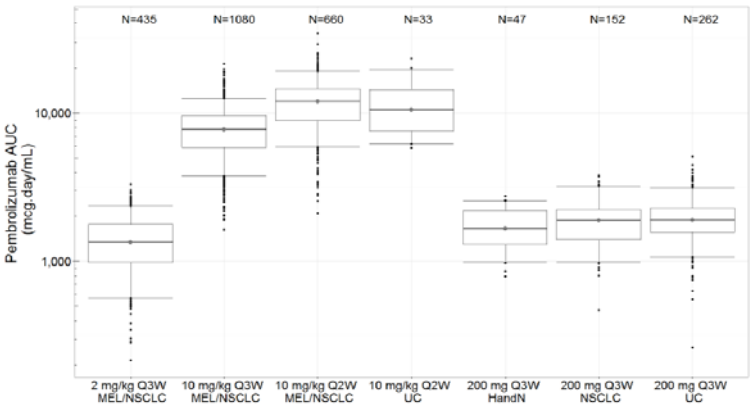
**Pembrolizumab (MK-3475) Exposure (AUC) Across Indications at Clinically Tested Doses (Log Scale)**

**First line (KN052)**




Note: Individual AUCss, 6 weeks estimates based on post-hoc clearance estimates.
Source: [Ref. 5.3.5.3: 04JR0J: Figure 6]

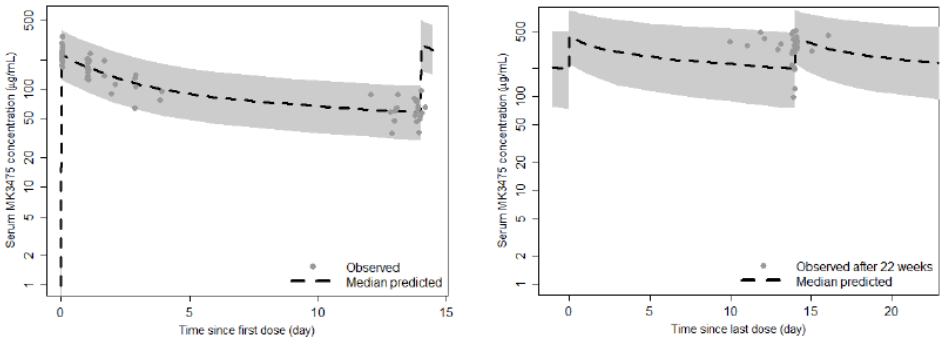
**Second line (KN045)**




Note: Individual AUCss, 6 weeks estimates based on post-hoc clearance estimates.
Source: [Ref. 5.3.5.3: 04JT5G: Figure 6]

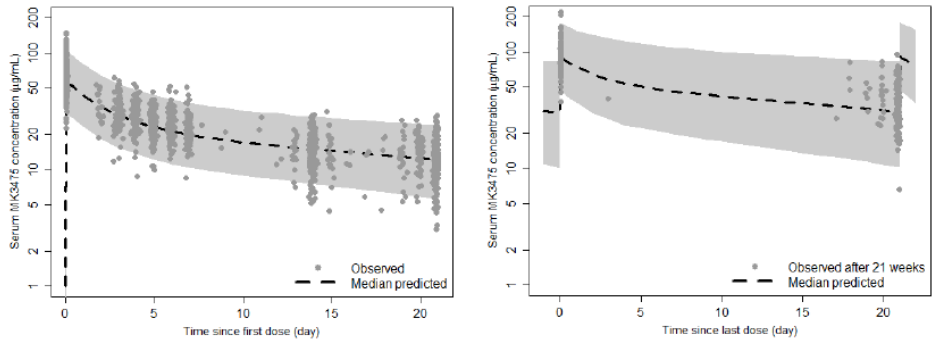
The figures below report the Pembrolizumab serum concentrations for the UC subjects treated with 10 mg/kg Q2W or 200 mg Q3W, together with a predicted concentration range (median and 90% prediction interval) from the definitive population PK model, based on the data from patients with melanoma or NSCLC.

**Consistency of Observed Concentrations in UC Subjects with Predictions Based on Definitive Population PK Model: Pembrolizumab (MK-3475) Concentration-Time Profiles during the First Dose (left panel) and at Steady State (right panel) of Repeated Dosing at 10 mg/kg Q2W**




Left panel: after first dose; right panel: at steady state (after 22 weeks). Dots are individual data from UC patients; Solid line is median prediction from the model for a regimen of 10 mg/kg Q2W and the shaded area represents the 90% prediction interval.
Reviewed per SOP-QP2-005

**Consistency of Observed Concentrations in UC Subjects with Predictions Based on Definitive Population PK Model: Pembrolizumab (MK-3475) Concentration-Time Profiles during the First Dose (left panel) and at Steady State (right panel) of Repeated Dosing at 200 mg Q3W**




Left panel: after first dose; right panel: at steady state (after 21 weeks). Dots are individual data from UC patients; Dashed line is median prediction from the model for a regimen of 200 mg Q3W and the shaded area represents the 90% prediction interval.
Reviewed per SOP-QP2-005

The MAH provided additional comparison of the observed PK data (trough and peak concentrations at each cycle) with those obtained with the 200 mg Q3W flat dose for UC and non-UC patients (1L NSCLC and HL) by means of tabular summaries of descriptive statistics and boxplots. Exposure reached in patients with UC is consistent with other indications at the same dose level.

## 2.3.5. Discussion on clinical pharmacology

The starting point for the population PK analysis submitted in this variation application was the previous population PK analysis 04DDV3 based on dataset including 2188 subjects across the melanoma and NSCLC indications (KN001, KN002 and KN006 studies). This analysis is considered the definitive population PK model to inform the label for pembrolizumab and no further model development was performed in the current analysis which incorporates data from UC patients recruited in studies KN012 (Cohort C), KN045 (second line) and KN052 (first line cisplatin ineligible).

Thus, the final dataset consists of a total of 14976 determinations of pembrolizumab concentrations from 2794 patients (606 UC out of 2794).

The approach taken was to utilise the definitve population PK model to predict pembrolizumab levels in UC patients after 200 mg Q3W and 10 mg/kg Q2W. The predictions were compared with observed levels determined in studies KN012 (Cohort C), KN045 and KN052.

Overall, the model proved adequate to capture pembrolizumab concentration indicating that the definitive population PK model provides an adequate representation of the pembrolizumab pharmacokinetics in UC, in addition to melanoma and NSCLC.

Observed plasma concentration in UC subjects both during the first dose (10 mg/kg or 200 mg Q3W) and at steady state after repeated doses (10 mg/kg or 200 mg Q3W) fall within the range of predicted concentration showing consistency in exposure between UC and other indications.

The PK report and the evaluation of studies KN012, KN045 and KN052 include descriptive statistics of serum concentration values of pembrolizumab following administration of multiple I.V 200 mg Q3W in UC patients and multiple 2 mg/kg I.V doses Q3W in KN001 melanoma and NSCLC patients.

Comparisons of peak and trough concentrations between indications showed that Pembrolizumab serum concentrations in cycle 1, 2 and 8 observed at 200 mg Q3W in UC patients are slightly higher compared to the range of concentrations at dose levels of 2 mg/kg Q3W observed in MEL and NSCLC patients.

The data presented showed that this difference in pembrolizumab concentration (higher value in UC patients after 200 mg Q3W compared to MEL and NSCLC after 2 mg/kg Q3W) is mainly evident in study KN045 (second line).

Generally, considering the flat relationship between dose and exposure, it is considerate unlikely that this difference could lead to a significant clinical effect.

However, all comparisons were made with other indications approved with the weight based dose regimen of 2 mg/kg, thus excluding indications approved with the flat dose of 200mg Q3W such us 1L NSCLC and HL. Similarly, the Boxplot reporting pembrolizumab exposure across indications did not consider the 200 mg Q3W dosing in 1L NSCLC (study KN024) and HL (study KN087).

Additional comparison of the observed PK data were provided (trough and peak concentrations at each cycle) with those obtained with the 200 mg Q3W flat dose for UC and non-UC patients (1L NSCLC and HL) by means of tabular summaries of descriptive statistics and boxplots.

The available concentrations after administration of the fixed dose of 200 mg Q3W for UC patients (KEYNOTE-052 and -45) were compared with those observed for 1L NSCLC patients (KN024), and cHL patients (KN087) for each cycle by time point. Exposure reached in patients with UC is consistent with other indications at the same dose level.

Moreover, a difference was observed in the PK profile of Pembrolizumab in UC patients when considering 1L and 2L studies separately, with lower exposure (AUC_ss) achieved in the first-line study KN052. To better address the comparability among UC patients and among other indications, Pembrolizumab (MK-3475) Exposure (AUC) Across Indications at Clinically Tested Doses in linear scale was provided.

As requested, the applicant elaborated on the comparison of PK in UC vs non-UC and among both UC patient groups (1L, 2L). PK differences that have been detected are deemed to be minor.

An integrated immunogenicity evaluation has been performed using data across studies keynote-001, -002, -006, -012, -013, -024, -045, -052, -055, -087 and -164. A total of 3727 subjects were included in the immunogenicity assessment across indications (1535 melanoma, 1238 NSCLC, 101 HNSCC, 45 MSI-H, 220 HL and 579 UC) and across doses (at 2 mg/kg Q3W, 10 mg/kg Q3W/Q2W and 200 mg Q3W). Out of the 3727 subjects included in the immunogenicity assessment, 2034 subjects were evaluable. The observed incidence of treatment emergent ADA in evaluable subjects based on the pooled analysis is 1.8% (36 out of 2034). Of the 36 treatment emergent positive subjects, 9 (1 melanoma, 5 NSCLC, 1 HL

and 2 UC) tested positive in the neutralizing assay. The 9 subjects positive in the neutralizing assay accounted for a total incidence rate of treatment neutralizing positive subjects of 0.4% (9 out of 2034) in the overall population.

The incidence of treatment emergent ADA in subjects with UC is comparable to the overall incidence and consistent with other indications. No impact of binding or neutralizing ADA on pembrolizumab exposure was observed.

### 2.3.6. Conclusions on clinical pharmacology

The pharmacology data submitted are considered appropriate and supportive for this application.

## *2.4. Clinical efficacy*

To support the Keytruda extension of indication in the treatment of locally advanced or metastatic urothelial carcinoma both for patients who have received prior chemotherapy and for those who are not eligible for cisplatin-containing chemotherapy, two single pivotal studies, each including patients in the two specific settings, have been submitted:

1. Study KEYNOTE-045, in a second-line setting for patients who progressed following treatment with platinum-containing chemotherapy, and
2. Study KEYNOTE-052 in patients previously untreated and not eligible to cisplatin-containing chemotherapy.

| Study ID / centres / locations | Study design | Treatment | No of pts planned / random / treated | Demographics | Primary endpoint | Secondary efficacy endpoints |
|---|---|---|---|---|---|---|
| **KEYNOTE-045**<br><br>120 enrolling centers in 29 countries:<br><br>Australia (3), Austria (4), Belgium (2), Canada (2), Chile (2), Denmark (4), France (5), Germany (4), Hungary (5), Ireland (1), Israel (7), Italy (6), Japan (20), Netherland (3), New Zealand (2), Norway (2), Peru (1), Poland (1), Portugal (2), Puerto Rico (1), Romania (2), Singapore (1), Spain (6), South Korea (3), Singapore (1), Sweden (1), Turkey (4), United Kingdom (2), United States (19), Taiwan (5). | Randomized (1:1), multicenter, open-label, active-controlled trial of pembrolizumab monotherapy vs investigator'choice in subjects with metastatic or locally advanced/unresectable urothelial carcinoma that had recurred or progressed following platinum-containing chemotherapy. | **pembrolizumab**<br>200 mg IV Q3W<br><br>**Investigator's choice**<br><br>paclitaxel<br>175 mg/m$^2$ IV Q3W<br>or<br><br>docetaxel<br>75mg/m$^2$ IV Q3W<br>or<br><br>vinflunine<br>320 mg/m$^2$ IV Q3W | 235/270/266<br><br>235/272/255<br><br>84 pts treated<br><br>84 pts treated<br><br>87 pts treated | Sex: 200M/70F<br><br>Median age (min/max): 67 years (29-88)<br><br>Sex: 202M/70F<br><br>Median age (min/max): 65 years (26-84) | **PFS**<br>(RECIST 1.1) by BICR<br><br>**OS** | **ORR**<br>(RECIST and mRECIST 1.1) by BICR<br><br>**DOR**<br>(RECIST 1.1) by BICR<br><br>**PFS**<br>(mRECIST 1.1) by BICR<br><br>**PFS**<br>At 6 and 12 mo<br>(RECIST 1.1) by BICR |

| | | | | | | |
|---|---|---|---|---|---|---|
| **KEYNOTE-052**<br><br>77 enrolling centers in 17 countries:<br><br>Australia (1), Canada (8), Denmark (2), Guatemala (2), Hungary (4), Ireland (1), Israel (5), Italy (3), Malaysia (1) Netherland (1), Puerto Rico (1), Singapore (2), Spain (9), Republic of Korea (3), United Kingdom (4), United States (28), Taiwan (2). | Non-randomized, multicenter, open-label trial, in subjects with metastatic or locally advanced/unresectable or metastatic urothelial carcinoma who have not received prior systemic chemotherapy, and who are not eligible to receive cisplatin. | **pembrolizumab**<br>200 mg IV Q3W | 350/370/370 | | **ORR**<br>(RECIST 1.1) by BICR<br>in<br>●all patients<br>●PD-L1 + (CPS≥1%)<br>●PD-L1 strongly + | **DOR**<br>(RECIST 1.1)<br>by BICR<br><br>**PFS**<br>(RECIST 1.1)<br>by BICR<br><br>**OS** |

## 2.4.1. Dose response study(ies)

A fixed-dose regimen of pembrolizumab 200 mg Q3W is administered in both pivotal studies for the treatment of urothelial carcinoma (UC). Thirty-three patients with heavily pre-treated urinary tract cancer received pembrolizumab 10 mg/kg Q2W in the phase Ib multi-cohort study KEYNOTE-012. Among the overall 27 patients PD-L1 ≥1% assessable for activity, an overall response rate of 26%, including 11% of complete responses (by independent central review per RECIST 1.1), was achieved. Overall, the median duration of response was 10 months, with 2 CR still ongoing after 13 months of median follow up (Plimack E R, et al Lancet Oncol 2017; 18:212-220).

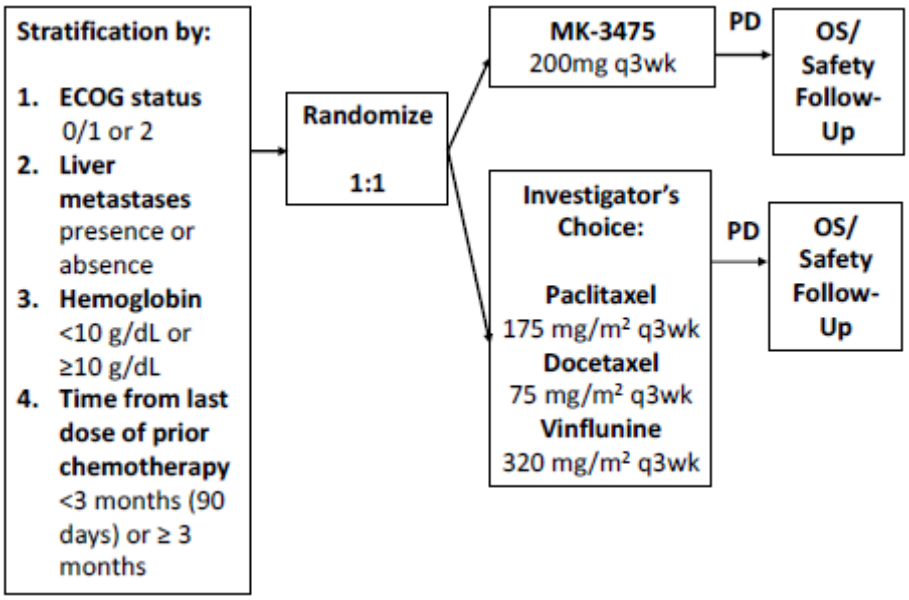
An integrated body of evidence suggests that 200 mg Q3W of pembrolizumab provides similar response to 2 mg/kg Q3W, 10 mg/kg Q3W, and 10 mg/kg Q2W.

Overall, the clinical data in urothelial carcinoma subjects, demonstrating efficacy at 200 mg Q3W and similarity of clinical response over a wide dose range (200 mg flat dose to 10 mg/kg), in conjunction with an integrated body of evidence in melanoma and NSCLC patients, support the use of pembrolizumab 200 mg Q3W fixed-dose as the appropriate dosing for urothelial carcinoma (see Section 2.3.4).

## 2.4.2. Main study(ies)

### Study Keynote-045: A Phase III Randomized Clinical Trial of Pembrolizumab versus Paclitaxel, Docetaxel or Vinflunine in Subjects with Recurrent or Progressive Metastatic Urothelial Cancer

**Figure: Trial design**




Note: The overall proportion of subjects receiving vinflunine in the control arm was initially planned to be capped at approximately 35%, however, the cap was never implemented. Vinflunine was only a comparator option in countries where vinflunine is approved for the treatment of metastatic urothelial cancer. Docetaxel was only a comparator option for subjects with a total bilirubin ≤1 x ULN, and an AST ≤ 1.5 x ULN if alkaline phosphatase is also >2.5 x ULN.

### *Methods*

### Study participants

*Main inclusion criteria*

- Histologically or cytologically confirmed diagnosis of urothelial cancer of the renal pelvis, ureter, bladder, or urethra. Both transitional cell and mixed transitional/nontransitional cell histologies were allowed, but transitional cell carcinoma had to be the predominant histology.
- Age ≥18 years
- Progression or recurrence of urothelial cancer following receipt of a 1st line platinum-containing regimen (eg, cisplatin or carboplatin) that was received:

a. in the metastatic setting or for inoperable locally advanced disease;

or

b. as adjuvant therapy following cystectomy for localized muscle-invasive urothelial cancer, with recurrence/progression ≤ 12 months following completion of therapy;

or

c. as neoadjuvant therapy prior to cystectomy for localized muscle-invasive urothelial cancer, with recurrence ≤ 12 months following completion of therapy.

*Notes: Primary chemo-radiation given for subjects who were not considered surgical candidates was not considered a line of therapy for the purpose of this study. Subjects with locally advanced unresectable disease who subsequently became eligible for surgery after platinum-containing therapy were not eligible for this study, unless they subsequently had disease recurrence in the metastatic setting.*

- No more than 2 prior lines of systemic chemotherapy for metastatic urothelial cancer. Subjects for whom the most recent therapy was a non-platinum-based regimen following progression/recurrence on platinum-based therapy (ie, third-line subjects) were eligible if they had progressed/recurred on their most recent therapy.

*Note: primary chemo-radiation for unresectable muscle-invasive bladder cancer with the aim of bladder preservation was not considered a prior line of systemic therapy for the purposes of determining study eligibility.*

- Provided tissue for biomarker analysis from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. A newly-obtained biopsy was strongly preferred but not required if archival tissue was adequate for analysis. Adequacy of the archived or freshly-obtained biopsy specimen had to be confirmed by the central laboratory during the screening period prior to enrollment.
- Measureable disease based on RECIST 1.1 as assessed by the Investigator/site radiologist. Tumor lesions situated in a previously irradiated area were considered measureable if progression had been demonstrated in such lesions.
- ECOG Performance Status of 0, 1, or 2, as assessed within 10 days prior to treatment initiation. Subjects with an ECOG-PS of 2 had to have a hemoglobin ≥ 10 g/dL, could not have liver metastases, and must have received the last dose of their last prior chemotherapy regimen ≥ 3 months (90 days) prior to enrollment.

*Main exclusion criteria*

- Disease suitable for local therapy administered with curative intent.
- Current or previous participation in a study of an investigational agent, with study therapy received or investigation device used within 4 weeks of the first dose of treatment.
- Diagnosis of immunodeficiency or ongoing systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids could have been approved after consultation with the Sponsor.

- Prior anticancer monoclonal antibody within 4 weeks prior to study Day 1 or not recovered (ie, ≤ Grade 1 or at baseline) from AEs due to agents administered more than 4 weeks earlier.
- Prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who had not recovered (ie, ≤ Grade 1 or at baseline) from AEs due to a previously administered agent.

*Notes: Subjects with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia are an exception to this criterion and could qualify for the study. If a subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.*

- Known additional malignancy progressing or requiring active treatment. Exceptions included basal cell carcinoma of the skin, squamous cell carcinoma of the skin that had undergone potentially curative therapy, or in situ cervical cancer. A history of prostate cancer identified incidentally following cysto-prostatectomy for bladder cancer was acceptable, provided that Stage was T2N0M0 or lower, Gleason score ≤ 6, and prostate-specific antigen undetectable.
- History of severe hypersensitivity reaction (eg, generalized rash/erythema, hypotension, bronchospasm, angioedema, or anaphylaxis) to paclitaxel or to other drugs formulated with polyoxyethylated castor oil, to docetaxel or other drugs formulated with polysorbate 80, or to vinflunine or other vinca alkaloids.
- History or current evidence of any condition, therapy, or laboratory abnormality that could confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or not in the best interest of the subject to participate, in the opinion of the treating Investigator.
- Prior therapy with an anti-PD-1, anti-PD-L1 agent, or with an agent directed to another co-inhibitory T-cell receptor (e.g. CTLA-4,OX-40, CD137).
- Known active central nervous system metastases and/or carcinomatous meningitis. Subjects with previously-treated brain metastases could participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of trial treatment and any neurologic symptoms had returned to baseline), had no evidence of new or enlarging brain metastases, and were not using steroids for at least 7 days prior to trial treatment. This exception did not include carcinomatous meningitis, which was excluded regardless of clinical stability.
- Active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that required systemic or immunosuppressive agents. Subjects with vitiligo, Type I diabetes, or resolved childhood asthma/atopy could be an exception to this rule. Subjects who required intermittent use of bronchodilators, inhaled steroids, or local steroid injections were not excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjögren's syndrome were not excluded from the study.
- Required ongoing therapy with a medication that was a strong inhibitor or inducer of the CYP3A4 enzymes.
- Administration of live vaccine within 30 days prior to the first administration of study medication.

## Treatments

- Pembrolizumab 200 mg administered as a 30 minute (-5 min/+10 min) IV infusion Q3W.
- Investigator's choice:
    - paclitaxel 175 mg/m$^2$ administered over 1 hours IV infusion Q3W
    - docetaxel 75 mg/m$^2$ administered over 1 hour IV infusion Q3W
    - vinflunine 320 mg/m$^2$ administered as a 20 minute IV infusion Q3W

The appropriate premedication regimen prior to paclitaxel and docetaxel administration may be determined by the investigator.

In case of mild hepatic impairment (total bilirubin ≥ 1.25 × ULN), paclitaxel was to be started at a dose of 135 mg/m$^2$.

Docetaxel was a comparator option only for subjects with a total bilirubin ≤ 1 × ULN, and an AST and/or ALT ≤ 1.5 × ULN if alkaline phosphatase was also > 2.5 × ULN.

Vinflunine was only a comparator option in countries where vinflunine was approved for the treatment of metastatic urothelial cancer. Vinflunine starting dose was to be modified in the following cases:

| | |
|---|---|
| ECOG-PS≥ 1 or ECOG-PS 0 and prior pelvic irradiation | 280 mg/m² Q3W<br>In the absence of any hematological toxicity during the first cycle causing treatment delay or dose reduction, the dose was to be increased to 320 mg/m$^2$ Q3W for the subsequent cycles |
| *Renal impairment*<br><br>moderate (40 ml/min≤CrCl≤60 ml/min)<br><br>severe (30 ml/min≤CrCl<40 ml/min) | <br><br>280 mg/m² Q3W<br><br>250 mg/m² Q3W |
| *Liver impairment*<br>Child-Pugh grade A or Prothrombin time ≥ 60% NV and 1.5xULN < Bilirubin ≤ xULN and presenting transaminases > ULN and/or GGT > 5xULN | 250 mg/m²Q3W |
| *Age ≥75 years*<br><br>≥75 years <80<br><br>≥80 years | <br><br>280 mg/m² Q3W<br><br>250 mg/m²Q3W |

Subjects continued with the assigned treatment until RECIST 1.1-defined progression confirmed by the investigator/site radiologist, unacceptable toxicity, intercurrent illness that prevented further administration of treatment, Investigator's decision to withdraw the subject, subject withdrew consent, confirmed positive pregnancy test, non-compliance with trial treatment or procedure requirements, the subject had received 24 months of pembrolizumab treatment or administrative reasons.

Despite RECIST 1.1 defined progression, pembrolizumab could have been continued while awaiting radiologic confirmation of PD. If repeat imaging still meets the threshold for PD (≥ 20% increase in tumor burden compared to nadir) but shows a reduction in tumor burden compared to the previous time point, treatment may be continued as per treatment calendar after consultation with Sponsor.

Patients who stopped pembrolizumab after receiving 24 months of treatment for reasons other than disease progression or intolerability, or after a complete response having received at least 24 weeks of pembrolizumab and at least 2 treatments beyond the date of initial CR declared, may have been eligible, at discretion of the investigator, for up to one year of retreatment upon experiencing disease progression (Second Course Phase).

Patients in the experimental arm were allowed to stay on treatment after PD based on RECIST 1.1 to account for pseudo-progressions and delayed responses. Overall, 98 patients were treated beyond first radiographic progression, and treatment was continued in 40% of them, including 17 patients who were not confirmed to be in progression and 22 patients with confirmed radiographic progression.

## Objectives

The study primary objective was to demonstrate the superiority of pembrolizumab versus Investigator's choice (paclitaxel, docetaxel or vinflunine) in terms of Progression Free Survival (PFS) per RECIST 1.1 by blinded independent central review (BICR), and of Overall Survival (OS) in all subjects with recurrent/progressive after platinum-based chemotherapy metastatic urothelial cancer, as well as in those with PD-L1 positive (CPS≥1%) and PD-L1 strongly positive (CPS≥10%) tumors.

The trial was considered to have met its primary objective if the pembrolizumab arm was superior to paclitaxel, docetaxel, or vinflunine in any of the following:

- H1: PFS in all subjects (regardless of PD-L1 expression)
- H2: OS in all subjects (regardless of PD-L1 expression)
- H3: PFS in subjects with PD-L1 positive expression (CPS≥1%)
- H4: OS in subjects with PD-L1 positive expression (CPS≥1%)
- H5: PFS in subjects with PD-L1 strongly positive expression (CPS≥10%)
- H6: OS in subjects with PD-L1 strongly positive expression (CPS≥10%)

As secondary objectives, Objective Response Rate (ORR) and response duration per RECIST 1.1 by BICR, ORR per modified RECIST (mRECIST) by BICR, PFS per mRECIST by BICR and per RECIST 1.1 from randomization to specific timepoints (6 months, 12 months), and safety and tolerability profile of pembrolizumab compared to Investigator's choice were evaluated in all subjects, as well as in those with PD-L1 positive (CPS≥1%) and PD-L1 strongly positive (CPS≥10%) recurrent/progressive metastatic urothelial cancer.

Other exploratory objectives were to evaluate changes in health-related quality of life assessment from baseline (eEORTC QLQ-C30), to characterize utilities (eEQ-5D), to investigate the relationship between

PD-L1 expression and response to pembrolizumab treatment, as well as between pembrolizumab treatment and biomarkers predicting response (eg, immunohistochemistry, proteomic signatures, genetic variation, and gene expression signatures) utilizing newly obtained or archival formalin-fixed, paraffin-embedded (FFPE) tumor tissue, and to evaluate PFS per RECIST 1.1 by Investigator review in the next line of therapy in patients treated with pembrolizumab in comparison to those who received paclitaxel, docetaxel or vinflunine.

## Outcomes / endpoints

The dual primary efficacy endpoints were PFS (i.e. time from randomization to the first documented disease progression per RECIST 1.1 based on BICR or death due to any cause, whichever occurs first), and OS (i.e. time from randomization to death due to any cause).

As secondary endpoints, ORR per RECIST 1.1 and mRECIST by BICR, duration response per RECIST 1.1 by BICR and PFS per mRECIST were evaluated.

ORR was defined as the proportion of the subjects in the analysis population who have a confirmed complete response (CR) or partial response (PR), based upon blinded independent central radiologists' review per RECIST 1.1.

Response duration was defined as the time from first documented evidence of confirmed CR or PR until disease progression or death. For subjects who had not progressed or died at the time of analysis, response duration was censored at the date of their last tumor assessment.

PFS and ORR per mRECIST were defined as for endpoints using RECIST 1.1, with the exception that a confirmation of progressive disease (PD) at least 4 weeks after the initial assessment was required for subjects who remained on treatment following a documented PD per RECIST 1.1. Subjects who discontinued treatment following a documented PD assessment per RECIST 1.1 were counted as having disease progression on the date of the documented PD assessment.

The assessment of response was performed initially at Week 9 (±7days), then every 6 weeks (±7 days) for the first year and every 12 weeks (±7 days) thereafter. Images obtained on study were submitted for BICR and were assessed based on the RECIST 1.1 for determination of ORR and PFS. Investigator/local site assessment of measurable disease, based on RECIST 1.1, was used to determine subject eligibility. Investigator assessment based on modified RECIST and site radiology reading(s) was used for treatment decisions and subject management.

Among the planned exploratory endpoints, results have been submitted for EORTC QLQ-C30 and EUROQoL EQ-5D. No formal hypotheses were formulated for PRO.

The global health status/quality of life scale from EORTC QLQ-C30, containing 5 functioning scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, nausea, pain), and six single item measures (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), was the key PRO endpoint, in particular in terms of mean score changes from baseline to week 15 and Time to deterioration (TTD), measured as the time point when the score decreases by ≥10 (out of 100), with or without subsequent confirmation. Supportive analyses included all QLQ-C30 sub-scales/items and alternative approaches such as estimating the effect of disease progression on HRQoL.

## Sample size

The trial planned to randomize 470 subjects in a 1:1 ratio between pembrolizumab and the standard treatment arm. The sample size calculation was driven by survival events. Assuming the prevalence rates of PD-L1 CPS ≥1% and PD-L1 CPS ≥10% subjects among the overall population of 55% and 33%, respectively, a sample size of 470 all subjects would provide approximately 260 PD-L1 CPS ≥1% subjects and 156 PD-L1 CPS ≥10% subjects.

The assumptions for the sample size and power calculation of PFS were that PFS follows an exponential distribution with a median of 4 months in the standard treatment arm; the true HR between pembrolizumab and standard therapy are 0.45, 0.5, and 0.5 for PD-L1 CPS ≥10%, PD-L1 CPS ≥1%, and all subjects, respectively; an enrollment period of 12 months; and a yearly drop-out rate of 5%.

Based on information from study KEYNOTE-052, indicating that the PD-L1 CPS ≥ 10% cutpoint is more meaningful than CPS ≥ 1% used in KEYNOTE-012, the study protocol was amended after IA1, and only the primary hypotheses for all comers and subjects with PD-L1 CPS >10% were retained.

The numbers of PFS events in PD-L1 CPS ≥ 10% and all subjects at the final PFS evaluation were estimated to be 137 and 420, respectively, with 97% power for the PFS hypothesis in PD-L1 CPS ≥ 10% subjects and >99% power for the PFS hypothesis in all subjects.

The sample size and power calculation of OS are based on the assumptions that OS follows an exponential distribution with a median of 8 months in the standard treatment arm; the hazard ratio for OS between pembrolizumab and standard treatment is 0.5, 0.6, and 0.7 for PD-L1 CPS ≥ 10%, PD-L1 CPS ≥ 1%, and all subjects, respectively (deemed to be clinically meaningful in this population); an enrollment period of 12 months and a minimum of 18 months follow-up after enrollment completion; and a yearly drop-out rate of 2%.

The final OS analysis was to be carried out after approximately 370 deaths in all subjects and 110 deaths in PD-L1 CPS ≥10% subjects had occurred between the pembrolizumab arm and the standard treatment arm for all subjects, barring early stopping for futility or efficacy. With the above numbers of events and before any alpha roll-over, the trial provides 88% and 86% power to demonstrate OS superiority of pembrolizumab compared to standard therapy at the pre-specified initial alpha (one-sided) levels in PD-L1 CPS ≥10% and all subjects, respectively.

The family-wise type I error rate is controlled at 2.5% (one-sided) with 0.5% allocated to the PFS hypotheses and 2.0% allocated to the OS hypotheses.

## Randomisation

Randomization (1:1) to pembrolizumab or the Investigator's choice (paclitaxel, docetaxel, or vinflunine) occurred centrally with block size of 2 within each of strata, using an interactive voice response system/integrated web response system (IVRS/IWRS). Investigators had to select 1 treatment among the control arm options before randomization occurred to use in the event that the subject was randomized to the control arm.

Randomized patients were stratified according to ECOG-PS (0/1 versus 2), presence or absence of liver metastases, Hemoglobin (≥10 g/dL versus <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥3 months).

## Blinding (masking)

Not applicable. This was an open label trial.

However, in order to ensure the unbiased use/ integrity of the PD-L1 analysis, the Medical Monitoring Team, consisting of clinical, statistical, statistical programming, and data management personnel, was blinded to treatment assignments and PD-L1 biomarker results (including CPS ≥1%), until the Cut-off value of PD-L1 expression level for CPS ≥10% was established and formally documented exclusively based on data outside of this trial.

## Statistical methods

Efficacy analyses were performed in the ITT population for all subjects, for subjects with CPS ≥ 10%, and for subjects with CPS ≥ 1% (only at the first interim analysis).

The treatment difference in PFS and OS was assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (i.e. hazard ratio) between the treatment arms.

In the PFS primary analysis, for the subjects who have PD, the true date of disease progression was approximated by the date of the first assessment at which PD is objectively documented per RECIST 1.1, regardless of discontinuation of study drug. Sensitivity analyses were performed for comparison of PFS based on investigator's assessment. In order to evaluate the robustness of the PFS endpoint, two sensitivity analyses with a different set of censoring rules were performed. The first sensitivity analysis censors at the last disease assessment without PD when PD or death is documented after more than one missed disease assessment. The second sensitivity analysis considers discontinuation of treatment or initiation of new anticancer treatment, whichever occurs later, to be a PD event for subjects without documented PD or death.

For the objective response rates (ORR) the Stratified Miettinen and Nurminen's method was used for comparison between the treatment groups. Sensitivity analyses were performed for comparison of ORR based on investigator's assessment and multiple imputation methods was considered to address the issue of informative missing data.

Response duration was summarised descriptively using Kaplan-Meier medians and quartiles. Only the subset of subjects who show a complete response or partial response was included in this analysis.

Longitudinal and descriptive data analyses were used to evaluate patient-reported outcomes (PRO). Several approaches were considered to address the issue of informative missing data: (1) truncating the analysis observation period at the visit closest to median duration of treatment in the comparator arm, (2) hierarchical pattern mixture models incorporating reasons for missingness, and (3) multiple imputation methods.

*Interim Analyses*

There were two planned PFS analyses and three planned OS analyses. Results of the first PFS analysis and the interim analysis of OS were to be reviewed by an external data monitoring committee (DMC). Timing, sample size and boundaries for decision guidance are displayed in the Table below.

The second interim analyses of OS was planned to be performed about 8 months after the first PFS analysis. The final OS analysis will be conducted after ~356 OS events are observed at the alpha level determined by the spending function boundaries and actual number of OS events.

**Summary of Timing, Sample Size and Decision Guidance at the Planned PFS and OS Analyses**

| Analysis | Criteria for Conduct of Analysis (Projected timing) | Value | Approx. Number of Events | Efficacy Boundary† | | |
|---|---|---|---|---|---|---|
| | | | | Z Statistic | p-value (1-sided) at Boundary | Approx. Observed HR at Boundary |
| IA 1:<br>PFS (H1, H3, H5)<br>OS (H2, H4, H6) | Full enrollment ~ 185 OS events (50% information) for all subjects | H1 PFS All Subjects | 273 | 3.500 | 0.0002 | 0.655 |
| | | H2 OS All Subjects | 185 | 3.494 | 0.0002 | 0.598 |
| | | H3 PFS PDL1 Positive | 151 | 3.500 | 0.0002 | 0.566 |
| | | H4 OS PDL1 Positive | 99 | 2.913 | 0.0018 | 0.557 |
| | | H5 PFS PDL1 Strongly Positive | 89 | 3.196 | 0.0007 | 0.508 |
| | | H6 OS PDL1 Strongly Positive | 55 | 3.384 | 0.0004 | 0.402 |
| IA 2:<br>PFS (H1 and H5)<br>OS (H2 and H6) | ~277 OS events (75% information) for all subjects and ~ 82 OS events (75% information) for PDL1 Strongly Positive Subjects | H1 PFS All Subjects | 357 | 3.345 | 0.0004 | 0.702 |
| | | H2 OS All Subjects | 277 | 2.683 | 0.0036 | 0.725 |
| | | H5 PFS PDL1 Strongly Positive | 116 | 2.865 | 0.0021 | 0.588 |
| | | H6 OS PDL1 Strongly Positive | 82 | 2.745 | 0.0030 | 0.546 |
| Final Analysis:<br>PFS (H1and H5)<br>OS (H2 and H6) | ~ 370 OS events for all subjects and ~110 OS events for PDL1 Strongly Positive Subjects | H1 PFS All Subjects | 420 | 3.182 | 0.0007 | 0.733 |
| | | H2 OS All Subjects | 370 | 2.381 | 0.0086 | 0.781 |
| | | H5 PFS PDL1 Strongly Positive | 137 | 2.782 | 0.0027 | 0.622 |
| | | H6 OS PDL1 Strongly Positive | 110 | 2.459 | 0.0070 | 0.625 |

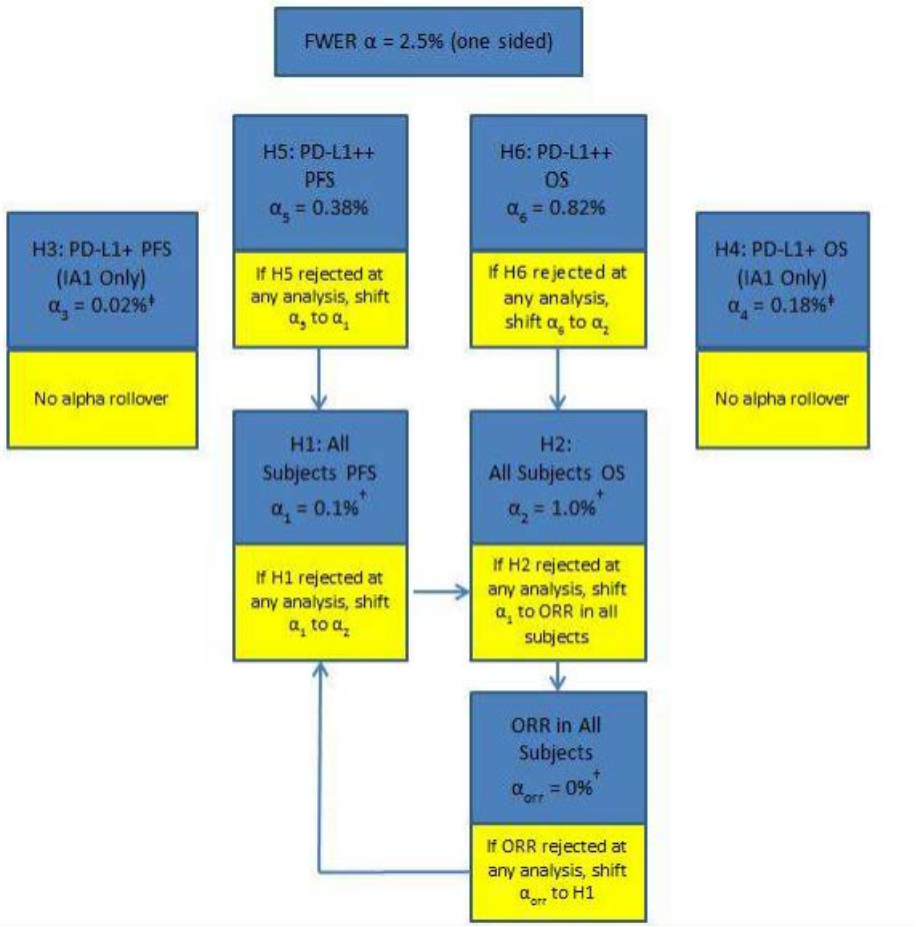
† Based on initially assigned type I error rate before any alpha roll-over and projected number of events at study mile stones. Actual efficacy boundaries will be based on actual numbers of events available at study milestones.

*Multiplicity Adjustment*

The family-wise type I error rate is controlled at 2.5% (one-sided) with 0.5% allocated to the PFS hypothesis and 2.0% allocated to the OS hypothesis. A strategy for the control of the family-wise type I error rate (FWER) was done to take into account the six primary hypotheses (two primary endpoints and three population) and the two planned interim analyses.

The alpha initially allocated among the six hypotheses, and the reallocation strategy according to the method of Maurer and Bretz, are displayed in the Figure below.

Type I Error Reallocation Strategy Following Closed Testing Principle




For each analysis (IA1, IA2 and final), alpha allocation was determined by applying a Hwang-Shih-DeCani alpha-spending function with the gamma parameter (-4).

As the biomarker strategy was changed (Amendment 13) and the hypotheses on PD-L1 positive (CPS ≥1%) were not be formally tested at the second interim analysis and the final analysis, the alpha allocation was revised accordingly to reflect the change in biomarker strategy. The reallocation of alpha occurred after the conduct of IA1. The type I error actually spent at IA1 was to be kept intact and the reallocation was to be applied only to the remaining unspent alpha, by first applying the same HSD gamma (-4) spending function and then updated based on the actual numbers of events (information fraction) and alpha roll-over.

The secondary hypotheses on PFS (modified RECIST 1.1), ORR (RECIST 1.1) and ORR (modified RECIST 1.1), were tested sequentially with alpha level depending on the alpha roll-over. The updated efficacy boundaries after taking into consideration of all alpha rollovers are summarized in the Table (see below).

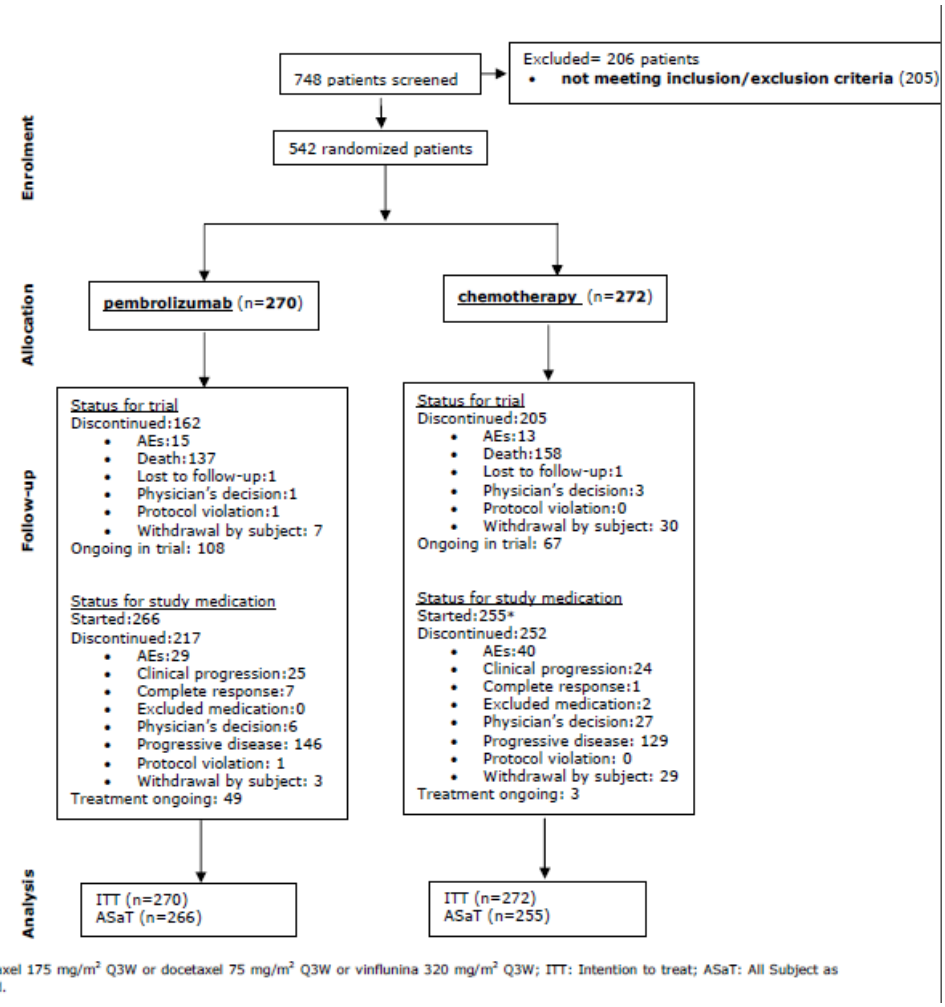
Updated Efficacy Boundary After Alpha Rollover

| Hypothesis | Alpha Allocation† for each Hypothesis after alpha roll-over | Updated Cumulative Alpha Spending (% of Overall Alpha) | | Updated Efficacy Boundary in p-Value (and Z-Statistic) at IA2 |
|---|---|---|---|---|
| | | IA1 | IA2 | |
| H1: PFS in All Subjects | 0.019212‡ | 0.012891 (67.1%) | 0.019212 (100%) | 0.0151 (2.168) |
| H2: OS in All Subjects | 0.018212♯ | 0.000674 (3.7%) | 0.012457 (68.4%) | 0.0123 (2.246) |
| H5: PFS in PD-L1 Strongly Positive | 0.003709 | 0.000867 (23.4%) | 0.003241 (87.4%) | 0.0029 (2.7590) |
| H6: OS in PD-L1 Strongly Positive | 0.008212 | 0.000584 (7.1%) | 0.006677 (81.3%) | 0.0065 (2.4836) |
| ORR in All Subjects | 0.018212$ | 0.003188 (17.5%) | 0.018212 (100%) | 0.0170 (2.1207) |

† The overall alpha allocated to the hypothesis, not the single analysis;
‡ Updated based on alpha rollover from H6, H2 and ORR in All Subjects;
♯ Updated based on alpha rollover from H6;
$ Updated based on alpha rollover from H6 and H2.

## *Results*

## Participant flow




*paclitaxel 175 mg/m² Q3W or docetaxel 75 mg/m² Q3W or vinflunina 320 mg/m² Q3W; ITT: Intention to treat; ASaT: All Subject as Treated.

## Recruitment

Overall, 542 patients were enrolled in 120 out of the 140 activated sites. The recruitment period lasted 1 year, with the first patient entered on 23 October 2014 and the last one randomized on 13 November 2015. The highest enrolling country was the US with a total of 105 subjects.

## Conduct of the study

A total of 14 amendments to the original protocol (dated 23 Jun 2014), including global and country-specific changes, were implemented during the study.

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

| Protocol Amendment | Most relevant changes |
|---|---|
| #01 (1 August 2014) | Country specific (Germany): the timing for follow-up radiographic imaging was changed to every 12 weeks (±7 days) following the initial radiographic assessment at 9 weeks or sooner if clinically indicated. |
| #2 (26 August 2014) | To include docetaxel as a comparator in the control arm. |
| # 3 (28 August 2014) | Country specific (Germany): to incorporate modifications as for Amendment #2. |
| #4 (not released) | To incorporate the agency feedback and to update the statistical analysis plan, including elevating PFS and OS in subjects with PD-L1 positive and PD-L1 strongly positive tumors to co-primary objectives. Due to a change in the biomarker strategy, this amendment was not released to the Health Authorities. |
| #5 (not released) | Country specific (Germany): to incorporate modifications as for Amendment #4. |
| #6 (15 January 2015) | Country specific (UK): to exclude subjects who required ongoing therapy with medications that are strong inducers of the CYP3A4 enzymes. |
| #7 (20 February 2015) | Country specific (France): to incorporate as Appendix the current Event of Clinical Interest (ECI) Guidance Document (18-Dec-2014 |
| #8 (not released) | Country specific (France): to incorporate modifications as for Amendment #4. |
| #9 (27 February 2016) | To include the planned changes for Amendment 04: incorporated agency feedback, and PFS and OS in subjects with PD-L1 positive (CPS ≥ 1%) and PD-L1 strongly positive tumors as co-primary objectives due to emerging evidence suggesting that PD-L1 status may correlate to outcomes. In addition, the statistical analysis plan was updated throughout to reflect the incorporation of the analyses of the primary hypotheses on PD-L1 positive (CPS ≥ 1%) |

| | |
|---|---|
| | and PD-L1 strongly positive subjects. |
| #10 (10 March 2016) | Country specific (Germany): to incorporate modifications as for Amendment #9. |
| #11 (26 May 2016) | To update the statistical analysis plan to account for the number of events in the PD-L1 positive (CPS ≥ 1%) subjects in timing and conduct of the interim and final analysis, because most of the alpha for testing OS was allocated to the PD-L1 positive(CPS ≥ 1%) biomarker subgroup. The statistical analysis plan was also updated to account for the possible postponement of the second interim analysis and/or the final analysis for up to 4 additional months to accrue enough OS events in the PD-L1 positive (CPS ≥ 1%) subjects after the planned number of OS events in all subjects is achieved. |
| #12 (21 June 2016) | Country specific (Germany): to incorporate modifications as for Amendment #11. |
| #13 (19 September 2016) | To clarify that the basis for PD-L1 positive and strongly positive categories using CPS cutpoints was determined from external data (ie, KEYNOTE-012, KEYNOTE-052, and epidemiologic studies).<br><br>The biomarker strategy was changed based on these emerging data. Primary hypotheses on PD-L1 positive (CPS ≥ 1%) subjects would not be formally tested at the second interim analysis and the final analysis. Alpha allocation among the primary hypotheses for interim and final analyses was revised accordingly to reflect the change in biomarker strategy. The reallocation of alpha occurs after the conduct of IA1, and proper adjustment was made to maintain the control of family-wise type I error rate (FWER) with implementation of this change |
| #14 (19 September 2016) | Country specific (Germany): to incorporate modifications as for Amendment #13. |

Clinically relevant protocol deviations were reported in a total of 28 patients, and concerned entry criteria (16 patients), discontinuation criteria (1 patient), and prohibited medication (11 patients). No subject was excluded from the analysis due to protocol deviation.

## Baseline data

Baseline characteristics of the ITT population are presented in the following Table:

**Table 1: Subjects Characteristics**

**All Subjects (ITT Population)- KEYNOTE-045**

| | Control | | Pembrolizumab | | Total | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Subjects in population | 272 | | 270 | | 542 | |
| **Gender** | | | | | | |
| Male | 202 | (74.3) | 200 | (74.1) | 402 | (74.2) |
| Female | 70 | (25.7) | 70 | (25.9) | 140 | (25.8) |
| **Age (Years)** | | | | | | |
| < 65 | 125 | (46.0) | 105 | (38.9) | 230 | (42.4) |
| >= 65 | 147 | (54.0) | 165 | (61.1) | 312 | (57.6) |
| Mean | 65.1 | | 66.0 | | 65.5 | |
| SD | 9.2 | | 10.2 | | 9.7 | |
| Median | 65.0 | | 67.0 | | 66.0 | |
| Range | 26 to 84 | | 29 to 88 | | 26 to 88 | |
| **Race** | | | | | | |
| Asian | 58 | (21.3) | 64 | (23.7) | 122 | (22.5) |
| Black Or African American | 4 | (1.5) | 5 | (1.9) | 9 | (1.7) |
| Multiple | 1 | (0.4) | 1 | (0.4) | 2 | (0.4) |
| White | 201 | (73.9) | 188 | (69.6) | 389 | (71.8) |
| Missing | 8 | (2.9) | 12 | (4.4) | 20 | (3.7) |
| **Ethnicity** | | | | | | |
| Hispanic Or Latino | 15 | (5.5) | 17 | (6.3) | 32 | (5.9) |
| Not Hispanic Or Latino | 235 | (86.4) | 221 | (81.9) | 456 | (84.1) |
| Not Reported | 16 | (5.9) | 28 | (10.4) | 44 | (8.1) |
| Unknown | 6 | (2.2) | 4 | (1.5) | 10 | (1.8) |
| **ECOG†** | | | | | | |
| [0] Normal Activity | 106 | (39.0) | 119 | (44.1) | 225 | (41.5) |
| [1] Symptoms, but ambulatory | 158 | (58.1) | 143 | (53.0) | 301 | (55.5) |
| [2] Ambulatory but unable to work | 4 | (1.5) | 2 | (0.7) | 6 | (1.1) |
| Missing | 4 | (1.5) | 6 | (2.2) | 10 | (1.8) |
| **Metastatic Staging** | | | | | | |
| MX | 0 | (0.0) | 2 | (0.7) | 2 | (0.4) |
| M0 | 10 | (3.7) | 10 | (3.7) | 20 | (3.7) |
| M1 | 261 | (96.0) | 258 | (95.6) | 519 | (95.8) |
| Missing | 1 | (0.4) | 0 | (0.0) | 1 | (0.2) |
| **Cancer Staging** | | | | | | |
| II | 0 | (0.0) | 1 | (0.4) | 1 | (0.2) |
| IV | 271 | (99.6) | 269 | (99.6) | 540 | (99.6) |
| Missing | 1 | (0.4) | 0 | (0.0) | 1 | (0.2) |

| | Control | | Pembrolizumab | | Total | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| **Prior Platinum Therapy** | | | | | | |
| Cisplatin | 213 | (78.3) | 198 | (73.3) | 411 | (75.8) |
| Carboplatin | 56 | (20.6) | 70 | (25.9) | 126 | (23.2) |
| Other (oxaliplatin,nedaplatin) | 2 | (0.7) | 1 | (0.4) | 3 | (0.6) |
| Missing | 1 | (0.4) | 1 | (0.4) | 2 | (0.4) |
| **Setting of Most Recent Prior Therapy** | | | | | | |
| Neo Adjuvant | 22 | (8.1) | 19 | (7.0) | 41 | (7.6) |
| Adjuvant | 31 | (11.4) | 12 | (4.4) | 43 | (7.9) |
| First Line | 157 | (57.7) | 183 | (67.8) | 340 | (62.7) |
| Second Line | 60 | (22.1) | 55 | (20.4) | 115 | (21.2) |
| Third Line | 1 | (0.4) | 0 | (0.0) | 1 | (0.2) |
| Missing | 1 | (0.4) | 1 | (0.4) | 2 | (0.4) |
| **Liver Metastases** | | | | | | |
| Absent | 176 | (64.7) | 179 | (66.3) | 355 | (65.5) |
| Present | 95 | (34.9) | 91 | (33.7) | 186 | (34.3) |
| Missing | 1 | (0.4) | 0 | (0.0) | 1 | (0.2) |
| **Baseline hemoglobin[‡]** | | | | | | |
| >=10 g/dL | 223 | (82.0) | 219 | (81.1) | 442 | (81.5) |
| <10 g/dL | 44 | (16.2) | 43 | (15.9) | 87 | (16.1) |
| Missing | 5 | (1.8) | 8 | (3.0) | 13 | (2.4) |
| **Time from Completion/Discontinuation of Most recent Prior Therapy to Baseline** | | | | | | |
| >=3 Months | 167 | (61.4) | 166 | (61.5) | 333 | (61.4) |
| <3 Months | 104 | (38.2) | 103 | (38.1) | 207 | (38.2) |
| Missing | 1 | (0.4) | 1 | (0.4) | 2 | (0.4) |
| **Prior Brain Metastasis Status** | | | | | | |
| Absent | 267 | (98.2) | 268 | (99.3) | 535 | (98.7) |
| Present | 5 | (1.8) | 2 | (0.7) | 7 | (1.3) |
| **Geographic Region EU** | | | | | | |
| EU | 117 | (43.0) | 106 | (39.3) | 223 | (41.1) |
| Non-EU | 155 | (57.0) | 164 | (60.7) | 319 | (58.9) |
| **Geographic Region US** | | | | | | |
| US | 59 | (21.7) | 47 | (17.4) | 106 | (19.6) |
| Non-US | 213 | (78.3) | 223 | (82.6) | 436 | (80.4) |
| **Geographic Region Asian** | | | | | | |
| East-Asian | 48 | (17.6) | 58 | (21.5) | 106 | (19.6) |
| Non-East Asian | 224 | (82.4) | 212 | (78.5) | 436 | (80.4) |

| | Control | | Pembrolizumab | | Total | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| **Study Medication Breakdown[§]** | | | | | | |
| Paclitaxel | 84 | (30.9) | 0 | (0.0) | 84 | (15.5) |
| Docetaxel | 84 | (30.9) | 0 | (0.0) | 84 | (15.5) |
| Vinflunine | 87 | (32.0) | 0 | (0.0) | 87 | (16.1) |
| Pembrolizumab | 0 | (0.0) | 266 | (98.5) | 266 | (49.1) |
| Missing | 17 | (6.3) | 4 | (1.5) | 21 | (3.9) |
| **Smoking Status** | | | | | | |
| Never Smoker | 83 | (30.5) | 104 | (38.5) | 187 | (34.5) |
| Ex Smoker | 148 | (54.4) | 136 | (50.4) | 284 | (52.4) |
| Current Smoker | 38 | (14.0) | 29 | (10.7) | 67 | (12.4) |
| Missing | 3 | (1.1) | 1 | (0.4) | 4 | (0.7) |
| **Histology** | | | | | | |
| Pure Transitional Cell | 197 | (72.4) | 186 | (68.9) | 383 | (70.7) |
| Predominantly Transitional Cell | 73 | (26.8) | 82 | (30.4) | 155 | (28.6) |
| Other | 0 | (0.0) | 2 | (0.7) | 2 | (0.4) |
| Missing | 2 | (0.7) | 0 | (0.0) | 2 | (0.4) |
| **PD-L1 CPS 1% Cutoff** | | | | | | |
| PD-L1 CPS < 1% | 147 | (54.0) | 151 | (55.9) | 298 | (55.0) |
| PD-L1 CPS >= 1% | 120 | (44.1) | 110 | (40.7) | 230 | (42.4) |
| Missing | 5 | (1.8) | 9 | (3.3) | 14 | (2.6) |
| **PD-L1 CPS 10% Cutoff** | | | | | | |
| PD-L1 CPS < 10% | 176 | (64.7) | 186 | (68.9) | 362 | (66.8) |
| PD-L1 CPS >= 10% | 90 | (33.1) | 74 | (27.4) | 164 | (30.3) |
| Missing | 6 | (2.2) | 10 | (3.7) | 16 | (3.0) |
| **Sum of Target Lesion at Baseline[§§]** | | | | | | |
| <Median | 117 | (43.0) | 132 | (48.9) | 249 | (45.9) |
| >=Median | 135 | (49.6) | 115 | (42.6) | 250 | (46.1) |
| Missing | 20 | (7.4) | 23 | (8.5) | 43 | (7.9) |
| **Risk Scores** | | | | | | |
| 0 | 44 | (16.2) | 54 | (20.0) | 98 | (18.1) |
| 1 | 97 | (35.7) | 96 | (35.6) | 193 | (35.6) |
| 2 | 80 | (29.4) | 66 | (24.4) | 146 | (26.9) |
| 3-4 | 45 | (16.5) | 45 | (16.7) | 90 | (16.6) |
| Missing | 6 | (2.2) | 9 | (3.3) | 15 | (2.8) |
| **Prior Cystectomy/Nephrectom** | | | | | | |
| No | 221 | (81.3) | 209 | (77.4) | 430 | (79.3) |
| Yes | 51 | (18.8) | 61 | (22.6) | 112 | (20.7) |

## Numbers analysed

The ITT population, including all randomized subjects in the treatment group to which they were assigned (270 in the pembrolizumab arm and 272 in the control arm), served as the primary efficacy analysis population.

For the analysis of pre-specified key exploratory PRO endpoints, a specific Full Analysis Set (FAS) population, that consisted of all randomized subjects who received at least one dose of study medication and completed at least one PRO instrument (266 subjects in the pembrolizumab arm and 254 subjects in the control arm), was considered.

The All Subject as Treated (ASaT) population, defined as all randomized subjects who received at least one dose of study treatment (266 in the pembrolizumab arm and 255 in the control arm) was used for the analysis of safety data.

## Outcomes and estimation

Results from the second interim analysis (cut-off date 07-Sep-2016) were provided for primary (PFS and OS) and secondary (ORR, DOR, and PFS/ORR per mRECIST) endpoints. Even if, based on external biomarker data only primary hypotheses of all comers and PD-L1 CPS ≥ 10% were included in the multiplicity-controlled statistical testing for the IA2, results in subjects with CPS ≥ 1% are also reported although p-value was not multiplicity-adjusted.

The median follow up duration was 10.3 (range 0.2 to 20.8) months in the pembrolizumab arm and 7.9 (range 0.3 to 20.3) months in the control arm.

***Primary endpoints***

***Overall Survival***

- All Subjects (ITT Population)

**Table 2: OS-All Subjects (ITT Population)**

**Data Cut-off date: 07 Sep 2016**

| Treatment | 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) | Pembrolizumab vs. Control | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Hazard Ratio‡ (95% CI)‡ | p-Value§ |
| Control | 272 | 179 (65.8) | 1935.1 | 9.3 | 7.4 (6.1, 8.3) | 56.7 (50.3, 62.6) | 30.7 (25.0, 36.7) | | |
| Pembrolizumab | 270 | 155 (57.4) | 2364.7 | 6.6 | 10.3 (8.0, 11.8) | 63.9 (57.9, 69.4) | 43.9 (37.8, 49.9) | 0.73 (0.59, 0.91) | 0.00224 |

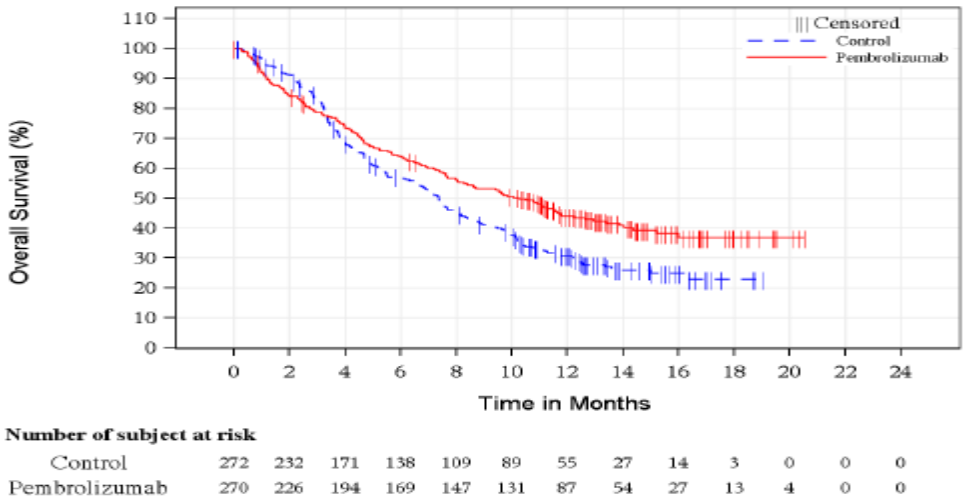
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on stratified Cox regression model with treatment as a covariate stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, hemoglobin (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥3 months)
§ One-sided p-value based on stratified log-rank test.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cutoff Date: 07SEP2016

Source: [P045V01: analysis-adsl; adtte]

**Figure: Kaplan-Meier estimates of OS**

**All Subjects (ITT Population)**

**Data Cut-off date: 07 Sep 2016**




**Number of subject at risk**

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Control | 272 | 232 | 171 | 138 | 109 | 89 | 55 | 27 | 14 | 3 | 0 | 0 | 0 |
| Pembrolizumab | 270 | 226 | 194 | 169 | 147 | 131 | 87 | 54 | 27 | 13 | 4 | 0 | 0 |

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine

(Database Cut-off date: 07SEP2016)

An updated analysis (cut-off date:18JAN2017) was conducted with a total of 366 OS events that are very close to the approximately 370 OS events defined in the protocol as the final analysis. The final study report is planned to be submitted in July 2018.

**Table 3: OS-All Subjects (ITT Population)**

**Data cut-off date: 18 Jan 2017**

| Treatment | 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) | Pembrolizumab vs. Control | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Hazard Ratio‡ (95% CI)‡ | p-Value§ |
| Control | 272 | 196 (72.1) | 2197.9 | 8.9 | 7.4 (6.3, 8.1) | 56.9 (50.6, 62.8) | 30.2 (24.6, 36.0) | | |
| Pembrolizumab | 270 | 170 (63.0) | 2795.5 | 6.1 | 10.3 (8.0, 12.3) | 63.9 (57.9, 69.4) | 44.4 (38.4, 50.3) | 0.70 (0.57, 0.86) | 0.00040 |

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

‡ Based on stratified Cox regression model with treatment as a covariate stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, hemoglobin (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥3 months)

§ One-sided p-value based on stratified log-rank test.

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

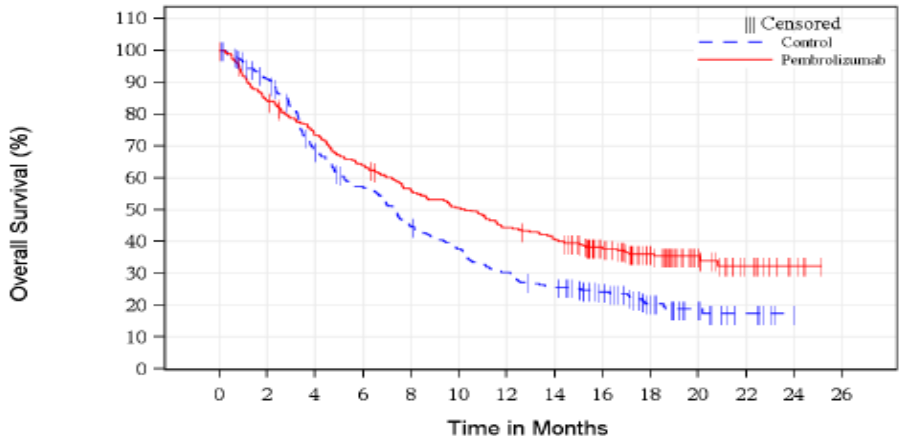
Database Cutoff Date: 18JAN2017

Source: [P045V01: analysis-adsl; adtte]

**Figure: Kaplan-Meier estimates of OS**

**All Subjects (ITT Population)**

**Data Cut-off date: 18 Jan 2017**




**Number of subject at risk**

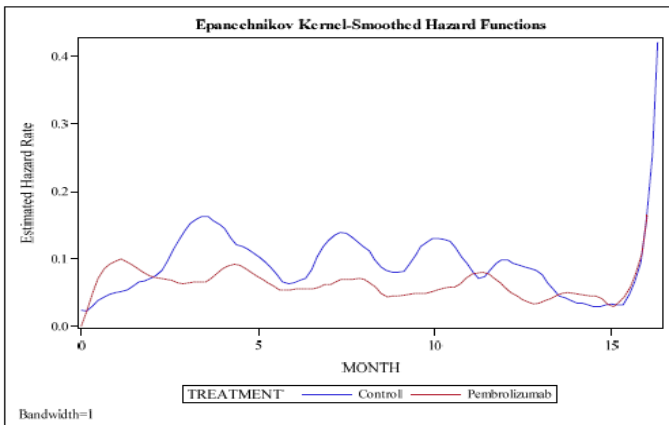
| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Control | 272 | 231 | 171 | 139 | 109 | 91 | 73 | 61 | 46 | 26 | 15 | 6 | 1 | 0 |
| Pembrolizumab | 270 | 226 | 194 | 169 | 147 | 132 | 116 | 106 | 79 | 52 | 27 | 12 | 4 | 0 |

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
(Database cutoff date: 18JAN2017)
Source: [P045V01: analysis-adsl; adtte]

Analysis of OS before Month 4

Due to the slope of KM curves, with an initial favourable treatment effect for the control arm followed by a convergence at approximately 2 months and a subsequent cross between Month 3 and Month 4, a review of OS events in the period from randomization to Month 4 was performed.

In order to understand in more detail the risk of death within the first 4 months, the instantaneous hazard rate over time was evaluated (see Figure below).




While the hazard rate for the pembrolizumab arm between 0 and approximately 2 months is above that of the control arm, thereafter the hazard rate in the pembrolizumab arm stays below the control arm. Subsequent analyses thus focused on the interval up to 2 months as well as up to 4 months.

In the interval from randomization to 2 months, there were more deaths but far fewer subjects censored in the pembrolizumab arm than the control arm (43 vs. 24 deaths, respectively; 3 vs. 17 censored,

respectively). Reasons for censoring were Withdrawal by Subject (2) and Lost to Follow-up (1) for the 3 patients on pembrolizumab arm, and Withdrawal by Subject for all 17 subjects on the control arm.

In the interval from 2 months to Month 4, twice as many subjects died in the control arm as in the pembrolizumab arm (56 vs. 28, respectively) with 4 subjects and 2 subjects censored, respectively.

Overall in the pembrolizumab arm there were 9 fewer deaths up to 4 months (71 deaths) compared to the control arm (80 deaths) and there were far fewer censored subjects (5 compared to 21).

For subjects that died or were censored in the first 2.1 months, there are modest imbalances in baseline risk factors between the treatment groups, including a higher prevalence of the presence of liver metastases and reduced treatment free interval (< 3 months) in subjects treated with pembrolizumab compared with control subjects.

To further assess potential factors that may influence the outcome in patients that might be treated with pembrolizumab compared to those on chemotherapy, a comparison of baseline characteristics between pembrolizumab and control arms of subjects who experienced early OS events (within 2.1 months) and of subjects who were censored for OS were each evaluated. It should be noted that the total number of subjects censored in the pembrolizumab arm within the first 2.1 months is small, 3 subjects, compared with 17 subjects in control arm, in part limiting the analysis.

The percentages of subjects at baseline with each individual Bellmunt risk factor of poor prognosis (ECOG PS > 0, presence of liver metastasis, hemoglobin < 10g/dL, time from prior chemotherapy < 3 months), Bellmunt risk scores ≥ 2, and additional characteristics of aggressive disease (baseline tumor burden ≥ median, and presence of visceral metastasis) among early deaths (within 2.1 months) and among early censoring events (within 2.1 months) are shown in the following Tables.

**Table 4: KN045 Percentage of Subjects with Risk Factors and Additional Characteristics of Aggressive Disease Among Early Overall Survival Events (< 2.1 months) - All Subjects Randomized (ITT Population)**

| | Control | Pembrolizumab |
|---|---|---|
| Risk Factor | | |
| ECOG > 0 | 79.1% | 69.7% |
| Liver metastasis | 66.7% | 74.4% |
| Hemoglobin < 10g/dL | 33.3% | 32.6% |
| Time from prior chemotherapy < 3 months | 37.5% | 51.2% |
| Bellmunt Risk Score ≥ 2 | 79.1% | 81.4% |
| Additional Characteristics of Poor Prognosis | | |
| Baseline tumor burden ≥ median | 75% | 74.4% |
| Visceral metastasis | 95.8% | 100% |

**Table 5: KN045 Percentage of Subjects with Risk Factors and Additional Characteristics of Aggressive Disease Among Early Overall Survival Censorings (<2.1 months) – All Subjects Randomized (ITT Population)**

| | Control | Pembrolizumab |
|---|---|---|
| **Risk Factor** | | |
| ECOG > 0 | 58.8% | 33.3% |
| Liver metastasis | 35.3% | 33.3% |
| Hemoglobin < 10g/dL | 17.6% | 0% |
| Time from prior chemotherapy < 3 months | 41.2% | 66.7% |
| Bellmunt ≥ 2 | 47.1% | 33.3% |
| **Additional Characteristics of Poor Prognosis** | | |
| Baseline tumor burden ≥ median | 58.8% | 33.3% |
| Visceral metastasis | 82.4% | 66.7% |

Among the deaths occurring within the first 2.1 months, a greater proportion of subjects in the pembrolizumab arm had liver metastasis and time from prior chemo <3 months. A higher proportion of subjects in the control arm had ECOG PS >0 and a similar proportion of subjects in both arms had haemoglobin <10 g/dL, Bellmunt Risk Score >2, baseline tumor burden > median and visceral metastasis. Among the early censored OS events, a greater proportion of subjects in the control arm had ECOG PS >0, Hb<10g/dL, Bellmunt risk scores >2, visceral metastasis and baseline tumor burden > median. A higher proportion of subjects in the pembrolizumab arm had time from prior chemotherapy < 3 months and a similar proportion of subjects in both arms had liver metastasis.

- OS results based on PD-L1 expression

**Table 6: OS - Subjects with PD-L1 CPS≥10%**

Cut-off Date:07Sep2016

| Treatment | 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) | Pembrolizumab vs. Control: Hazard Ratio‡ (95% CI)‡ | Pembrolizumab vs. Control: p-Value§ |
|---|---|---|---|---|---|---|---|---|---|
| Control | 90 | 60 (66.7) | 570.3 | 10.5 | 5.2 (4.0, 7.4) | 47.2 (36.0, 57.6) | 26.9 (17.5, 37.2) | | |
| Pembrolizumab | 74 | 44 (59.5) | 589.1 | 7.5 | 8.0 (5.0, 12.3) | 58.5 (46.3, 68.9) | 39.8 (28.0, 51.3) | 0.57 (0.37, 0.88) | 0.00483 |

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on stratified Cox regression model with treatment as a covariate stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, hemoglobin (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥3 months)
§ One-sided p-value based on stratified log-rank test.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cutoff Date: 07SEP2016

Source: [P045V01: analysis-adsl; adtte]

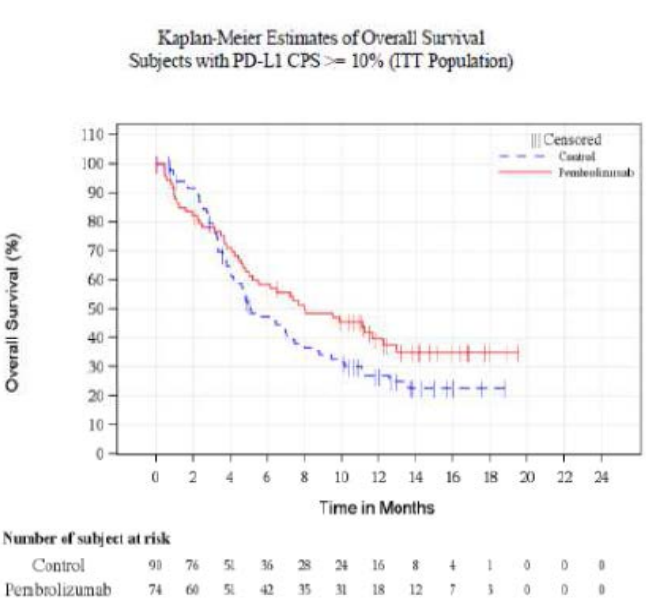
**Table 7: OS - Subjects with PD-L1 CPS≥1%**

Cut-off Date:07Sep2016

| Treatment | 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) | Pembrolizumab vs. Control | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Hazard Ratio‡ (95% CI)‡ | p-Value§ |
| Control | 120 | 81 (67.5) | 823.0 | 9.8 | 6.9 (4.7, 8.8) | 51.6 (41.9, 60.4) | 28.8 (20.4, 37.7) | | |
| Pembrolizumab | 110 | 61 (55.5) | 971.1 | 6.3 | 11.3 (7.7, 16.0) | 65.9 (56.1, 73.9) | 46.5 (36.4, 55.8) | 0.61 (0.43, 0.86) | 0.00239 |

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on stratified Cox regression model with treatment as a covariate stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, hemoglobin (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥3 months)
§ One-sided p-value based on stratified log-rank test.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cutoff Date: 07SEP2016

Source: [P045V01: analysis-adsl; adtte]



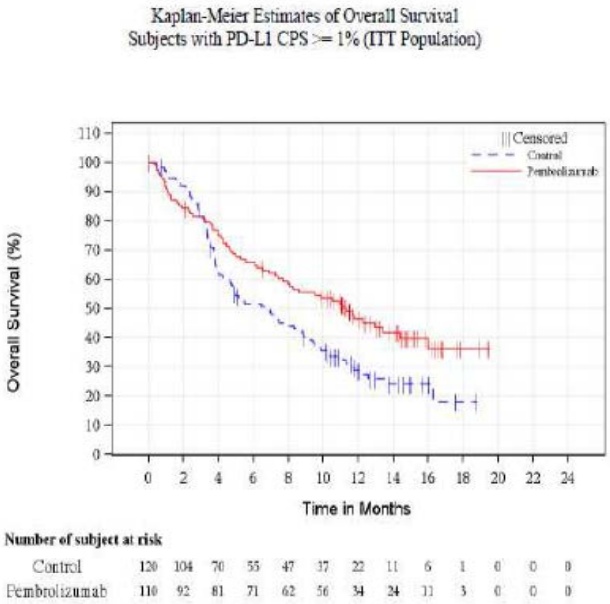




**Table 8: Summary of OS results**

Cut- off date: 18Jan2017

| Treatment group | Control N = 272 | Pembrolizumab N = 270 | Pembrolizumab vs. Control | |
|---|---|---|---|---|
| | Median, months (95% CI) | | HR (95% CI) | p-value |
| OS | | | | |
| ITT | N = 272 | N = 270 | | |
| | 7.4 (6.3, 8.1) | 10.3 (8.0, 12.3) | 0.70 (0.57, 0.86) | 0.00040 |
| CPS ≥ 10% | N = 74 | N = 90 | | |
| | 5.2 (4.0, 7.4) | 8.0 (5.0, 12.3) | 0.57 (0.38, 0.86) | 0.00335 |
| CPS ≥ 1% | N = 120 | N = 110 | | |
| | 6.9 (4.7, 8.8) | 11.3 (7.7, 16.0) | 0.59 (0.42, 0.83) | 0.00092* |
| CPS < 10% | N = 176 | N = 186 | | |
| | 7.7 (6.8, 9.7) | 10.8 (8.0, 13.9) | 0.76 (0.58, 0.98) | |
| CPS < 1% | N = 147 | N = 151 | | |
| | 7.5 (6.6, 9.7) | 9.6 (6.9, 11.6) | 0.89 (0.66, 1.20) | |

***Progression Free Survival per RECIST 1.1 by Central Radiology Assessment***

- All Subjects (ITT Population)

**Table 9: PFS based on RECIST 1.1 per central radiology assessment**

**All Subjects (ITT Population)**

Data cut-off: 07 Sep 2016

| Treatment | N | Number of Events (%) | Person-Months | Event Rate/ 100 Person-Months (%) | Median PFS† (Months) (95% CI) | PFS Rate at Months 6 in %† (95% CI) | PFS Rate at Months 12 in %† (95% CI) | Pembrolizumab vs. Control | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Hazard Ratio‡ (95% CI)‡ | p-Value§ |
| Control | 272 | 219 (80.5) | 1014.1 | 21.6 | 3.3 (2.3, 3.5) | 26.8 (21.2, 32.6) | 6.2 (3.3, 10.2) | | |
| Pembrolizumab | 270 | 218 (80.7) | 1206.7 | 18.1 | 2.1 (2.0, 2.2) | 28.8 (23.5, 34.3) | 16.8 (12.3, 22.0) | 0.98 (0.81, 1.19) | 0.41648 |

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.

‡ Based on stratified Cox regression model with treatment as a covariate stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, hemoglobin (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥3 months)

§ One-sided p-value based on stratified log-rank test.

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

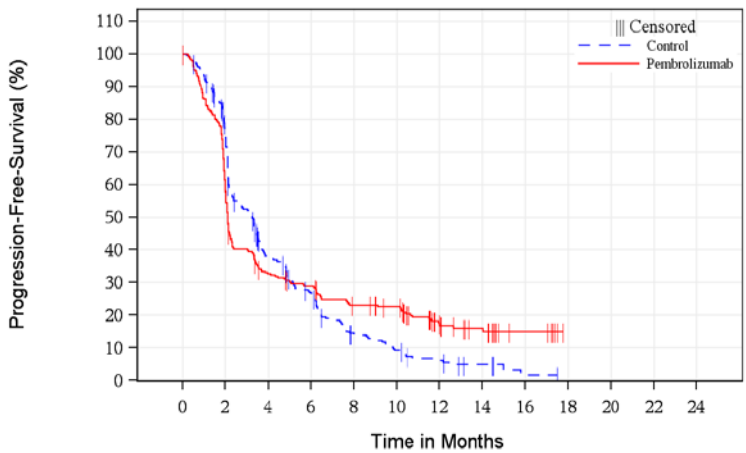
Database Cutoff Date: 07SEP2016

Source: [P045V01: analysis-adsl; adtte]

**Figure: Kaplan-Meier estimates of PFS based on RECIST 1.1 per central radiology assessment (Primary Censoring Rule)**

**All Subjects (ITT Population)**

Data cut- off: 07 Sep 2016




**Number of subject at risk**

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Control | 272 | 188 | 85 | 56 | 27 | 17 | 10 | 5 | 1 | 0 | 0 | 0 | 0 |
| Pembrolizumab | 270 | 165 | 85 | 73 | 56 | 51 | 23 | 16 | 7 | 0 | 0 | 0 | 0 |

**Table 10: PFS based on RECIST 1.1 per central radiology assessment**

**All Subjects (ITT Population)**

Data cut-off: 18 Jan 2017

| Treatment | N | Number of Events (%) | Person-Months | Event Rate/ 100 Person-Months (%) | Median PFS† (Months) (95% CI) | PFS Rate at Months 6 in % † (95% CI) | PFS Rate at Months 12 in % † (95% CI) | Pembrolizumab vs. Control | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Hazard Ratio‡ (95% CI)‡ | p-Value§ |
| Control | 272 | 227 (83.5) | 1110.7 | 20.4 | 3.3 (2.4, 3.5) | 28.4 (22.8, 34.2) | 7.9 (4.8, 12.0) | | |
| Pembrolizumab | 270 | 219 (81.1) | 1371.2 | 16.0 | 2.1 (2.0, 2.2) | 28.8 (23.5, 34.3) | 17.6 (13.2, 22.6) | 0.96 (0.79, 1.16) | 0.32274 |

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.

‡ Based on stratified Cox regression model with treatment as a covariate stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, hemoglobin (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥3 months)

§ One-sided p-value based on stratified log-rank test.

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

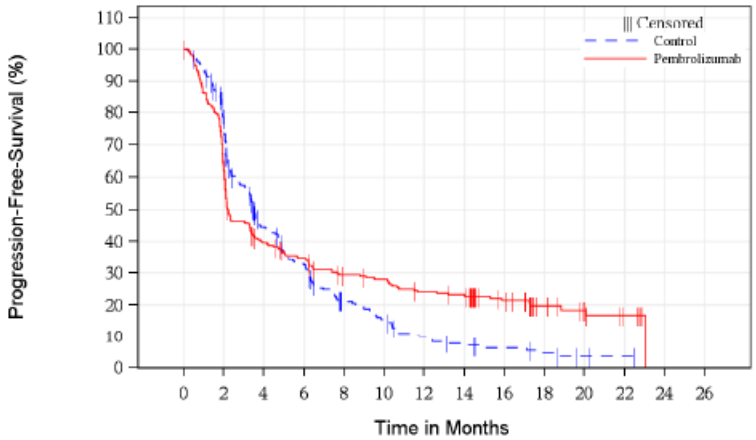
Database Cutoff Date: 18JAN2017

Source: [P045V01: analysis-adsl; adtte]

**Figure: Kaplan-Meier estimates of PFS based on RECIST 1.1 per central radiology assessment (Primary Censoring Rule)**

**All Subjects (ITT Population)**

Data cut- off: 18 Jan 2017




**Number of subject at risk**

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Control | 272 | 192 | 98 | 70 | 40 | 28 | 17 | 11 | 8 | 5 | 2 | 1 | 0 | 0 |
| Pembrolizumab | 270 | 173 | 101 | 86 | 68 | 64 | 54 | 51 | 32 | 17 | 11 | 5 | 0 | 0 |

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
(Database cutoff date: 18JAN2017)
Source: [P045V01: analysis-adsl; adtte]

- PFS results based on PD-L1 expression

**Table 11: PFS based on RECIST 1.1 per Central Radiology Assessment Subjects with PD-L1 CPS≥10%**

Cut- off Date: 07Sep2016

| Treatment | N | Number of Events (%) | Person-Months | Event Rate/ 100 Person-Months (%) | Median PFS† (Months) (95% CI) | PFS Rate at Months 6 in % † (95% CI) | PFS Rate at Months 12 in % † (95% CI) | Pembrolizumab vs. Control | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Hazard Ratio‡ (95% CI)‡ | p-Value§ |
| Control | 90 | 72 (80.0) | 283.8 | 25.4 | 3.1 (2.2, 3.4) | 18.5 (10.6, 28.1) | 3.7 (0.7, 10.9) | | |
| Pembrolizumab | 74 | 59 (79.7) | 316.4 | 18.6 | 2.1 (1.9, 2.1) | 24.7 (15.5, 34.9) | 17.7 (9.5, 27.9) | 0.89 (0.61, 1.28) | 0.23958 |

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.
‡ Based on stratified Cox regression model with treatment as a covariate stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, hemoglobin (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥3 months)
§ One-sided p-value based on stratified log-rank test.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cutoff Date: 07SEP2016

Source: [P045V01: analysis-adsl; adtte]

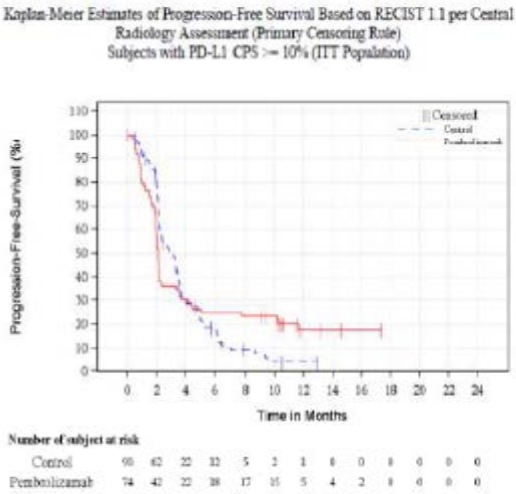
**Table 12: PFS based on RECIST 1.1 per Central Radiology Assessment Subjects with PD-L1 CPS≥1%**

Cut-off Date: 07Sep2016

| Treatment | N | Number of Events (%) | Person-Months | Event Rate/ 100 Person-Months (%) | Median PFS† (Months) (95% CI) | PFS Rate at Months 6 in % † (95% CI) | PFS Rate at Months 12 in % † (95% CI) | Pembrolizumab vs. Control | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Hazard Ratio‡ (95% CI)‡ | p-Value§ |
| Control | 120 | 98 (81.7) | 421.3 | 23.3 | 3.2 (2.2, 3.4) | 20.5 (13.3, 28.8) | 4.4 (1.4, 10.4) | | |
| Pembrolizumab | 110 | 85 (77.3) | 509.8 | 16.7 | 2.1 (2.0, 2.4) | 28.4 (20.3, 37.1) | 20.9 (13.6, 29.3) | 0.91 (0.68, 1.24) | 0.26443 |

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.
‡ Based on stratified Cox regression model with treatment as a covariate stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, hemoglobin (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥3 months)
§ One-sided p-value based on stratified log-rank test.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cutoff Date: 07SEP2016

Source: [P045V01: analysis-adsl; adtte]



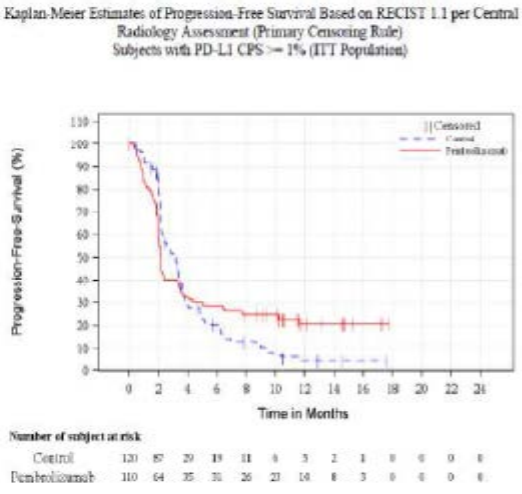




**Table 13: Summary of PFS results**

Cut- off date: 18Jan2017

| Treatment group | Control N = 272 | Pembrolizumab N = 270 | Pembrolizumab vs. Control | |
|---|---|---|---|---|
| | Median, months (95% CI) | | HR (95% CI) | p-value |
| **PFS** | | | | |
| **ITT** | N = 272 | N = 270 | | |
| | 3.3 (2.4, 3.5) | 2.1 (2.0, 2.2) | 0.96 (0.79, 1.16) | 0.32274 |
| **CPS ≥ 10%** | N = 90 | N = 74 | | |
| | 3.2 (2.2, 3.5) | 2.1 (1.9, 2.1) | 0.94 (0.65, 1.35) | 0.33449 |
| **CPS ≥ 1%** | N = 120 | N = 110 | | |
| | 3.2 (2.2, 3.4) | 2.1 (2.0, 2.4) | 0.92 (0.68, 1.24) | 0.26416* |
| **CPS < 10%** | N = 176 | N = 186 | | |
| | 3.3 (2.2, 4.2) | 2.1 (2.0, 2.3) | 1.00 (0.79, 1.26) | |
| **CPS < 1%** | N = 147 | N = 151 | | |
| | 3.3 (2.2, 4.7) | 2.1 (2.0, 2.3) | 1.07 (0.82, 1.39) | |

***Secondary endpoints***

***Objective Response Rate per confirmed RECIST 1.1 by Central Radiology Assessment***

- All Subjects (ITT Population)

The ORR was 21.1% (95% CI: 16.4, 26.5) in the pembrolizumab arm compared to 11.4% (95% CI: 7.9, 15.8) in the control arm, with an estimated difference of 9.6% (95% CI: 3.5, 15.9; p=0.001).

**Table 14: Summary of Best Overall Response based on RECIST 1.1 by Central Radiology Assessment;** Cut- off Date: 07Sep2016

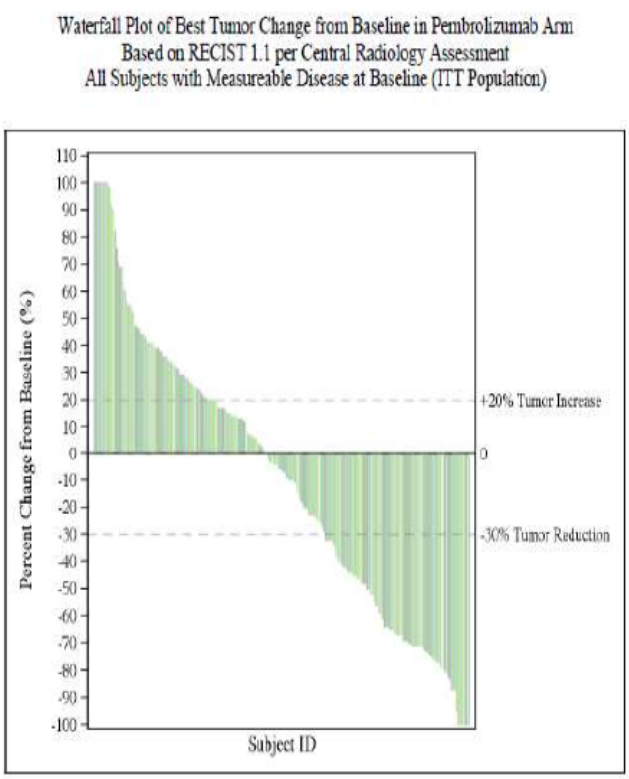
| Response Evaluation | Control (N=272) | | | Pembrolizumab (N=270) | | |
|---|---|---|---|---|---|---|
| | n | % | 95% CI† | n | % | 95% CI† |
| Complete Response (CR) | 9 | 3.3 | (1.5, 6.2) | 19 | 7.0 | (4.3, 10.8) |
| Partial Response (PR) | 22 | 8.1 | (5.1, 12.0) | 38 | 14.1 | (10.2, 18.8) |
| **Objective Response (CR+PR)** | **31** | **11.4** | **(7.9, 15.8)** | **57** | **21.1** | **(16.4, 26.5)** |
| Stable Disease (SD) | 91 | 33.5 | (27.9, 39.4) | 47 | 17.4 | (13.1, 22.5) |
| **Disease Control (CR+PR+SD)** | **122** | **44.9** | **(38.8, 51.0)** | **104** | **38.5** | **(32.7, 44.6)** |
| Progressive Disease (PD) | 90 | 33.1 | (27.5, 39.0) | 131 | 48.5 | (42.4, 54.7) |
| Non-evaluable (NE) | 9 | 3.3 | (1.5, 6.2) | 4 | 1.5 | (0.4, 3.7) |
| No Assessment | 51 | 18.8 | (14.3, 23.9) | 31 | 11.5 | (7.9, 15.9) |

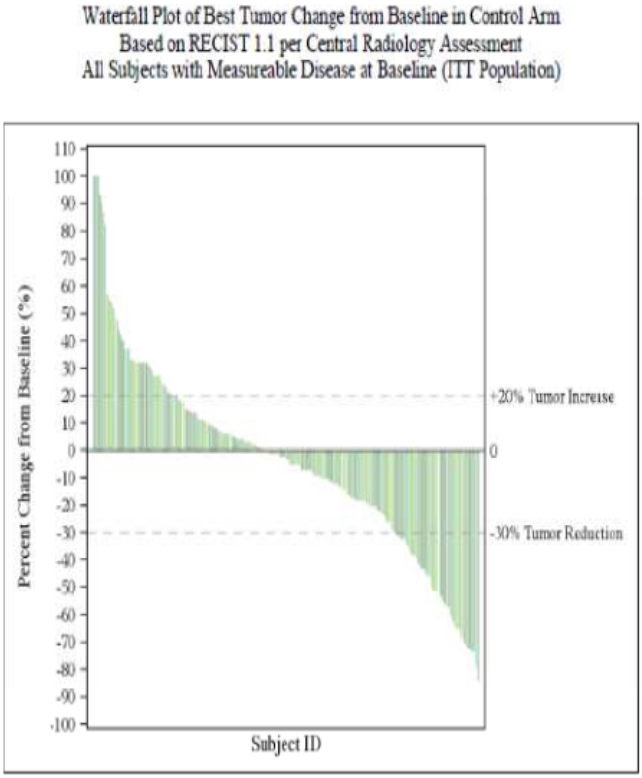
Confirmed responses are included.
† Based on binomial exact confidence interval method.
Non-evaluable: subject had post-baseline imaging and the BOR was determined to be NE per RECIST 1.1.
No Assessment: subject had no post-baseline imaging.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cutoff Date: 07SEP2016

Source: [P045V01: analysis-adsl; adopa]

The median follow-up in patients with confirmed CR and PR was 13.4 (7.3-19.1) months in the control arm and 14.1 (10.2-20.8) months in the pembrolizumab group.

Across arms, the reduction of tumour burden in patients with at least 1 baseline imaging assessment was 53.9% (118 of 219 subjects) in the pembrolizumab arm, and 54.5% (109 of 200 subjects) in the control arm, as shown in the following figures:




Percentage changes >100% were truncated at 100%.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cutoff Date: 07SEP2016

**Table 15: Summary of Best Overall Response based on RECIST 1.1**

**by Central Radiology Assessment**

**Cutoff Date:18Jan2017**

| Response Evaluation | Control (N=272) | | | Pembrolizumab (N=270) | | |
|---|---|---|---|---|---|---|
| | n | % | 95% CI† | n | % | 95% CI† |
| Complete Response (CR) | 8 | 2.9 | (1.3, 5.7) | 21 | 7.8 | (4.9, 11.6) |
| Partial Response (PR) | 22 | 8.1 | (5.1, 12.0) | 36 | 13.3 | (9.5, 18.0) |
| **Objective Response (CR+PR)** | **30** | **11.0** | **(7.6, 15.4)** | **57** | **21.1** | **(16.4, 26.5)** |
| Stable Disease (SD) | 92 | 33.8 | (28.2, 39.8) | 47 | 17.4 | (13.1, 22.5) |
| **Disease Control (CR+PR+SD)** | **122** | **44.9** | **(38.8, 51.0)** | **104** | **38.5** | **(32.7, 44.6)** |
| Progressive Disease (PD) | 90 | 33.1 | (27.5, 39.0) | 131 | 48.5 | (42.4, 54.7) |
| Non-evaluable (NE) | 9 | 3.3 | (1.5, 6.2) | 4 | 1.5 | (0.4, 3.7) |
| No Assessment | 51 | 18.8 | (14.3, 23.9) | 31 | 11.5 | (7.9, 15.9) |

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.

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

Database Cutoff Date: 18JAN2017

Source: [P045V01: analysis-adsl; adopa]

- ORR Results based on PD-L1 expression

**Table 16: Summary of Best Overall Response based on RECIST 1.1** by Central Radiology Assessment; (ITT Population) Cut-off Date: 07Sep2016

| Response evaluation | **PD-L1 CPS≥10%** | | **PD-L1 CPS≥1%** | |
|---|---|---|---|---|
| | **Control (N=90)** | **Pembrolizumab (N=74)** | **Control (N=120)** | **Pembrolizumab (N=110)** |
| | n (%) 95% CI° | n(%) 95% CI° | n(%) 95% CI° | n(%) 95% CI° |
| Complete response (CR) | 2 (2.2) (0.3,7.8) | 5 (6.8) (2.2,15.1) | 5 (4.2) (1.4,9.5) | 10 (9.1) (4.4,16.1) |
| Partial response (PR) | 4 (4.4) (1.2,11.0) | 11 (14.9) (7.7,25.0) | 5 (4.2) (1.4,9.5) | 16 (14.5) (8.5,22.5) |
| **Objective response (CR+PR)** | **6 (6.7) (2.5,13.9)** | **16 (21.6) (12.9,32.7)** | **10 (8.3) (4.1,14.8)** | **26 (23.6) (16.1,32.7)** |
| Stable disease (SD) | 32 (35.6) (25.7,46.3) | 9 (12.2) (5.7,21.8) | 42 (35.0) (26.5,44.2) | 17 (15.5) (9.3,23.6) |
| **Disease control (CR+PR+SD)** | **38 (42.2) (31.9,53.1)** | **25 (33.8) (23.2,45.7)** | **52 (43.3) (34.3,52.7)** | **43 (39.1) (29.9,48.9)** |
| Progressive disease (PD) | 28 (31.1) (21.8,41.7) | 37 (50.0) (38.1,61.9) | 38 (31.7) (23.5,40.8) | 53 (48.2) (38.6,57.9) |

| | | | | |
|---|---|---|---|---|
| Non-evaluable (NE) | 4 (4.4)<br>(1.2,11.0) | 0 (0.0)<br>(0.0,4.9) | 4 (3.3)<br>(0.9,8.3) | 0 (0.0)<br>(0.0,3.3) |
| No Assessment | 20 (22.2)<br>(14.1,32.2) | 12(16.2)<br>(8.7,26.6) | 26 (21.7)<br>(14.7,30.1) | 14 (12.7)<br>(7.1,20.4) |

°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: subjects had no post-baseline imaging.

**Table 17: Summary of ORR results – Cut-off date: 18Jan2017**

| Treatment group | Control<br>N = 272 | Pembrolizumab<br>N = 270 | Pembrolizumab vs. Control | |
|---|---|---|---|---|
| | Median, months (95% CI) | | HR (95% CI) | p-value |
| **ORR analysis** | (BICR-RECIST 1.1)<br>% (95% CI) | | Difference (95% CI) | p-value |
| **ITT** | N = 272 | N = 270 | | |
| | 11.0 (7.6, 15.4) | 21.1 (16.4, 26.5) | 10.0 (3.9,16.2) | 0.00068 |
| **CPS ≥ 10%** | N = 90 | N = 74 | | |
| | 6.7 (2.5, 13.9) | 20.3 (11.8, 31.2) | 17.2 (6.8,29.4) | 0.00061* |
| **CPS ≥ 1%** | N = 120 | N = 110 | | |
| | 8.3 (4.1, 14.8) | 22.7 (15.3, 31.7) | 15.6 (6.5,25.7) | 0.00049* |
| **CPS < 10%** | N = 176 | N = 186 | | |
| | 13.6 (8.9,19.6) | 19.4 (13.9,25.8) | 5.1 (-2.6,12.8) | |
| **CPS < 1%** | N = 144 | N = 151 | | |
| | 13.6 (8.5,20.2) | 17.9 (12.1,24.9) | 3.9 (-4.5,12.3) | |

*Time to Response (TTR) and Response Duration (DOR) by Central Radiology Assessment*

- All Subjects (ITT Population)

**Table 18: Summary of TTR and DOR based on RECIST 1.1 per BICR**

**in subjects with confirmed response**

**All Subjects (ITT Population)**

| | Control<br>(N=272) | Pembrolizumab<br>(N=270) |
|---|---|---|
| Number of Subjects with Response[†] | 31 | 57 |
| Time to Response[†] (months) | | |
| Mean (SD) | 2.4 (0.8) | 2.7 (1.2) |
| Median (Range) | 2.1 (1.7-4.9) | 2.1 (1.4-6.3) |
| Response Duration[†] (months) | | |
| Median (Range)[§] | 4.3 (1.4+ - 15.4+) | Not reached (1.6+ - 15.6+) |
| Number of Subjects with Response ≥ 6 Months (%)[‡] | 7 (40) | 41 (78) |
| Number of Subjects with Response ≥ 12 Months (%)[‡] | 3 (35) | 14 (68) |

[†]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 the response duration is censored.

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

Database Cutoff Date: 07SEP2016

Source: [P045V01: analysis-adsl; adtte]

- PD-L1 CPS≥10% and PD-L1 CPS≥1% Populations

**Table 19: Summary of TTR and DOR based on RECIST 1.1 per BICR in subjects with confirmed response**

**Subjects with PD-L1 CPS≥10% and Subjects with PD-L1 CPS≥1%**

**(ITT Population)**

| | **PD-L1 CPS≥10%** | | **PD-L1 CPS≥1%** | |
|---|---|---|---|---|
| | **Control (N=90)** | **Pembrolizumab (N=74)** | **Control (N=120)** | **Pembrolizumab (N=110)** |
| Number of subjects with response° | 6 | 16 | 10 | 26 |
| Time to Response° (months) | | | | |
| Mean (SD) | 2.0 (0.1) | 2.5 (1.0) | 2.0 (0.1) | 2.6 (1.0) |
| Median (Range) | 2.1 (1.9-2.2) | 2.1 (1.4-5.3) | 2.1 (1.9-2.2) | 2.2 (1.4-5.3) |
| Response Duration* (months) | | | | |
| Median (Range) | 4.4 (1.5+-10.8+) | NR (1.6+-15.4+) | NR (1.5+-15.4+) | NR (1.6+-15.6+) |
| N. of subjects with response ≥6 months (%)* | 1 (40) | 14 (93) | 3 (56) | 21 (88) |
| N. of subjects with response ≥12 months (%)* | 0 | 3 (76) | 2 (56) | 7 (78) |

Table made by the Assessor from Table 11-9 and Table 14.2-51 in KEYNOTE-045 CSR v.01

NR: Not reached

°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.

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

Database Cut-off Date: 07SEP2016

Results of PFS and ORR analysis per mRECIST by BICR were consistent with those per RECIST 1.1.

**Summary of updated efficacy results (Data Cut-off: 18 Jan 2017)**

**Table 20: KN045 Summary of Efficacy Results – All Subjects Randomized (ITT Population) - 18-Jan-2017**

| Treatment group | Control N = 272 | Pembrolizumab N = 270 | Pembrolizumab vs. Control | |
|---|---|---|---|---|
| | Median, months (95% CI) | | HR (95% CI) | p-value |
| **OS** | | | | |
| **ITT** | N = 272 | N = 270 | | |
| | 7.4 (6.3, 8.1) | 10.3 (8.0, 12.3) | 0.70 (0.57, 0.86) | 0.00040 |
| **CPS ≥ 10%** | N = 74 | N = 90 | | |
| | 5.2 (4.0, 7.4) | 8.0 (5.0, 12.3) | 0.57 (0.38, 0.86) | 0.00335 |
| **CPS ≥ 1%** | N = 120 | N = 110 | | |
| | 6.9 (4.7, 8.8) | 11.3 (7.7, 16.0) | 0.59 (0.42, 0.83) | 0.00092* |
| **CPS < 10%** | N = 176 | N = 186 | | |
| | 7.7 (6.8, 9.7) | 10.8 (8.0, 13.9) | 0.76 (0.58, 0.98) | |
| **CPS < 1%** | N = 147 | N = 151 | | |
| | 7.5 (6.6, 9.7) | 9.6 (6.9, 11.6) | 0.89 (0.66, 1.20) | |
| **PFS** | | | | |
| **ITT** | N = 272 | N = 270 | | |
| | 3.3 (2.4, 3.5) | 2.1 (2.0, 2.2) | 0.96 (0.79, 1.16) | 0.32274 |
| **CPS ≥ 10%** | N = 90 | N = 74 | | |
| | 3.2 (2.2, 3.5) | 2.1 (1.9, 2.1) | 0.94 (0.65, 1.35) | 0.33449 |
| **CPS ≥ 1%** | N = 120 | N = 110 | | |
| | 3.2 (2.2, 3.4) | 2.1 (2.0, 2.4) | 0.92 (0.68, 1.24) | 0.26416* |
| **CPS < 10%** | N = 176 | N = 186 | | |
| | 3.3 (2.2, 4.2) | 2.1 (2.0, 2.3) | 1.00 (0.79, 1.26) | |
| **CPS < 1%** | N = 147 | N = 151 | | |
| | 3.3 (2.2, 4.7) | 2.1 (2.0, 2.3) | 1.07 (0.82, 1.39) | |
| **ORR analysis** | (BICR-RECIST 1.1) % (95% CI) | | Difference (95% CI) | p-value |
| **ITT** | N = 272 | N = 270 | | |
| | 11.0 (7.6, 15.4) | 21.1 (16.4, 26.5) | 10.0 (3.9,16.2) | 0.00068 |
| **CPS ≥ 10%** | N = 90 | N = 74 | | |
| | 6.7 (2.5, 13.9) | 20.3 (11.8, 31.2) | 17.2 (6.8,29.4) | 0.00061* |
| **CPS ≥ 1%** | N = 120 | N = 110 | | |
| | 8.3 (4.1, 14.8) | 22.7 (15.3, 31.7) | 15.6 (6.5,25.7) | 0.00049* |
| **CPS < 10%** | N = 176 | N = 186 | | |
| | 13.6 (8.9,19.6) | 19.4 (13.9,25.8) | 5.1 (-2.6,12.8) | |
| **CPS < 1%** | N = 147 | N = 151 | | |
| | 13.6 (8.5,20.2) | 17.9 (12.1,24.9) | 3.9 (-4.5,12.3) | |

* Not multiplicity controlled.

Abbreviations: BICR=blinded independent central review; CI=confidence interval; CPS=combined proportion score; ITT=intent-to-treat; OS=overall survival; PFS=progression-free survival; ORR=objective response rate.

***Exploratory endpoints- Patient-reported Outcome Analyses***

***EORTC QLQ-C30***

- EORTC QLQ-C30 score change from baseline to week 9 and week 15

At Week 9, the global health status/QoL score was stable from baseline in the pembrolizumab arm (LS mean = -1.37 points; 95% CI: -4.10, 1.35), and a greater worsening of -5.75 points (95% CI: -8.62,-2.87) was observed in the control, with a difference between arms at Week 9 of 4.38 points (95% CI: 0.59, 8.16; two-sided $p$=0.02, not controlled for multiplicity).

An even greater difference in LS means was reported at Week 15 between pembrolizumab and control (9.05 points; 95% CI: 4.61, 13.48; two-sided $p$<0.001, not controlled for multiplicity).

- EORTC QLQ-C30 Global Health Status Score at each visit to week 27

**Table 21: Summary of QLQ-C30 Global Health Status/QoL at Study Visit (FAS Population)**

| Study Visit | Treatment | | | |
|---|---|---|---|---|
| | Control (N†=254) | | Pembrolizumab (N†=266) | |
| | n | Mean (SE) | n | Mean (SE) |
| BASELINE | 243 | 59.1 (1.4) | 260 | 61.5 (1.4) |
| WEEK 3 | 220 | 57.7 (1.5) | 238 | 63.2 (1.4) |
| WEEK 6 | 199 | 58.9 (1.6) | 215 | 64.3 (1.6) |
| WEEK 9 | 176 | 58.5 (1.6) | 200 | 63.0 (1.6) |
| WEEK 15 | 118 | 57.9 (1.8) | 157 | 67.6 (1.8) |
| WEEK 21 | 73 | 60.5 (2.2) | 126 | 67.4 (1.8) |
| WEEK 27 | 46 | 59.4 (3.4) | 105 | 67.3 (2.3) |

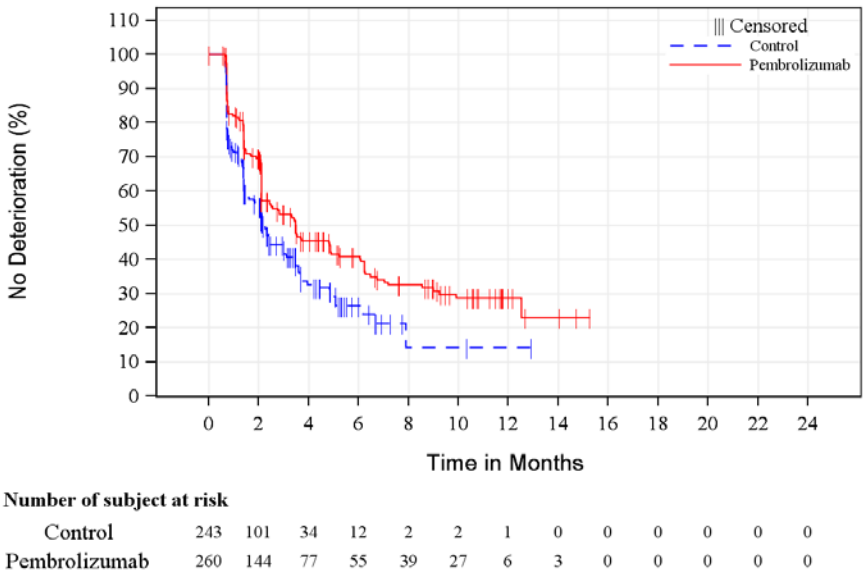
†: Number of subjects in Full Analysis Set population.
Database Cutoff: 07SEP2016

Source: [P045V01: analysis-adsl; adpro]

- Time to Deterioration analysis of EORTC QLQ-C30 Global Health Status/QoL score

A longer time to deterioration was registered with pembrolizumab compared to the control arm (HR = 0.70; 95% CI:0.55, 0.90; two-sided *p*=0.002, not controlled for multiplicity).

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




**Number of subject at risk**

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Control | 243 | 101 | 34 | 12 | 2 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pembrolizumab | 260 | 144 | 77 | 55 | 39 | 27 | 6 | 3 | 0 | 0 | 0 | 0 | 0 |

- Additional EORTC QLQ-C30 analyses

**Table 22: Analysis of Change from Baseline of EORTC QLQ-C30 Global health status / QoL at Week 9 by Progressive Disease (PD) Status (FAS Population)**

| Treatment | Without PD LS Mean (95% CI)† | With PD LS Mean (95% CI)† | Difference by PD Status LS Mean (95% CI)† |
|---|---|---|---|
| Pembrolizumab | 3.13 (-0.03, 6.30) | -6.87 (-10.34, -3.41) | -10.01 (-13.94, -6.07) |
| Control | -2.23 (-5.43, 0.97) | -12.30 (-15.80, -8.79) | -10.06 (-13.08, -7.05) |

† Based on cLDA model with the PRO scores as the response variable, treatment by study visit interaction, and stratification factors: Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, hemoglobin ( =10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or =3 months), PD status and PD status by treatment arm as covariates.
LS Mean: Least square mean; CI: Confidence interval.
Database Cutoff: 07SEP2016

Source: [P045V01: analysis-adsl; adpro]

**Table 23: Analysis of Change from Baseline of EORTC QLQ-C30 Global health status / QoL at Week 15 by Progressive Disease (PD) Status (FAS Population)**

| Treatment | Without PD LS Mean (95% CI)† | With PD LS Mean (95% CI)† | Difference by PD Status LS Mean (95% CI)† |
|---|---|---|---|
| Pembrolizumab | 5.97 (2.48, 9.46) | -3.54 (-6.95, -0.13) | -9.52 (-12.88, -6.15) |
| Control | -4.31 (-8.02, -0.60) | -13.95 (-17.75, -10.15) | -9.64 (-12.21, -7.07) |

† Based on cLDA model with the PRO scores as the response variable, treatment by study visit interaction, and stratification factors: Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, hemoglobin ( =10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or =3 months), PD status and PD status by treatment arm as covariates.
LS Mean: Least square mean; CI: Confidence interval.
Database Cutoff: 07SEP2016

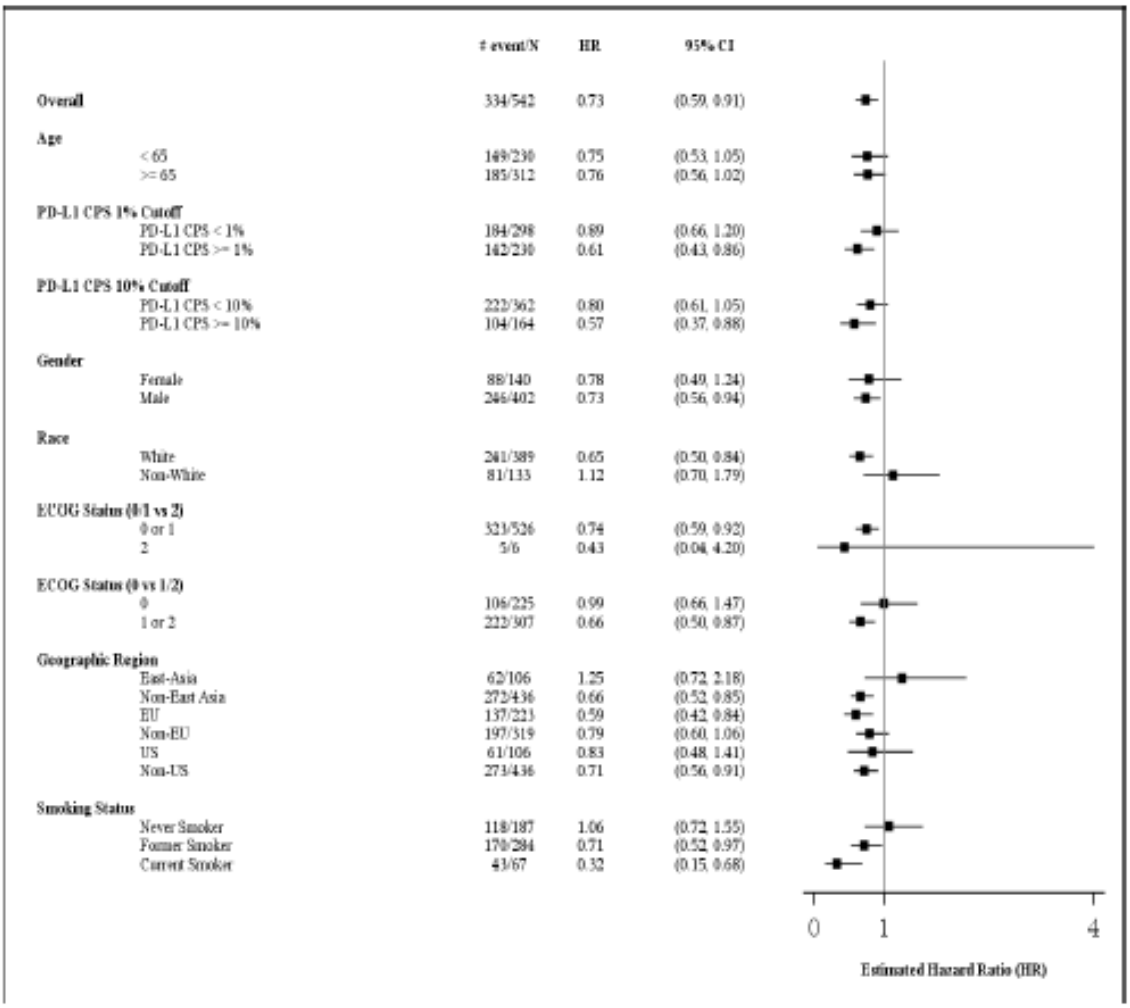
Source: [P045V01: analysis-adsl; adpro]

## Ancillary analyses

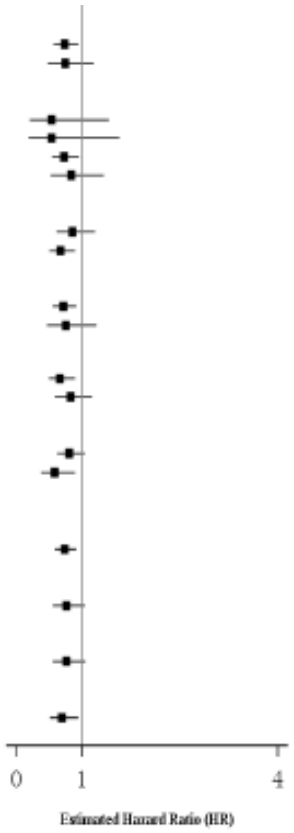
*OS*

*Subgroup analysis*

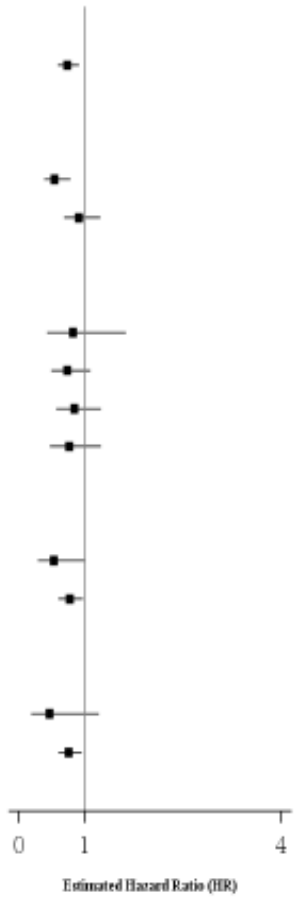
**Figure: Overall Survival by Subgroup Factors, Point Estimate and Nominal 95% Confidence Interval, All Subjects (ITT Population)**



| | | | |
|---|---|---|---|
| **Prior Platinum Therapy** | | | |
| Cisplatin | 248/411 | 0.73 | (0.56, 0.94) |
| Carboplatin | 82/126 | 0.74 | (0.47, 1.18) |
| **Most Recent Prior Therapy** | | | |
| Neo Adjuvant | 22/41 | 0.53 | (0.20, 1.41) |
| Adjuvant | 27/43 | 0.53 | (0.18, 1.57) |
| 1L Metastatic | 203/340 | 0.72 | (0.54, 0.95) |
| 2L Metastatic | 80/115 | 0.83 | (0.52, 1.33) |
| **Liver Metastases at Baseline** | | | |
| Presence | 145/186 | 0.85 | (0.61, 1.20) |
| Absence | 189/355 | 0.67 | (0.50, 0.89) |
| **Baseline Hemoglobin** | | | |
| >=10 g/dL | 257/442 | 0.71 | (0.55, 0.91) |
| <10 g/dL | 71/87 | 0.75 | (0.46, 1.22) |
| **Time from Most Recent Chemo Therapy** | | | |
| >=3 Months | 193/333 | 0.66 | (0.49, 0.89) |
| <3 Months | 140/207 | 0.82 | (0.58, 1.15) |
| **Histology** | | | |
| Transitional Cell | 240/383 | 0.80 | (0.62, 1.04) |
| Mixed Transitional/non-transitional histology | 93/155 | 0.58 | (0.37, 0.89) |
| **Brain Metastasis Status** | | | |
| Prior Brain Metastasis | 6/7 | NA | (NA, NA) |
| No Prior Brain Metastasis | 328/535 | 0.73 | (0.58, 0.91) |
| **MK-3475 vs. Paclitaxel** | | | |
| MK-3475 vs. Paclitaxel | 208/350 | 0.76 | (0.55, 1.04) |
| **MK-3475 vs. Docetaxel** | | | |
| MK-3475 vs. Docetaxel | 203/350 | 0.76 | (0.55, 1.05) |
| **MK-3475 vs. Vinflunine** | | | |
| MK-3475 vs. Vinflunine | 216/353 | 0.69 | (0.51, 0.94) |




| | # event/N | HR | 95% CI |
|---|---|---|---|
| **Overall** | 334/542 | 0.73 | (0.59, 0.91) |
| **Burden of Disease on Baseline Tumor Volume** | | | |
| < Median | 131/249 | 0.54 | (0.38, 0.78) |
| >= Median | 183/250 | 0.91 | (0.68, 1.23) |
| **Risk Scores** | | | |
| 0 | 35/98 | 0.82 | (0.42, 1.62) |
| 1 | 104/193 | 0.73 | (0.49, 1.08) |
| 2 | 111/146 | 0.84 | (0.56, 1.24) |
| 3 or 4 | 76/90 | 0.76 | (0.47, 1.24) |
| **Site of Primary Tumor** | | | |
| Upper Tract | 48/75 | 0.53 | (0.28, 1.01) |
| Lower Tract | 286/466 | 0.77 | (0.60, 0.97) |
| **Visceral Disease at Baseline** | | | |
| Lymph Node Only | 22/67 | 0.46 | (0.18, 1.21) |
| Visceral Disease | 312/473 | 0.75 | (0.60, 0.95) |



Based on Cox regression model with treatment as covariates and stratified by ECOG Performance Scale (0/1 vs. 2), presence or absence of liver metastases, hemoglobin (>=10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or >=3 months).

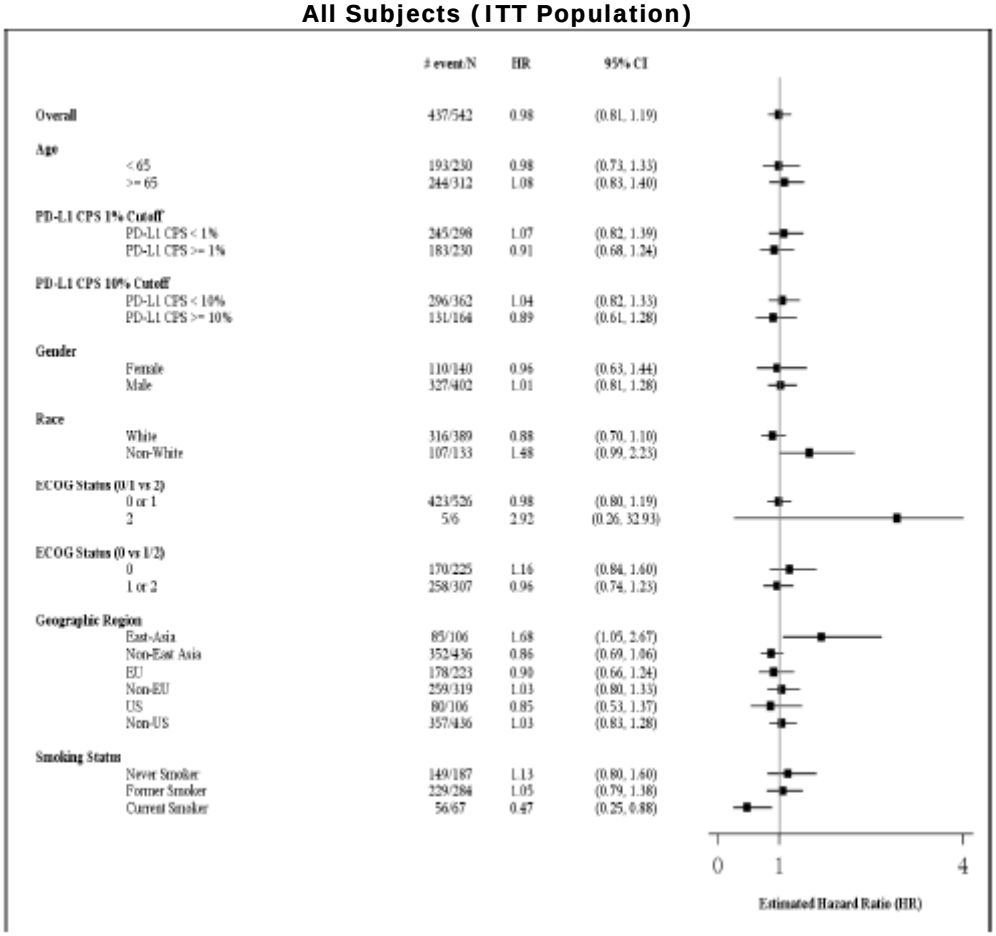
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

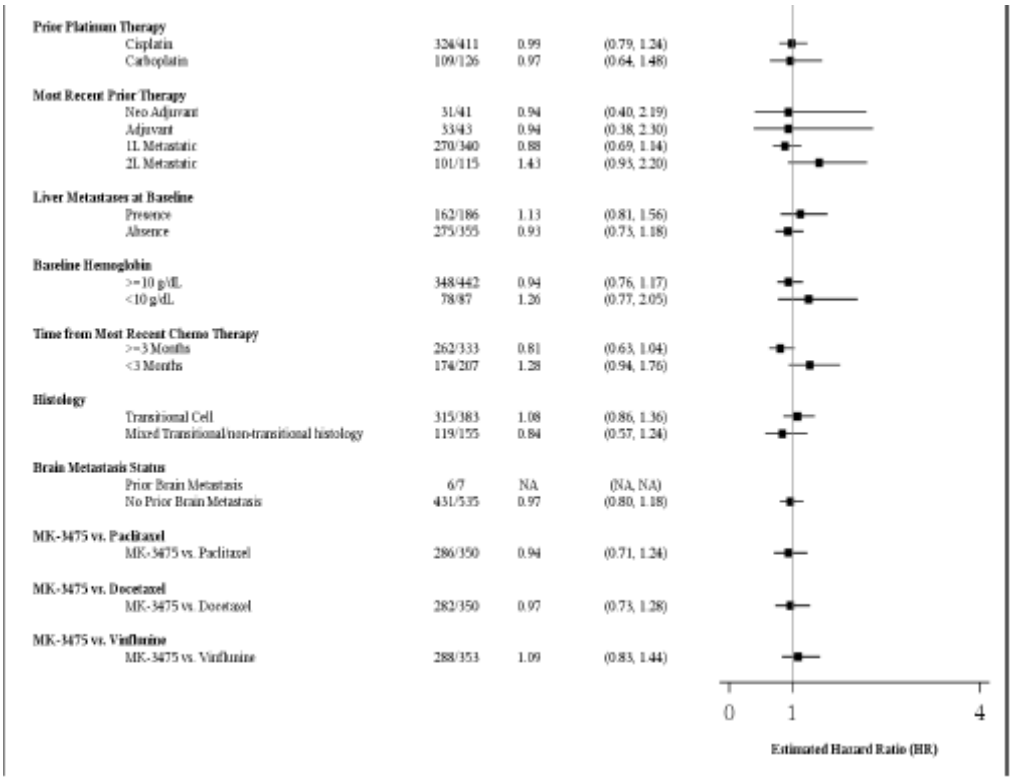
Database Cut-off Date: 07SEP2016

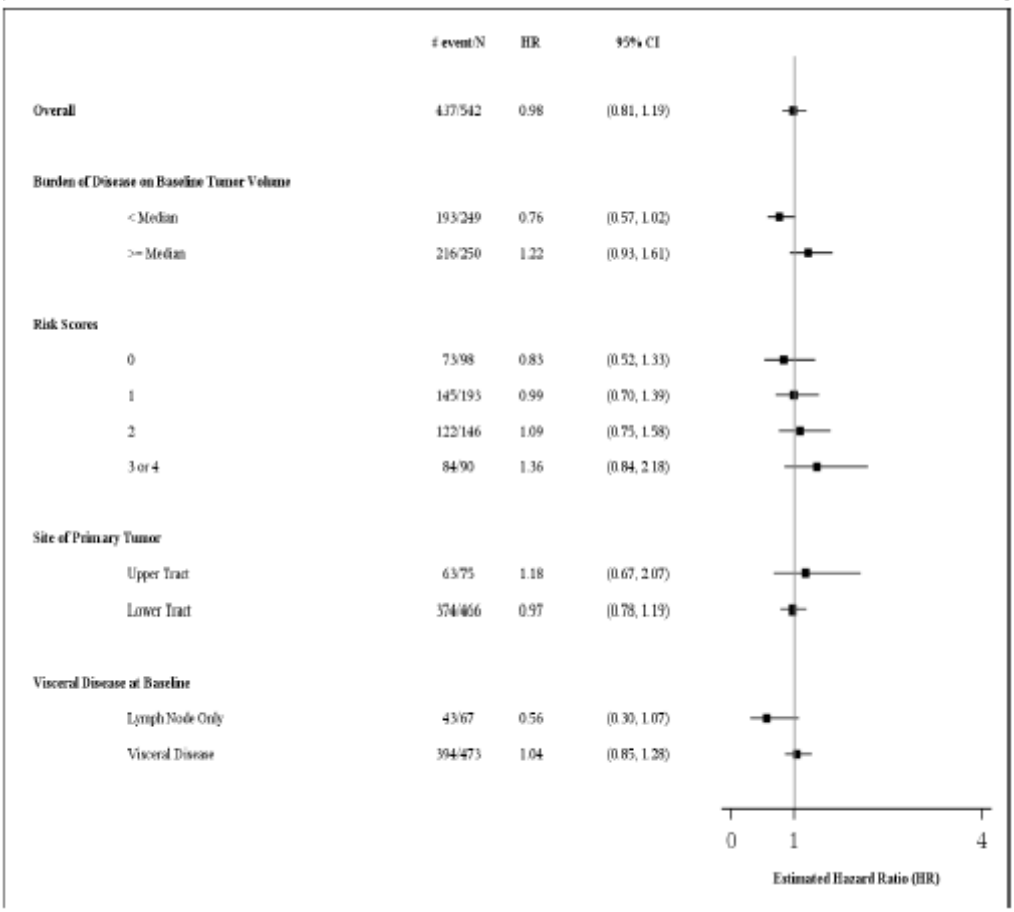
*PFS*

*Subgroup analysis*

**Figure: PFS based on RECIST 1.1 per central radiology assessment by Subgroup Factors Point Estimate and Nominal 95% Confidence Interval All Subjects (ITT Population)**






Based on Cox regression model with treatment as covariates and stratified by ECOG Performance Scale (0/1 vs. 2), presence or absence of liver metastases, hemoglobin (>=10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or >=3 months).
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

*Sensitivity analyses*

The results of the PFS analyses per RECIST 1.1 by Central Radiology Assessment according to Sensitivity Censoring Rules are reported in the following Table:

**Table 24: Analysis of PFS based on RECIST 1.1 per Central Radiology Assessment Sensitivity Censoring Rules 1,2 and 3 All Subjects (ITT Population)**

| | N | N. events (%) | Person-Months | Event Rate/ 100 Person-Months (%) | Median PFS* (months) (95% CI) | PFS Rate 6 months (%)* (95% CI) | PFS Rate 12 months (%)* (95% CI) | Pem vs control | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | HR (95%CI)° | p-value |
| **Sensitivity Censoring Rule 1** | | | | | | | | | |
| control | 272 | 199 (73.2) | 885.7 | 22.5 | 3.0 (2.2, 3.4) | 24.3 (18.7, 30.3) | 6.1 (3.0, 10.7) | 0.99 (0.81, 1.21) | 0.462 |
| pembro | 270 | 214 (79.3) | 1161.6 | 18.4 | 2.1 (2.0, 2.2) | 28.5 (23.1, 34.0) | 16.4 (11.8, 21.6) | | |
| | **Sensitivity Censoring Rule 2** | | | | | | | | |
| control | 272 | 264 (97.1) | 994.5 | 26.5 | 2.7 (2.2, 3.3) | 20.8 (16.2, 25.9) | 2.3 (0.9, 4.6) | 0.86 (0.71, 1.03) | 0.042 |
| pembro | 270 | 239 (88.5) | 1172.3 | 20.4 | 2.1 (2.0, 2.2) | 26.8 (21.6, 32.2) | 11.5 (7.9, 15.9) | | |
| | **Sensitivity Censoring Rule 3** | | | | | | | | |
| control | 272 | 212 (77.9) | 985.7 | 21.5 | 3.3 (2.3, 3.5) | 26.4 (20.8, 32.3) | 6.6 (3.6, 10.9) | 0.98 (0.80, 1.19) | 0.392 |
| pembro | 270 | 212 (78.5) | 1179.0 | 18.0 | 2.1 (2.0, 2.2) | 29.2 (23.8, 34.8) | 16.6 (12.0, 21.9) | | |

Table made by Assessor from Table 14.2-1, Table 14.2-2 and Table 14.2-3.
Sensitivity Censoring Rule 1: data for any subject who misses two or more consecutive disease assessments (with or without a subsequent death or progression) are censored at the last disease assessment prior to missing visits.
Sensitivity Censoring Rule 2: discontinuation of treatment or initiation of new anticancer treatment subsequent to discontinuation of study specified treatments, whichever occurs later, is a PD event for subjects without documented PD or death.
Sensitivity Censoring Rule 3: censoring of subjects with any of the following two clinical scenarios before PD or death at the time of last disease assessment prior to the clinical scenarios: (1) use of radiotherapy before study treatment discontinuation; (2) occurrence of a skeletal-related event (e.g., fracture) in patients with bone metastases at study entry.

*From product-limit (Kaplan-Meier) method for censored data.
°Based on stratified Cox regression model with treatment as a covariate stratified by ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, hemoglobin (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥ 3 months)
One-sided p-value based on stratified log-rank test.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cut-off Date: 07SEP2016

The results of the PFS analyses per RECIST 1.1 by Site Radiology Assessment for all subjects in the ITT population were similar compared to those by Central Radiology assessment.

*Analyses of OS/PFS and ORR by age group*

| | control | | | | pembrolizumab | | | |
|---|---|---|---|---|---|---|---|---|
| | **<65** | **65-74** | **75-84** | **85+** | **<65** | **65-74** | **75-84** | **85+** |
| N. Subject | 125 | 104 | 43 | 0 | 105 | 113 | 46 | 6 |
| **OS** | | | | | | | | |
| *n. of events* | 85 | 70 | 24 | 0 | 64 | 61 | 28 | 2 |
| *Median OS (months) (95%CI)* | 7.5 (6.3, 9.7) | 6.8 (4.7, 8.0) | 8.9 (3.6, ...) | NA | 8.0 (6.0, 11.8) | 10.5 (8.0, 16.0) | 10.3 (4.7, 15.2) | Not reached (11.6,..) |
| *OS at 6 months (%) (95%CI)* | 60.5 (51.0, 68.7) | 52.6 (42.1, 62.1) | 55.7 (39.2, 69.4) | NA | 60.7 (50.7, 69.3) | 65.7 (56.0, 73.7) | 62.3 (46.5, 74.6) | 100.0 (...,...) |
| *OS at 12 months (%) (95%CI)* | 29.7 (21.5, 38.4) | 29.0 (20.0, 38.6) | 38.3 (22.9, 53.5) | NA | 40.1 (30.4, 49.6) | 46.2 (36.5, 55.4) | 42.2 (27.8, 56.0) | 83.3 (27.3, 97.5) |
| *pem vs. control Hazard Ratio (95% CI)* | | | | | 0.75 (0.53, 1.05) | 0.64 (0.45, 0.92) | 1.52 (0.79, 2.89) | |
| *p-Value* | | | | | 0.045 | 0.007 | 0.897 | |
| **PFS** | | | | | | | | |
| *n. of events* | 105 | 81 | 33 | 0 | 88 | 87 | 38 | 5 |
| *Median PFS (months) (95%CI)* | 2.3 (2.1, 3.4) | 3.3 (2.6, 4.2) | 3.7 (2.1, 5.2) | NA | 2.0 (1.9, 2.1) | 2.2 (2.1, 3.4) | 2.1 (2.0, 4.8) | 2.7 (1.9, ...) |
| *PFS at 6 months (%) (95%CI)* | 21.8 (14.5, 30.1) | 32.0 (22.5, 41.9) | 28.6 (15.3, 43.5) | NA | 23.6 (15.9, 32.1) | 30.7 (22.4, 39.4) | 35.6 (22.0, 49.3) | 33.3 (4.6, 67.6) |
| *PFS at 12months (%) (95%CI)* | 2.3 (0.5, 7.2) | 9.4 (4.1, 17.4) | 9.1 (1.8, 23.7) | NA | 16.0 (9.3, 24.3) | 19.7 (12.5, 28.2) | 11.2 (3.0, 25.7) | 16.7 (0.8, 51.7) |
| *pem vs. control Hazard Ratio (95% CI)* | | | | | 0.98 (0.73, 1.33) | 1.00 (0.73, 1.38) | 1.52 (0.88, 2.64) | |
| *p-Value* | | | | | 0.457 | 0.504 | 0.931 | |
| **ORR** | | | | | | | | |
| *ORR (%)* | 6.4 | 11.5 | 25.6 | NA | 18.1 | 23.0 | 21.7 | 33.3 |
| *(95%CI)* | (2.8, 12.2) | (6.1, 19.3) | (13.5, 41.2) | | (11.3, 26.8) | (15.6, 31.9) | (10.9, 36.4) | (4.3, 77.7) |
| *pem vs. control Estimate (95% CI)* | | | | | 12.7 (4.3, 22.2) | 10.6 (0.5, 21.1) | -8.0 (-27.7,11.3) | |
| *p-Value* | | | | | 0.001 | 0.019 | 0.790 | |

Table made by the Assessor from Tables 14.2-12 to 14.2-15 (OS), from Tables 14.2-7 to 14.2-10 (PFS) and from Tables 14.2-35 to 14.2-38 (ORR) in KEYNOTE-045 CSR v01

## *Summary of main study(ies)*

The following table summarises 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 25: Summary of Efficacy for trial KEYNOTE-045**

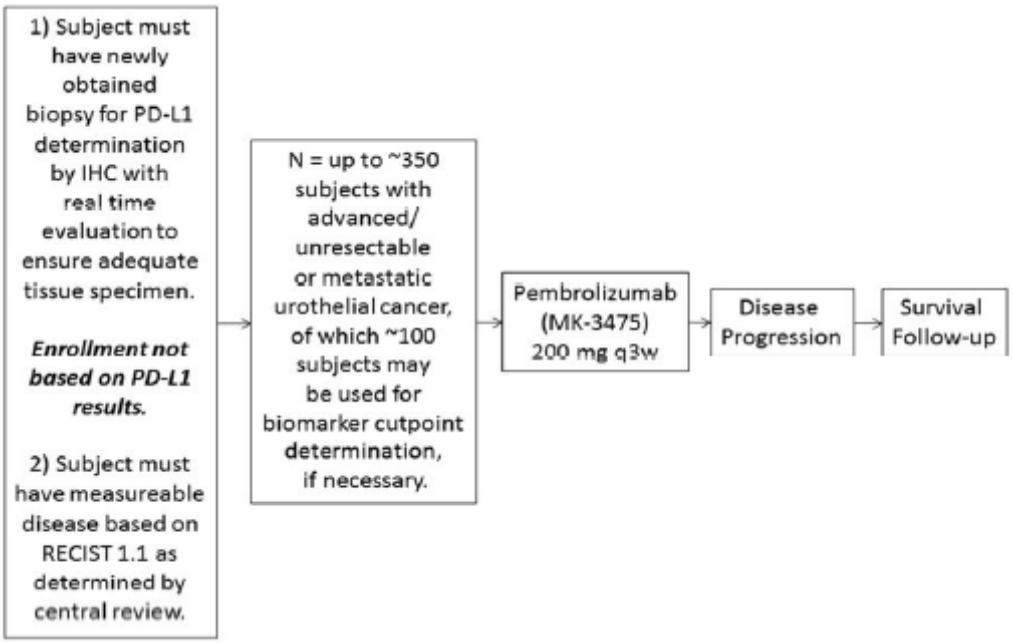
| **Title: A Phase III Randomized Clinical Trial of Pembrolizumab (MK-3475) versus Paclitaxel, Docetaxel or Vinflunine in Subjects with Recurrent or Progressive Metastatic Urothelial Cancer** | | | |
|---|---|---|---|
| Study identifier | EudraCT number: 2014-002009-40 | | |
| Design | Randomized, active-controlled, multicenter, open-label trial of IV pembrolizumab monotherapy vs the investigator's choice of paclitaxel, docetaxel or vinflunine in locally advanced or metastatic urothelial carcinoma patients who have received prior platinum-containing therapy. | | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | | not applicable<br>not applicable<br>not applicable |
| Hypothesis | Superiority | | |
| Treatments groups | pembrolizumab | | 200 mg IV Q3W<br><br>270 enrolled patients |
| | Investigator's choice | | paclitaxel 175 mg/m$^2$ Q3W<br><br>OR<br><br>docetaxel 75 mg/m$^2$ Q3W<br><br>OR<br><br>vinflunine 320 mg/m$^2$ Q3W<br><br>272 enrolled patients |
| Endpoints and definitions | Co-Primary endpoint | OS | time from randomization to death due to any cause |
| | Co-primary endpoint | PFS | time from randomization to documented progressive disease per RECIST 1.1 based on BICR or death due to any cause, whichever occurred first |
| | Secondary endpoint | ORR | Proportion of patients in the analysis population with a CR or PR, based on BICR review per RECIST 1.1 |
| | Secondary endpoint | Time to response | Time from randomization to the first assessment of CR or PR. Only confirmed CR/PR were included in the analysis. |
| | Secondary endpoint | Response duration | Time from the first CR/PR to documented PD. Only confirmed CR/PR were included in the analysis. |
| Cut-off date<br>Database lock | 07-SEP-2016<br>07-OCT- 2016 | | |
| **Results and Analysis** | | | |
| **Analysis description** | **Primary Analysis** | | |
| Analysis population and time point description | Intent to treat | | |

| | | | |
|---|---|---|---|
| Descriptive statistics and effect estimate per comparison | Treatment group | Pembrolizumab 200 mg | Control |
| | All subject (N) | 270 | 272 |
| | **Dual Primary endpoints** | | |
| | **OS**<br>N. with events<br>n (%) | 155 (57.4) | 179 (65.8) |
| | Median OS months<br>(95% CI) | 10.3<br>(8.0,11.8) | 7.4<br>(6.1, 8.3) |
| | Hazard Ratio<br>Pembrolizumab vs control<br>(95% CI) | 0.73<br>(0.59, 0.91) | |
| | p-value<br>(one sided log-rank test) | 0.002 | |
| | **PFS** (BICR RECIST 1.1)<br>N. with events (%) | 218 (80.7) | 219 (80.5) |
| | Median PFS months<br>(95% CI) | 2.1<br>(2.0,2.2) | 3.3<br>(2.3,3.5) |
| | Hazard Ratio<br>Pembrolizumab vs control<br>(95% CI) | 0.98<br>(0.81, 1.19) | |
| | p-value<br>(one sided log-rank test) | 0.416 | |
| | **Secondary endpoints** | | |
| | **ORR** (BICR-RECIST 1.1)<br>(95% CI) | 21.1<br>(16.4, 26.5) | 11.4<br>(7.9, 15.8) |
| | Difference % vs control<br>(95% CI) | 9.6<br>(3.5, 15.9) | |
| | p-value<br>(one sided) | 0.001 | |
| | Number of subjects with response | 57 | 31 |
| | **Time to response**<br>Median (months)<br>range | 2.1<br>(1.4, 6.3) | 2.1<br>(1.7, 4.9) |
| | **Response duration**<br>Median (months)<br>range | Not reached<br>(1.6+, 15.6+) | 4.3<br>(1.4+, 15.4+) |

- **Main study** (Urothelial carcinoma ineligible for cisplatin-based chemotherapy)

***Study KEYNOTE-052*: A Phase II Clinical Trial of Pembrolizumab (MK-3475) in Subjects with Advanced/Unresectable or Metastatic Urothelial Cancer**

**Figure: Trial design**




***Methods***

**Study participants**

*Main inclusion criteria*

- Histologically or cytologically confirmed diagnosis of advanced/unresectable (inoperable) or metastatic urothelial cancer of the renal pelvis, ureter, bladder, or urethra. Both transitional cell and mixed transitional/non-transitional cell histologies were allowed.
- Age ≥18 years.
- Cisplatin-ineligibility to receive cisplatin-based combination therapy, 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
  *Note: Subjects with a creatinine clearance (calculated or measured) <30 mL/min or on dialysis are excluded from the trial*

- 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

*Note: In the event that subjects are enrolled for the purposes of determining the biomarker cut-point prior to the start of the main body of this study, these subjects are not required to be cisplatin-ineligible and the above criteria does not apply.*

- No prior systemic chemotherapy for advanced/unresectable (inoperable) or metastatic urothelial cancer.
  - Adjuvant platinum based chemotherapy, following radial cystectomy, with recurrence >12 months from completion of therapy is permitted
  - Neoadjuvant platinum based chemotherapy, with recurrence >12 months since completion of therapy is permitted
    *Note: Low-dose chemotherapy (eg, low dose cisplatin, cisplatin+5FU, mytomycin+5FU, or cisplatin+paclitaxel) given concurrent with radiation to the primary tumor site is not considered as systemic therapy.*

- Provided tissue for biomarker analysis from a newly obtained core or excisional biopsy of a tumor lesion not previously irradiated (mandatory). Adequacy of the biopsy specimen for PD-L1 biomarker analysis must be confirmed by the central laboratory.

- Measureable disease based on RECIST 1.1 as assessed by central review. Tumor lesions situated in a previously irradiated area were considered measureable if progression had been demonstrated in such lesions.

- ECOG Performance Status of 0, 1, or 2, as assessed within 10 days prior to treatment initiation.

*Main exclusion criteria*

- Disease suitable for local therapy administered with curative intent.

- Current or previous participation in a study of an investigational agent, with study therapy received or investigation device used within 4 weeks of the first dose of treatment.

- Prior anticancer monoclonal antibody for direct anti-neoplastic treatment within 4 weeks prior to study Day 1 or not recovered (ie, ⩽ Grade 1 or at baseline) from AEs due to agents administered more than 4 weeks earlier.

- Prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to

study Day 1 or who had not recovered (ie, ⩽ Grade 1 or at baseline) from AEs due to a previously administered agent.

*Notes: Subjects with neuropathy or ⩽ Grade 2 alopecia were an exception to this criterion and may qualify for the study. If a subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.*

- Known additional malignancy progressing or requiring active treatment. Exceptions included basal cell carcinoma of the skin, squamous cell carcinoma of the skin that had undergone potentially curative therapy, or in situ cervical cancer. A history of prostate cancer identified incidentally following cysto-prostatectomy for bladder cancer was acceptable, provided that Stage was T2N0M0 or lower, Gleason score ⩽6, and prostate-specific antigen undetectable.

- Known active central nervous system metastases and/or carcinomatous meningitis. Subjects with previously-treated brain metastases may participate provided they were stable (without evidence of progression by imaging, confirmed by CT scan or MRI if used as prior imaging, for at least 4 weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and were not using steroids for at least 7 days prior to trial treatment. This exception did not include carcinomatous meningitis, which was excluded regardless of clinical stability.

- Active autoimmune disease requiring systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considere d a form of systemic treatment.

- History or current evidence of any condition, therapy, or laboratory abnormality that could confound the results of the trial, interfere with the subject' s participation for the full duration of the trial, or not in the best interest of the subject to participate, in the opinion of the treating Investigator.

- Prior therapy with an anti-PD-1, anti-PD-L1 agent, or with anagent directed to another co-inhibitory T-cell receptor (eg, CTLA-4,OX-40, CD137).

- Known history of Human Immunodeficiency Virus (HIV) (HIV-1/2 antibodies).

- Administration of live vaccine within 30 days prior to the first administration of study medication.

## Treatments

Pembrolizumab was administered at the fixed dosing regimen of 200 mg as a 30 minute (-5 min/+10 min) IV infusion Q3W.
Treatment could be continued until confirmed radiographic disease progression by RECIST 1.1, unacceptable adverse experiences, intercurrent illness that prevented further administration of treatment, Investigator's decision to withdraw the subject, confirmed positive pregnancy test, non-compliance with trial treatment or procedure requirements, completed 24 months of pembrolizumab treatment or administrative reasons.
Despite RECIST 1.1 defined progression, pembrolizumab could have been continued while awaiting radiologic confirmation of PD. If repeat imaging still meets the threshold for PD (⩾ 20% increase in tumor

burden compared to nadir) but shows a reduction in tumor burden compared to the previous time point, treatment may be continued as per treatment calendar after consultation with Sponsor.
Patients who stopped pembrolizumab after receiving 24 months of treatment for reasons other than disease progression or intolerability, or after a complete response having received at least 24 weeks of pembrolizumab and at least 2 treatments beyond the date of initial CR declared, may have been eligible for up to one additional year of retreatment upon experiencing disease progression.

## Objectives

The study primary objective was to evaluate the anti-tumor activity of pembrolizumab in terms of Objective Response Rate (ORR) per RECIST 1.1 by independent radiology review in all subjects with advanced/unresectable or metastatic urothelial carcinoma who are ineligible to receive cisplatin-based therapy, as well as in those with PD-L1 positive (CPS≥1%) and PD-L1 strongly positive (CPS cut point determined from biomarker discovery population) tumors.

As secondary objectives, the pembrolizumab activity was evaluated in terms of duration of response (DOR) per RECIST 1.1 by independent radiology review, PFS per RECIST 1.1 by independent radiology review (including PFS rate at 6 and 12 months), and OS (including OS rate at 6 and 12 months).
In addition, the anti-tumor activity in terms of ORR, DOR and PFS based on modified RECIST 1.1 by independent radiology review, the relationship between candidate efficacy/resistance biomarkers and pembrolizumab anti-tumor activity based on pre- and post-treatment tumor biopsies and blood sampling, the PK profile of pembrolizumab 200 mg Q3W, the changes in health-related quality-of-life assessments from baseline using the EORTC QLQ-C30, and the characterization of utilities using the EQ-5D were evaluated as exploratory objectives in PD-L1 strongly positive, PD-L1 positive, and all subjects.

## Outcomes/endpoints

The primary efficacy endpoint was objective response rate (ORR) based on RECIST 1.1 criteria assessed by independent radiology review of imaging studies performed at both planned and unplanned time points during the study. ORR was estimated for all subjects, for subjects with PD-L1 expression (CPS) ⩾1%, and for subjects with strongly positive CPS expression (CPS) ⩾10%, that was determined as a secondary study objective of the trial, based on assessment of activity in the biomarker discovery cohort (the first 100 subjects enrolled). All other efficacy analyses involving subsets of the population defined in terms of the strongly positive CPS cutpoint were conducted among the PD-L1 ≥10% from the validation cohort, with the exclusion of patients in the discovery cohort.

Additional secondary efficacy endpoints were DOR (RECIST 1.1 by independent radiology review); PFS (RECIST 1.1 by independent radiology review); overall survival (OS); PFS (RECIST 1.1 by independent radiology review) rate and OS rate at 6 months and 12 months.

Additional exploratory endpoints were to investigate the relationship between biomarkers and anti-tumor activity, to evaluate the pembrolizumab anti-tumor activity by ORR, DOR and PFS based on modified RECIST 1.1 by independent radiology review, and to evaluate changes in health-related quality-of-life assessments from baseline using the EORTC QLQ-C30.
The definition of primary and secondary endpoints is reported in the below Table "*Summary of Efficacy for trial KEYNOTE-052*".

Response to treatment was assessed with radiographic imaging at 9 weeks (63 ± 7 days) after the first dose of pembrolizumab and every 6 weeks thereafter (42 days ± 7 days). Subjects who remained on treatment beyond 1 year had imaging assessments performed every 12 weeks (84 ± 7 days). All on-trial imaging was submitted to the central vendor for BICR review per RECIST 1.1 for determination of ORR and PFS. The Investigator may have chosen to treat beyond RECIST 1.1 defined progression if subjects continued deriving clinical benefit and were clinically stable.

The APT population, including all enrolled subjects who received at least 1 dose of pembrolizumab, served as the primary population for the efficacy analyses. Supportive analyses were to be conducted in the Full Analysis Set (FAS) population, consisting of all enrolled subjects who received at least 1 dose of pembrolizumab and had measureable disease at baseline. In this case, the APT and FAS populations overlapped, and therefore supportive analyses were not performed.

Additional not protocol-specified analyses were conducted to further characterize pembrolizumab efficacy and safety profile in the target population. In order to determine the influence on the primary endpoint estimation of the duration of follow up and of radiology reader variability ORR was determined among subjects with longer follow-up than the total APT population and by investigator per RECIST v1.1.

Although the primary analysis for CPS ⩾10% was conducted on the validation cohort, a supportive analysis combining the biomarker discovery and validation cohorts was performed in order to assess the ORR in strongly positive across the entire study population.

## Sample size

The sample size calculation was driven by the primary efficacy estimation for PD -L1 CPS ⩾10% subjects. Up to 350 subjects were to be enrolled. Assuming a 33% prevalence rate of PD-L1 CPS ⩾10% subjects and 100 subjects in the biomarker discovery population, there was an 88% chance to have at least 75 PD-L1 CPS ⩾10% subjects and 99.9% chance to have at least 60 PD-L1 CPS ⩾10% subjects in the validation cohort (N ≈ 250).

## Randomisation

Treatment allocation was performed centrally using an interactive voice response system/integrated web response system (IVRS/IWRS) by non-random assignment.

## Blinding (masking)

Not applicable. This is an open label trial.

## Statistical methods

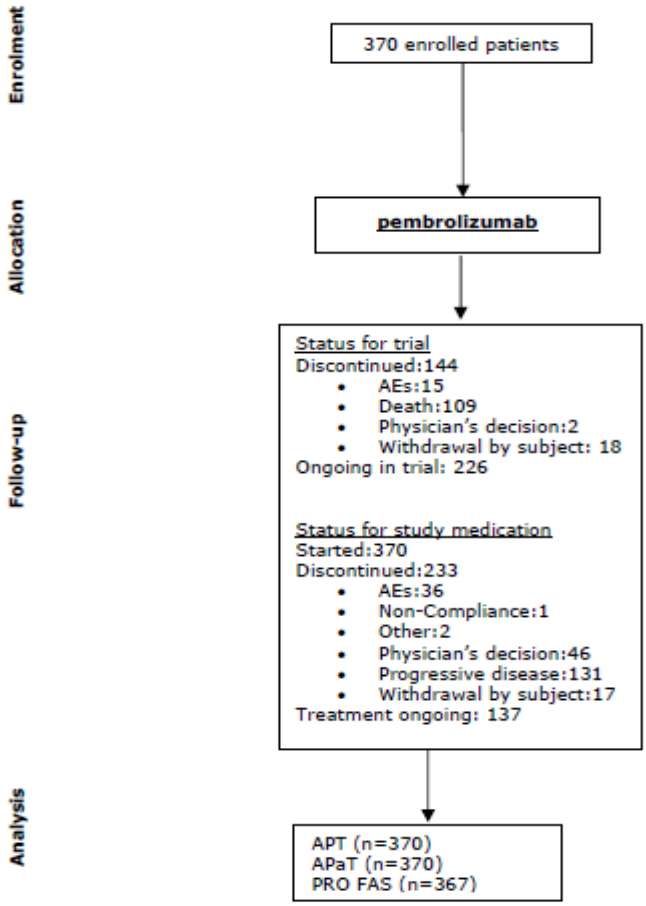
A preliminary assessment of clinical activity within the discovery cohort to determine the strongly positive cut-off as a function of ORR was performed in the first 100 subjects. The APT population, consisting of all enrolled subjects who received at least one dose of study treatment, served as the primary population for the analyses of efficacy data in this trial. The biomarker discovery population, subjects in this trial used for the determination of the PD-L1 strongly positive cut-point, was to be excluded from efficacy analyses for the PD-L1 strongly positive population. These subjects were still to be included in the efficacy analyses for all and PD-L1 positive subjects. Efficacy analyses were conducted according to the methods reported in the table below.

| Endpoint/Variable+ (Description, Time Point) | Statistical Method | Analysis Population | Missing Data Approach |
|---|---|---|---|
| Primary Objectives: | | | |
| RECIST1.1 ORR by independent radiology review for PD-L1 strongly positive subjects, PD-L1 positive subjects, and all subjects | Exact method based on binomial distribution | APT/FAS | Subjects with missing data are considered non-responders |
| Secondary Objectives: | | | |
| Duration of Response, RECIST1.1 by independent radiology review, for PD-L1 strongly positive subjects, PD-L1 positive subjects, and all subjects | Summary statistics /Kaplan-Meier method | APT/FAS | Non-responders are excluded in analysis |
| Progression-free survival, RECIST1.1 by independent radiology review, for PD-L1 strongly positive subjects, PD-L1 positive subjects, and all subjects | Summary statistics /Kaplan-Meier method | APT/FAS | Censored at last assessment |
| Overall survival, for PD-L1 strongly positive subjects, PD-L1 positive subjects, and all subjects | Summary statistics /Kaplan-Meier method | APT/FAS | Censored at last assessment |
| 95% confidence interval is determined by the upper and lower 97.5% one-sided confidence bounds. | | | |

An interim efficacy evaluation was performed in which enrollment of PD-L1 negative (CPS <1%) subjects could have been stopped if the ORR was low and substantial enrollment remained. This futility analysis was based on the evaluable PD-L1 negative subjects in the biomarker discovery population (up to the first 25 subjects). If the number of PD-L1 negative subjects in the biomarker subgroup was less than 20, additional PD-L1 negative subjects could be included until the number reached at least 20. The non-binding rule for futility required that the upper limit of the 95% confidence interval (CI) (2-sided) for the ORR be less than 20% (needed at least 1 response in N < 26 subjects and at least 2 responses in N = 26 to 40 subjects).

***Results***

## Participant flow




APT: All Patients Treated; APaT: All Patients as Treated; PRO FAS: Patient Reported Outcomes Full Analysis Set.

## Recruitment

Overall, 370 patients were enrolled and treated in 77 activated centers from 20 April 2015 to 21 June 2016. The highest enrolling country was the US with a total of 159 subjects.

## Conduct of the study

The original protocol (dated 29 August 2014) was amended twice during the study conduction.
The key changes introduced by the protocol amendments are summarized below:

| Protocol Amendment | Most relevant changes |
|---|---|
| #01 (8 October 2014) | Clarification that subjects must be refractory to available or standard therapy for treatment of their bladder cancer in order to participate in the biomarker cut-point determination part of the Study, if they do not meet cisplatin-ineligible criteria. |

| | |
|---|---|
| | Safety and tolerability were to be evaluated in all subjects regardless of PD-L1 status.<br><br>The screening window for the new core or excisional biopsy for biomarker analysis was increased to 56 days (8 weeks). |
| #2 (11 March 2016) | Addition to indicate that PD-L1 positive was prospectively defined as subjects with Combined Positive Score (CPS) ⩾1%.<br><br>Removal of hypotheses testing since the objective of the trial was to estimate efficacy, and the success of the trial was determined by clinically meaningful ORRs and durability of the response.<br><br>The number of subjects to be used for the biomarker cut-point analysis was updated from ~150 subjects to ~100 subjects.<br><br>Clarification that bone scans must have been submitted for review at baseline to the central imaging vendor even though bone scans were not part of determining RECIST measurability.<br><br>The 56 day screening window requirement for the new core or excisional biopsy was removed from the protocol to offer more operational flexibility, as long as the subject has not received any intervening systemic therapy from the time the tissue was collected until the time the subject enters the study.<br><br>The All-Patients-Treated (APT) population was identified as the primary efficacy and safety analysis population, based on FDA requirement for single arm trials. |

There were 9 major protocol deviations deemed clinically relevant from 6 different sites, 3 in Spain, 1 in the US, and 2 in Italy. Two clinically relevant major protocol deviations were categorized as entry criteria deviations and pertained to allocation/treatment despite creatinine and bilirubin being above allowable limits. A third subject was allocated/treated despite having a history of Gleason 8 prostate cancer. Two major protocol deviations occurred when 2 subjects each were treated with corticosteroids for non-ECI AEs during the trial which was prohibited except to treat pre-defined immune-related AEs. For 4 subjects, clinically relevant major protocol deviations occurred in relation to bone scan efficacy assessments, as they did not have follow-up scans despite the presence of osseous metastatic disease at study entry. No subjects were excluded from the analysis due to a protocol deviation.

For 2 additional subjects, the blinded central independent radiology vendor notified sites that the subjects had RECIST-measurable disease. However, when the imaging data for these subjects was formally analyzed for outcome, no target lesions were identified. Being treated, subjects were included in the analysis in the denominator of the ORR calculations as per the protocol statistical analysis plan, but they were not counted as complete or partial responders.

## Baseline data

### Table 26: Subjects Characteristics

### All Subjects (ITT Population)- KEYNOTE-052

| | 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) |
| **Ethnicity** | | |
| Hispanic Or Latino | 22 | (5.9) |
| Not Hispanic Or Latino | 319 | (86.2) |
| Not Reported | 21 | (5.7) |
| Unknown | 8 | (2.2) |
| **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 | 133 | (35.9) |
| [2] Ambulatory but unable to work | 156 | (42.2) |
| [3] Limited selfcare | 1 | (0.3) |

| | Pembrolizumab | |
|---|---|---|
| | n | (%) |
| **Metastatic Staging** | | |
| M0 | 47 | (12.7) |
| M1 | 323 | (87.3) |
| **Chemotherapy Naïve (Y/N)** | | |
| No | 67 | (18.1) |
| Yes | 303 | (81.9) |
| **Baseline Hemoglobin** | | |
| >=10 g/dL | 329 | (88.9) |
| <10 g/dL | 41 | (11.1) |
| **Liver Metastasis (Y/N)** | | |
| No | 292 | (78.9) |
| Yes | 78 | (21.1) |
| **Prior Adjuvant or Neoadjuvant Platinum-based Chemotherapy** | | |
| No | 334 | (90.3) |
| Yes | 36 | (9.7) |
| **Prior BCG Therapy** | | |
| No | 316 | (85.4) |
| Yes | 54 | (14.6) |
| **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 | 182 | (49.2) |
| ECOG 2 and Renal Dysfunction | 35 | (9.5) |
| Other Reasons‡ | 33 | (8.9) |

†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.
M stage Database Cutoff Date: 14FEB2017
Database Cutoff Date: 01SEP2016

Source: [P052V01MK3475: analysis-adsl]

## Numbers analysed

The same patient population, consisting of the 370 subjects who were enrolled and treated in the trial, served as the primary population for the efficacy analyses (APT: All-Patients-Treated population) and was used for the analysis of safety data (APaT: All Patients as Treated population).
A biomarker discovery population cohort including the first 100 subjects enrolled and treated served for determination of the PD-L1 strongly positive cut-point.
Analyses of the pre-specified patient reported outcomes (PRO) from the EORTC QLC-C30 and EQ-5D questionnaires were conducted in the PRO-specific full analysis set (FAS) population, including 367 patients who received at least 1 dose of study medication and completed at least 1 PRO instrument.

## Outcomes and estimation

The activity reported in the biomarker discovery cohort, including the first 100 subjects enrolled and treated, served for determination of the PD-L1 strongly positive cut-point.
The biomarker discovery cohort was excluded from the primary efficacy analyses for subjects in the

validation cohort whose tumors were PD-L1 strongly positive.
In the initial submission (cut-off data:01-Sep-2016), the median duration of follow-up for all subjects in the APT population was 5 months (range 0.1-16.5 months). An updated analysis (Cut-off data: 09Mar2017) was conducted at a median follow-up of 9.5 months (0.1-22.7). For the tables below, first the 01-Sep-2016 cut-off is presented, followed by a presentation of the same data with the 09-Mar-2017 cut-off.

***Primary endpoint***

***Objective Response Rate***

- *All Subjects (APT Population)*

**Table 27: Summary of Best Overall Response with Confirmation Based on RECIST 1.1 per Central Radiology Assessment**
**All Subjects (APT Population)**
(Cut-off date: 01-Sep-2016)

| Response Evaluation | Pembrolizumab (N=370) | | |
|---|---|---|---|
| | n | % | 95% CI[†] |
| Complete Response (CR) | 17 | 4.6 | (2.7, 7.3) |
| Partial Response (PR) | 72 | 19.5 | (15.5, 23.9) |
| **Objective Response (CR+PR)** | **89** | **24.1** | **(19.8, 28.7)** |
| Stable Disease (SD) | 84 | 22.7 | (18.5, 27.3) |
| **Disease Control (CR+PR+SD)** | **173** | **46.8** | **(41.6, 52.0)** |
| Progressive Disease (PD) | 156 | 42.2 | (37.1, 47.4) |
| Non-evaluable (NE) | 10 | 2.7 | (1.3, 4.9) |
| 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: 01SEP2016

Source: [P052V01MK3475: analysis-adsl; adopa]

**Table 28: Summary of Best Overall Response with Confirmation Based on RECIST 1.1 per Central Radiology Assessment**

**All Subjects (APT Population)**

(Cut-off date: 09-Mar-2017)

| Response Evaluation | Pembrolizumab (N=370) | | |
|---|---|---|---|
| | n | % | 95% CI† |
| Complete Response (CR) | 27 | 7.3 | (4.9, 10.4) |
| Partial Response (PR) | 81 | 21.9 | (17.8, 26.5) |
| Objective Response (CR+PR) | 108 | 29.2 | (24.6, 34.1) |
| Stable Disease (SD) | 67 | 18.1 | (14.3, 22.4) |
| Disease Control (CR+PR+SD) | 175 | 47.3 | (42.1, 52.5) |
| Progressive Disease (PD) | 155 | 41.9 | (36.8, 47.1) |
| Non-evaluable (NE) | 9 | 2.4 | (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: 09MAR2017

Source: [P052V01MK3475: analysis-adsl; adopa]

- *Subjects with PD-L1 CPS≥1%*

**Table 29: Summary of Best Overall Response with Confirmation Based on RECIST 1.1 per Central Radiology Assessment Subjects with PD-L1 CPS≥1% (APT Population)**

Cut-off date: 01-Sep-2016

| Response Evaluation | Pembrolizumab (N=282) | | |
|---|---|---|---|
| | n | % | 95% CI† |
| Complete Response (CR) | 14 | 5.0 | (2.7, 8.2) |
| Partial Response (PR) | 61 | 21.6 | (17.0, 26.9) |
| **Objective Response (CR+PR)** | **75** | **26.6** | **(21.5, 32.2)** |
| Stable Disease (SD) | 72 | 25.5 | (20.5, 31.0) |
| **Disease Control (CR+PR+SD)** | **147** | **52.1** | **(46.1, 58.1)** |
| Progressive Disease (PD) | 109 | 38.7 | (32.9, 44.6) |
| Non-evaluable (NE) | 6 | 2.1 | (0.8, 4.6) |
| No Assessment | 20 | 7.1 | (4.4, 10.7) |

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: 01SEP2016

Source: [P052V01MK3475: analysis-adsl; adopa]

**Table 30: Summary of Best Overall Response with Confirmation Based on RECIST 1.1 per Central Radiology Assessment Subjects with PD-L1 CPS≥1% (APT Population)**

Cut-off date: 09-Mar-2017

| Response Evaluation | Pembrolizumab (N=282) | | |
|---|---|---|---|
| | n | % | 95% CI† |
| Complete Response (CR) | 24 | 8.5 | (5.5, 12.4) |
| Partial Response (PR) | 68 | 24.1 | (19.2, 29.5) |
| **Objective Response (CR+PR)** | **92** | **32.6** | **(27.2, 38.4)** |
| Stable Disease (SD) | 57 | 20.2 | (15.7, 25.4) |
| **Disease Control (CR+PR+SD)** | **149** | **52.8** | **(46.8, 58.8)** |
| Progressive Disease (PD) | 108 | 38.3 | (32.6, 44.2) |
| Non-evaluable (NE) | 5 | 1.8 | (0.6, 4.1) |
| No Assessment | 20 | 7.1 | (4.4, 10.7) |

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: 09MAR2017

Source: [P052V01MK3475: analysis-adsl; adopa]

- *Subjects with PD-L1 CPS≥10%*

The PD-L1 CPS strongly positive cut point for efficacy was determined among subjects in the discovery cohort to be CPS ≥10% through a systematic assessment that included analysis of the positive and negative predictive values and receiver operating characteristics (ROC) across a wide range of potential CPS cut points. Table 31, depicts the results for the Biomarker Discovery population and Table 32 depicts the results for the Biomarker validation population. Tables 33 and 34 present the summary of best overall response for the total population with PD-L1 CPS≥10%, first according to the 01-Sep-2016 cut-off, followed by the data from the 08-Mar-2017 cut-off. Tables 35 and 36 represent the data for the <1% CPS and <10% CPS populations, respectively, for the most recent data cut-off point.

**Table 31: Summary of Best Overall Response with Confirmation Based on RECIST 1.1 per Central Radiology Assessment Subjects with PD-L1 CPS≥10% (APT Population) Biomarker Discovery Population**

Cut-off date: 01-Sep-2016

| Response Evaluation | Pembrolizumab (N=30) | | |
|---|---|---|---|
| | n | % | 95% CI† |
| Complete Response (CR) | 5 | 16.7 | (5.6, 34.7) |
| Partial Response (PR) | 6 | 20.0 | (7.7, 38.6) |
| **Objective Response (CR+PR)** | **11** | **36.7** | **(19.9, 56.1)** |
| Stable Disease (SD) | 7 | 23.3 | (9.9, 42.3) |
| **Disease Control (CR+PR+SD)** | **18** | **60.0** | **(40.6, 77.3)** |
| Progressive Disease (PD) | 11 | 36.7 | (19.9, 56.1) |
| Non-evaluable (NE) | 0 | 0.0 | (0.0, 11.6) |
| No Assessment | 1 | 3.3 | (0.1, 17.2) |

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: 01SEP2016

Source: [P052V01MK3475: analysis-adsl; adopa]

**Table 32: Summary of Best Overall Response with Confirmation Based on RECIST 1.1 per Central Radiology Assessment Subjects with PD-L1 CPS≥10% (APT Population) Efficacy Validation Population**

Cut-off date: 01-Sep-2016

| Response Evaluation | Pembrolizumab (N=80) | | |
|---|---|---|---|
| | n | % | 95% CI† |
| Complete Response (CR) | 8 | 10.0 | (4.4, 18.8) |
| Partial Response (PR) | 23 | 28.8 | (19.2, 40.0) |
| **Objective Response (CR+PR)** | **31** | **38.8** | **(28.1, 50.3)** |
| Stable Disease (SD) | 24 | 30.0 | (20.3, 41.3) |
| **Disease Control (CR+PR+SD)** | **55** | **68.8** | **(57.4, 78.7)** |
| Progressive Disease (PD) | 20 | 25.0 | (16.0, 35.9) |
| Non-evaluable (NE) | 0 | 0.0 | (0.0, 4.5) |
| No Assessment | 5 | 6.3 | (2.1, 14.0) |

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: 01SEP2016

Source: [P052V01MK3475: analysis-adsl; adopa]

**Table 33: Summary of Best Overall Response with Confirmation Based on RECIST 1.1 per Central Radiology Assessment**

**Subjects with PD-L1 CPS ≥ 10% (APT Population)**

Cut-off date: 01-Sep-2016

| Response Evaluation | Pembrolizumab (N=110) | | |
|---|---|---|---|
| | n | % | 95% CI† |
| Complete Response (CR) | 13 | 11.8 | (6.4, 19.4) |
| Partial Response (PR) | 29 | 26.4 | (18.4, 35.6) |
| **Objective Response (CR+PR)** | **42** | **38.2** | **(29.1, 47.9)** |
| Stable Disease (SD) | 31 | 28.2 | (20.0, 37.6) |
| **Disease Control (CR+PR+SD)** | **73** | **66.4** | **(56.7, 75.1)** |
| Progressive Disease (PD) | 31 | 28.2 | (20.0, 37.6) |
| Non-evaluable (NE) | 0 | 0.0 | (0.0, 3.3) |
| No Assessment | 6 | 5.5 | (2.0, 11.5) |

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: 01SEP2016

Source: [P052V01MK3475: analysis-adsl; adopa]

**Table 34: Summary of Best Overall Response with Confirmation Based on RECIST 1.1 per Central Radiology Assessment Subjects with PD-L1 CPS≥10% (APT Population)**

Cut-off date: 09-Mar-2017

| Response Evaluation | Pembrolizumab (N=110) | | |
|---|---|---|---|
| | n | % | 95% CI† |
| Complete Response (CR) | 18 | 16.4 | (10.0, 24.6) |
| Partial Response (PR) | 34 | 30.9 | (22.4, 40.4) |
| **Objective Response (CR+PR)** | **52** | **47.3** | **(37.7, 57.0)** |
| Stable Disease (SD) | 22 | 20.0 | (13.0, 28.7) |
| **Disease Control (CR+PR+SD)** | **74** | **67.3** | **(57.7, 75.9)** |
| Progressive Disease (PD) | 30 | 27.3 | (19.2, 36.6) |
| Non-evaluable (NE) | 0 | 0.0 | (0.0, 3.3) |
| No Assessment | 6 | 5.5 | (2.0, 11.5) |

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: 09MAR2017

Source: [P052V01MK3475: analysis-adsl; adopa]

- *Subjects with PD-L1 CPS<1% and subjects with PD-L1 CPS<10%*

**Table 35: Summary of Best Overall Response with Confirmation Based on RECIST 1.1 per Central Radiology Assessment Subjects with PD-L1 CPS <1% (APT Population)**

Cut-off date: 09-Mar-2017

| Response Evaluation | Pembrolizumab (N=79) | | |
|---|---|---|---|
| | n | % | 95% CI† |
| Complete Response (CR) | 2 | 2.5 | (0.3, 8.8) |
| Partial Response (PR) | 11 | 13.9 | (7.2, 23.5) |
| **Objective Response (CR+PR)** | **13** | **16.5** | **(9.1, 26.5)** |
| Stable Disease (SD) | 9 | 11.4 | (5.3, 20.5) |
| **Disease Control (CR+PR+SD)** | **22** | **27.8** | **(18.3, 39.1)** |
| Progressive Disease (PD) | 43 | 54.4 | (42.8, 65.7) |
| Non-evaluable (NE) | 4 | 5.1 | (1.4, 12.5) |
| No Assessment | 10 | 12.7 | (6.2, 22.0) |

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: 09MAR2017

Source: [P052V01MK3475: analysis-adsl; adopa]

**Table 36: Summary of Best Overall Response with Confirmation Based on RECIST 1.1 per Central Radiology Assessment Subjects with PD-L1 CPS <10% (APT Population)**

Cut-off date: 09-Mar-2017

| Response Evaluation | Pembrolizumab (N=251) | | |
|---|---|---|---|
| | n | % | 95% CI† |
| Complete Response (CR) | 8 | 3.2 | (1.4, 6.2) |
| Partial Response (PR) | 45 | 17.9 | (13.4, 23.2) |
| **Objective Response (CR+PR)** | **53** | **21.1** | **(16.2, 26.7)** |
| Stable Disease (SD) | 44 | 17.5 | (13.0, 22.8) |
| **Disease Control (CR+PR+SD)** | **97** | **38.6** | **(32.6, 45.0)** |
| Progressive Disease (PD) | 121 | 48.2 | (41.9, 54.6) |
| Non-evaluable (NE) | 9 | 3.6 | (1.7, 6.7) |
| No Assessment | 24 | 9.6 | (6.2, 13.9) |

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: 09MAR2017

Source: [P052V01MK3475: analysis-adsl; adopa]

- *Subjects with PD-L1 CPS≥1% to<10%*

**Table 37: Summary of Best Overall Response with Confirmation Based on RECIST 1.1 per Central Radiology Assessment Subjects with PD-L1 CPS ≥ 1% to < 10% (APT Population)**

Cut-off date: 09-Mar-2017

| Response Evaluation | Pembrolizumab (N=172) | | |
|---|---|---|---|
| | n | % | 95% CI[†] |
| Complete Response (CR) | 6 | 3.5 | (1.3, 7.4) |
| Partial Response (PR) | 34 | 19.8 | (14.1, 26.5) |
| **Objective Response (CR+PR)** | **40** | **23.3** | **(17.2, 30.3)** |
| Stable Disease (SD) | 35 | 20.3 | (14.6, 27.1) |
| **Disease Control (CR+PR+SD)** | **75** | **43.6** | **(36.1, 51.4)** |
| Progressive Disease (PD) | 78 | 45.3 | (37.8, 53.1) |
| Non-evaluable (NE) | 5 | 2.9 | (1.0, 6.7) |
| No Assessment | 14 | 8.1 | (4.5, 13.3) |

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: 09MAR2017

Source: [P052V01MK3475: analysis-adsl; adopa]

***Secondary endpoints***

***Duration of Response***

**Table 38: Time to Response and Response Duration Based on RECIST 1.1 per Central Radiology Assessment in Subjects with Confirmed Response**

Cut-off date: 09-Mar-2017

| **All subjects (APT Population)** | **Pembrolizumab (N=370)** |
|---|---|
| N. subjects with response* | 108 |
| Time to Response* (months)<br>• Mean (SD)<br>• Median (Range) | <br>2.5 (1.1)<br>2.1 (1.3-9.0) |
| Response Duration° (months)<br>• Median (Range) | <br>Not reached (1.4+ - 19.6+) |
| N. subjects with response≥6 months° (%) | 77 (82) |
| **PD-L1 CPS≥1%** | **Pembrolizumab (N=282)** |
| N. subjects with response* | 92 |
| Time to Response* (months)<br>• Mean (SD)<br>• Median (Range) | <br>2.5 (1.1)<br>2.1 (1.3-9.0) |
| Response Duration° (months)<br>• Median (Range) | <br>Not reached (1.4+ - 19.2+) |
| N. subjects with response≥6 months° (%) | 64 (81) |
| **PD-L1 CPS≥10%** | **Pembrolizumab (N=110)** |
| N. subjects with response* | 52 |
| Time to Response* (months)<br>• Mean (SD) | <br>2.4 (0.9) |

| | |
|---|---|
| • Median (Range) | 2.1 (1.3-6.1) |
| Response Duration° (months)<br>• Median (Range) | <br>12.6 (1.4+ - 18.3+) |
| N. subjects with response≥6 months° (%) | 35 (79) |
| **PD-L1 CPS<1%** | **Pembrolizumab (N=79)** |
| N. subjects with response* | 13 |
| Time to Response* (months)<br>• Mean (SD)<br>• Median (Range) | <br>2.5 (1.2)<br>2.1 (1.9-5.9) |
| Response Duration° (months)<br>Median (Range) | <br>11.3 (1.4+ - 15.8+) |
| N. subjects with response≥6 months° (%) | 10 (83) |
| **PD-L1 CPS<10%** | **Pembrolizumab (N=251)** |
| N. subjects with response* | 53 |
| Time to Response* (months)<br>• Mean (SD)<br>• Median (Range) | <br>2.6 (1.3)<br>2.1 (1.6-9.0) |
| Response Duration° (months)<br>Median (Range) | <br>Not reached (1.4+ - 19.2+) |
| N. subjects with response≥6 months° (%) | 39 (84) |
| **PD-L1 CPS≥1% to <10%** | **Pembrolizumab (N=172)** |
| N. subjects with response* | 40 |
| Time to Response* (months)<br>• Mean (SD)<br>• Median (Range) | <br>2.6 (1.3)<br>2.1 (1.6-9.0) |
| Response Duration° (months)<br>Median (Range) | <br>Not reached (3.2 - 19.2+) |
| N. subjects with response≥6 months° (%) | 29 (84) |
| Table made by Assessor.<br>*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.<br>°Median and percentage are calculated from product-limit (Kaplan-Meier) method for censored data.<br>"+" indicates there is no progressive disease by the time of last disease assessment.<br>Database Cut-off Date: 09 MAR2017 | |

***Progression Free Survival***

**Table 39: Progression Free Survival Based on RECIST 1.1 per Central Radiology Assessment**

Cut-off Date: 01Sep2016

| N | N. events (%) | Person-Months | Event Rate/ 100 Person-Months (%) | Median PFS* (months) (95% CI) | PFS Rate 6 months (%)* (95% CI) | PFS Rate 12 months (%)* (95% CI) |
|---|---|---|---|---|---|---|
| **All subjects (APT Population)** | | | | | | |
| 370 | 248 (67.0) | 1259.9 | 19.7 | 2.1 (2.1, 3.0) | 30.0 (24.8, 35.3) | 18.6 (12.8, 25.2) |
| **PD-L1 CPS≥1%** | | | | | | |
| 282 | 177 (62.8) | 982.1 | 18.0 | 3.0 (2.1, 3.5) | 32.7 (26.5, 39.0) | 21.3 (14.0, 29.7) |
| **PD-L1 CPS≥10%** | | | | | | |
| 80 | 37 (46.3) | 300.8 | 12.3 | 4.9 (3.5,..) | 45.6 (31.9, 58.3) | Not reached |
| Table made by Assessor from Table 11-17, Table 11-18 and Table 11-19.<br>*From product-limit (Kaplan-Meier) method for censored data.<br>Database Cut-off Date: 01SEP2016 | | | | | | |

**Kaplan-Meier of Progression Free Survival based on RECIST 1.1 per Central Radiology Assessment**
**All subjects (APT Population)**

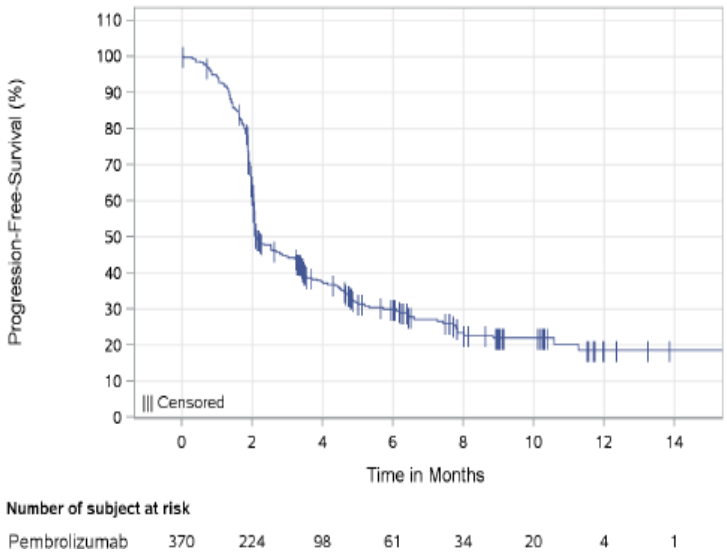



**Table 40: Progression Free Survival Based on RECIST 1.1 per Central Radiology Assessment All Subjects (APT Population)**
Cut-off Date: 09-Mar-2017

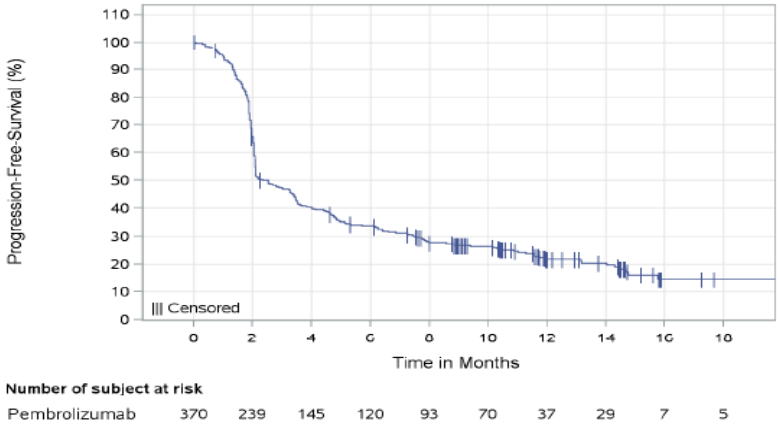
| Treatment | N | Number of Events (%) | Person-Months | Event Rate/ 100 Person-Months (%) | Median PFS† (Months) (95% CI) | PFS Rate at Months 6 in % † (95% CI) | PFS Rate at Months 12 in % † (95% CI) |
|---|---|---|---|---|---|---|---|
| Pembrolizumab | 370 | 284 (76.8) | 1878.3 | 15.1 | 2.3 (2.1, 3.4) | 33.8 (29.0, 38.7) | 21.8 (17.4, 26.6) |

Progression-free survival is defined as time from the first dose to disease progression, or death, whichever occurs first. Time to scheduled tumor assessment visit rather than the actual tumor assessment visit is used in the analysis. Patients without post-baseline tumor assessment are censored at time of the first dose.
† From product-limit (Kaplan-Meier) method for censored data.
Database Cutoff Date: 09MAR2017

Source: [P052V01MK3475: analysis-adsl; adtte]

**Kaplan-Meier of Progression Free Survival based on RECIST 1.1 per Central Radiology Assessment**

**All subjects (APT Population)**




(Database cutoff date: 09MAR2017)
Source: [P052V01MK3475: analysis-adsl; adtte]

***Overall Survival***

**Table 41: Overall Survival**

Cut- off date: 01-Sep-2016

| N | N. events (%) | Person-Months | Event Rate/ 100 Person-Months (%) | Median OS* (months) (95% CI) | OS Rate 6 months (%)* (95% CI) | OS Rate 12 months (%)* (95% CI) |
|---|---|---|---|---|---|---|
| **All subjects (APT Population)** | | | | | | |
| 370 | 130 (35.1) | 2056.6 | 6.3 | 10.9 (9.7, ...) | 67.4 (61.7, 72.5) | 41.2 (31.4, 50.7) |
| **PD-L1 CPS≥1%** | | | | | | |
| 282 | 85 (30.1) | 1584.9 | 5.4 | 11.6 (10.1,...) | 70.5 (64.0, 76.1) | 49.3 (37.6, 60.0) |
| **PD-L1 CPS≥10%** | | | | | | |
| 80 | 18 (22.5) | 409.0 | 4.4 | Not reached (8.4,..) | 76.5 (63.4, 85.5) | Not reached |

Database cut-off date: 01-Sep-2017
Tables 7, 45 and 46 Response to RSI
*From product-limit (Kaplan-Meier) method for censored data.

***Exploratory endpoints***

**Table 42: Summary of Best Overall Response with Confirmation Based on Modified RECIST 1.1 per Central Radiology Assessment**
**All Subjects (APT Population)**
Cut-off Date: 09Mar2017

| Response Evaluation | Pembrolizumab (N=370) | | |
|---|---|---|---|
| | n | % | 95% CI[†] |
| Complete Response (CR) | 27 | 7.3 | (4.9, 10.4) |
| Partial Response (PR) | 86 | 23.2 | (19.0, 27.9) |
| **Objective Response (CR+PR)** | **113** | **30.5** | **(25.9, 35.5)** |
| Stable Disease (SD) | 76 | 20.5 | (16.5, 25.0) |
| **Disease Control (CR+PR+SD)** | **189** | **51.1** | **(45.9, 56.3)** |
| Progressive Disease (PD) | 142 | 38.4 | (33.4, 43.5) |
| Non-evaluable (NE) | 9 | 2.4 | (1.1, 4.6) |
| No Assessment | 30 | 8.1 | (5.5, 11.4) |

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: 09MAR2017

Source: [P052V01MK3475: analysis-adsl; adopa]

**Table 43: Summary of PFS**
**Based on Modified RECIST 1.1 per Central Radiology Assessment All Subjects (APT Population)**
Cut-off Date: 09Mar2017

| Treatment | N | Number of Events (%) | Person-Months | Event Rate/ 100 Person-Months (%) | Median PFS[†] (Months) (95% CI) | PFS Rate at Months 6 in %[†] (95% CI) | PFS Rate at Months 12 in %[†] (95% CI) |
|---|---|---|---|---|---|---|---|
| Pembrolizumab | 370 | 248 (67.0) | 1991.0 | 12.5 | 3.4 (2.5, 4.7) | 40.4 (35.2, 45.5) | 28.3 (23.2, 33.6) |

Progression-free survival is defined as time from the first dose to disease progression, or death, whichever occurs first. Time to scheduled tumor assessment visit rather than the actual tumor assessment visit is used in the analysis. Patients without post-baseline tumor assessment are censored at time of the first dose.
[†] From product-limit (Kaplan-Meier) method for censored data.
Database Cutoff Date: 09MAR2017

Source: [P052V01MK3475: analysis-adsl; adtte]

***Patient Reported Outcomes***

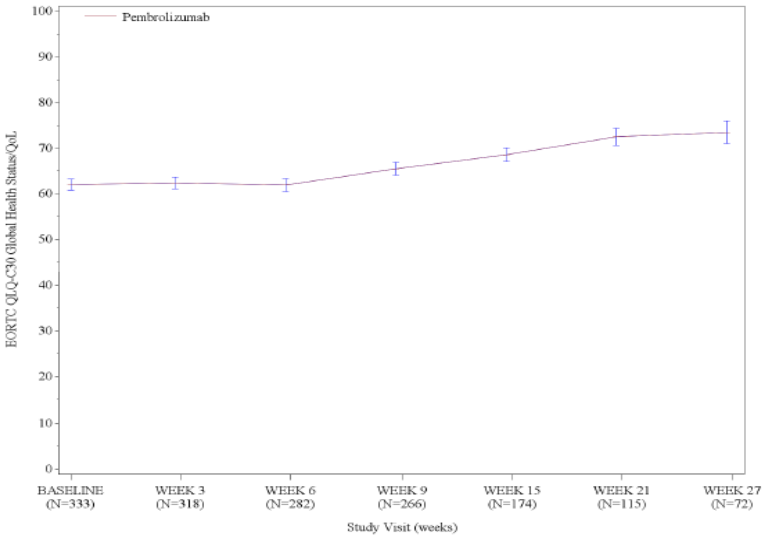
EORTC QLQ-C30 and EQ-5D Compliance Rate and Completion Rate

Compliance rates for both the EORTC QLQ-C30 and EQ-5D were 90% or above at baseline, and over 86% at Week 9. Completion rates, calculated for each visit from baseline to Week 57, remained above 70% at each time point after baseline, until Week 9, when they dropped as patients discontinued the study due to disease progression, physician decision, AEs, or death.

EORTC QLQ-C30 analysis

At week 9, the majority of the subjects experienced improvement of 10 or more points (31%) or stable global health status/QoL (42%). This was observed for all EORTC functioning and symptom domains. An improved quality of life was registered for patients who remained on treatment, although scores after Week 9 should be interpreted with caution due to the small sample size.

**Figure: Summary of EORTC QLQ-C30 Global health status/QoL at Study Visit**
**Mean +/- SE**
**(FAS Population)**

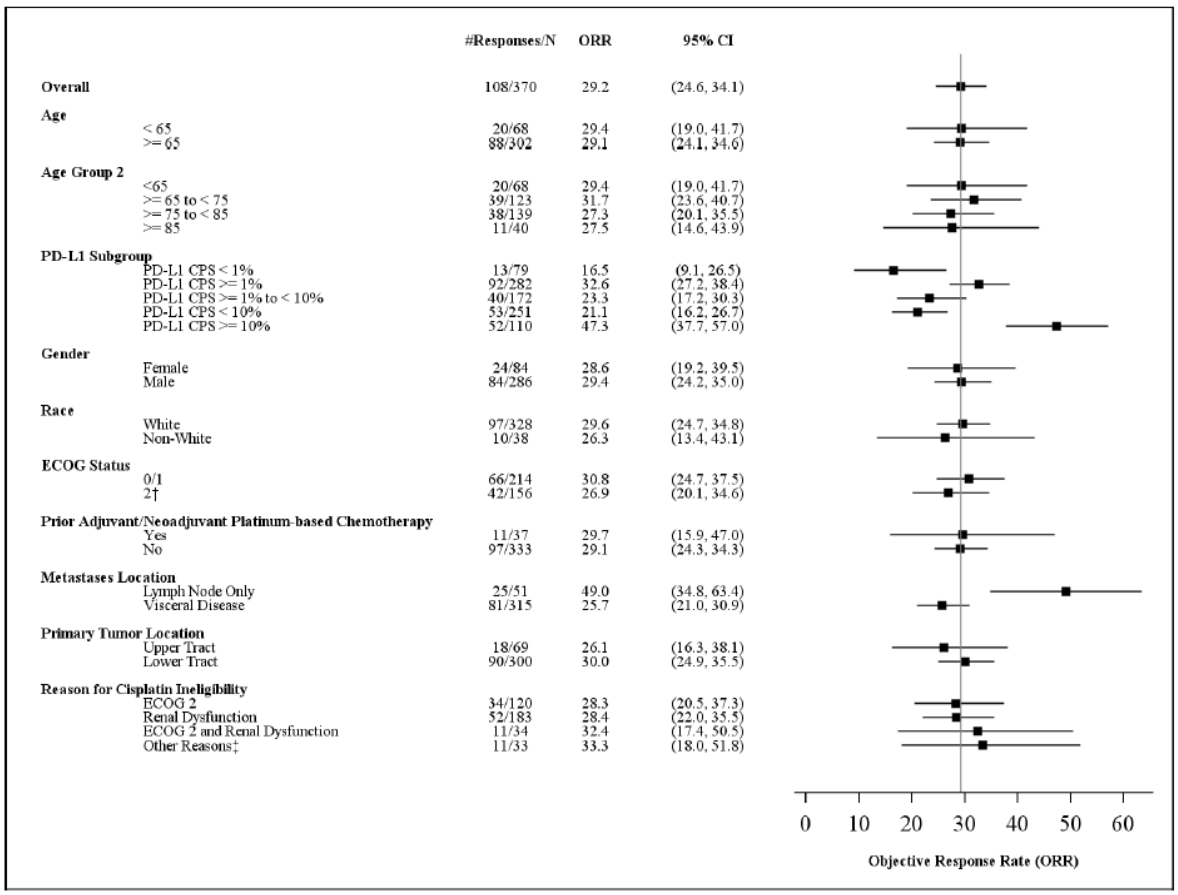



Database Cutoff: 01SEP2016
(Source: [P052V01MK3475: analysis-ads1; adpro])

**Ancillary analyses**

*Objective Response Rate in protocol-specified subgroups*

**Figure: ORR 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 Cut-off Date: 09 March 2017
Source: [P052V01MK3475: analysis-adsl; adopa]

**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 44: Summary of Efficacy for trial KEYNOTE-052**

| **Title: A Phase II Clinical Trial of Pembrolizumab (MK-3475) in Subjects with Advanced/Unresectable or Metastatic Urothelial Cancer** | | | |
|---|---|---|---|
| Study identifier | EudraCT number: 2014-002206-20 | | |
| Design | Non-randomized, multicenter, open-label, trial of IV pembrolizumab monotherapy in subjects with advanced/unresectable or metastatic urothelial carcinoma, who have not received prior systemic chemotherapy and who are not eligible to receive cisplatin. | | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | | not applicable<br>not applicable<br>not applicable |
| Hypothesis | Not applicable | | |
| Treatments groups | pembrolizumab | | 200 mg IV Q3W<br><br>370 subjects treated |
| Endpoints and definitions | Primary endpoint | ORR | Percentage of patients having a CR or PR during the trial, based on BICR review per RECIST 1.1. |
| | Secondary endpoint | Response duration | Time from first RECIST 1.1 response to disease progression assessed by BICR in subjects who achieve a PR or CR. |
| | Secondary endpoint | OS | Time from allocation to death due to any cause |
| | Secondary endpoint | PFS | Time from allocation to the first documented disease progression according to RECIST 1.1 based on BICR or death due to any cause, whichever occurred first. |
| Data Cut-off | 01-SEP-2016/ 09-MAR-2017 | | |
| **Results and Analysis** | | | |
| **Analysis description** | **Primary Analysis** | | |

| | | | |
|---|---|---|---|
| Analysis population and time point description | All-Patients-Treated (APT)<br>All Subjects | | |
| Descriptive statistics and effect estimate per comparison | Treatment group | Pembrolizumab<br>200 mg | |
| | Number of subject | 370 | |
| | **Primary endpoint** | | |
| | | Data Cut-off: 1st September 2016 | Data cut-off: 9th March 2017 |
| | **ORR** (BICR-RECIST 1.1)<br>n (%) (95% CI) | 89 (24.1)<br>(19.8, 28.7) | 108 (29.2)<br>(24.6, 34.1) |
| | **Secondary endpoints** | | |
| | **Time to response**<br>Median (months)<br>(range) | 2.0 (0.2-4.8) | 2.1 (1.3-9.0) |
| | **Response duration**<br>Median (months)<br>(range) | Not reached (1.0+ - 13.6+) | Not reached (1.4+ -19.6) |
| | **PFS** N. with events<br>n (%) | 248 (67.0) | 284 (76.8) |
| | Median PFS months<br>(95% CI) | 2.1 (2.1, 3.0) | 2.3 (2.1, 3.4) |
| | PFS rate at 6 months (%)<br>(95% CI) | 30.0 (24.8, 35.3) | 33.8 (29.0, 38.7) |
| | PFS rate at 12 months (%)<br>(95% CI) | 18.6 (12.8, 25.2) | 21.8 (17.4, 26.6) |
| | **OS** N. with events<br>n (%) | 130 (35.1) | 188 (50.8) |
| | Median OS months<br>(95% CI) | 10.9 (9.7, ...) | 11.0 (10.0, 13.6) |
| | OS rate at 6 months (%)<br>(95% CI) | 67.4 (61.7, 72.5) | 67.4 (62.3, 72.0) |
| | OS rate at 12 months (%)<br>(95% CI) | 41.2 (31.4, 50.7) | 46.8 (41.1, 52.3) |

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

A systematic literature review and meta-analysis to compile ORR, DOR and OS to historical first line therapies for advanced/metastatic urothelial cancer was submitted.

PUBMED (Medline), Cochrane, and EMBASE databases were searched to identify clinical trials published in English language since 1 January 1991. Randomized controlled trials, single arm trials, retrospective studies and observational studies were included in the initial step of the review. Any agent given in the

first line setting for subjects with advanced or metastatic urothelial cancer who are cisplatin-ineligible (i.e. single agent or combination therapy, including, but not limited to, carboplatin, gemcitabine, paclitaxel, methotrexate, vinflunine, vinblastine, epirubicin, docetaxel, oxaliplatin and doxorubicin) were defined as comparator therapies.

*Systematic Review*

The combined literature searches (PUBMED, Cochrane, Embase), identified a total of 3297 references. A comprehensive search strategy was used to identify references that addressed the 1L therapy of cisplatin-ineligible subjects with advanced/metastatic urothelial cancer, thus resulting in 97 references. However, the majority of these 97 references included subjects with good performance status and adequate renal function. In order to generate the most appropriate reference data for KN052, only references with similar inclusion criteria in terms of performance status and renal function were included in the meta-analysis. At the end of the filtering process, 18 publications, representing 21 treatment arms (12 carboplatin based; 13 gemcitabine based; 8 carboplatin/gemcitabine), that unambiguously reported responses in cisplatin-ineligible subjects being treated in the first line setting for advanced/metastatic urothelial cancer, were included. Only one Phase III study was reported for the scenario of interest, while the other identified studies were mostly Phase II studies or retrospective studies. For many combinations, multiple studies were unavailable, and hence meta-analysis was not feasible.

The pooled analysis yielded an ORR of 36% (95% CI: 30%, 42%). Median duration of response (DOR) was 6.52 months (95% CI: 5.47-7.76), and median overall survival (OS) was 9.84 months (95% CI: 8.37-11.57). Heterogeneity among studies was performed through the $I^2$ statistic and resulted to be substantial for ORR and OS data (60.4% and 81.5% respectively).

## 2.4.3. Discussion on clinical efficacy

The Keytruda extension of indication in the treatment of locally advanced or metastatic urothelial carcinoma is sought concomitantly in two specific settings, each one based on one single pivotal trial:

1. Study KEYNOTE-045, in advanced or metastatic urothelial carcinoma progressing after platinum-based chemotherapy
2. Study KEYNOTE-052, in patients previously untreated and not eligible to cisplatin-containing chemotherapy.

In both studies, patients were enrolled independently from PD-L1 expression, with the provision of tissue for biomarker analysis as a requirement for eligibility, and the PD-L1 status was defined based on a Combined Positive Score (CPS), including the PD-L1 expression on both tumor and infiltrating immune cells. This scoring system was selected based on the results from an earlier study KEYNOTE-012, in which two different scoring systems, one based on tumour cell staining alone and the other based on staining in both tumour cells and inflammatory cells, were evaluated to analyse the relationship between PD-L1 expression and clinical response. Results from this post-hoc analysis showed the importance to incorporate inflammatory cells into the determination of PD-L1 status for the selection of patients more likely to respond to pembrolizumab. In both urothelial carcinoma studies, two PD-L1 CPS cut-off were evaluated: PD-L1 CPS ≥ 1% determined exclusively using KN012 data, and the CPS ≥ 10% defined based on the first 100 subjects in KN052 which served as the training data set.

***Study KEYNOTE-045 in advanced or metastatic urothelial carcinoma patients progressing after platinum-based chemotherapy***

**Design and conduct of clinical study**

This is a phase III randomized trial of pembrolizumab versus Investigator's choice (paclitaxel, docetaxel or vinflunine) in subjects with recurrent or metastatic urothelial carcinoma who experienced progression after a platinum-based regimen.

Overall, 542 patients were randomized in the trial and allocated with a 1:1 ratio in the pembrolizumab arm (270 patients) and in the chemotherapy group (272 patients). Inclusion criteria allowed the enrolment in the trial of a quite heterogeneous population in terms of prior treatments and ECOG PS. Indeed, differently from studies with other checkpoint inhibitors in patients progressing after platinum-based chemotherapy, ECOG PS2 patients were considered eligible, but only in selected conditions (i.e, haemoglobin ≥ 10 g/dL, no liver metastases, treatment interval before enrollment ≥ 3 months). In the absence of a well globally established standard of care, the proposed comparators are deemed acceptable. Indeed, taxanes are commonly used off-label in clinical practice, and vinflunine is approved only in EU for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen. On this basis, an imbalance in the number of patients allocated to each regimen in the control arm could have been expected. However, the number of patients allocated to each chemotherapy regimen was quite well balanced (i.e. 84 patients with paclitaxel; 84 patients with docetaxel; 85 patients with vinflunine).

PFS per RECIST 1.1 based on BICR and OS were selected as dual primary endpoints, meaning that the study could be considered to have met its primary objective if superiority was demonstrated for PFS **or** OS in the overall population or in any of the subgroups analysed based on PD-L1 expression. As secondary endpoints, confirmed ORR per RECIST 1.1 and mRECIST by BICR, duration response per RECIST 1.1 by BICR and PFS per mRECIST were also evaluated. The statistical assumptions for the definition of sample size can be considered reasonable, providing enough power for the comparison also in PD-L1 CPS ≥ 10% subjects. There are two planned PFS analyses (IA1 and final), and three planned OS analyses (IA1, IA2 and final). The statistical plan includes a set of comprehensive subgroup analyses, taking into account the most relevant prognostic factors, which is considered appropriate. Overall, the statistical methods are acceptable. The control for multiplicity is considered appropriate.

The choice to include patients regardless of PD-L1 status is acceptable based on the lack of sufficient data to justify enrichment at the time the study started. For the same reason PD-L1 status was not even considered as a stratification factor. However, based on emerging evidence on the correlation between PD-L1 status and outcomes, the statistical analysis plan was updated while the study was ongoing to incorporate new primary hypotheses for PD-L1 positive (CPS≥1%) and strongly positive (CPS≥10%) subjects (Amendment#9). Further changes to the biomarker strategy were then introduced based on external results coming KN052, and the formal test for hypotheses on PD-L1 CPS≥ 1% was deleted through Amendment# 13, released after IA1 and data cut-off date. A reallocation of alpha with proper adjustment to maintain the control of family-wise type I error rate (FWER) was made. Even if the adopted strategy of alpha re-allocation seems to be in principle reasonable, the lack of a rigorous approach in the specification of the statistical methods in the protocol, before any interim analysis was conducted, is noted.

Stratification has been performed according to well recognised prognostic factors in second line setting (ECOG PS 0/1 vs 2; presence or absence of liver metastases; Haemoglobin ≥10 g/dL vs <10 g/dL; time from completion of most recent chemotherapy <3 months vs ≥3 months).

Baseline characteristics were overall well balanced in the two treatment arms. The median age of patients was slightly higher in the pembrolizumab arm (67 vs 65 years), with 61.1% of patients ≥65 years compared to 54% in the control arm. Fifty-five percent of patients were PD-L1 <1% (56% in the pembrolizumab arm and 54% in the control group), while respectively 33% in the control arm and 27.4% in the pembrolizumab group were PD-L1≥10%.

In general eligibility criteria are considered adequate to define a 2L+ UC patient population (including subjects with failure of neoadjuvant/adjuvant treatment within 12 months). However subjects with poor prognostic /baseline characteristics are not fully represented (e.g. ECOG PS 2 subjects could not have additional unfavourable prognostic factors, subjects with more than 2 prior lines of systemic chemotherapy for metastatic disease, active brain metastases or inadequate organ function were excluded). Lastly, only 6 patients with ECOG PS of 2 (1.1% of study population) were included, which is seen as critical considering the general high proportion of patients with reduced performance status in patients with advanced / metastatic UC. Only 7 patients (1.3%) were included with brain metastases and only 21% had two prior treatments. Most patients (76%) had been eligible to receive Cisplatin as prior platinum therapy. In this context it is notable that 27% of screened subjects were non-randomized, because they did not meet eligibility criteria. Most of these (nearly 80%) were not included in the study due to unfavourable prognostic factors or comorbidities.

15 subjects in the control arm withdrew consent after randomisation before start of treatment (none in the pembrolizumab treatment arm). Moreover a higher proportion of subjects discontinued studied medication due to withdrawal by subjects or physician decision in the control arm (n=56) compared to the pembrolizumab arm (n=9). It may be assumed that this at least partly reflects that assignment to the chemotherapy arm did not meet expectations of patients and physicians in this open-label trial. This high rate of (premature) withdrawals raises concerns with regards to a possible underperformance of the control arm in an ITT analysis. However a consistent benefit in OS favouring pembrolizumab versus chemotherapy has been reported by sensitivity analyses, even when patients not treated or discontinued due to withdrawal by subject or physician decision were excluded.

**Efficacy data and additional analyses**

The MAH submitted OS results from IA2, with 334 OS events in all comer patients and 104 in PD-L1 CPS≥10% patients. Even if, with 36 additional OS events, results are not expected to significantly change, the final analysis data should be provided and this is requested as a post-authorisation efficacy study.

Overall, a statistically significant gain of 3 months in OS is reported in the overall population (HR:0.73, 95% CI 0.59, 0.91, p=0.002). The median OS in the chemotherapy arm (7.4 months, 95% CI 6.1, 8.3) is consistent with historical data from single-agent second line treatment.

Consistently, a significant OS increase was observed in PD-L1 strongly positive patients (CPS≥10%) treated with pembrolizumab compared to chemotherapy (HR:0.57, 95% CI 0.37, 0.88, p=0.004). In addition, even though p-value was not multiplicity-adjusted, results in PD-L1 positive patients (CPS≥1%) showed a similar magnitude of OS benefit (HR:0.61, 95% CI 0.43, 0.86, p=0.002) compared to PD-L1 strongly positive.

The visual inspection of the KM curves of OS shows an initial favourable effect in the control arm followed by a cross between month 3 and month 4 from the start of treatment. A review of early events in order to clarify potential factors influencing such outcome was provided: apart from the number of censoring in the first 2 months that was much higher in the control arm compared to the pembrolizumab arm (17 vs 3), an excess of deaths in the pembrolizumab arm was observed in the first two months (43 in pembrolizumab vs 24 in control arm). Liver metastases and time from most recent prior therapy of < 3

months were identified as possible factors associated to the higher risk of early death. No benefit (instead a detrimental effect) was observed for pembrolizumab in terms of median PFS per RECIST 1.1 based on BICR in the ITT population. This is not an unexpected finding, considering the different mechanism of action of chemotherapy and immune checkpoint inhibitors, and taking into account the possibility of a delayed response not captured by RECIST 1.1. As observed for OS curves, the slope of the KM curves shows an initial unfavourable treatment effect for pembrolizumab followed by a cross at Month 5 and a trend to diverge after 6 months, with a PFS rate at 12 months of 6.2% in the control arm and 16.8% with pembrolizumab.

A similar trend of PFS KM-curves was observed in patients with PD-L1 positive tumour (CPS ≥10% and ≥1%), with consistent median PFS value across subpopulations and a sustained effect in a subset of patients. PFS based on modified RECIST in these subgroups also showed similar results.

Since patients could stay on treatment beyond progression to account for the possibility of pseudo-progression and delayed response, PFS based on modified RECIST was also analysed, showing however similar findings.

A higher ORR has been consistently reported in the pembrolizumab arm compared to chemotherapy in the total population (21.1% vs 11.4%), in PD-L1 CPS≥10% (21.6% vs 6.7%) and in PD-L1 CPS≥1% (23.6% vs 8.3%). On the other hand, chemotherapy produced disease stabilisation in a larger number of patients (33.5% vs 17.4% in the total population; 35.6% vs 12.2% in PD-L1 CPS≥10%; 35% vs 15.5% in PD-L1 CPS≥1%). Waterfall Plots of Best Tumour Change from Baseline were provided showing a higher frequency of deep responses with pembrolizumab compared to chemotherapy. ORR differences for pembrolizumab vs. control in subjects with PD-L1 CPS <1% and PD-L1 <10% were lower compared to those of the higher PD-L1 subgroups, but ORR results for pembrolizumab still remained favourable compared to the chemotherapy control group.

No differences in the median time to tumour response were observed among arms in all populations, but responses were considerably longer with pembrolizumab (median time not reached with the current data cut-off for pembrolizumab and 4.3 months in the control arm).

Efficacy results for all endpoints were confirmed by the performed sensitivity analyses.

More than half of included patients were PD-L1 negative (CPS <1%) in both arms (54% in the control arm and 56% in the pembrolizumab arm). Efficacy results, in subgroups with PD-L1 CPS <1% and PD-L1 <10%, show that OS, PFS, ORR and best change from tumor baseline were overall consistent with the results in the overall population.

Indeed, contrasting evidences on the role of PD-L1 expression as biomarker for response are provided by other immune checkpoint inhibitors. In the phase II, single arm study CheckMate 275, responses to nivolumab were seen irrespective of PD-L1 expression (Sharma P, Lancet 2017). On the other hand, a higher immune-cell PD-L1 expression was associated with higher atezolizumab response in the phase II, single arm IMvigor 210 study (Rosemberg JE, Lancet 2016). However the randomized phase III study (IMvigor 211) of atezolizumab vs. chemotherapy control demonstrated a negative prognostic value of PD-L1 expression in immune cells (i.e. higher PD-L1 expression was associated with worse outcome in both, the atezolizumab treatment group and the control arm), but PD-L1 expression was not predictive.

An updated efficacy analysis for KN045 was performed with a cut-off date of 18JAN2017 and a total of 366 OS events. A robust OS improvement favoring pembrolizumab as compared with chemotherapy control continues to be noted in the overall population [OS HR: 0.70 (0.57, 0.86), p-value:0.0004]. No improvement in PFS for pembrolizumab compared with chemotherapy control is observed [PFS HR: 0.96 (0.79, 1.16), p-value:0.322] albeit a plateau in the tail of the Kaplan-Meier curves suggest durable clinical benefit for a subset of patients. The improvement in response rates compared with the

chemotherapy control was confirmed at the longer follow-up in the overall population (21.1% vs 11%), as well as in PD-L1 CPS≥10% (20.3% vs 6.7%) and in PD-L1 CPS≥1% (22.7% vs 8.3%).

Results of analyses on exploratory biomarkers (proteomic signatures, genetic variation, and gene expression signatures) will be part of the final KN045 CSR that is planned to be submitted as a Post-Authorisation Efficacy Study (PAES) in July 2018.

Patient-reported outcomes (PROs) were assessed using EORTC QLQ-C30. A prolonged time to deterioration in EORTC QLQ-C30 global health status/QoL was observed for patients treated with pembrolizumab compared to investigator's choice chemotherapy (HR 0.70; 95% CI 0.55-0.90). Over 15 weeks of follow-up, patients treated with pembrolizumab had stable global health status/QoL, while those treated with investigator's choice chemotherapy had a decline in global health status/QoL, however these results should be interpreted in the context of the open-label study design and therefore taken cautiously.

***Study KEYNOTE-052: patients previously untreated and not eligible to cisplatin-containing chemotherapy***

**Design and conduct of clinical study**

This is a Phase II single arm trial of pembrolizumab in first-line cisplatin-ineligible advanced/unresectable or metastatic urothelial carcinoma. Overall, the eligibility criteria are acceptable. In particular, the criteria for cisplatin-ineligibility are deemed acceptable and reflect the standard criteria used in clinical practice.

Patients were enrolled irrespective of PD-L1 status. In comparison to study KN-045, only freshly-obtained biopsy specimen was required for PD-L1 biomarker analysis. A total of 370 patients were enrolled. A biomarker discovery cohort, including the first 100 subjects enrolled and treated, served for determination of the PD-L1 strongly positive cut-point. This population was excluded from efficacy analyses for the PD-L1 strongly positive population, which were conducted on the biomarker validation cohort (n = 270 overall). 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 (RECIST 1.1 by independent radiology review); PFS (RECIST 1.1 by independent radiology review); OS; PFS (RECIST 1.1 by independent radiology review) rate and OS rate at 6 months and 12 months were among secondary endpoints.

The sample size was initially driven by the primary efficacy hypothesis of a true ORR > 30% and 2.5% (one-sided) type 1 error in PD -L1 positive subjects. Based on amendment#2 the efficacy hypothesis on ORR was removed with the justification that the success of the study was to be determined by clinically meaningful ORRs and durability of the response.

As expected based on eligibility criteria, the enrolled population was mostly ≥ 65 years (81.6%), with a median age of 74 years. The most common reasons for cisplatin ineligibility were renal dysfunction (50%), ECOG PS 2 (32.4) or both renal dysfunction and ECOG PS 2 (9%). In addition, the majority of patients (85.1%) had visceral metastases. As concern PD-L1 expression, 21.4% were PD-L1<1%, while most of patients (46.5%) of had a PD-L1 CPS in the range of 1% to 10%. A discrepancy is noted between the prevalence of PD-L1< 1% patients in Study KN052 and Study KN045 that could not be explained by the MAH, but will be further evaluated in future clinical trials in UC.

Pembrolizumab was administered at the fixed dosing regimen of 200 mg Q3W, which is acceptable.

**Efficacy data and additional analyses**

An ORR of 24.1% (95% CI 19.8, 28.7) was reported in the overall population. In 282 PD-L1 positive patients ORR was 26.6% (95% CI 21.5, 32.2). When considering the subgroup of PD-L1 strongly positive patients from the validation cohort, a higher ORR was reported 38.8% (95% CI 28.1, 50.3).

In the first-line therapy of urothelial carcinoma, an ORR up to 30%-40% with a median OS of 9 months has been reported with carboplatin-containing (De Santis M, J Clin Oncol 2012).

Updated results with a median follow-up of 9.5 months showed an improvement in ORR in the overall population [29.2% (95% CI 24.6, 34.1)]. Median DOR has not been reached yet, thus responses with pembrolizumab last longer compared to those achieved by chemotherapy in the submitted meta-analysis (median DOR 6.52, upper 95% CI 7.76 months). Although the ORR was higher in PD-L1 CPS $\geq$ 10% patients [47.3% (95% CI: 37.7, 57.0)], responses were also registered in PD-L1 CPS < 10% and CPS <1% patients [21.1% (95% CI: 16.2, 26.7) and 16.5% (95% CI: 9.1, 26.5), respectively]. The disease control rate, which includes subjects with CR, PR, and stable disease was 47.3% (95% CI: 42.1, 52.5), suggesting that there is a larger pool of subjects who may benefit from pembrolizumab beyond those who experience a confirmed response as measured by RECIST 1.1.

With 67 additional PFS events at longer follow up, a slight improvement compared to the original analysis has been reported in terms of median PFS [2.3 months (95% CI: 2.1, 3.4) versus 2.1 months (95% CI: 2.1, 3.3)], PFS rate at 6 months [33.8% (95% CI: 29.0%, 38.7%) versus 30.6% (95% CI: 25.2%, 36.2%)] and PFS rate at 12 months [21.8% (95% CI: 17.4%, 26.6%) versus 19.0% (95% CI: 13.0%, 25.8%)].

Compared to the original submission, a consistent median OS (11 months) was reported, with a slight increase in the OS rate at 12 months [46.8 (41.1, 52.3) versus 41.2 (31.4, 50.7)].

Median PFS data remained unfavourable in comparison to chemotherapy despite a small improvement with longer duration of follow-up; however benefits of pembrolizumab might not been captured by median PFS values. Durable responses appear to be reflected in a plateau in the tail of the KM curve beginning at approximately 8 months.
In order to provide information for contextualisation of the results in cisplatin ineligible patients, the MAH conducted and provided a systematic literature review and meta-analysis. The pooled analysis yielded an ORR of 36% (95% CI: 30%, 42%). Median duration of response (DOR) was 6.52 months (95% CI: 5.47-7.76), and median overall survival (OS) was 9.84 months (95% CI: 8.37-11.57). Heterogeneity among studies was performed through the $I^2$ statistic and resulted to be substantial for ORR and OS data (60.4% and 81.5% respectively). The quality of trials included in the meta-analysis was assessed by the MAH to evaluate the risk of bias (including selection bias, performance bias, detection bias, attrition bias or reporting bias) that resulted to be high in most of the trials. This can be explained considering that only one of them was a phase III study, while the others were phase II trials with a small sample size. Overall, the quality of the included trials is not fully reassuring on the validity of the results of the meta-analysis.

In the context of scientific advice (EMEA/H/SA/2437/14/2016/II) it was recommended to capture in Study KN052 post-progression treatments and responses to treatments to assess the impact of 2nd-line chemotherapies. Overall, post-progression systemic therapy was reported in 88 subjects (24%), and most of them (56 patients) received carboplatin/gemcitabine combination. However, post-progression treatment responses were not captured for KN052 subjects.

Patient reported outcomes were assessed using EORTC QLQ-C30. At week 9, the majority of the subjects experienced improvement or stable global health status/QoL across all EORTC functioning and symptom domains, although scores after Week 9 should be interpreted with caution due to the small sample size. Both the EQ-5D VAS score and the EQ-5D Utility scores were stable over time.

Additional efficacy data will be provided with the following Post-Authorisation Efficacy Study (PAES):

- Study KN361 comparing pembrolizumab with or without platinum-based combination chemotherapy and chemotherapy alone in both cisplatin-eligible and ineligible patients.

- Study P045 comparing pembrolizumab versus Paclitaxel, Docetaxel or Vinflunine in Subjects with Recurrent or Progressive Metastatic Urothelial Cancer.

- Study P052, evaluating pembrolizumab in patients with Advanced/Unresectable or Metastatic Urothelial Cancer.

### 2.4.4. Conclusions on the clinical efficacy

Based on efficacy results from study KN045, a broad indication, including patients with locally advanced or metastatic urothelial carcinoma who have received prior chemotherapy, regardless of PD-L1 expression, has been requested by the MAH. Statistically significant and clinically meaningful gains in OS were reported across population (all-comers, PD-L1 CPS ≥1% and PD-L1 CPS ≥10%).

Even if the efficacy of pembrolizumab in the 1L cisplatin-ineligible UC population is only based on a single non-randomized study, with still an insufficient duration of follow-up and observed response rates slightly lower compared to historical data for chemotherapy, results compare rather favourable with chemotherapy in terms of duration of responses and OS.

Additional efficacy data from the ongoing Studies should be provided in order to obtain further efficacy data as Post-Authorisation Efficacy Studies (PAES):
- Study P361 comparing pembrolizumab with or without platinum-based combination chemotherapy and chemotherapy alone in both cisplatin-eligible and ineligible patients.
- Study P045 comparing pembrolizumab versus Paclitaxel, Docetaxel or Vinflunine in Subjects with Recurrent or Progressive Metastatic Urothelial Cancer.
- Study P052, evaluating pembrolizumab (MK-3475) in Subjects with Advanced/Unresectable or Metastatic Urothelial Cancer.

## *2.5. Clinical safety*

### *Introduction*

The known pembrolizumab safety profile, evaluated across clinical studies in advanced melanoma (1567 patients from studies KEYNOTE-001, KEYNOTE-002 and KEYNOTE-006), advanced NSCLC (1386 patients from studies KEYNOTE-001, KEYNOTE-010 and KEYNOTE-024), and classical Hodgkin Lymphoma (241 patients from studies KEYNOTE-087 and KEYNOTE-013) is mainly associated with immune-related adverse reactions and characterized by general (fatigue), gastrointestinal (diarrhoea and nausea) and skin (rash and pruritus) disorders. The majority of adverse reactions reported were of Grade 1 or 2 severity and the most serious were immune-related adverse reactions and severe infusion-related reactions.

Within this application safety results have been presented by:

- Study KEYNOTE-045, including 266 locally advanced or metastatic urothelial carcinoma patients previously treated with platinum-containing chemotherapy, who received at least 1 dose of

pembrolizumab (data Cut-off date: 07 September 2016; updated data Cut-off date: 18 Jan 2017).

- Study KEYNOTE-052, including 370 locally advanced or metastatic urothelial carcinoma patients previously untreated and cisplatin-ineligible, who received at least 1 dose of pembrolizumab (data Cut-off date: 01 September 2016; updated data Cut-off date: 09 Mar 2017).
- Reference Safety Dataset, a pooled population of 3,194 subjects, including patients with NSCLC (studies KN-001, KN-010 and KN-024), melanoma (studies KN-001, KEYNOTE-002, KEYNOTE-006), Hodgkin's Lymphoma (studies KN-013 and KN-087) and urothelial carcinoma ( studies KN-045 and KN-052), which is used to compare with studies KEYNOTE-045 and -052.
- Cumulative Running Safety Dataset, including cumulative pembrolizumab safety data from all studies reported to the regulatory authority, provided to demonstrate no meaningful safety related difference between the cumulative dataset and the reference safety dataset.

## *Patient exposure*

Overall, the median exposure to pembrolizumab was shorter in urothelial carcinoma patients compared to the Reference dataset (see Table below):

**Table 45: Summary of Drug Exposure**

**Studies KN045, KN052, and Reference Safety Dataset**

**(APaT Population)**

| | KN045 and KN052 for MK-3475 | Refrence Safety Dataset for MK-3475[††] | Cumulative Safety Dataset for MK-3475[§§] |
|---|---|---|---|
| | N=636 | N=3194 | N=3830 |
| Time on Therapy (months) | | | |
| Mean | 5.68 | 6.65 | 6.49 |
| Median | 3.42 | 4.86 | 4.71 |
| SD | 5.66 | 5.79 | 5.78 |
| Range | 0.03 to 22.80 | 0.03 to 30.39 | 0.03 to 30.39 |
| Number of Administrations | | | |
| Mean | 8.81 | 11.23 | 10.83 |
| Median | 5.50 | 8.00 | 8.00 |
| SD | 7.87 | 9.45 | 9.25 |
| Range | 1.00 to 34.00 | 1.00 to 59.00 | 1.00 to 59.00 |

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

[††] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN013 Cohort 3 (Hodgkin´s Lymphoma), KN024, and KN087.

[§§] Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN013 Cohort 3 (Hodgkin´s Lymphoma), KN024, KN045, KN052, and KN087.

(KN001 Database Cutoff Date for Melanoma: 18APR2014).
(KN001 Database Cutoff Date for Lung Cancer: 23JAN2015).
(KN002 Database Cutoff Date: 28FEB2015).
(KN006 Database Cutoff Date: 03MAR2015).
(KN010 Database Cutoff Date: 30SEP2015).
(KN013 Database Cutoff Date for Hodgkin´s Lymphoma: 27SEP2016).
(KN024 Database Cutoff Date: 09MAY2016).
(KN045 Database Cutoff Date: 18JAN2017).
(KN052 Database Cutoff Date: 09MAR2017).
(KN087 Database Cutoff Date: 25SEP2016).

In study KEYNOTE-045 the duration of exposure was 3.45 months for the pembrolizumab arm at the last updated data Cut-off, with a median number of 6 administrations. At the initial data Cut-off, a total of 139 (52.2%) and 95 (35.7%) subjects received pembrolizumab for ≥3 months and for ≥6 months,

respectively. The exposure to pembrolizumab was 1 year or longer for 43 (16 %) patients. In contrast, of the 255 subjects in the control arm, only 29 (11.4%) received treatment for ≥ 6 months and 3 (1.2%) received treatment for ≥ 12 months.

The duration of exposure was similar in study KEYNOTE-052, with a median time on therapy of 3.40 months and a median number of 5 administrations.At the initial data Cut-off, a total of 157 (42.4%) patients were treated for at least 3 months, 72 (19.5%) for at least 6 months and 9 (2.4%) patients exposed ≥ 1 year to pembrolizumab.

In comparison to the reference safety dataset, patients in both KN-045 and KN-052 were mostly male (74.4% and 77.3%, respectively, versus 59.3%), older, as demonstrated by the higher percentage of subjects ≥65 years (61.3% and 81.6%, respectively, versus 43.3%), and had ECOG PS of 2 (1.5% and 42.2%, respectively versus 0).

### *Adverse events*

In both studies KN-045 and KN-052 pembrolizumab safety and tolerability has been evaluated during the treatment period up to two different cut-off dates, 7-Sep-2016 (Table 46) and 18-Jan-2017 (Table 47). Adverse events, which occurred from the first dose up to 30 days after the last dose, were reported and coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 19.0 and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.

**Table 46: AEs Summary Study KN045**

**(APaT Population)**

| | **KN045** | |
|---|---|---|
| | control<br>n (%) | pembrolizumab<br>n (%) |
| Subjects in population | 255 | 266 |
| with one or more adverse events | 250 (98.0) | 248 (93.2) |
| with no adverse event | 5 (2.0) | 18 (6.8) |
| with drug-related[†] adverse events | 230 (90.2) | 162 (60.9) |
| with toxicity grade ≥3 AEs | 160 (62.7) | 139 (52.3) |
| with toxicity grade ≥3 drug-related AEs | 126 (49.4) | 40 (15.0) |
| with serious adverse events | 104 (40.8) | 104 (39.1) |
| with serious drug-related AEs | 57 (22.4) | 27 (10.2) |
| who died | 8 (3.1) | 13 (4.9) |
| who died due to a drug-related AE | 4 (1.6) | 4 (1.6) |
| discontinued[‡] due to an adverse event | 32 (12.5) | 22 (8.3) |
| discontinued due to a drug-related AE | 28 (11.0) | 15 (5.6) |
| discontinued due to a serious AE | 12 (4.7) | 15 (5.6) |
| discontinued due to a serious drug-related AE | 10 (3.9) | 9 (3.4) |

Data cut-off 7-Sept-2016

The overall pembrolizumab safety profile favorably compares with chemotherapy in study KN045, with a lower rate of drug-related AEs (60.9% vs 90.2%), drug-related Grade≥3 AEs (15% vs 49.4%), serious drug-related AEs (10.2 vs 22.4%) and discontinuations due to drug-related AEs (11% vs 5.6%).

**Table 47: Adverse Event Summary Studies KN045, KN052, KN001, KN002, KN006, KN010, KN013, KN024, and KN087**

**(APaT Population)**

| | KN045 for MK-3475 | | Refrence Safety Dataset for MK-3475†† | | Cumulative Safety Dataset for MK-3475§§ | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Subjects in population | 266 | | 3,194 | | 3,460 | |
| with one or more adverse events | 249 | (93.6) | 3,107 | (97.3) | 3,356 | (97.0) |
| with no adverse event | 17 | (6.4) | 87 | (2.7) | 104 | (3.0) |
| with drug-related† adverse events | 163 | (61.3) | 2,340 | (73.3) | 2,503 | (72.3) |
| with toxicity grade 3-5 adverse events | 145 | (54.5) | 1,421 | (44.5) | 1,566 | (45.3) |
| with toxicity grade 3-5 drug-related adverse events | 44 | (16.5) | 456 | (14.3) | 500 | (14.5) |
| with non-serious adverse events | 244 | (91.7) | 3,046 | (95.4) | 3,290 | (95.1) |
| with serious adverse events | 108 | (40.6) | 1,154 | (36.1) | 1,262 | (36.5) |
| with serious drug-related adverse events | 31 | (11.7) | 329 | (10.3) | 360 | (10.4) |
| with dose modification§ due to an adverse event | 80 | (30.1) | 1,021 | (32.0) | 1,101 | (31.8) |
| who died | 13 | (4.9) | 121 | (3.8) | 134 | (3.9) |
| who died due to a drug-related adverse event | 4 | (1.5) | 11 | (0.3) | 15 | (0.4) |
| discontinued‡ due to an adverse event | 26 | (9.8) | 362 | (11.3) | 388 | (11.2) |
| discontinued due to a drug-related adverse event | 18 | (6.8) | 169 | (5.3) | 187 | (5.4) |
| discontinued due to a serious adverse event | 19 | (7.1) | 274 | (8.6) | 293 | (8.5) |
| discontinued due to a serious drug-related adverse event | 12 | (4.5) | 117 | (3.7) | 129 | (3.7) |

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

‡ Study medication withdrawn.

§ Defined as overall action taken of dose reduced, drug interrupted or drug withdrawn.

MedDRA version used is 19.1.

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 MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN013 Cohort 3 (Hodgkin´s Lymphoma), KN024, and KN087.

§§ Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN013 Cohort 3 (Hodgkin´s Lymphoma), KN024, KN045, and KN087.

(KN001 Database Cutoff Date for Melanoma: 18APR2014).

(KN001 Database Cutoff Date for Lung Cancer: 23JAN2015).

(KN002 Database Cutoff Date: 28FEB2015).

(KN006 Database Cutoff Date: 03MAR2015).

(KN010 Database Cutoff Date: 30SEP2015).

(KN013 Database Cutoff Date for Hodgkin´s Lymphoma: 27SEP2016).

(KN024 Database Cutoff Date: 09MAY2016).

(KN045 Database Cutoff Date: 18JAN2017).

(KN087 Database Cutoff Date: 25SEP2016).

Source: [ISS: analysis-adsl; adaeosi; aeplus]

Data cut-off 18-Jan-2017

In study KN-045, the most frequent AEs in the pembrolizumab arm were fatigue (25.6%), pruritus (23.7%), decreased appetite (21.4%) and nausea (20.7%). In the control arm, AEs observed in ≥ 20% of the subjects were alopecia (38.8%), anemia (35.7%), fatigue (33.7%), constipation (31.8%), nausea (28.6%), decreased appetite (20.8 %) and asthenia (20.8%).

**Table 48: Adverse Event Summary (incidence ≥10% in One or More Groups) All Subjects in Study KN045**

**(APaT Population)**

| | Control | | Pembrolizumab | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| Subjects in population | 255 | | 266 | |
| with one or more adverse events | 250 | (98.0) | 248 | (93.2) |
| with no adverse events | 5 | (2.0) | 18 | (6.8) |
| **Blood and lymphatic system disorders** | **130** | **(51.0)** | **53** | **(19.9)** |
| Anaemia | 91 | (35.7) | 46 | (17.3) |
| Neutropenia | 43 | (16.9) | 0 | (0.0) |
| **Endocrine disorders** | **4** | **(1.6)** | **28** | **(10.5)** |
| **Gastrointestinal disorders** | **174** | **(68.2)** | **150** | **(56.4)** |
| Abdominal pain | 34 | (13.3) | 34 | (12.8) |
| Constipation | 81 | (31.8) | 50 | (18.8) |
| Diarrhoea | 48 | (18.8) | 43 | (16.2) |
| Nausea | 73 | (28.6) | 55 | (20.7) |
| Vomiting | 34 | (13.3) | 39 | (14.7) |
| **General disorders and administration site conditions** | **184** | **(72.2)** | **153** | **(57.5)** |
| Asthenia | 53 | (20.8) | 30 | (11.3) |
| Fatigue | 86 | (33.7) | 69 | (25.9) |
| Oedema peripheral | 40 | (15.7) | 26 | (9.8) |
| Pyrexia | 33 | (12.9) | 36 | (13.5) |
| **Infections and infestations** | **94** | **(36.9)** | **105** | **(39.5)** |
| Urinary tract infection | 34 | (13.3) | 39 | (14.7) |
| **Investigations** | **89** | **(34.9)** | **77** | **(28.9)** |
| Neutrophil count decreased | 38 | (14.9) | 1 | (0.4) |
| **Metabolism and nutrition disorders** | **97** | **(38.0)** | **101** | **(38.0)** |
| Decreased appetite | 53 | (20.8) | 56 | (21.1) |
| **Musculoskeletal and connective tissue disorders** | **95** | **(37.3)** | **113** | **(42.5)** |
| Arthralgia | 30 | (11.8) | 24 | (9.0) |
| Back pain | 21 | (8.2) | 37 | (13.9) |
| Pain in extremity | 28 | (11.0) | 21 | (7.9) |
| **Nervous system disorders** | **105** | **(41.2)** | **58** | **(21.8)** |
| Neuropathy peripheral | 31 | (12.2) | 1 | (0.4) |
| Peripheral sensory neuropathy | 28 | (11.0) | 2 | (0.8) |
| **Psychiatric disorders** | **43** | **(16.9)** | **38** | **(14.3)** |
| **Renal and urinary disorders** | **45** | **(17.6)** | **72** | **(27.1)** |
| Haematuria | 20 | (7.8) | 30 | (11.3) |
| **Respiratory, thoracic and mediastinal disorders** | **75** | **(29.4)** | **91** | **(34.2)** |
| Cough | 18 | (7.1) | 38 | (14.3) |
| Dyspnoea | 23 | (9.0) | 33 | (12.4) |
| **Skin and subcutaneous tissue disorders** | **127** | **(49.8)** | **114** | **(42.9)** |
| Alopecia | 99 | (38.8) | 2 | (0.8) |
| Pruritus | 14 | (5.5) | 62 | (23.3) |
| Rash | 16 | (6.3) | 29 | (10.9) |
| **Vascular disorders** | **32** | **(12.5)** | **39** | **(14.7)** |

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.
MedDRA V19.0 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.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cutoff Date: 07SEP2016 .

Source: [P045V01: analysis-adsl] [P045V01: tabulations-aeplus]

In study KN052, the most common reported AEs were fatigue (31.1%), decreased appetite (21.6%), and constipation (21.1%).

The frequency of AEs was generally comparable between both populations in studies KN045 and KN052, and the Reference Safety Dataset.

**Table 49: Adverse Event Summary (incidence ≥5% in One or More Groups) Studies KN045, KN052 and Reference Safety Dataset by Body System or Organ Class and PT**

**(APaT Population)**

| | **KN045**<br><br>n (%) | **KN052**<br><br>n (%) | **Reference Safety Dataset***<br><br>n (%) |
|---|---|---|---|
| Subjects in population | 266 | 370 | 2,799 |
| with one or more adverse events | 248 (93.2) | 354 (95.7) | 2,727 (97.4) |
| with no adverse event | 18 (6.8) | 16 (4.3) | 72 (2.6) |
| **Blood and lymphatic system disorders** | **53 (19.9)** | **73 (19.7)** | **487 (17.4)** |
| Anaemia | 46 (17.3) | 61 (16.5) | 347 (12.4) |
| **Cardiac disorders** | **15 (5.6)** | **28 (7.6)** | **253 (9.0)** |
| **Endocrine disorders** | **28 (10.5)** | **38 (10.3)** | **335 (12.0)** |
| Hypothyroidism | 17 (6.4) | 24 (6.5) | 236 (8.4) |
| **Eye disorders** | **20 (7.5)** | **17 (4.6)** | **358 (12.8)** |
| **Gastrointestinal disorders** | **150 (56.4)** | **202 (54.6)** | **1,705 (60.9)** |
| Abdominal pain | 34 (12.8) | 40 (10.8) | 274 (9.8) |
| Constipation | 50 (18.8) | 78 (21.1) | 497 (17.8) |
| Diarrhoea | 43 (16.2) | 69 (18.6) | 625 (22.3) |
| Dry mouth | 7 (2.6) | 18 (4.9) | 142 (5.1) |
| Nausea | 55 (20.7) | 68 (18.4) | 685 (24.5) |
| Vomiting | 39 (14.7) | 46 (12.4) | 387 (13.8) |
| **General disorders and administration site conditions** | **153 (57.5)** | **211 (57.0)** | **1,856 (66.3)** |
| Asthenia | 30 (11.3) | 38 (10.3) | 362 (12.9) |
| Chest pain | 5 (1.9) | 13 (3.5) | 165 (5.9) |
| Chills | 5 (1.9) | 21 (5.7) | 153 (5.5) |
| Fatigue | 69 (25.9) | 115 (31.1) | 1,044 (37.3) |
| Oedema peripheral | 26 (9.8) | 50 (13.5) | 285 (10.2) |

| | | | |
|---|---|---|---|
| Pyrexia | 36 (13.5) | 41 (11.1) | 357 (12.8) |
| **Infections and infestations** | **105 (39.5)** | **146 (39.5)** | **1,180 (42.2)** |
| Nasopharyngitis | 14 (5.3) | 1 (0.3) | 182 (6.5) |
| Pneumonia | 12 (4.5) | 15 (4.1) | 140 (5.0) |
| Upper respiratory tract infection | 7 (2.6) | 12 (3.2) | 182 (6.5) |
| Urinary tract infection | 39 (14.7) | 70 (18.9) | 162 (5.8) |
| **Injury, poisoning and procedural complications** | **25 (9.4)** | **42 (11.4)** | **362 (12.9)** |
| **Investigations** | **77 (28.9)** | **128 (34.6)** | **865 (30.9)** |
| Alanine aminotransferase increased | 14 (5.3) | 23 (6.2) | 172 (6.1) |
| Aspartate aminotransferase increased | 14 (5.3) | 25 (6.8) | 168 (6.0) |
| Blood alkaline phosphatase increased | 9 (3.4) | 21 (5.7) | 112 (4.0) |
| Blood creatinine increased | 13 (4.9) | 41 (11.1) | 108 (3.9) |
| Weight decreased | 24 (9.0) | 37 (10.0) | 219 (7.8) |
| **Metabolism and nutrition disorders** | **101 (38.0)** | **157 (42.4)** | **1,109 (39.6)** |
| Decreased appetite | 56 (21.1) | 80 (21.6) | 630 (22.5) |
| Hyperglycaemia | / | 33 (8.9) | 130 (4.6) |
| Hyperkalaemia | / | 24 (6.5) | 61 (2.2) |
| Hyponatraemia | 15 (5.6) | 36 (9.7) | 146 (5.2) |
| **Musculoskeletal and connective tissue disorders** | **113 (42.5)** | **145 (39.2)** | **1,411 (50.4)** |
| Arthralgia | 24 (9.0) | 37 (10.0) | 504 (18.0) |
| Back pain | 37 (13.9) | 42 (11.4) | 349 (12.5) |
| Musculoskeletal pain | 13 (4.9) | 16 (4.3) | 226 (8.1) |
| Myalgia | 14 (5.3) | 15 (4.1) | 253 (9.0) |
| Pain in extremity | 21 (7.9) | 22 (5.9) | 237 (8.5) |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | **18 (6.8)** | **16 (4.3)** | **256 (9.1)** |
| **Nervous system disorders** | **58 (21.8)** | **97 (26.2)** | **1,037 (37.0)** |
| Dizziness | 15 (5.6) | 24 (6.5) | 244 (8.7) |
| Headache | 13 (4.9) | 13 (3.5) | 400 (14.3) |

| | | | |
|---|---|---|---|
| **Psychiatric disorders** | **38 (14.3)** | **55 (14.9)** | **523 (18.7)** |
| Anxiety | 8 (3.0) | 9 (2.4) | 141 (5.0) |
| Insomnia | 16 (6.0) | 23 (6.2) | 218 (7.8) |
| **Renal and urinary disorders** | **72 (27.1)** | **111 (30.0)** | **271 (9.7)** |
| Acute kidney injury | 15 (5.6) | 21 (5.7) | 40 (1.4) |
| Haematuria | 30 (11.3) | 48 (13.0) | 39 (1.4) |
| **Reproductive system and breast disorders** | **18 (6.8)** | **24 (6.5)** | **129 (4.6)** |
| **Respiratory, thoracic and mediastinal disorders** | **91 (34.2)** | **118 (31.9)** | **1,391 (49.7)** |
| Cough | 38 (14.3) | 51 (13.8) | 615 (22.0) |
| Dyspnoea | 33 (12.4) | 39 (10.5) | 534 (19.1) |
| Productive cough | 6 (2.3) | 14 (3.8) | 142 (5.1) |
| **Skin and subcutaneous tissue disorders** | **114 (42.9)** | **139 (37.6)** | **1,360 (48.6)** |
| Dry skin | 14 (5.3) | 11 (3.0) | 165 (5.9) |
| Pruritus | 62 (23.3) | 70 (18.9) | 562 (20.1) |
| Rash | 29 (10.9) | 46 (12.4) | 499 (17.8) |
| Vitiligo | 1 (0.4) | 0 (0.0) | 171 (6.1) |
| **Vascular disorders** | **39 (14.7)** | **42 (11.4)** | **410 (14.6)** |

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

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 MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010.

(KN001 Database Cut-off Date for Melanoma: 18APR2014).

(KN001 Database Cut-off Date for Lung Cancer: 23JAN2015).

(KN002 Database Cut-off Date: 28FEB2015).

(KN006 Database Cut-off Date: 03MAR2015).

(KN010 Database Cut-off Date: 30SEP2015).

Across both studies in Urothelial cancer, *Urinary tract infection* and *Haematuria*, as well as increase of *Blood alkaline phosphatase* and *Blood creatinine* in study KN052, occurred more frequently than in the reference safety dataset. Upon medical review, these events were deemed unlikely related to pembrolizumab and more likely associated with the underlying disease condition, medical history, or medical procedures (eg, cystoscopy). None of these AEs represents a new safety signal for pembrolizumab.

*Grade 3-5 Adverse Events*

A lower rate of subjects in the pembrolizumab arm of Study KN045 experienced Grade ≥3 AEs (52.3%) compared to the control arm (62.7%).

**Table 50: Grade ≥3 Adverse Events (incidence ≥5% in One or More Groups) All Subjects in Study KN045 (APaT Population)**

| | Control | | Pembrolizumab | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| Subjects in population | 255 | | 266 | |
| with one or more adverse events | 160 | (62.7) | 139 | (52.3) |
| with no adverse events | 95 | (37.3) | 127 | (47.7) |
| Anaemia | 31 | (12.2) | 22 | (8.3) |
| Neutropenia | 37 | (14.5) | 0 | (0.0) |
| Neutrophil count decreased | 32 | (12.5) | 1 | (0.4) |
| Fatigue | 15 | (5.9) | 10 | (3.8) |
| Febrile neutropenia | 19 | (7.5) | 0 | (0.0) |
| Asthenia | 13 | (5.1) | 2 | (0.8) |
| White blood cell count decreased | 14 | (5.5) | 1 | (0.4) |

Every subject is counted a single time for each applicable specific adverse event.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA V19.0 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.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cutoff Date: 07SEP2016

Source: [P045V01: analysis-adsl] [P045V01: tabulations-aeplus]

In study KN052, 53.8% of subjects experienced at least 1 Grade ≥3 AEs, and the most commonly reported were urinary tract infection (9.5%) and anemia (7.0%), see Table 51.

**Table 51: Grade ≥3 Adverse Events (incidence ≥5% in One or More Groups) All Subjects in Study KN052 (APaT Population)**

| | Pembrolizumab | |
|---|---|---|
| | n | (%) |
| Subjects in population | 370 | |
| with one or more adverse events | 199 | (53.8) |
| with no adverse events | 171 | (46.2) |
| Urinary tract infection | 35 | (9.5) |
| Anaemia | 26 | (7.0) |

Every subject is counted a single time for each applicable specific adverse event.
A specific adverse event appears on this report only if its incidence meets the incidence criterion in the report title, after rounding.
MedDRA V19 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Database Cutoff Date: 01SEP2016

Source: [P052V01MK3475: analysis-adsl] [P052V01MK3475: tabulations-aeplus]

*Drug-related Adverse Events*

In Study KN045, fewer subjects in the pembrolizumab arm than in the control arm experienced drug-related AEs (60.9% vs 90.2%, respectively). In the pembrolizumab arm, the most frequently observed drug-related AEs were *Pruritus* (19.5%), *Fatigue* (13.9%) and *Nausea* (10.9%). In the control arm, drug-related AEs observed in ≥10% of the subjects were *Alopecia* (37.6%), *Fatigue* (27.8%), *Anemia* (24.7%), *Nausea* (24.3%), *Constipation* (20.4%), *Decreased appetite* (16.1%), *Neutropenia* (15.3%), *Asthenia* (14.1%), *Neutrophil count decreased* (14.1%), *Diarrhea* (12.9%), *Peripheral sensory neuropathy* (11.0%), and *Neuropathy peripheral* (10.6%).

With the exception of *Pruritus*, all most common drug-related AEs observed in the pembrolizumab group were reported in a lower or similar frequency compared to control, while all most common drug-related AEs observed in the control arm were reported in higher or similar frequency in comparison to patients receiving pembrolizumab.

In Study KN052, The most commonly reported drug-related AEs were *Fatigue* (16.8%), *Pruritus* (14.6%) and *Rash* (9.7%).

Overall, the pattern of drug-related adverse events in KN045 and KN052 is comparable to the reference safety dataset as shown in Table 52, which was compiled from the most recent data-cut-off for KN045 and KN052 (18-Jan-2017 and 8-Mar-2017, respectively).

**Table 52: Drug-related Adverse Events (incidence >2 in KN045 and KN052) Studies KN045, KN052, KN001, KN002, KN006, KN010, KN013, KN024 and KN087 by Body System or Organ Class and PT**
**(APaT Population)**

| | **KN045 and KN052**<br>n (%) | **Reference Safety Dataset**°<br>n (%) | **Cumulative Safety Dataset***<br>n (%) |
|---|---|---|---|
| Subjects in population<br>with one or more adverse events<br>with no adverse event | 636<br>406 (63.8)<br>230 (36.2) | 3,194<br>2,340 (73.3)<br>854 (26.7) | 3,830<br>2,746 (71.7)<br>1,084 (28.3) |
| **Blood and lymphatic system disorders**<br>Anaemia<br>Eosinophilia Haemolytic<br>Thrombocytopenia | **24 (3.8)**<br>18 (2.8)<br>2 (0.3)<br>3 (0.5) | **185 (5.8)**<br>104 (3.3)<br>17 (0.5)<br>26 (0.8) | **209 (5.5)**<br>122 (3.2)<br>19 (0.5)<br>29 (0.8) |
| **Cardiac disorders**<br>Myocarditis | **3 (0.5)**<br>2 (0.3) | **30 (0.9)**<br>1 (0.0) | **33 (0.9)**<br>3 (0.1) |
| **Ear and labyrinth disorders** | **2 (0.3)** | **20 (0.6)** | **22 (0.6)** |
| **Endocrine disorders**<br>Adrenal insufficiency<br>Hyperthyroidism<br>Hypophysitis<br>Hypothyroidism<br>Thyroiditis | **72 (11.3)**<br>5 (0.8)<br>18 (2.8)<br>2 (0.3)<br>53 (8.3)<br>3 (0.5) | **348 (10.9)**<br>15 (0.5)<br>99 (3.1)<br>8 (0.3)<br>255 (8.0)<br>16 (0.5) | **420 (11.0)**<br>20 (0.5)<br>117 (3.1)<br>10 (0.3)<br>308 (8.0)<br>19 (0.5) |
| **Eye disorders**<br>Dry eye | **11 (1.7)**<br>2 (0.3) | **134 (4.2)**<br>32 (1.0) | **145 (3.8)**<br>34 (0.9) |

| | | | |
|---|---|---|---|
| Lacrimation increased | 2 (0.3) | 11 (0.3) | 13 (0.3) |
| **Gastrointestinal disorders** | **149 (23.4)** | **897 (28.1)** | **1,046 (28.5)** |
| Abdominal discomfort | 2 (0.3) | 15 (0.5) | 17 (0.4) |
| Abdominal distension | 2 (0.3) | 23 (0.7) | 25 (0.7) |
| Abdominal pain | 9 (1.4) | 74 (2.3) | 83 (2.2) |
| Abdominal pain upper | 4 (0.6) | 27 (0.8) | 31 (0.8) |
| Colitis | 13 (2.0) | 42 (1.3) | 55 (1.4) |
| Constipation | 18 (2.8) | 103 (3.2) | 121 (3.2) |
| Diarrhoea | 56 (8.8) | 386 (12.1) | 442 (11.5) |
| Dry mouth | 15 (2.4) | 81 (2.5) | 96 (2.5) |
| Dyspepsia | 5 (0.8) | 13 (0.4) | 18 (0.5) |
| Flatulence | 3 (0.5) | 4 (0.1) | 7 (0.2) |
| Nausea | 60 (9.4) | 335 (10.5) | 395 (10.3) |
| Oral pain | 2 (0.3) | 4 (0.1) | 6 (0.2) |
| Stomatitis | 8 (1.3) | 40 (1.3) | 48 (1.3) |
| Vomiting | 25 (3.9) | 121 (3.8) | 146 (3.8) |
| **General disorders and administration site conditions** | **182 (28.6)** | **1,178 (36.9)** | **1,360 (35.5)** |
| Asthenia | 32 (5.0) | 228 (7.1) | 260 (6.8) |
| Chest pain | 2 (0.3) | 20 (0.6) | 22 (0.6) |
| Chills | 13 (2.0) | 88 (2.8) | 101 (2.6) |
| Face oedema | 2 (0.3) | 8 (0.3) | 10 (0.3) |
| Fatigue | 104 (16.4) | 716 (22.4) | 820 (21.4) |
| Influenza like illness | 14 (2.2) | 49 (1.5) | 63 (1.6) |
| Malaise | 5 (0.8) | 26 (0.8) | 31 (0.8) |
| Mucosal inflammation | 5 (0.8) | 23 (0.7) | 28 (0.7) |
| Oedema peripheral | 12 (1.9) | 60 (1.9) | 72 (1.9) |
| Pyrexia | 31 (4.9) | 164 (5.1) | 195 (5.1) |
| Xerosis | 2 (0.3) | 13 (0.4) | 15 (0.4) |
| **Hepatobiliary disorders** | **7 (1.1)** | **34 (1.1)** | **41 (1.1)** |
| Hepatitis | 3 (0.5) | 4 (0.1) | 7 (0.2) |
| **Immune system disorders** | **2 (0.3)** | **36 (1.1)** | **38 (1.0)** |
| **Infections and infestations** | **33 (5.2)** | **160 (5.0)** | **193 (5.0)** |
| Cellulitis | 2 (0.3) | 1 (0.0) | 3 (0.1) |
| Conjunctivitis | 2 (0.3) | 16 (0.5) | 18 (0.5) |
| Fungal skin infection | 2 (0.3) | 2 (0.1) | 4 (0.1) |
| Herpes zoster | 2 (0.3) | 6 (0.2) | 8 (0.2) |
| Oral fungal infection | 2 (0.3) | 7 (0.2) | 9 (0.2) |
| Rash pustular | 3 (0.5) | 2 (0.1) | 5 (0.1) |
| Rhinitis | 3 (0.5) | 5 (0.2) | 8 (0.2) |
| Urinary tract infection | 5 (0.8) | 5 (0.2) | 10 (0.3) |
| **Injury, poisoning and procedural complications** | **4 (0.6)** | **53 (1.7)** | **57 (1.5)** |
| **Investigations** | **84 (13.2)** | **446 (14.0)** | **530 (13.8)** |
| Alanine aminotransferase increased | 20 (3.1) | 111 (3.5) | 131 (3.4) |
| Aspartate aminotransferase increased | 21 (3.3) | 106 (3.3) | 127 (3.3) |
| Blood alkaline phosphatase increased | 11 (1.7) | 40 (1.3) | 51 (1.3) |
| Blood bilirubin increased | 7 (1.1) | 27 (0.8) | 34 (0.9) |
| Blood creatinine increased | 9 (1.4) | 40 (1.3) | 49 (1.3) |
| Blood thyroid stimulating hormone increased | 5 (0.8) | 36(1.1) | 41 (1.1) |
| Lymphocyte count decreased | 3 (0.5) | 24 (0.8) | 27 (0.7) |
| Platelet count decreased | 6 (0.9) | 17 (0.5) | 23 (0.6) |
| Weight decreased | 14 (2.2) | 70 (2.2) | 84 (2.2) |
| **Metabolism and nutrition disorders** | **94 (14.8)** | **428 (13.4)** | **522 (13.6)** |
| Decreased appetite | 61 (9.6) | 275 (8.6) | 336 (8.8) |
| Dehydration | 6 (0.9) | 18 (0.6) | 24 (0.6) |
| Hyperglycaemia | 8 (1.3) | 17 (0.5) | 25 (0.7) |
| Hyperuricaemia | 4 (0.6) | 10 (0.3) | 14 (0.4) |
| Hyponatraemia | 9 (1.4) | 23 (0.7) | 32 (0.8) |
| Hypophosphataemia | 5 (0.8) | 22 (0.7) | 27 (0.7) |
| **Musculoskeletal and connective tissue disorders** | **64 (10.1)** | **594 (18.6)** | **658 (17.2)** |
| Arthralgia | 18 (2.8) | 305 (9.5) | 323 (8.4) |
| Arthritis | 5 (0.8) | 28 (0.9) | 33 (0.9) |
| Back pain | 5 (0.8) | 54 (1.7) | 59 (1.5) |
| Muscle spasms | 6 (0.9) | 46 (1.4) | 52 (1.4) |
| Muscular weakness | 7 (1.1) | 24 (0.8) | 31 (0.8) |
| Musculoskeletal pain | 3 (0.5) | 33 (1.0) | 36 (0.9) |
| Myalgia | 15 (2.4) | 155 (4.9) | 170 (4.4) |
| Pain in extremity | 5 (0.8) | 45 (1.4) | 50 (1.3) |

| | | | |
|---|---|---|---|
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | **2 (0.3)** | **25 (0.8)** | **27 (0.7)** |
| **Nervous system disorders** | **51 (8.0)** | **353 (11.1)** | **404 (10.5)** |
| Dizziness | 12 (1.9) | 49 (1.5) | 61 (1.6) |
| Dysgeusia | 15 (2.4) | 47 (1.5) | 62 (1.6) |
| Headache | 7 (1.1) | 126 (3.9) | 133 (3.5) |
| Lethargy | 6 (0.9) | 9 (0.3) | 15 (0.4) |
| Peripheral sensory neuropathy | 2 (0.3) | 14 (0.4) | 16 (0.4) |
| Tremor | 3 (0.5) | 6 (0.2) | 9 (0.2) |
| **Psychiatric disorders** | **8 (1.3)** | **73 (2.3)** | **81 (2.1)** |
| Confusional state | 2 (0.3) | 7 (0.2) | 9 (0.2) |
| Insomnia | 5 (0.8) | 29 (0.9) | 34 (0.9) |
| **Renal and urinary disorders** | **13 (2.0)** | **48 (1.5)** | **61 (1.6)** |
| Acute kidney injury | 3 (0.5) | 8 (0.3) | 11 (0.3) |
| **Reproductive system and breast disorders** | **6 (0.9)** | **30 (0.9)** | **36 (0.9)** |
| **Respiratory, thoracic and mediastinal disorders** | **59 (9.3)** | **402 (12.6)** | **461 (12.0)** |
| Cough | 17 (2.7) | 130 (4.1) | 147 (3.8) |
| Dyspnoea | 16 (2.5) | 123 (3.9) | 139 (3.6) |
| Pneumonitis | 20 (3.1) | 98 (3.1) | 118 (3.1) |
| **Skin and subcutaneous tissue disorders** | **195 (30.7)** | **1,107 (34.7)** | **1,302 (34.0)** |
| Alopecia | 2 (0.3) | 28 (0.9) | 30 (0.8) |
| Dermatitis | 14 (2.2) | 54 (1.6) | 68 (1.7) |
| Dry skin | 11 (1.7) | 105 (3.3) | 116 (3.0) |
| Erythema | 8 (1.3) | 51 (1.6) | 59 (1.5) |
| Pruritus | 100 (15.7) | 584 (18.2) | 684 (17.8) |
| Rash | 22 (8.3) | 36 (9.7) | 386 (13.8) |
| Urticaria | 6 (0.9) | 13 (0.4) | 19 (0.5) |
| **Vascular disorders** | **11 (1.7)** | **86 (2.7)** | **97 (2.5)** |
| Hypertension | 2 (0.3) | 14 (0.4) | 16 (0.4) |

Every subject is counted a single time for each applicable row and column.
MedDRA version used is 19.1.

° Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN013 Cohort 3 (Hodgkin's Lymphoma), KN024 an KN087.

* Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010, KN013 Cohort 3 (Hodgkin's Lymphoma), KN024, KN045, KN052 and KN087.

(KN001 Database Cut-off Date for Melanoma: 18APR2014).
(KN001 Database Cut-off Date for Lung Cancer: 23JAN2015).
(KN002 Database Cut-off Date: 28FEB2015).
(KN006 Database Cut-off Date: 03MAR2015).
(KN010 Database Cut-off Date: 30SEP2015).
(KN013 Database Cut-off Date for Hodgkin's Lymphoma: 27SEP2016).
(KN024 Database Cut-off Date: 09MAY2016).
(KN087 Database Cut-off Date: 27SEP2016).

Database Cut-off KN045 Date: 18 JAN 2017.
Database Cut-off KN052 Date: 09 MAR 2017.

Overall, a total of 28 (10.5%) patients treated with pembrolizumab in Study KN045 and 43 (11.6%) patients in Study KN052 had a drug-related AE resulting in treatment interruption. The most common events leading to treatment interruption were *Colitis* and *Diarrhea* (1.1% each) in KN045, and *Alanine aminotransferase increased* (1.6%), *Aspartate aminotransferase increased* and *Diarrhea* (1.1% each) in Study KN052.

In the control arm of Study KN045, treatment was interrupted due to drug-related AE in a total of 40 (15.7%) patients, and the most frequent events were *Anemia* (4.7%), *Neutropenia* (2.0%), *Asthenia* (1.6%), *Neutrophil count decrease* (1.6%), and *Infusion-related reaction* (1.2%).

*Drug-related Grade 3-5 Adverse Events*

In Study KN045, a lower frequency of subjects in the pembrolizumab arm experienced drug-related Grade ≥3 AEs compared to the control (15% vs 49.4%). In the pembrolizumab arm, the most commonly reported events were pneumonitis (1.5%), AST increased (1.1%), diarrhea (1.1%), and fatigue (1.1%) in the pembrolizumab arm, and neutropenia (13.3%), neutrophil count decreased (12.2%), anemia (7.8%), febrile neutropenia (7.1%), and white blood cell decreased (5.1%) in the control arm. Two Grade≥3 *Anemia* events were considered drug-related by the Investigator. However, based on evaluation of the available information for these events, they were finally deemed unlikely related to pembrolizumab, and more likely related to the underlying medical condition.

All the drug-related Grade ≥3 AEs observed in ≥5% of subjects in the control arm were reported with a frequency < 1% in the pembrolizumab arm.

In Study KN052, 15.7% of subjects experienced at least 1 Grade ≥3 AEs, and the most commonly reported were *Fatigue* (2.2%), Blood alkaline phosphatase increased (1.4%), Colitis (1.1%) and Muscular weakness (1.1%). There were no drug-related Grade≥ 3 AEs reported with incidence ≥3%. One Grade≥ 3 *Anemia* and 1 Grade≥ 3 *Urinary tract infection* were considered drug-related by the Investigator. However, upon medical review of the available information, both *Anemia* and *Urinary tract infections* cases were deemed more likely related to the underlying medical condition.

**Serious adverse event / deaths / other significant events**

*Serious Adverse Events (SAEs)*

Overall, in Study KN045, 39.1% of patients in the pembrolizumab arm and 40.8% in the control arm experienced at least 1 SAEs up to 90 days after the last dose of study treatment. In the pembrolizumab arm, the SAEs observed at frequency ≥1% were *Urinary tract infection* (4.5%), *Pneumonia* (3.4%), *Anemia* (2.6%), *Pneumonitis* (2.3%), *Hematuria* (1.9%), *Pyrexia* (1.9%), *Acute kidney injury* (1.5%), *Cancer pain* (1.5%), *Urosepsis* (1.5%), *Colitis* (1.5%), *Dehydration* (1.1% vs 0.8%), *Diarrhea* (1.1%), *Dyspnea* (1.1%), *Urinary tract obstruction* (1.1%), *Device dislocation* (1.1%), and *General physical health deterioration* (1.1%). With the exception of pneumonitis and colitis, all these events were reported in a lower or similar frequency in the pembrolizumab group compared to control.

In the control arm, the SAE reported in ≥5% of subjects was febrile neutropenia (5.9%).

Table 53 shows the subject incidence and frequencies of drug-related SAEs observed in Study KN045. Most of the events were reported once on both groups but pembrolizumab was associated with a higher frequency of immune-mediated pneumonitis compared to the control arm (Table 55)

**Table 53: Drug-related Serious Adverse Events Up to 90 Days After Last Dose (Incidence >0% in One or More Treatment Groups) Study KN045 All Subjects (APaT Population)**

| | Control | | Pembrolizumab | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| Subjects in population | 255 | | 266 | |
| with one or more adverse events | 57 | (22.4) | 27 | (10.2) |
| with no adverse events | 198 | (77.6) | 239 | (89.8) |
| **Blood and lymphatic system disorders** | **28** | **(11.0)** | **0** | **(0.0)** |
| Anaemia | 5 | (2.0) | 0 | (0.0) |
| Febrile neutropenia | 15 | (5.9) | 0 | (0.0) |
| Leukopenia | 1 | (0.4) | 0 | (0.0) |
| Neutropenia | 5 | (2.0) | 0 | (0.0) |
| Normochromic normocytic anaemia | 1 | (0.4) | 0 | (0.0) |
| Pancytopenia | 2 | (0.8) | 0 | (0.0) |
| Thrombocytopenia | 1 | (0.4) | 0 | (0.0) |
| **Endocrine disorders** | **0** | **(0.0)** | **1** | **(0.4)** |
| Adrenal insufficiency | 0 | (0.0) | 1 | (0.4) |
| **Gastrointestinal disorders** | **20** | **(7.8)** | **5** | **(1.9)** |
| Colitis | 0 | (0.0) | 4 | (1.5) |
| Constipation | 7 | (2.7) | 0 | (0.0) |
| Diarrhoea | 1 | (0.4) | 2 | (0.8) |
| Ileus | 2 | (0.8) | 0 | (0.0) |
| Ileus paralytic | 2 | (0.8) | 0 | (0.0) |
| Intestinal obstruction | 5 | (2.0) | 0 | (0.0) |
| Large intestinal obstruction | 1 | (0.4) | 0 | (0.0) |
| Nausea | 1 | (0.4) | 0 | (0.0) |
| Neutropenic colitis | 1 | (0.4) | 0 | (0.0) |
| Subileus | 1 | (0.4) | 0 | (0.0) |
| Vomiting | 1 | (0.4) | 0 | (0.0) |
| **General disorders and administration site conditions** | **5** | **(2.0)** | **3** | **(1.1)** |
| Death | 1 | (0.4) | 1 | (0.4) |
| Fatigue | 1 | (0.4) | 1 | (0.4) |
| Influenza like illness | 0 | (0.0) | 1 | (0.4) |
| Malaise | 1 | (0.4) | 0 | (0.0) |
| Mucosal inflammation | 1 | (0.4) | 0 | (0.0) |
| Pyrexia | 1 | (0.4) | 0 | (0.0) |
| **Hepatobiliary disorders** | **1** | **(0.4)** | **0** | **(0.0)** |
| Jaundice | 1 | (0.4) | 0 | (0.0) |
| **Infections and infestations** | **10** | **(3.9)** | **2** | **(0.8)** |
| Lung infection | 0 | (0.0) | 1 | (0.4) |

| | Control | | Pembrolizumab | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| **Infections and infestations** | **10** | **(3.9)** | **2** | **(0.8)** |
| Pneumocystis jirovecii infection | 1 | (0.4) | 0 | (0.0) |
| Pneumonia | 1 | (0.4) | 1 | (0.4) |
| Sepsis | 2 | (0.8) | 0 | (0.0) |
| Septic shock | 1 | (0.4) | 0 | (0.0) |
| Upper respiratory tract infection | 1 | (0.4) | 0 | (0.0) |
| Urinary tract infection | 4 | (1.6) | 0 | (0.0) |
| **Investigations** | **4** | **(1.6)** | **2** | **(0.8)** |
| Alanine aminotransferase increased | 0 | (0.0) | 1 | (0.4) |
| Aspartate aminotransferase increased | 0 | (0.0) | 1 | (0.4) |
| Neutrophil count decreased | 3 | (1.2) | 0 | (0.0) |
| Platelet count decreased | 1 | (0.4) | 0 | (0.0) |
| Transaminases increased | 0 | (0.0) | 1 | (0.4) |
| **Metabolism and nutrition disorders** | **3** | **(1.2)** | **1** | **(0.4)** |
| Decreased appetite | 1 | (0.4) | 0 | (0.0) |
| Dehydration | 1 | (0.4) | 0 | (0.0) |
| Fluid retention | 1 | (0.4) | 0 | (0.0) |
| Hyponatraemia | 0 | (0.0) | 1 | (0.4) |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | **0** | **(0.0)** | **1** | **(0.4)** |
| Malignant neoplasm progression | 0 | (0.0) | 1 | (0.4) |
| **Nervous system disorders** | **1** | **(0.4)** | **1** | **(0.4)** |
| Encephalopathy | 0 | (0.0) | 1 | (0.4) |
| Posterior reversible encephalopathy syndrome | 1 | (0.4) | 0 | (0.0) |
| **Renal and urinary disorders** | **3** | **(1.2)** | **4** | **(1.5)** |
| Acute kidney injury | 2 | (0.8) | 0 | (0.0) |
| Autoimmune nephritis | 0 | (0.0) | 1 | (0.4) |
| Nephritis | 0 | (0.0) | 1 | (0.4) |
| Renal failure | 1 | (0.4) | 0 | (0.0) |
| Renal injury | 0 | (0.0) | 1 | (0.4) |
| Urinary tract obstruction | 0 | (0.0) | 1 | (0.4) |
| **Reproductive system and breast disorders** | **0** | **(0.0)** | **1** | **(0.4)** |
| Female genital tract fistula | 0 | (0.0) | 1 | (0.4) |

| | | | | |
|---|---|---|---|---|
| **Respiratory, thoracic and mediastinal disorders** | **2** | **(0.8)** | **7** | **(2.6)** |
| Chronic obstructive pulmonary disease | 0 | (0.0) | 1 | (0.4) |
| Dyspnoea | 1 | (0.4) | 0 | (0.0) |
| Interstitial lung disease | 0 | (0.0) | 1 | (0.4) |
| Pneumonitis | 0 | (0.0) | 5 | (1.9) |
| Pulmonary hypertension | 1 | (0.4) | 0 | (0.0) |
| **Skin and subcutaneous tissue disorders** | **0** | **(0.0)** | **1** | **(0.4)** |
| Rash maculo-papular | 0 | (0.0) | 1 | (0.4) |
| **Vascular disorders** | **1** | **(0.4)** | **0** | **(0.0)** |
| Deep vein thrombosis | 1 | (0.4) | 0 | (0.0) |

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA V19.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Serious adverse events up to 90 days of last dose are included.
Grades are based on NCI CTCAE version 4.0.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cutoff Date: 07SEP2016

Source: [P045V01: analysis-adsl] [P045V01: tabulations-aeplus]

In Study KN052, the frequency of subjects with 1 or more SAEs up to 90 days after the last pembrolizumab dose was 41.4%, and the most commonly reported events were *Urinary tract infection* (6.2%), *Acute kidney injury*, *Hematuria*, *Pneumonia*, and *Urosepsis* (2.7% each).

The drug-related SAEs observed in ≥1% of pembrolizumab treated patients across the urothelial cancer population (Study KN045 and Study KN052) and the Reference Safety Dataset are reported in the following Table (Table 54).

**Table 54: Drug-related Serious Adverse Events Up to 90 Days After Last Dose (Incidence >1% in One or More Treatment Groups) Pembrolizumab treated patients in Studies KN045, KN052 and Reference Safety Dataset by Body System or Organ Class and PT (APaT Population)**

| | **KN045**<br>n (%) | **KN052**<br>n (%) | **Reference Safety Dataset***<br>n (%) |
|---|---|---|---|
| Subjects in population<br>with one or more adverse events<br>with no adverse event | 266<br>27 (10.2)<br>239 (89.8) | 370<br>36 (9.7)<br>334 (90.3) | 2,799<br>281 (10.0)<br>2,518 (90.0) |
| **Endocrine disorders** | **1 (0.4)** | **6 (1.6)** | **27 (1.0)** |
| **Gastrointestinal disorders**<br>Colitis | **5 (1.9)**<br>4 (1.5) | **5 (1.4)**<br>2 (0.5) | **60 (2.1)**<br>25 (0.9) |
| **General disorders and administration site conditions**<br>Pyrexia | **3 (1.1)**<br>0 (0.0) | **5 (1.4)**<br>4 (1.1) | **24 (0.9)**<br>10 (0.4) |
| **Hepatobiliary disorders** | **0 (0.0)** | **4 (1.1)** | **15 (0.5)** |
| **Infections and infestations** | **2 (0.8)** | **5 (1.4)** | **20(0.7)** |
| **Metabolism and nutrition disorders** | **1 (0.4)** | **5 (1.4)** | **25 (0.9)** |
| **Musculoskeletal and connective tissue disorders** | **0 (0.0)** | **5 (1.4)** | **13 (0.5)** |
| **Renal and urinary disorders** | **4 (1.5)** | **3 (0.8)** | **13 (0.5)** |
| **Respiratory, thoracic and mediastinal disorders**<br>Pneumonitis | **7 (2.6)**<br>5 (1.9) | **2 (0.5)**<br>2 (0.5) | **66 (2.4)**<br>44 (1.6) |

Table 5.3.5.3.3-urothelial:28 (ISS KN045) and Table 5.3.5.3.3-urothelial:29 (ISS KN052).
Every subject is counted a single time for each applicable row and column.

MedDRA version used is 19.0.
*Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010.
(KN001 Database Cut-off Date for Melanoma: 18APR2014).
(KN001 Database Cut-off Date for Lung Cancer: 23JAN2015).
(KN002 Database Cut-off Date: 28FEB2015).
(KN006 Database Cut-off Date: 03MAR2015).
(KN010 Database Cut-off Date: 30SEP2015).

*Deaths*

In Study KN045, a total of 13 patients (4.9%) in the pembrolizumab arm and 8 patients (3.1%) in the control group had AEs resulting in death within 90 days of the last dose (Table 55).

**Table 55: Subjects With Adverse Events Resulting in Death Up to 90 Days After Last Dose (Incidence >0% in One or More Treatment Groups) Study KN045 All Subjects (APaT Population)**

| | Control | | Pembrolizumab | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| Subjects in population | 255 | | 266 | |
| with one or more adverse events | 8 | (3.1) | 13 | (4.9) |
| with no adverse events | 247 | (96.9) | 253 | (95.1) |
| **Gastrointestinal disorders** | **0** | **(0.0)** | **1** | **(0.4)** |
| Gastrointestinal perforation | 0 | (0.0) | 1 | (0.4) |
| **General disorders and administration site conditions** | **4** | **(1.6)** | **2** | **(0.8)** |
| Death | 4 | (1.6) | 1 | (0.4) |
| General physical health deterioration | 0 | (0.0) | 1 | (0.4) |
| **Infections and infestations** | **4** | **(1.6)** | **5** | **(1.9)** |
| Atypical pneumonia | 0 | (0.0) | 1 | (0.4) |
| Pneumonia | 1 | (0.4) | 3 | (1.1) |
| Sepsis | 2 | (0.8) | 0 | (0.0) |
| Septic shock | 1 | (0.4) | 0 | (0.0) |
| Urosepsis | 0 | (0.0) | 1 | (0.4) |
| **Metabolism and nutrition disorders** | **0** | **(0.0)** | **2** | **(0.8)** |
| Cachexia | 0 | (0.0) | 2 | (0.8) |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | **0** | **(0.0)** | **1** | **(0.4)** |
| Malignant neoplasm progression | 0 | (0.0) | 1 | (0.4) |
| **Renal and urinary disorders** | **0** | **(0.0)** | **1** | **(0.4)** |
| Urinary tract obstruction | 0 | (0.0) | 1 | (0.4) |
| **Respiratory, thoracic and mediastinal disorders** | **0** | **(0.0)** | **1** | **(0.4)** |
| Pneumonitis | 0 | (0.0) | 1 | (0.4) |

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 V19.0 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.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cutoff Date: 07SEP2016

Source: [P045V01: analysis-adsl] [P045V01: tabulations-aeplus]

Upon medical review, the fatal pneumonitis event was consistent with the previously described immune-mediated events related to pembrolizumab. Based on available information, the remaining AEs with a fatal outcome in subjects receiving pembrolizumab were deemed more likely related to either malignant neoplasm progression, infections (common among subjects with cancer), or related to complication of surgery for gastrointestinal perforation. No new safety signal was identified upon review of these fatal events.

In Study KN052, 18 (4.9%) patients died due to an AE during the trial. A summary of all AEs resulting in death is provided in the following Table (Table 56).

**Table 56: Subjects With Adverse Events Resulting in Death Up to 90 Days After Last Dose (Incidence >0%) Study KN052**
**All Subjects (APaT Population)**

| | Pembrolizumab | |
|---|---|---|
| | n | (%) |
| Subjects in population | 370 | |
| with one or more adverse events | 18 | (4.9) |
| with no adverse events | 352 | (95.1) |
| **Cardiac disorders** | **1** | **(0.3)** |
| Ischaemic cardiomyopathy | 1 | (0.3) |
| **Gastrointestinal disorders** | **2** | **(0.5)** |
| Duodenal obstruction | 1 | (0.3) |
| Large intestine perforation | 1 | (0.3) |
| **General disorders and administration site conditions** | **1** | **(0.3)** |
| Death | 1 | (0.3) |
| **Infections and infestations** | **8** | **(2.2)** |
| Pneumonia | 3 | (0.8) |
| Sepsis | 2 | (0.5) |
| Urosepsis | 3 | (0.8) |
| **Metabolism and nutrition disorders** | **1** | **(0.3)** |
| Type 2 diabetes mellitus | 1 | (0.3) |
| **Musculoskeletal and connective tissue disorders** | **1** | **(0.3)** |
| Myositis | 1 | (0.3) |
| **Nervous system disorders** | **1** | **(0.3)** |
| Cerebrovascular accident | 1 | (0.3) |
| **Renal and urinary disorders** | **3** | **(0.8)** |
| Acute kidney injury | 1 | (0.3) |
| Chronic kidney disease | 1 | (0.3) |
| Renal failure | 1 | (0.3) |
| **Respiratory, thoracic and mediastinal disorders** | **2** | **(0.5)** |
| Aspiration | 1 | (0.3) |
| **Respiratory, thoracic and mediastinal disorders** | **2** | **(0.5)** |
| Respiratory failure | 1 | (0.3) |

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence meets the incidence criterion in the report title, after rounding.
MedDRA V19 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Database Cutoff Date: 01SEP2016

Source: [P052V01MK3475: analysis-adsl] [P052V01MK3475: tabulations-aeplus]

All fatal events, including those reported only once, were medically reviewed. The only fatal event reported as drug-related by the Investigator refers to a patient who developed *Thyroiditis* (Grade 3 with hyperthyroidism followed by hypothyroidism), immune-mediated *Myositis* (Grade 5), *Myocarditis* (Grade 4), *Hepatitis* (Grade 3) and *Pneumonia* (Grade 3), approximately 20 days after initiation of pembrolizumab. Despite treatment, including steroid therapy, IV immunoglobulin and thyroid hormone replacement, the subject experienced respiratory insufficiency and pneumonia with a fatal outcome. In total, the patient received 2 doses prior to drug discontinuation. The Investigator considered the SAEs of thyroiditis, myositis, myocarditis, hepatitis, and pneumonia to be immune related, related to the study therapy, and events of clinical interest. According to the MAH, the available information permit to conclude the correlation of the reported SAEs *Thyroiditis* and *Myositis* with pembrolizumab administration, while SAEs of *Hepatitis* and *Myocarditis* were not related to pembrolizumab considering that there was no biopsy confirming the immune mediated nature of these events. This is the first reported fatal case of *Myositis* with pembrolizumab.

For the remaining cases, based on available information, the fatal outcomes of *Pneumonia* (3 subjects), *Urosepsis* (3 subjects), and *Sepsis* (2 subjects) were more likely related to the underlying medical condition or confounded by a medical procedure.

Two additional fatal cases (PTs *septic shock and malignant neoplasm progression;* PT *Clostridium difficile infection*) were reported at the updated safety analysis.

No new safety signal was identified upon review of the fatal events reported in both Study KN045 and Study KN052.

*Adverse Events of Special Interest (AEOSI)*

The AEOSI, including immune-mediated AEs and infusion-related reactions considered to be identified or potential risk for pembrolizumab, are characterized in an ongoing manner as part of the pembrolizumab development program. A pre-specified list of PTs was developed for assessing AEOSI.

**Table 57: Subjects with AEOSI (Incidence>0% in One or More Treatment Group) Study KN045 All Subjects (APaT Population)**

| | Control | | Pembrolizumab | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| Subjects in population | 255 | | 266 | |
| with one or more adverse events | 19 | (7.5) | 45 | (16.9) |
| with no adverse events | 236 | (92.5) | 221 | (83.1) |
| **Adrenal Insufficiency** | **0** | **(0.0)** | **1** | **(0.4)** |
| Adrenal insufficiency | 0 | (0.0) | 1 | (0.4) |
| **Colitis** | **1** | **(0.4)** | **6** | **(2.3)** |
| Colitis | 1 | (0.4) | 5 | (1.9) |
| Enterocolitis | 0 | (0.0) | 1 | (0.4) |
| **Hyperthyroidism** | **1** | **(0.4)** | **10** | **(3.8)** |
| Hyperthyroidism | 1 | (0.4) | 10 | (3.8) |
| **Hypothyroidism** | **3** | **(1.2)** | **17** | **(6.4)** |
| Hypothyroidism | 3 | (1.2) | 17 | (6.4) |
| **Infusion Related Reactions** | **10** | **(3.9)** | **2** | **(0.8)** |
| Hypersensitivity | 2 | (0.8) | 1 | (0.4) |
| Infusion related reaction | 8 | (3.1) | 1 | (0.4) |
| **Myositis** | **1** | **(0.4)** | **0** | **(0.0)** |
| Myositis | 1 | (0.4) | 0 | (0.0) |
| **Nephritis** | **0** | **(0.0)** | **2** | **(0.8)** |
| Autoimmune nephritis | 0 | (0.0) | 1 | (0.4) |
| Nephritis | 0 | (0.0) | 1 | (0.4) |
| **Pneumonitis** | **1** | **(0.4)** | **11** | **(4.1)** |
| Interstitial lung disease | 1 | (0.4) | 1 | (0.4) |
| Pneumonitis | 0 | (0.0) | 10 | (3.8) |
| **Severe Skin Reactions** | **3** | **(1.2)** | **2** | **(0.8)** |
| Jaundice | 1 | (0.4) | 0 | (0.0) |
| Dermatitis exfoliative | 0 | (0.0) | 1 | (0.4) |
| Drug eruption | 1 | (0.4) | 0 | (0.0) |
| Pruritus | 1 | (0.4) | 0 | (0.0) |
| Rash | 0 | (0.0) | 1 | (0.4) |
| **Thyroiditis** | **0** | **(0.0)** | **2** | **(0.8)** |
| Autoimmune thyroiditis | 0 | (0.0) | 1 | (0.4) |
| **Thyroiditis** | **0** | **(0.0)** | **2** | **(0.8)** |
| Thyroiditis | 0 | (0.0) | 1 | (0.4) |

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 V19.0 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.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cutoff Date: 07SEP2016

Source: [P045V01: analysis-adsl; adae] [P045V01: tabulations-aeplus]

**Table 58: Subjects with AEOSI (Incidence>0% in One or More Treatment Group) Study KN052 All Subjects (APaT Population)**

| | Pembrolizumab | |
|---|---|---|
| | n | (%) |
| Subjects in population | 370 | |
| with one or more adverse events | 63 | (17.0) |
| with no adverse events | 307 | (83.0) |
| **Adrenal Insufficiency** | **5** | **(1.4)** |
| Adrenal insufficiency | 5 | (1.4) |
| **Colitis** | **9** | **(2.4)** |
| Colitis | 8 | (2.2) |
| Enterocolitis | 1 | (0.3) |
| **Hepatitis** | **4** | **(1.1)** |
| Autoimmune hepatitis | 1 | (0.3) |
| Hepatitis | 3 | (0.8) |
| **Hyperthyroidism** | **9** | **(2.4)** |
| Hyperthyroidism | 9 | (2.4) |
| **Hypophysitis** | **2** | **(0.5)** |
| Hypophysitis | 1 | (0.3) |
| Hypopituitarism | 1 | (0.3) |
| **Hypothyroidism** | **24** | **(6.5)** |
| Hypothyroidism | 24 | (6.5) |
| **Infusion Related Reactions** | **1** | **(0.3)** |
| Hypersensitivity | 1 | (0.3) |
| **Myositis** | **1** | **(0.3)** |
| Myositis | 1 | (0.3) |
| **Nephritis** | **1** | **(0.3)** |
| Tubulointerstitial nephritis | 1 | (0.3) |
| **Pneumonitis** | **7** | **(1.9)** |
| Pneumonitis | 7 | (1.9) |
| **Severe Skin Reactions** | **4** | **(1.1)** |
| Dermatitis bullous | 1 | (0.3) |
| Lichen planus | 1 | (0.3) |
| Pruritus | 1 | (0.3) |
| Rash | 1 | (0.3) |
| Rash maculo-papular | 1 | (0.3) |
| **Thyroiditis** | **3** | **(0.8)** |
| Thyroid disorder | 1 | (0.3) |
| Thyroiditis | 2 | (0.5) |
| **Type 1 Diabetes Mellitus** | **4** | **(1.1)** |
| Diabetic ketoacidosis | 2 | (0.5) |
| Type 1 diabetes mellitus | 3 | (0.8) |

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
MedDRA version used is 19.0
Database Cutoff Date: 01SEP2016 .
Source: [P052V01MK3475: analysis-adsl; adae] [P052V01MK3475: tabulations-aeplus]

In general, the frequency and severity of each AEOSI observed in Study KN045 and KN052 were in line with the previously described characterization of the pembrolizumab safety profile. No new immune-mediated event causally associated with pembrolizumab and indication-specific was identified.

One fatal case each was reported in Study KN045 (*Pneumonitis*) and in Study KN052 (*Myositis*).

**Laboratory findings**

Laboratory abnormalities were analysed based on the highest CTCAE grade reported for each subject, in order to assess the clinically meaningful changes from baseline, defined as a shift from less than Grade 3 to Grade≥ 3 or a shift from Grade 0 to Grade 2.

In the pembrolizumab arm of Study KN045, the most frequently reported laboratory values with a clinically meaningful worsening in CTCAE grade from baseline were *Lymphocytes decreased* (25.6%), *Phosphate decreased* (23.7%). The rate of these laboratory abnormalities was higher in the control arm (34.9% and 27.5%, respectively). Additional laboratory findings with a clinically meaningful worsening most commonly observed in the control group were *Neutrophils decreased* (52.2%) and *Leukocytes decreased* (47.8%).

In Study KN052, the most common clinically meaningful worsened laboratory values were *Lymphocytes decreased* (21.9%) and *Albumin decreased* (13.8%). The most frequent liver function finding observed was *Alkaline phosphatase* ≥1.5 ULN (24.5%).

As concern the liver functioning test, in both studies the most frequent finding observed was *Alkaline phosphatase* ≥1.5 ULN (31.6% with pembrolizumab and 28.5% in the control group in KN045; 24.5% in KN052). Overall, no liver function abnormalities consistent with severe drug injury (Hy's Law: AST or ALT ≥3 ULN, total bilirubin ≥2 ULN and an alkaline phosphatase <2 X ULN) were reported. However, 4 (1.6%) subjects in the control arm and 8 (3.2%) subjects in the pembrolizumab arm of Study KN045, and 4 (1.1%) patients in Study KN052 had either an AST or ALT value ≥3 ULN with a total bilirubin value ≥2 ULN.

The frequency of subjects with clinically meaningful worsening in laboratory CTCAE grades in Study KN045, Study KN052 and in the reference safety data set is reported in the below Table (Table 59)

**Table 59: Summary of clinically meaningful worsening in laboratory CTCAE Grades from baseline Pembrolizumab treated patients in Studies KN045, KN052, and Reference Safety Dataset (APaT Population)**

| Laboratory test | KN045 (n=266) | KN052 (n=370) | Reference Safety Dataset (n=2,799) |
|---|---|---|---|
| APTT increased | 1 (0.4) | 7 (1.9) | 16 (0.6) |
| Alanine Aminotransferase Increased | 9 (3.4) | 21 (5.7) | 114 (4.1) |
| Albumin decreased | 40 (15.0) | 51 (13.8) | 252 (9.0) |
| Alkaline phosphatase increased | 25 (9.4) | 30 (8.1) | 122 (4.4) |
| Amylase increased | 0 (0.0) | 2 (0.5) | 7 (0.3) |
| Aspartate Aminotransferase Increased | 15 (5.6) | 22 (5.9) | 122 (4.4) |
| Bilirubin increased | 17 (6.4) | 12 (3.2) | 91(3.3) |
| Calcium decreased | 21 (7.9) | 18 (4.9) | 108 (3.9) |
| Calcium increased | 5 (1.9) | 7 (1.9) | 36 (1.3) |
| Creatinine increased | 21 (7.9) | 30 (8.1) | 57 (2.0) |
| Gamma glutamyl transferase increased | 10 (3.8) | 5 (1.4) | 23 (0.8) |
| Glucose decreased | 1 (0.4) | 5 (1.4) | 40 (1.4) |
| Glucose increased | 42 (15.8) | 48 (13.0) | 296 (10.6) |
| Haemoglobin decreased | 46 (17.3) | 45 (12.2) | 122 (4.4) |
| Leukocytes decreased | 1 (0.4) | 7 (1.9) | 69 (2.5) |
| Lymphocytes decreased | 68 (25.6) | 81 (21.9) | 438 (15.6) |
| Lymphocytes increased | 1 (0.4) | 2 (0.5) | 2 (0.1) |
| Neutophils decreased | 9 (3.4) | 18 (4.9) | 67 (2.4) |
| Phosphate decreased | 63 (23.7) | 48 (13.0) | 470 (16.8) |
| Platelet decreased | 8 (3.0) | 5 (1.4) | 46 (1.6) |
| Potassium decreased | 4 (1.5) | 3 (0.8) | 50 (1.8) |
| Potassium increased | 19 (7.1) | 28 (7.6) | 114 (4.1) |
| Prothrombin INR increased | 3 (1.1) | 8 (2.2) | 29 (1.0) |
| Sodium decreased | 21 (7.9) | 43 (11.6) | 185 (6.6) |
| Sodium increased | 1 (0.4) | 0 (0.0) | 4 (0.1) |
| Triacylglycerol lipase increased | 2 (0.8) | 2 (0.5) | 5 (0.2) |

## *Safety in special populations*

*Age*

In Study KN045, the percentage of AEs was generally comparable between age categories in both treatment arms (Table 60).

**Table 60: Adverse Events Summary by Age Study KN045**
**All Subjects**
**(APaT Population)**

| | Age (Years) | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Control | | | | | | | | Pembrolizumab | | | | | | | |
| | < 65 | | >= 65 to < 75 | | >= 75 to < 85 | | >= 85 | | < 65 | | >= 65 to < 75 | | >= 75 to < 85 | | >= 85 | |
| | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) |
| Subjects in Population | 118 | | 94 | | 43 | | 0 | | 103 | | 111 | | 46 | | 6 | |
| with one or more adverse events | 116 | (98.3) | 91 | (96.8) | 43 | (100.0) | 0 | | 96 | (93.2) | 104 | (93.7) | 42 | (91.3) | 6 | (100.0) |
| who died | 4 | (3.4) | 1 | (1.1) | 3 | (7.0) | 0 | | 5 | (4.9) | 5 | (4.5) | 3 | (6.5) | 0 | (0.0) |
| with serious adverse events | 44 | (37.3) | 44 | (46.8) | 16 | (37.2) | 0 | | 31 | (30.1) | 49 | (44.1) | 20 | (43.5) | 4 | (66.7) |
| discontinued† due to an adverse event | 18 | (15.3) | 8 | (8.5) | 6 | (14.0) | 0 | | 6 | (5.8) | 10 | (9.0) | 6 | (13.0) | 0 | (0.0) |
| CNS (confusion/extrapyramidal) | 10 | (8.5) | 6 | (6.4) | 3 | (7.0) | 0 | | 6 | (5.8) | 7 | (6.3) | 2 | (4.3) | 1 | (16.7) |
| AE related to falling | 2 | (1.7) | 6 | (6.4) | 4 | (9.3) | 0 | | 5 | (4.9) | 7 | (6.3) | 5 | (10.9) | 2 | (33.3) |
| CV events | 20 | (16.9) | 15 | (16.0) | 7 | (16.3) | 0 | | 15 | (14.6) | 28 | (25.2) | 5 | (10.9) | 1 | (16.7) |
| Cerebrovascular events | 0 | (0.0) | 1 | (1.1) | 0 | (0.0) | 0 | | 1 | (1.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Infections | 41 | (34.7) | 37 | (39.4) | 16 | (37.2) | 0 | | 36 | (35.0) | 47 | (42.3) | 18 | (39.1) | 4 | (66.7) |

† Study medication withdrawn
MedDRA V19.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
AEs were followed 30 days after last dose of study treatment; SAEs were followed 90 days after last dose of study treatment
(Database Cutoff Date: 07SEP2016).

Source: [P045V01: analysis-adsl] [P045V01: tabulations-aeplus]

Overall, no impact of age was identified for pembrolizumab in both Study KN045 and KN052 populations in comparison to the Reference Safety Dataset (Table 61).

**Table 61: AEs Summary by Age (<65, ≥65)**
**Pembrolizumab treated patients in Studies KN045, KN052, and Reference Safety Dataset**
**(APaT Population)**

| | KN045 | | KN052 | | Reference Safety Dataset* | |
|---|---|---|---|---|---|---|
| | <65 | ≥65 | <65 | ≥65 | <65 | ≥65 |
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Subjects in population | 103 | 163 | 68 | 302 | 1,587 | 1,212 |
| with one or more AEs | 96 (93.2) | 152 (93.3) | 65 (95.6) | 289 (95.7) | 1,547(97.5) | 1,180 (97.4) |
| with no AE | 7 (6.8) | 11 (6.7) | 3 (4.4) | 13 (4.3) | 40 (2.5) | 32 (2.6) |
| with drug-related° AEs | 62 (60.2) | 100 (61.3) | 37 (54.4) | 192 (63.6) | 1,164 (73.3) | 898 (74.1) |
| with toxicity Grade≥3 AEs | 47 (45.6) | 92 (56.4) | 34 (50.0) | 165 (54.6) | 695 (43.8) | 578 (47.7) |
| with toxicity Grade≥3 drug-related AEs | 13 (12.6) | 27 (16.6) | 10 (14.7) | 48 (15.9) | 202 (12.7) | 184 (15.2) |
| with serious AEs | 31 (30.1) | 73 (44.8) | 26 (38.2) | 127 (42.1) | 553 (34.8) | 488 (40.3) |
| with serious drug-related AEs | 7 (6.8) | 20 (12.3) | 8 (11.8) | 28 (9.3) | 145 (9.1) | 136 (11.2) |
| who died | 5 (4.9) | 8 (4.9) | 3 (4.4) | 15 (5.0) | 46 (2.9) | 64 (5.3) |
| who died due to drug-related AEs | 2 (1.9) | 2 (1.2) | 0 (0.0) | 1 (0.3) | 4 (0.3) | 6 (0.5) |
| discontinued due to AE | 6 (5.8) | 16 (9.8) | 9 (13.2) | 32 (10.6) | 164 (10.3) | 170 (14.0) |
| discontinued due to drug-related AE | 3 (2.9) | 12 (7.4) | 4 (5.9) | 15 (5.0) | 66 (4.2) | 80 (6.6) |
| discontinued due to serious AE | 6 (5.8) | 9 (5.5) | 8 (11.8) | 26 (8.6) | 123 (7.8) | 130 (10.7) |
| discontinued due to serious drug-related AE | 3 (2.9) | 6 (3.7) | 3 (4.4) | 11 (3.6) | 47 (3.0) | 54 (4.5) |

Table made by the Assessor from Table 2.7.4:16 (CSR KN045) and Table 2.7.4:15 (CSR KN052).
°determined by the Investigator to be related to the drug
*Includes all subjects who received at least one dose of MK-3475 in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase), KN006, KN010.
(KN001 Database Cut-off Date for Melanoma: 18APR2014).
(KN001 Database Cut-off Date for Lung Cancer: 23JAN2015).
(KN002 Database Cut-off Date: 28FEB2015).
(KN006 Database Cut-off Date: 03MAR2015).
(KN010 Database Cut-off Date: 30SEP2015).

*Gender*

Pembrolizumab was similarly well tolerated in either male or female patients enrolled in Study KN045, on the basis of lower frequency of drug-related AEs, Grade≥ 3 AEs, Grade≥3 drug-related AEs, and drug-related SAEs (Table 62).

**Table 62: Adverse Events Summary by Gender Study KN045 -All Subjects (APaT Population)**

| | Control | | | | Pembrolizumab | | | |
|---|---|---|---|---|---|---|---|---|
| | Male | | Female | | Male | | Female | |
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Subjects in population | 192 | | 63 | | 198 | | 68 | |
| with one or more adverse events | 188 | (97.9) | 62 | (98.4) | 185 | (93.4) | 63 | (92.6) |
| with no adverse event | 4 | (2.1) | 1 | (1.6) | 13 | (6.6) | 5 | (7.4) |
| with drug-related† adverse events | 173 | (90.1) | 57 | (90.5) | 125 | (63.1) | 37 | (54.4) |
| with toxicity grade 3-5 adverse events | 117 | (60.9) | 43 | (68.3) | 107 | (54.0) | 32 | (47.1) |
| with toxicity grade 3-5 drug-related adverse events | 92 | (47.9) | 34 | (54.0) | 31 | (15.7) | 9 | (13.2) |
| with serious adverse events | 74 | (38.5) | 30 | (47.6) | 80 | (40.4) | 24 | (35.3) |
| with serious drug-related adverse events | 41 | (21.4) | 16 | (25.4) | 22 | (11.1) | 5 | (7.4) |
| who died | 6 | (3.1) | 2 | (3.2) | 8 | (4.0) | 5 | (7.4) |
| who died due to a drug-related adverse event | 3 | (1.6) | 1 | (1.6) | 3 | (1.5) | 1 | (1.5) |
| discontinued‡ due to an adverse event | 25 | (13.0) | 7 | (11.1) | 15 | (7.6) | 7 | (10.3) |
| discontinued due to a drug-related adverse event | 22 | (11.5) | 6 | (9.5) | 11 | (5.6) | 4 | (5.9) |
| discontinued due to a serious adverse event | 9 | (4.7) | 3 | (4.8) | 10 | (5.1) | 5 | (7.4) |
| discontinued due to a serious drug-related adverse event | 7 | (3.6) | 3 | (4.8) | 7 | (3.5) | 2 | (2.9) |

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
MedDRA V19.0 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.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cutoff Date: 07SEP2016

Source: [P045V01: analysis-adsl] [P045V01: tabulations-aeplus]

The frequency of AEs by Gender in Study KN045 population was similar to that in the Reference Safety Dataset, while female patients in Study KN052 experienced a higher rate of SAEs and Grade ≥3 AEs in comparison to those in the reference safety dataset (50% vs 35.5% and 63.1% vs 45.1%, respectively. These findings should be evaluated with caution given the low number of females (n=84) in Study KN052.

*ECOG Status*

Pembrolizumab was consistently well tolerated in ECOG PS 0 or ECOG PS 1 patients treated in Study KN045, with a better tolerability profile in both subgroups in terms of drug-related AEs, Grade ≥3 drug-related AEs, and drug-related SAEs, compared to the control (Table 63).

**Table 63: Adverse Events Summary by ECOG Status Study KN045**
**All Subjects**
**(APaT Population)**

| | Control | | | | | | | | Pembrolizumab | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | [0] Normal Activity | | [1] Symptoms, But Ambulatory | | [2] Ambulatory But Unable To Work | | Null | | [0] Normal Activity | | [1] Symptoms, But Ambulatory | | [2] Ambulatory But Unable To Work | | Null | |
| | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) |
| Subjects in population | 100 | | 148 | | 3 | | 4 | | 119 | | 140 | | 2 | | 5 | |
| with one or more adverse events | 97 | (97.0) | 146 | (98.6) | 3 | (100.0) | 4 | (100.0) | 113 | (95.0) | 129 | (92.1) | 2 | (100.0) | 4 | (80.0) |
| with no adverse event | 3 | (3.0) | 2 | (1.4) | 0 | (0.0) | 0 | (0.0) | 6 | (5.0) | 11 | (7.9) | 0 | (0.0) | 1 | (20.0) |
| with drug-related† adverse events | 90 | (90.0) | 134 | (90.5) | 2 | (66.7) | 4 | (100.0) | 81 | (68.1) | 78 | (55.7) | 0 | (0.0) | 3 | (60.0) |
| with toxicity grade 3-5 adverse events | 59 | (59.0) | 96 | (64.9) | 1 | (33.3) | 4 | (100.0) | 57 | (47.9) | 80 | (57.1) | 1 | (50.0) | 1 | (20.0) |
| with toxicity grade 3-5 drug-related adverse events | 51 | (51.0) | 71 | (48.0) | 1 | (33.3) | 3 | (75.0) | 18 | (15.1) | 22 | (15.7) | 0 | (0.0) | 0 | (0.0) |
| with serious adverse events | 32 | (32.0) | 67 | (45.3) | 2 | (66.7) | 3 | (75.0) | 44 | (37.0) | 57 | (40.7) | 1 | (50.0) | 2 | (40.0) |
| with serious drug-related adverse events | 19 | (19.0) | 35 | (23.6) | 1 | (33.3) | 2 | (50.0) | 13 | (10.9) | 14 | (10.0) | 0 | (0.0) | 0 | (0.0) |
| who died | 2 | (2.0) | 6 | (4.1) | 0 | (0.0) | 0 | (0.0) | 7 | (5.9) | 6 | (4.3) | 0 | (0.0) | 0 | (0.0) |
| who died due to a drug-related adverse event | 2 | (2.0) | 2 | (1.4) | 0 | (0.0) | 0 | (0.0) | 2 | (1.7) | 2 | (1.4) | 0 | (0.0) | 0 | (0.0) |
| discontinued‡ due to an adverse event | 9 | (9.0) | 21 | (14.2) | 2 | (66.7) | 0 | (0.0) | 10 | (8.4) | 12 | (8.6) | 0 | (0.0) | 0 | (0.0) |
| discontinued due to a drug-related adverse event | 8 | (8.0) | 18 | (12.2) | 2 | (66.7) | 0 | (0.0) | 6 | (5.0) | 9 | (6.4) | 0 | (0.0) | 0 | (0.0) |
| discontinued due to a serious adverse event | 3 | (3.0) | 8 | (5.4) | 1 | (33.3) | 0 | (0.0) | 6 | (5.0) | 9 | (6.4) | 0 | (0.0) | 0 | (0.0) |
| discontinued due to a serious drug-related adverse event | 3 | (3.0) | 6 | (4.1) | 1 | (33.3) | 0 | (0.0) | 3 | (2.5) | 6 | (4.3) | 0 | (0.0) | 0 | (0.0) |

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
MedDRA V19.0 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.
Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
Database Cutoff Date: 07SEP2016

Source: [P045V01: analysis-adsl] [P045V01: tabulations-aeplus]

In general, the overall frequency of AEs in patients with ECOG-PS 0 or 1 reported in both Study KN045 and Study KN052 was similar to the Reference Safety Dataset for these respective groups.

Patients with ECOG PS 2 were only included in Study KN052, and therefore the comparison of AEs frequency versus the Reference Safety Dataset cannot be made (Table 64).

**Table 64: Adverse Events Summary by ECOG Status Study KN052**
**All Subjects**
**(APaT Population)**

| | Pembrolizumab | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | [0] Normal Activity | | [1] Symptoms, But Ambulatory | | [2] Ambulatory But Unable To Work | | [3] Limited Selfcare | |
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Subjects in population | 80 | | 133 | | 156 | | 1 | |
| with one or more adverse events | 75 | (93.8) | 131 | (98.5) | 147 | (94.2) | 1 | (100.0) |
| with no adverse event | 5 | (6.3) | 2 | (1.5) | 9 | (5.8) | 0 | (0.0) |
| with drug-related† adverse events | 55 | (68.8) | 89 | (66.9) | 84 | (53.8) | 1 | (100.0) |
| with toxicity grade 3-5 adverse events | 39 | (48.8) | 77 | (57.9) | 82 | (52.6) | 1 | (100.0) |
| with toxicity grade 3-5 drug-related adverse events | 11 | (13.8) | 24 | (18.0) | 22 | (14.1) | 1 | (100.0) |
| with serious adverse events | 26 | (32.5) | 61 | (45.9) | 65 | (41.7) | 1 | (100.0) |
| with serious drug-related adverse events | 7 | (8.8) | 14 | (10.5) | 14 | (9.0) | 1 | (100.0) |
| who died | 4 | (5.0) | 5 | (3.8) | 9 | (5.8) | 0 | (0.0) |
| who died due to a drug-related adverse event | 0 | (0.0) | 1 | (0.8) | 0 | (0.0) | 0 | (0.0) |
| discontinued‡ due to an adverse event | 9 | (11.3) | 14 | (10.5) | 17 | (10.9) | 1 | (100.0) |
| discontinued due to a drug-related adverse event | 4 | (5.0) | 7 | (5.3) | 7 | (4.5) | 1 | (100.0) |
| discontinued due to a serious adverse event | 8 | (10.0) | 12 | (9.0) | 13 | (8.3) | 1 | (100.0) |
| discontinued due to a serious drug-related adverse event | 3 | (3.8) | 5 | (3.8) | 5 | (3.2) | 1 | (100.0) |

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
MedDRA V19 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: 01SEP2016

Source: [P052V01MK3475: analysis-adsl] [P052V01MK3475: tabulations-aeplus]

*Region*

The overall summary by region (EU versus non-EU) for KN045 showed similar results for the EU compared to non-EU (Table 65).**Table 65: Adverse Events Summary by Region (EU vs Non-EU) Study KN045 - All Subjects**

**(APaT Population)**

| | Control | | | | Pembrolizumab | | | |
|---|---|---|---|---|---|---|---|---|
| | EU | | Non-EU | | EU | | Non-EU | |
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Subjects in population | 112 | | 143 | | 104 | | 162 | |
| with one or more adverse events | 111 | (99.1) | 139 | (97.2) | 98 | (94.2) | 150 | (92.6) |
| with no adverse event | 1 | (0.9) | 4 | (2.8) | 6 | (5.8) | 12 | (7.4) |
| with drug-related† adverse events | 101 | (90.2) | 129 | (90.2) | 66 | (63.5) | 96 | (59.3) |
| with toxicity grade 3-5 adverse events | 60 | (53.6) | 100 | (69.9) | 53 | (51.0) | 86 | (53.1) |
| with toxicity grade 3-5 drug-related adverse events | 45 | (40.2) | 81 | (56.6) | 18 | (17.3) | 22 | (13.6) |
| with serious adverse events | 52 | (46.4) | 52 | (36.4) | 38 | (36.5) | 66 | (40.7) |
| with serious drug-related adverse events | 32 | (28.6) | 25 | (17.5) | 9 | (8.7) | 18 | (11.1) |
| who died | 4 | (3.6) | 4 | (2.8) | 4 | (3.8) | 9 | (5.6) |
| who died due to a drug-related adverse event | 3 | (2.7) | 1 | (0.7) | 0 | (0.0) | 4 | (2.5) |
| discontinued‡ due to an adverse event | 13 | (11.6) | 19 | (13.3) | 7 | (6.7) | 15 | (9.3) |
| discontinued due to a drug-related adverse event | 11 | (9.8) | 17 | (11.9) | 5 | (4.8) | 10 | (6.2) |
| discontinued due to a serious adverse event | 8 | (7.1) | 4 | (2.8) | 2 | (1.9) | 13 | (8.0) |
| discontinued due to a serious drug-related adverse event | 7 | (6.3) | 3 | (2.1) | 0 | (0.0) | 9 | (5.6) |

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

‡ Study medication withdrawn.

MedDRA V19.0 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.

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.

Database Cutoff Date: 07SEP2016

Source: [P045V01: analysis-adsl] [P045V01: tabulations-aeplus]

## *Discontinuation due to adverse events*

In Study KN045, a total of 22 (8.3%) patients in the pembrolizumab arm and 32 (12.5%) patients in the control group had an AE resulting in treatment discontinuation. The most common AEs leading to discontinuation were *Pneumonitis* (1.9%) in patients treated with pembrolizumab, and *Peripheral sensory neuropathy* (2.0%) and *Neuropathy peripheral* (1.6%) in patients who received chemotherapy.

In Study KN052, a total of 41 (11.1%) subjects discontinued treatment due to AEs. None of these events was reported in a frequency >1%.

**Immunogenicity**

A total of 3727 subjects were included in the immunogenicity assessment across indications (1,535 melanoma, 1,238 NSCLC, 101 HNSCC, 54 MSI-H, 220 HL, and 579 urothelial carcinoma subjects) and across doses (at 2 mg/kg Q3W, 10 mg/kg Q3W/ Q2W, and 200 mg Q3W).

The observed frequency of treatment-emergent anti-drug antibodies (ADA) in evaluable subjects from this pooled analysis across indications is 1.8% (36 out of 2034). Exposure to pembrolizumab was not compromised by the observed immune response. Indeed, in the 36 subjects with a treatment-emergent immunogenicity response pembrolizumab exposure was in the range of those observed for non-positive subjects treated with pembrolizumab in the same regimen. The treatment emergent positive subjects did not have any AEs associated with neutralizing antibodies, such as hypersensitivity events (e.g. anaphylaxis, urticaria, angioedema) or injection site reactions.

In the subgroup of urothelial carcinoma subjects (pooled across KN012, KN045 and KN052), the incidence for treatment-emergent ADA in evaluable subjects is 1.4% (7 of 509; 497 negative, 5 non-treatment emergent positive and 7 treatment emergent positive), in line with the overall incidence.

### *Post marketing experience*

The Keytyruda Periodic Safety Update Report (PSUR), covering the reporting period 04 March 2016 to 03 September 2016, has been just reviewed by the PRAC. Assessment of the signal for sarcoidosis led to the conclusion that a causal association cannot be excluded and reflection in the SmPC and Package Leaflet was requested accordingly.

## 2.5.1. Discussion on clinical safety

The pembrolizumab safety profile in locally advanced or metastatic urothelial carcinoma has been presented in 266 subjected previously treated with platinum-containing chemotherapy (study KEYNOTE-045), and in 370 patients previously untreated and cisplatin-ineligible (study KEYNOTE-052). In addition, safety data from a Reference Safety Dataset including overall 3,194 patients treated with pembrolizumab across different trials (studies KEYNOTE-001, KEYNOTE-002 and KEYNOTE-006 in melanoma; studies KEYNOTE-001, KEYNOTE-010 and KEYNOTE-024 in NSCLC; studies KEYNOTE-013 Cohort 3 and KEYNOTE-087 in Hodgkin's Lymphoma) have been submitted, in order to allow a comparison with the already established pembrolizumab safety profile. At a median follow up of 12 months in study KN045 and of 11 months in study KN052, a shorter median time on therapy was reported in both KN045 and KN052 studies compared to the Reference Safety Dataset (3.45 months and 3.40 respectively, versus 4.86 months), resulting into a reduced number of administered doses ( 6 and 5 respectively, versus 8).

Consistently with the epidemiologic pattern of urothelial carcinoma, in comparison to the reference safety dataset, patients in both KN-045 and KN-052 were mostly male (74.4% and 77.3%, respectively, versus 59.3%), and ≥65 years (61.3% and 81.6%, respectively, versus 43.3%). ECOG PS2 patients were 42.2% in Study KN-052 and 1.5% in Study KN-045

In study KN045, pembrolizumab treatment favorably compares with chemotherapy in terms of drug-related AEs (60.9% vs 90.2%), Grade≥3 AEs (52.3% vs 62.7%), drug-related Grade≥3 AEs (15% vs 49.4%), serious drug-related AEs (10.2 vs 22.4%), treatment interruption due to drug-related AEs (10.5% vs 15.7%) and treatment discontinuation due to drug-related AEs (11% vs 5.6%). As expected, pembrolizumab showed a well different safety profile compared to chemotherapy, with a higher rate in the control arm of AEs in SOCs *General disorders and administration site conditions* (72.2% vs 57.5%), *Gastrointestinal disorders* (68.2% vs 56.4%), *Blood and lymphatic system disorders* (51% vs 19.9%), *Nervous system disorders* (41.2% vs 21.8%) and *Investigations* (34.9% vs 28.9%), and a higher frequency in pembrolizumab arm of AEs in SOCs *Musculoskeletal and connective tissue disorders* (42.5% vs 37.3%), *Respiratory, thoracic and mediastinal disorders* (34.2% vs 29.4%), *Renal and urinary disorders* (27.1% vs 17.6%) and *Endocrine disorders* (10.5% vs 1.6%). Among the most common PTs, *Pruritus* and *Decreased appetite* were the only registered at higher frequency in the pembrolizumab arm (23.3% vs 5.5% and 21.1% vs 20.8%, respectively). In terms of drug-related AEs, the most frequently observed events in the pembrolizumab arm were *Pruritus* (19.5%), *Fatigue* (13.9%) and *Nausea* (10.9%) while in the control arm patients mostly experienced *Alopecia* (37.6%), *Fatigue* (27.8%), *Anemia* (24.7%), *Nausea* (24.3%), *Constipation* (20.4%), *Decreased appetite* (16.1%), *Neutropenia* (15.3%), *Asthenia* (14.1%), *Neutrophil count decreased* (14.1%), *Diarrhea* (12.9%), *Peripheral sensory neuropathy* (11.0%), and *Neuropathy peripheral* (10.6%).

Overall, in patients treated with pembrolizumab, no major differences in the safety profile were observed between both populations in studies KN045 and KN052 and in the Reference Safety Dataset. The

frequency and severity of AEOSI in both UC populations were also in line with those previously described. However, a higher frequency of *Urinary tract infection* and *Haematuria* was registered across UC studies in comparison to the Reference Safety Dataset, together with an increase of *Blood alkaline phosphatase* and *Blood creatinine* specifically in study KN052. *Urinary tract infection* was also the most commonly reported Grade≥3 AE (9.5%) in study KN052. Even though the underlying disease condition can possibly explain the higher than previously reported rate of these AEs, the contribution of pembrolizumab cannot be ignored: in the comparative study KN045, patients treated with pembrolizumab experienced more frequently that those treated with chemotherapy *Acute kidney injury* (5.6% vs 2.7%), *Haematuria* (11.3% vs 7.8%) and *Urinary tract infection* (14.7% vs 13.3%). In study KN052, consistently with the Reference Safety Dataset, the most commonly reported drug-related AEs were Fatigue (16.8% and 24.2%), Pruritus (14.6% and 16.7%) and *Rash* (9.7% and 13.8%). *Pneumonitis* and *Colitis* were the most common drug-related SAEs in KN045 (1.9% and 1.5%) and in the Reference Safety Dataset (1.6% and 0.9%).

Overall, a total of 31 fatal cases, 13 in study KN045 and 18 in study KN052, occurred within 90 days from the last pembrolizumab dose. The frequency of patients with AE leading to fatal outcome was comparable in KN045 (4.9%), KN052 (4.9%) and in the Reference Safety Dataset (3.9%), even though a higher number of deaths was reported in cisplatin-ineligible patients compared to platinum-pretreated ones. This difference can be explained considering the baseline characteristics of the patient population in study KN052. Indeed, 15 out of the 18 dead patients were ≥65 years old, including 10 patients aged ≥75 years and 4 patients older than 85 years. No new safety signal was identified from fatal cases. One AEOSI with fatal outcome was reported each in Study KN045 (*Pneumonitis*) and in Study KN052 (*Myositis*); while fatal *Pneumonitis* events were already reported, this is the first fatal case of *Myositis* and the information has been included in Section 4.4 of the SmPC.

The frequency of clinically meaningful laboratory abnormalities was overall comparable among Study KN045, Study KN052 and the reference safety data set, with the exception of *Albumin decreased*, *Creatinine increased*, *Haemoglobin decreased* that were more pronounced in the urothelial cancer population possibly due to the baseline medical condition.

No major and unexpected differences in the tolerability of pembrolizumab treatment were observed across the different classes of age (<65 years, ≥65 to <75 years,≥75 to <85 years, ≥85 years), ECOG Performance Status categories (PS 0/1), and gender (Male/Female). ECOG PS≥2 patients were only included in Study KN052. Based on the overall 157 patients included, no impact on the pembrolizumab tolerability can be assumed.

In the application which was submitted also a change to section 4.4 of the SmPC was proposed, adding possible hypersensitivity and anaphylaxis as part of infusion reactions. These changes have been considered acceptable and were included in the SmPC.

## 2.5.2. Conclusions on clinical safety

Overall, the safety profile of pembrolizumab in the UC population does not seem to be significantly influenced by prior platinum-treatment (KN045) or baseline patient characteristics leading to cisplatin-ineligibility (KN052). Available safety data are in general consistent with those previously reported in the SmPC. New warnings were added under section 4.4 regarding the delayed onset of the effect of pembrolizumab to be considered when treating patients with poorer prognosis; the lack of data in frailer patients (e.g ECOG ≥3) ineligible for chemotherapy and the first reported fatal case of myositis. The incidences of adverse reactions under section 4.8 of the SmPC were updated to reflect the totality of the data.

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

The PRAC considered that the risk management plan version 7.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 7.2 with the following content:

### *Safety concerns*

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | **Immune-Related Adverse Reactions**<br>- Immune-related pneumonitis<br>- Immune-related colitis<br>- Immune-related hepatitis<br>- Immune-related nephritis<br>- Immune-related endocrinopathies<br>• Hypophysitis (including hypopituitarism and secondary adrenal insufficiency)<br>• Thyroid Disorder (hypothyroidism, hyperthyroidism, thyroiditis)<br>• Type 1 diabetes mellitus<br>- Other immune-related adverse reactions<br>• Uveitis<br>• Myositis<br>• Pancreatitis<br>• Severe Skin Reactions<br>• Guillain-Barre Syndrome<br>**Infusion-Related Reactions** |
| Important potential risks | **Immune-Related Adverse Events**<br>• Gastrointestinal perforation secondary to colitis<br>**Immunogenicity** |
| Missing information | - Safety in patients with moderate or severe hepatic impairment<br>- Safety in patients with severe renal impairment<br>- Safety in patients with active systemic autoimmune disease<br>- Safety in patients with HIV or Hepatitis B or Hepatitis C<br>- Safety in pediatric patients<br>- Reproductive and lactation data<br>- Long term safety<br>- Safety in various ethnic groups<br>- Potential pharmacodynamic interaction with systemic |

| Summary of safety concerns | |
|---|---|
| | immunosuppressants<br>- Safety in patients with previous hypersensitivity to another monoclonal antibody<br>- Safety in patients with severe (grade 3) immune-related (ir)AEs on prior ipilimumab (ipi) requiring corticosteroids for > 12 weeks, or life-threatening irAEs on prior ipi, or with ongoing ipi-related AEs |

Having considered the updated data in the safety specification, no new safety concerns were included as part of this extension of indication. The list of safety concerns remains unchanged.

## *Pharmacovigilance plan*

Completed, ongoing and planned studies in the PhV development plan

| **Activity/Study title (type of activity, study title, category 1-3)*** | **Objectives** | **Safety concerns addressed** | **Status Planned, started,** | **Date for submission of interim or final reports (planned or actual)** |
|---|---|---|---|---|
| *Validation report for anti-MK-3475 neutralizing antibody assay*<br>*(Category 3)* | *To validate the assay for the determination of neutralizing capacity of anti-MK-3475 antibodies and to report the results in an assay validation report.* | *Important potential risk (Immunogenicity)* | *Started* | *Final assay validation report September 2016* |
| *Clinical trial Phase I Study of Single Agent MK-3475 in Patients with Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, and Non-Small Cell Lung Carcinoma (P001)*<br>*(Category 3)* | *To evaluate and characterize the tolerability and safety profile of single agent MK-3475 in adult patients with unresectable advanced carcinoma (including NSCLC or MEL).* | *-Important identified risks (Immune-related adverse reactions, Infusion-related reactions)*<br>*-Important potential risks (Immune-related adverse events, Immunogenicity)*<br>*-Long term safety* | *Started* | *Final study report December 2016* |
| *Clinical trial Randomized, Phase II Study of MK-3475 versus Chemotherapy in Patients with Advanced Melanoma (P002) (Category 3)* | *To evaluate the progression-free-survival (PFS) in patients with ipilimumab refractory advanced MEL receiving either MK-3475 or chemotherapy.* | *-Important identified risks (Immune-related adverse reactions, Infusion-related reactions)*<br>*-Important potential risks* | *Started* | *Final study report January 2017* |

| Activity / Study title (type of activity, study title, category 1-3)* | Objectives | Safety concerns addressed | Status Planned, started, | Date for submission of interim or final reports (planned or actual) |
|---|---|---|---|---|
| | | *(Immune-related adverse events, Immunogenicity)*<br>*-Long term safety* | | |
| *Clinical trial A Multicenter, Randomized, Controlled, Three-Arm, Phase III Study to Evaluate the Safety and Efficacy of Two Dosing Schedules of MK-3475 Compared to IPI in Patients with Advanced Melanoma (P006) (Category 3)* | *To evaluate progression-free-survival (PFS) in patients with advanced MEL receiving either MK-3475 or IPI* | *-Important identified risks (Immune-related adverse reactions, Infusion-related reactions)*<br>*-Important potential risks (Immune-related adverse events, Immunogenicity)*<br>*-Long term safety* | *Started* | *Final study report January 2017* |
| *Clinical trial A Phase II/III Randomized Trial of Two Doses of MK-3475 (SCH900475) versus Docetaxel in Previously Treated Subjects with Non-Small Cell Lung Cancer (P010) (Category 3)* | *To compare the overall survival (OS) of previously-treated subjects with NSCLC in the strongly positive PD-L1 stratum treated with MK-3475 compared to docetaxel* | *-Important identified risks (Immune-related adverse reactions, Infusion-related reactions*<br>*-Important potential risks (Immune-related adverse events, Immunogenicity)*<br>*-Long term safety* | *Started* | *Final study report August 2019* |
| *Clinical trial A Randomized Open-Label Phase III Trial of Pembrolizumab versus Platinum based Chemotherapy in 1L Subjects with PD-L1 Strong Metastatic Non-Small Cell Lung Cancer (P024) (Category 3)* | *To compare the Progression Free Survival (PFS) per RECIST 1.1 as assessed by blinded independent central radiologists' review in subjects with PDL1 strong, 1L metastatic NSCLC treated with pembrolizumab compared to standard of* | *-Important identified risks (Immune-related adverse reactions, Infusion-related reactions)*<br>*-Important potential risks (Immune-related* | *Started* | *Final study report September 2018* |

| Activity / Study title (type of activity, study title, category 1-3)* | Objectives | Safety concerns addressed | Status Planned, started, | Date for submission of interim or final reports (planned or actual) |
|---|---|---|---|---|
| | *care (SOC) chemotherapies.* | *adverse events, Immunogenicity)*<br>*-Long term safety* | | |
| *Clinical trial A Randomized, Open Label, Phase III Study of Overall Survival Comparing Pembrolizumab (MK-3475) versus Platinum Based Chemotherapy in Treatment Naïve Subjects with PD-L1 Positive Advanced or Metastatic Non-Small Cell Lung Cancer (P042) (Category 3)* | *To compare the overall survival (OS) in subjects with PD-L1 strongly positive, 1L advanced/metastatic NSCLC treated with pembrolizumab compared to standard of care (SOC) chemotherapies.* | *-Important identified risks (Immune-related adverse reactions, Infusion-related reactions)*<br>*-Important potential risks (Immune-related adverse events, Immunogenicity)*<br>*-Long term safety* | *Started* | *Final study report December 2019* |
| *Clinical trial*<br>*A Phase I/II Study of Pembrolizumab (MK-3475) in Children with advanced melanoma or a PD-L1 positive advanced, relapsed or refractory solid tumor or lymphoma (P051) (Category 3)* | *To define the rate of dose-limiting toxicities (DLTs) at the maximum tolerated dose (MTD) or maximum administered dose (MAD) of pembrolizumab when administered as monotherapy to children from 6 months to < 18 years of age pooled across all indications including advanced melanoma or a PD-L1 positive advanced, relapsed or refractory solid tumor or lymphoma.* | *Important identified risks (Immune-related adverse reactions, Infusion-related reactions)*<br>*-Important potential risks (Immune-related adverse events)*<br>*-Safety in pediatric patients* | *Started* | *Final Study Report*<br>*July 2019* |

No changes to the PhV plan have been proposed as part of this extension of indication. The post-authorisation PhV development plan remains sufficient to identify and characterise the risks of the product.

## *Risk minimisation measures*

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| **Important Identified Risk** | | |
| Immune-related Pneumonitis | The risk of the immune-related adverse reaction of pneumonitis 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. | Educational materials |
| Immune-related Colitis | The risk of the immune-related adverse reaction of colitis 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. | Educational materials |
| Immune-related Hepatitis | The risk of the immune-related adverse reaction of hepatitis 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. | Educational materials |
| Immune-related Nephritis | The risk of the immune-related adverse reaction of nephritis 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. | Educational materials |
| Immune-related Endocrinopathies<br><br>-Hypophysitis (including hypopituitarism and secondary adrenal insufficiency)<br>- Thyroid Disorder ( Hypothyroidism, Hyperthyroidism, thyroiditis)<br>- Type 1 Diabetes Mellitus | The risk of the immune-related endocrinopathies [Hypophysitis (including hypopituitarism and secondary adrenal insufficiency); Thyroid Disorder ( Hypothyroidism, Hyperthyroidism, thyroiditis); Type 1 Diabetes Mellitus] associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4 and 4.8 and appropriate advice is provided to the prescriber to minimize the risk. | Educational materials |
| Other Immune-related adverse reactions | The risk of other immune-related adverse reactions (uveitis, myositis, | Educational materials |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| -Uveitis, Myositis, Pancreatitis, Severe Skin Reactions, Guillain-Barre Syndrome | pancreatitis, severe skin reactions, Guillain-Barre syndrome) associated with the use of pembrolizumab is described in the SmPC, Section 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk. | |
| Infusion-Related Reactions | The risk of infusion-related reactions 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. | Educational materials |
| **Important Potential Risk** | | |
| Gastrointestinal perforation secondary to colitis | The risk of the immune-related adverse event of gastrointestinal perforation secondary to colitis associated with the use of pembrolizumab is described in the SmPC, Section 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk. | None |
| Immunogenicity | The risk of immunogenicity associated with the use of pembrolizumab is described in the SmPC, Section 4.8. | None |
| **Missing Information** | | |
| Safety in patients with moderate or severe hepatic impairment and patients with severe renal impairment | The missing information of safety in these patients is described in the SmPC, Section 4.2, 4.4. | None |
| Safety in patients with active systemic autoimmune disease | The missing information of safety in patients with active systemic autoimmune disease is described in the SmPC, Section 4.4, 5.1 | None |
| Safety in patients with HIV or Hepatitis B or Hepatitis C | The missing information of safety in patients with patients with HIV or Hepatitis B or Hepatitis C is described in the SmPC, Section 4.4, 5.1. | None |
| Safety in Pediatric patients | The missing information of safety in pediatric patients is described in the SmPC, Section 4.2 | None |
| Reproductive and lactation data | Use during pregnancy and use in nursing mothers is described in the SmPC, Section 4.6, 5.3 | None |
| Long term safety | None | None |
| Safety in various ethnic groups | None | None |
| Potential pharmacodynamic interaction with systemic | The missing information of potential pharmacodynamic interaction with | None |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| immunosuppressants | systemic immunosuppressants is described in the SmPC, Section 4.4, 4.5 | |
| Safety in patients with previous hypersensitivity to another monoclonal antibody | The missing information of safety in patients with previous hypersensitivity to another monoclonal antibody is described in the SmPC, Section 4.4, 5.1 | None |
| Safety in patients with severe (grade 3) immune-related (ir)AEs on prior ipilimumab (ipi) requiring corticosteroids for > 12 weeks, or life-threatening irAEs on prior ipi, or with ongoing ipi-related AEs | The missing information of safety in patients with severe (grade 3) immune-related (ir)AEs on prior ipilimumab (ipi) requiring corticosteroids for > 12 weeks, or life-threatening irAEs on prior ipi, or with ongoing ipi-related AEs is described in the SmPC, Section 4.4, 5.1 | None |

The risk minimisation measures have not changed. The existing risk minimisation measures remain sufficient to minimise the risks of the product in the proposed indication.

## *2.7. Update of the Product information*

As a consequence of these new indications, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated and the Package Leaflet has been updated accordingly. Further, a change to section 4.4 of the SmPC adding possible hypersensitivity and anaphylaxis as part of infusion reactions, have been included.

### 2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant. Even though the justification can be considered in principle acceptable due to the limited changes to the package leaflet, since the readability test was performed several modification have been implemented based on variations.

The CHMP recommends an abridged testing of the current version of the package leaflet and Instruction for HPs should be performed with the next relevant submitted variation. This testing on package leaflet should be carried out with 5 participants (patients or caregivers) for each round (two); moreover, at least three HPs should be involved for an abridged test focused on the Instructions for preparation and administration and posology section. The relevant questions of the initial questionnaire should be used to reflect all amendments adequately.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

*KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior chemotherapy.*

The MAH agrees to revise the above indication taking into account that only patients previously treated with platinum-based chemotherapy were included in the pivotal trial (revised indication: *"KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who were previously treated with platinum-based chemotherapy".)*

*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.*

### 3.1.2. Available therapies and unmet medical need

Failing first-line platinum-based chemotherapy, the prognosis is compromised with a median OS reduced to 5 to 7 months (Bellmunt J, J Clin Oncol 2009). In this setting, there is no globally recognized standard of care. Vinflunine is the only drug approved in EU.

More than 50% of patients are unfit for cisplatin due to poor performance status, impaired renal function, or specific comorbidities. For these patients, NCCN Guidelines (version 2.2017) and ESMO Practice Guideline (Bellmunt J, Annals of Oncology 2014) recommend carboplatin-based regimens or single agent taxane or gemcitabine. A median OS of 9 months has been reported with the carboplatin/gemcitabine combination (De Santis M, J Clin Oncol 2012). In case of patients with PS ≥2 and poor renal function, the participation in clinical trials or BSC is recommended by ESMO guidelines.

### 3.1.3. Main clinical studies

Advanced or metastatic urothelial carcinoma progressing after prior chemotherapy

To support this indication, results of a phase III randomized (1:1) open-label clinical trial (KEYNOTE-045) of pembrolizumab versus Investigator's choice (paclitaxel, docetaxel or vinflunine) in 542 subjects with recurrent or metastatic urothelial carcinoma who experienced progression after a platinum-based regimen, enrolled regardless PD-L1 expression status were provided.

Previously untreated cisplatin-ineligible advanced/unresectable or metastatic urothelial carcinoma

To support this indication, results of a phase II single-arm clinical trial (KEYNOTE-052) of pembrolizumab in 370 cisplatin-ineligible subjects with locally advanced unresectable or metastatic urothelial carcinoma, enrolled regardless PD-L1 expression status were provided.

In order to provide information for contextualization of the results in cisplatin ineligible patients, the MAH conducted and provided a systematic literature review and meta-analysis.

## *3.2. Favourable effects*

Advanced or metastatic urothelial carcinoma progressing after prior chemotherapy

Overall, a statistically significant gain of 3 months in OS is reported in the overall population (HR:0.73, 95% CI 0.59, 0.91, p=0.002). The median OS in the chemotherapy arm (7.4 months, 95% CI 6.1, 8.3) is consistent with historical data from single-agent second line treatment. Consistently, a significant OS increase was observed in PD-L1 strongly positive patients treated with pembrolizumab compared to chemotherapy (HR:0.57, 95% CI 0.37, 0.88, p=0.004). In addition, even though p-value was not multiplicity-adjusted, results in PD-L1 positive patients showed a similar magnitude of OS benefit (HR:0.61, 95% CI 0.43, 0.86, p=0.002) compared to PD-L1 strongly positive. A prolonged time to deterioration in EORTC QLQ-C30 global health status/QoL was observed for patients treated with pembrolizumab compared to chemotherapy (HR 0.70; 95% CI 0.55-0.90) which remained at over 15 weeks of follow-up.

Previously untreated cisplatin-ineligible advanced/unresectable or metastatic urothelial carcinoma

An ORR of 24.1% (95% CI 19.8, 28.7) was reported in the overall population. In 282 PD-L1 positive patients ORR was 26.6% (95% CI 21.5, 32.2). When considering the subgroup of PD-L1 strongly positive patients from the validation cohort, a higher ORR of 38.8% (95% CI 28.1, 50.3) was reported.

Response rates improved with longer follow and responses remained durable (see efficacy results of updated analyses in effects tables below).

## *3.3. Uncertainties and limitations about favourable effects*

Advanced or metastatic urothelial carcinoma progressing after prior chemotherapy

An excess of deaths in the pembrolizumab arm was observed in the first two months (43 in pembrolizumab vs. 24 in control arm) leading to an initial favourable effect for the control arm in OS K-M curves, followed by a crossing around 3-4 months from the start of treatment. In this regard, liver metastases and time from most recent prior therapy of < 3 months were identified as possible factors associated to the higher risk of early death. Hence, a warning has been added in section 4.4 of the SmPC as follows: “Physicians should consider the delayed onset of pembrolizumab effect before initiating treatment in patients with poorer prognostic features and/or aggressive disease. In urothelial cancer, a higher number of deaths within 2 months were observed in pembrolizumab compared to chemotherapy (see section 5.1).”

Improvement in patient-reported outcomes by EORTC QLQ-C30 such as prolonged time to deterioration in EORTC QLQ-C30 global health status/QoL was observed for patients treated with pembrolizumab compared to investigator’s choice chemotherapy (HR 0.70; 95% CI 0.55-0.90) and its maintenance over 15 weeks of follow-up, was a significant result, however such results should be interpreted in the context of the open-label study design and therefore taken cautiously (See SmPC).

Previously untreated cisplatin-ineligible advanced/unresectable or metastatic urothelial carcinoma

Only data from an uncontrolled trial (KN052) were submitted to support this indication. A systematic review and meta-analysis of the literature was performed, however this systematic review presents some limitations. Taking into account the historical data in the target population, observed ORR data are not that compelling, even in the PD-L1 strongly positive cohort. Data on the median duration of response compare favourably, but are still immature. The same applies for time to event endpoints PFS and OS. Moreover the duration of follow-up is still insufficient. Efficacy updates will be provided with the final CSR (see RMP).

Unmet medical need is considered high in UC in general, but new therapies would be especially needed for cisplatin-ineligible and chemotherapy-ineligible patients; however these patients are not represented in the study population of KN-052, hence the following warning has been added in section 4.4 of the

SmPC: " The baseline and prognostic disease characteristics of the study population of KEYNOTE-052 included a proportion of patients eligible for a carboplatin-based combination or mono-chemotherapy. In the absence of comparative data, pembrolizumab should be used with caution in this population after careful consideration of the potential risk-benefit on an individual basis."

Results from the on-going randomized studies P045, P052 and P361 and are requested as part of a Post-Authorisation Efficacy Study (PAES).

## 3.4. Unfavourable effects

In patients previously treated with platinum-containing chemotherapy (study KN045), pembrolizumab favorably compares with chemotherapy in terms of drug-related AEs (60.9% vs 90.2%), Grade≥3 AEs (52.3% vs 62.7%), drug-related Grade≥3 AEs (15% vs 49.4%), serious drug-related AEs (10.2 vs 22.4%), treatment interruption due to drug-related AEs (10.5% vs 15.7%) and treatment discontinuation due to drug-related AEs (11% vs 5.6%). In terms of drug-related AEs, the most frequently observed events in the pembrolizumab arm were *Pruritus* (19.5%), *Fatigue* (13.9%) and *Nausea* (10.9%) while in the control arm patients mostly experienced *Alopecia* (37.6%), *Fatigue* (27.8%), *Anemia* (24.7%), *Nausea* (24.3%), *Constipation* (20.4%), *Decreased appetite* (16.1%), *Neutropenia* (15.3%), *Asthenia* (14.1%), *Neutrophil count decreased* (14.1%), *Diarrhea* (12.9%), *Peripheral sensory neuropathy* (11.0%), and *Neuropathy peripheral* (10.6%).

In UC patients treated with pembrolizumab, no major differences in the safety profile were observed despite prior treatment and eligibility to cisplatin in studies KN045 and KN052 and in comparison to the Reference Safety Dataset. In study KN052, consistently with the Reference Safety Dataset, the most commonly reported drug-related AEs were Fatigue (16.8% and 24.2%), Pruritus (14.6% and 16.7%) and *Rash* (9.7% and 13.8%).

One fatal case of myositis was reported in KN052. This is the first registered with pembrolizumab.

## 3.5. Uncertainties and limitations about unfavourable effects

A higher number of deaths within 2 months was observed in pembrolizumab compared to chemotherapy which was attributed to the delayed onset of effect of pembrolizumab; this factor should be considered before initiating treatment in patients with poorer prognostic features and/or aggressive disease (see SmPC section 4.4).

No safety and efficacy data are available in frailer patients (e.g., ECOG performance status 3) considered not eligible for chemotherapy. In the SmPC section 4.4 it is stated that 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.

Longer safety follow up is needed and will be provided with the final reports from studies 045 and 052. Additional safety information for pembrolizumab with or without Platinum-Based Combination Chemotherapy versus Chemotherapy in advanced or metastatic Urothelial Carcinoma, will be provided with the results of study P361.

## *3.6. Effects Table*

**Table 68**: Effects Table for Keytruda in the treatment of recurrent or progressive metastatic urothelial carcinoma previously treated with platinum-based chemotherapy (Study KEYNOTE-045; Cut-off date: 7 SEP 2016)

| Effect | Short Description | Unit | Treatment | Control | Uncertainties / Strength of evidence | Ref |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| **All population** | | | | | | |
| OS | Time from randomization to death due to any cause | months (95% CI) | 10.3 (8.0,11.8) | 7.4 (6.1, 8.3) | Significant gain in OS and a trend to PFS improvement after 6 months reported across population (all-comers, PD-L1 CPS ≥1% and PD-L1 CPS ≥10%).<br><br>Updated results (data Cut-off: 18 Jan2017):<br><br>Results based on PD-L1 expression (below and above the pre-specified cut-off of CPS 1% and 10%) did not show important differences in favourable effects. | |
| | | HR (95% CI) | 0.73 (0.59, 0.91) | | | |
| | | p-value | 0.002 | | | |
| PFS | time from randomization to documented PD (RECIST 1.1 by BICR) or death due to any cause, whichever occurred first | months (95% CI) | 2.1 (2.0,2.2) | 3.3 (2.3,3.5) | | |
| | | HR (95% CI) | 0.98 (0.81, 1.19) | | | |
| | | p-value | 0.416 | | | |
| | | | | | | |
| | | | | | | |
| **Unfavourable Effects** | | | | | | |
| Tolerability | drug related AEs | % | 60.9 | 90.2 | . | KN045 CSR |
| | drug related Gr≥3 AE | % | 15.0 | 49.4 | The Pembrolizumab safety profile favourably compared to that of chemotherapy and importantly differed in the most frequent types of AEs.<br><br>More frequent with pembrolizumab *Acute kidney injury* (5.6% vs 2.7%), *Haematuria* (11.3% vs 7.8%) and *Urinary tract infection* (14.7% vs 13.3%) | |
| | drug related SAEs | % | 10.2 | 22.4 | | |
| | death drug related | % | 1.6 | 1.6 | | |
| | discontinuation drug related AEs | % | 5.6 | 11.0 | | |
| | discontinuation drug related SAEs | % | 3.4 | 3.9 | | |
| Drug-related AEs | Pruritus | % | 19.5 | 2.7 | | |
| | Fatigue | % | 13.9 | 27.8 | | |
| | Nausea | % | 10.9 | 24.3 | | |
| | Alopecia | % | 37.6 | 0.0 | | |
| | Anemia | % | 24.7 | 3.4 | | |
| | Constipation | % | 2.3 | 20.4 | | |
| | Diarrhoea | % | 9.0 | 12.9 | | |

**Table 69**: Effects Table for Keytruda in the treatment of advanced/unresectable or metastatic urothelial carcinoma previously untreated with systemic chemotherapy and not eligible to cisplatin. (Study KEYNOTE-052; Cut-off date: 1 SEP 2016)

| Effect | Short Description | Unit | Treatment | Uncertainties / Strength of evidence | Ref. |
|---|---|---|---|---|---|
| **Favourable Effects** | | | | | |
| **All Population** | | | | | |
| ORR | Proportion of patients with a CR or PR | % (95% CI) | 24.1 (19.8, 28.7)<br><br>CR 4.6 (2.7, 7.3) | Updated results (data Cut-off: 09Mar2017):<br><br>ORR: 29.2% (24.6, 34.1)<br>CR: 7.3% (4.9, 10.4)<br>DOR: Not reached (1.4+,19.6+)<br>ORR: 29.2% (24.6, 34.1) ) | |
| DOR | Time from the first CR/PR to documented PD<br><br>*% at 6 months* | months (95% CI) | Not reached (1.0+, 13.6+) | Demonstration of efficacy based on a single non-randomized study. Duration of follow up still insufficient to fully evaluate clinical benefit. ORR not clearly outstanding. However, DOR superior to historical chemotherapy | |
| **Unfavourable Effects** | | | | | |
| Tolerability | drug related AEs | % | 61.9 | Safety profile is in line with that reported in KN045 and in the reference melanoma and NSCLC population.<br><br>One *Myositis* fatal case was reported. | KN052 CSR |
| | drug related Gr≥3 AE | % | 15.7 | | |
| | drug related SAEs | % | 9.7 | | |
| | death drug related | % | 0.3 | | |
| | discontinuation drug related AEs | % | 5.1 | | |
| | discontinuation drug related SAEs | % | 3.8 | | |
| Drug-related AEs | Fatigue | % | 16.8 | | |
| | Pruritus | % | 14.6 | | |
| | Rash | % | 9.7 | | |

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

Advanced or metastatic urothelial carcinoma progressing after prior chemotherapy

Pembrolizumab favorably compares with chemotherapy in terms of drug-related AEs (60.9% vs 90.2%), Grade≥3 AEs (52.3% vs 62.7%), drug-related Grade≥3 AEs (15% vs 49.4%), serious drug-related AEs (10.2 vs 22.4%), treatment interruption due to drug-related AEs (10.5% vs 15.7%) and treatment discontinuation due to drug-related AEs (11% vs 5.6%). No major differences in the safety profile were observed in comparison to the Reference Safety Dataset.

Previously untreated cisplatin-ineligible advanced/unresectable or metastatic urothelial carcinoma

The effect observed in terms ORR in the uncontrolled trial KN052 is not outstanding compared to historical data in the target population, even in the PD-L1 strongly positive cohort. Data on the median Duration of Response and other time to event endpoints PFS and OS are still immature to draw sound conclusions.

The safety profile observed in cisplatin ineligible UC patients was consistent to that observed in study KN045, and no new safety signals emerged compared to the Reference Safety Dataset.

### 3.7.2. Balance of benefits and risks

Advanced or metastatic urothelial carcinoma progressing after prior chemotherapy

Based on OS results from study KN045, a benefit is claimed in the overall population. However, patients' characteristics influencing a higher risk of early death during treatment need to be further discussed, in order to include detailed information in the product SmPC.

The safety profile in the UC patient population does not significantly differ from the well-known limited risks associated with pembrolizumab therapy, far more manageable and less impacting on patients' quality of life than those associated with chemotherapy.

Previously untreated cisplatin-ineligible advanced/unresectable or metastatic urothelial carcinoma

However, duration of responses is clearly superior and OS compares rather favourable to those achieved by chemotherapy in the submitted meta-analysis.

The safety profile in the sought indication does not raise new concerns and seems to favorably compare to chemotherapy.

### 3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

## *3.8. Conclusions*

Based on the totality of the evidence, the benefit-risk balance of the use of pembrolizumab in 2nd line UC and in 1st line cisplatin-ineligible UC **is considered positive.**

# 4. Recommendations

## *Outcome*

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends by a majority of 24 out of 28 votes, the variations to the terms of the Marketing Authorisation, concerning the following changes:

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

Extension of Indication to add treatment as monotherapy of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy based on the results from study KEYNOTE-045; a phase 3, randomized, active-controlled, multi-site, open-label trial evaluating pembrolizumab administered at 200 mg Q3W versus investigators' choice of paclitaxel, docetaxel, or vinflunine in patients previously treated with chemotherapy.

Extension of Indication to add treatment as monotherapy of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy based on the results from study KEYNOTE-52; a phase 2, single-arm, multisite, open-label trial of pembrolizumab at 200 mg Q3W in the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy.

As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated and the Package Leaflet has been updated accordingly.

Further, the MAH is taking the opportunity to implement a change to section 4.4 of the SmPC adding possible hypersensitivity and anaphylaxis as part of infusion reactions

In addition, Annex II has been updated to include new Post-authorisation efficacy studies (PAES) as obligations under 'conditions or restrictions with regard to the safe and effective use of the medicinal product'.

An updated RMP version 7.2 was agreed during the procedure.

This recommendation is subject to the following new conditions:

## *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:

| | |
|---|---|
| 5. Post-authorisation efficacy study (PAES): In order to further evaluate the efficacy of Pembrolizumab versus Paclitaxel, Docetaxel or Vinflunine in Subjects with Recurrent or Progressive Metastatic Urothelial Cancer, the MAH should conduct and submit the results of study P045 | 3Q 2018 |
| 6 Post-authorisation efficacy study (PAES): In order to further evaluate the efficacy of Pembrolizumab in patients with Advanced/Unresectable or Metastatic Urothelial Cancer, the MAH should conduct and submit the final results of study P052 | 2Q 2019 |
| 7. Post-authorisation efficacy study (PAES): In order to further evaluate the efficacy of Pembrolizumab with or without Platinum-Based Combination Chemotherapy versus Chemotherapy in Subjects with Advanced or Metastatic Urothelial Carcinoma, the MAH should conduct and submit the results of study P361 | 2Q 2019 |

The recommendation is also subject to the following modified condition:

### *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:

| | |
|---|---|
| 4. The value of biomarkers to predict the efficacy of pembrolizumab should be further explored, specifically:<br><br>Additional biomarkers other than PD-L1 expression status by Immunohistochemistry (IHC) (e.g. PD-L2, RNA signature, etc.) predictive of pembrolizumab efficacy should be investigated together with more information regarding the pattern of expression of PD-L1 obtained in the ongoing NSCLC studies (P001, P010, P024 and P042)<br>and urothelial carcinoma studies (KN045, KN052):<br>• Data on the Nanostring RNA gene signature<br>• IHC staining for PD-L2<br>• Data on RNA and proteomic serum profiling | 2Q 2020<br>2Q 2019 |

Divergent positions to the majority recommendation are appended to this report.

# APPENDIX 1

**Divergent position dated 20.07.2017**

DIVERGENT POSITION DATED 20 July 2017

Keytruda EMEA/H/C/003820/II/23/G

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the extension of the indication for Keytruda (pembrolizumab) in the 1st-line cisplatin-ineligible urothelial carcinoma (UC) for the following reasons:

- Current evidence on efficacy and safety in first-line cisplatin-ineligible patients only comprises a single-arm study, i.e. KEYNOTE-052. Upon indirect comparison of the Keytruda results obtained the first-line cisplatin-ineligible urothelial carcinoma population to control (i.e. gemcitabine-carboplatin) chemotherapy), the primary endpoint ORR results are not compelling and PFS compares unfavourably. Depending on the source of information, the OS of Keytruda compares either unfavourably or is suggested being similar. DoR is still immature. Moreover, the lack of direct comparative efficacy data with first line agents precludes a determination of the extent of any potential "loss of chance", in particular for the patients who do not respond to Keytruda.

  It is acknowledged that safety seems to be more favourable when compared to chemotherapy.

- In conclusion, we consider that in the 1st-line cisplatin-ineligible UC population the results obtained with Keytruda are on itself not convincing and accompanied with large uncertainties associated with the single, non-comparative study design and a limited duration of follow-up. The current evidence is not compelling enough to support a positive B/R and, as a consequence, considered insufficient for approval.

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Alexandre Moreau (FR)

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Romaldas Maciulaitis (LT)

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Johann Lodewijk Hillege (NL)

…….
Sinan B.Sarac (DK)

…….
Svein Rune Anderson (NO)