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Horizon Scanning in Oncology

Pembrolizumab (Keytruda®) as second-line treatment for patients with advanced urothelial carcinoma (UC)

Ludwig Boltzmann Institut
Health Technology Assessment

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Health Technology Assessment

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Abstract

Introduction

Urothelial carcinoma (UC) is a malignant tumour, derived from the transitional epithelium (urothelium), which most commonly forms in the bladder, but can also arise in the upper urinary tract. Recently, pembrolizumab (Keytruda®) was approved for the treatment of patients with locally advanced or metastatic UC following platinum-containing chemotherapy by the Food and Drug Administration (FDA). Pembrolizumab is a humanised monoclonal immunoglobulin (Ig) G4 antibody that blocks the interaction between the transmembrane programmed cell death-1 (PD-1) protein and its ligands. Thus, pembrolizumab potentiates T-cell responses, including anti-tumour responses and cancer-specific T-cells.

Methodology

Published and grey literature were identified by searching the Cochrane Library, CRD Database, Embase, Ovid Medline, PubMed, Internet sites and contacting the manufacturer. To assess the risk of bias at the study level, the assessment of the methodological quality of the evidence was conducted based on the EUnetHTA internal validity for randomised controlled trials. Furthermore, to stratify the magnitude of clinical benefit that can be expected from pembrolizumab, the original as well as an adapted version of the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology was used.

Results of the KEYNOTE-045 trial

Between 5 November 2014 and 13 November 2015, 542 patients were randomly assigned to receive either pembrolizumab (n = 270) or investigator's choice of chemotherapy (n = 272). After the early termination of the trial (second interim analysis), the co-primary endpoint overall survival (OS) was statistically significantly longer in the total as well as in the PD-L1 ≥10% population; with a gain in median OS of 2.9 and 2.8 months in the total and PD-L1 ≥10% population, respectively. Moreover, the objective response rate (ORR) was also statistically significantly higher in the pembrolizumab group; however, the duration of progression-free survival (PFS) did not differ between treatment groups. Treatment-related adverse events (AEs) of any grade, as well as of grades 3–5, were more common in control group. The most frequent treatment-related AEs of any grade in the pembrolizumab arm were pruritus, fatigue and nausea. However, patient-reported outcomes, like quality of life (QoL), are only available in abstract form.

Conclusion

Overall, the treatment with pembrolizumab offers a statistically significant improvement in OS, independent of the PD-L1 status, with a superior safety profile compared to chemotherapy at high costs. However, due to the early termination of the trial, a systematic overestimation of the treatment effect of pembrolizumab is possible, leading to a need of long-term data. In addition, the identification of a robust predictive biomarker to identify the most suitable patients will be crucial in the future. Finally, head-to-head comparison trials comparing pembrolizumab to nivolumab and atezolizumab are essential to investigate which second-line treatment option UC patients benefit the most from.

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1 Research questions

The HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals was used for structuring this report [1]. The Model organises HTA information according to pre-defined generic research questions. Based on these generic questions, the following research questions were answered in the assessment.

EUnetHTA HTA Core Model®

Element ID	Research question
Description of the technology	
B0001	What is pembrolizumab?
A0022	Who manufactures pembrolizumab?
A0007	What is the target population in this assessment?
A0020	For which indications has pembrolizumab received marketing authorisation?
Health problem and current use	
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A0006	What are the consequences of urothelial carcinoma for the society?
A0023	How many people belong to the target population?
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A0021	What is the reimbursement status of pembrolizumab?

2 Drug description

Generic/Brand name/ATC code:

Pembrolizumab/Keytruda®/L01XC18

B0001: What is pembrolizumab?

humanised monoclonal IgG4 antibody

Pembrolizumab is a humanised monoclonal immunoglobulin (Ig) G4 antibody that blocks the interaction between the transmembrane programmed cell death-1 (PD-1) protein, which is expressed on the cell surface of activated T-cells, and its ligands PD-L1 and PD-L2 [2-5]. The PD-1 receptor, a negative T-cell activity regulator, has been shown to be involved in the control of T-cell immune responses. By blocking the interaction of PD-1 and its ligands, pembrolizumab potentiates T-cell responses, including anti-tumour responses and cancer-specific T-cells [3, 5].

administration as an intravenous infusion every 3 weeks

Pembrolizumab should be administered as an intravenous infusion over 30 minutes every three weeks. In clinical trials investigating urothelial carcinoma patients, 200 mg of pembrolizumab were administered intravenously every three weeks until disease progression or unacceptable toxicity [6]. For other indications the recommended dose for non-small cell lung cancer (NSCLC) that has not been previously treated with chemotherapy is 200 mg. For NSCLC patients who received prior chemotherapy, as well as for melanoma patients, the recommend dose is 2 mg/kg [3].

A0022: Who manufactures pembrolizumab?

Merck Sharp & Dohme Corp.

3 Indication

A0007: What is the target population in this assessment?

2nd-line treatment of patients with advanced UC

Pembrolizumab is indicated for the second-line treatment of patients with advanced UC of the renal pelvis, ureter, bladder, or urethra that has recurred or progressed following platinum-based chemotherapy.

4 Current regulatory status

A0020: For which indications has pembrolizumab received marketing authorisation?

not approved for UC by the EMA, but for several other indications

To date, pembrolizumab is not approved for the second-line treatment of patients with UC by the European Medicines Agency (EMA). However, the EMA granted marketing authorisation of pembrolizumab for the following indications [3]:

- as monotherapy for the treatment of patients with advanced unresectable or metastatic melanoma (July 2015)
- for the treatment of locally advanced or metastatic NSCLC patients, whose tumours express PD-L1, and who have received at least one prior chemotherapy regimen (July 2016)
- as monotherapy for the first-line treatment of metastatic NSCLC patients, whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutation (January 2017)
- as monotherapy for the treatment of patients with relapsed or refractory classical Hodgkin lymphoma (cHL), who have failed autologous stem cell transplant and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV (March 2017)

FDA approval for UC since May 2017

In May 2017, the US Food and Drug Administration (FDA) approved pembrolizumab for the treatment of locally advanced or metastatic UC patients, who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. Furthermore, the FDA also granted accelerated approval to pembrolizumab for the treatment of patients with locally advanced or metastatic UC, who are not eligible for cisplatin-containing chemotherapy [7].

FDA approved indications of pembrolizumab

Moreover, pembrolizumab has also received marketing authorisation by the FDA for the following indications [7]:

- for the treatment of patients with unresectable or metastatic melanoma (September 2014)
- for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma with disease progression on or after platinum-containing chemotherapy (August 2016)
- for the treatment of patients with metastatic NSCLC
  - whose tumours have high PD-L1 expression (≥50% TPS) with no EGFR and ALK genomic tumour aberration, as a first-line therapy (October 2016)
  - whose tumours express PD-L1 (TPS ≥1%) with disease progression on or after platinum-containing chemotherapy (October 2016)
  - as a first-line therapy in combination with pemetrexed and carboplatin for non-squamous NSCLC (May 2017)

- for the treatment of patients with refractory cHL, or those who have relapsed after three or more prior lines of therapy (March 2017)

5 Burden of disease

A0002: What is urothelial carcinoma?

most common form of UC is bladder cancer

The majority of cancers that form in the bladder, the renal pelvises, the ureters, and the proximal urethra are UCs (also known as transitional cell carcinomas) that arise from the transitional epithelium (urothelium). UC is the predominant histologic type of all diagnosed bladder cancers in the United States and in Europe, where it accounts for about 90% of all bladder cancer cases. Therefore, the following information will focus on urothelial bladder cancer [8-10].

A0004: What is the natural course of urothelial carcinoma?

variable course of disease: high- or low-grade, muscle-invasive or non-muscle-invasive bladder cancer

UC of the bladder can either be low-grade or high-grade. In respect of low-grade, bladder cancer recurrence after respective treatment often occurs, but it rarely invades the muscular wall of the bladder or spreads to other parts of the body. High-grade bladder cancer frequently recurs, has a high tendency to invade the muscular wall of the bladder and can spread to other parts of the body. Based on the invasion of the muscularis propria (detrusor muscle), a muscle of the bladder wall, bladder cancer can also be divided into muscle-invasive and non-muscle-invasive disease [9].

A0006: What are the consequences of urothelial carcinoma for the society?

increasing incidence of cancer

Due to the aging population and in combination with the fact that higher age is a main risk factor for cancer, the incidence of cancer is increasing over time [11]. Globally, UC of the bladder is the most frequent malignancy involving the urinary system and the ninth most common malignancy worldwide [12]. However, incidence rates are also influenced by risk factor prevalence of past years. Since cigarette smoking is one of the most important risk factors, a decrease in the cigarette smoking rate may also impact the incidence rate of bladder cancer [13].

cigarette smoking rates influence bladder incidence rate

A0023: How many people belong to the target population?

incidence rate of bladder cancer in Austria: 17.3 per 100,000 persons/year

In Austria, 1,427 new cases of bladder cancer were diagnosed in 2014 with a corresponding age standardised incidence rate for the European Standard Population of 17.3 cases per 100,000 persons. Moreover, around 65.0% of female bladder cancer patients (7.1/100,000/year) and 71.0% of male bladder cancer patients (31.6/100,000/year) are alive at least five years after diagnosis. About two-thirds of all diagnosed cases in Austria are identified in a localised tumour stage, whereas metastatic disease at the time of diagnosis accounts for about 4.0% of patients. In addition, men have higher incidence and mortality rates; 70.5% of deaths and 76.4% of newly diagnosed cases oc-

curred in men [14]. The median age at diagnosis of bladder cancer is 69 years in men and 71 in women [12].

A0005: What are the symptoms and the burden of urothelial carcinoma?

most common presentation: gross or microscopic haematuria

In the majority of patients with UC of the bladder, gross or microscopic haematuria is present. Symptoms like urinary frequency, nocturia, urgency and dysuria can occur less often. These presentations are more common in patients with carcinomas in situ [9]. Patients with upper urinary tract UCs may show pain symptoms due to the obstruction by the tumour [9, 15].

A0003: What are the known risk factors for urothelial carcinoma?

main risk factors: occupational carcinogen exposures & cigarette smoking

Several risk factors have been identified for UC of the bladder. The most important risk factors are cigarette smoking and various occupational carcinogen exposures [12]. Other risk factors include: age, family history of bladder cancer and genetic mutations (men are more often affected than women) [9].

A0024: How is urothelial carcinoma currently diagnosed according to published guidelines and in practice?

gold standard for the initial diagnosis: cystoscopy

The gold standard for the initial diagnosis of UC of the bladder is cystoscopy in combination with urine cytology to detect lesions of the upper urinary tract (ureter or renal pelvis) [9, 15]. To identify papillary and carcinoma in situ lesions, novel endoscopic imaging techniques like narrow-band imaging and fluorescence cystoscopy may be applied. To assess the depth of invasion (mucosa, submucosa and muscularis) and the histologic grade, initial staging either using biopsy or transurethral resection of the bladder tumour (TURBT), combined with a pelvic examination under anaesthesia, is required. To rule out secondary tumours imaging of the upper urinary tract by computed tomography, magnetic resonance imaging with intravenous contrast or retrograde ureter pyelography are performed [15].

TNM system incorporates the depth of invasion of the primary tumour

Since the depth of invasion (T = depth of invasion of the primary tumour) for patients with disease limited to the bladder is the most important prognostic variable, it is integrated into the standard staging system, the tumour, node, metastasis (TNM) system [16]:

- Ta: papillary (exophytic) lesions
- Tis (carcinoma in situ): high-grade intraepithelial neoplasm without invasion into subepithelial connective tissue
- T1: invasion of the submucosa or lamina propria (usually high grade)
- T2: invasion into muscle (increased probability of nodal and distant metastases)
- T3: extension beyond muscle into the perivesical fat.
- T4: extension into adjacent organs; tumours invading the prostate, vagina, uterus, or bowel are classified as T4a, while tumours fixed to the abdominal wall, pelvic wall, or other organs are classified as T4b

6 Current treatment

A0025: How is urothelial carcinoma currently managed according to published guidelines and in practice?

mainstay of treatment of muscle-invasive urothelial bladder cancer: radical cystectomy

Muscle-invasive urothelial bladder cancer is generally treated by radical cystectomy, removal of the bladder and/or adjacent organs and/or regional lymph nodes, accompanied with neoadjuvant and/or adjuvant cisplatin-based combination chemotherapy. Combined-modality approaches, like maximal TURBT, radiation therapy, and concurrent chemotherapy are options for patients who are not candidates for radical cystectomy [15, 17, 18].

standard 1st-line treatment options: platinum-based chemotherapy

First-line platinum-based chemotherapy (e.g., gemcitabine plus cisplatin or a combination of methotrexate, vinblastine, doxorubicin, and cisplatin) is the preferred initial approach for systemic therapy in patients with metastatic UC of the bladder and urinary tract. The particular chemotherapy regimen depends on the presence or absences of medical comorbidities (e.g., renal impairment) of the patient. Thus, non-cisplatin-containing regimens (e.g., gemcitabine, carboplatin) may be considered in patients with comorbidities [15, 17, 18].

2nd-line treatment options: platinum-based chemotherapy, gemcitabine and/or paclitaxel, vinflunine

Current second-line treatment options include vinflunine, gemcitabine and/or paclitaxel, or a re-challenge with a platinum-based chemotherapy [17]. Three checkpoint inhibitors – nivolumab, atezolizumab and pembrolizumab – were recently approved by the FDA for the treatment of patients with locally advanced or metastatic UC, who have disease progression during or following platinum-containing chemotherapy [15]. However, they have not yet received marketing authorisation for this indication in Europe.

7 Evidence

systematic literature search in 5 databases: 63 hits

A literature search was conducted on 15 May 2017 in five databases: the Cochrane Library, CRD Database, Embase, Ovid Medline and PubMed. Search terms were “pembrolizumab”, “keytruda”, “urothelial cancer”, “urothelial carcinoma”, “bladder cancer” and “transitional cell carcinoma”. The manufacturer was also contacted and submitted six references (three of which had already been identified by systematic literature search). A manual search identified 28 additional references (web documents and journal articles).

manual search: 28 additional references

overall: 91 references included: 2 studies

Overall, 91 references were identified. Included in this reported are:

- KEYNOTE-045, phase III [6, 19]
- KEYNOTE-012, phase Ib [20]

study level risk of bias assessed based on EUnetHTA internal validity for RCTs

To assess the risk of bias at the study level, the assessment of the methodological quality of the evidence was conducted based on the EUnetHTA internal validity for randomised controlled trials (RCTs) [21]. Evidence was assessed based on the adequate generation of the randomisation sequence, allocation concealment, blinding of patient and treating physician, selective

outcome reporting and other aspects that may increase the risk of bias. Study quality details are reported in Table 5 of the Appendix.

magnitude of clinically meaningful benefit assessed based on ESMO-MCBS

To evaluate the magnitude of "clinically meaningful benefit" that can be expected from a new anti-cancer treatment, the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology (ESMO-MCBS) was used [22]. Additionally, an adapted version (due to perceived limitations) of the ESMO-MCBS was applied [23]. Details of the magnitude of the clinically meaningful benefit scale are reported in Table 3.

7.1 Clinical efficacy and safety – Phase III studies

KEYNOTE-045: open-label, randomised, international, phase III study

KEYNOTE-045 [6, 19], an open-label, international, randomised phase III study, was conducted to assess the efficacy and safety of pembrolizumab in patients with UC (renal pelvis, ureter, bladder or urethra) that has recurred or progressed following platinum-based chemotherapy. A total of 542 patients were randomly assigned in a 1:1 ratio to receive either pembrolizumab (n = 270, 200 mg) or the investigator's choice of chemotherapy (n = 272), paclitaxel (175 mg/m^2), docetaxel (75 mg/m^2) or vinflunine (320 mg/m^2) every three weeks. The stratification of randomisation was based on the Eastern Cooperative Oncology Group (ECOG) performance-status score (0 or 1 versus 2), the presence of liver metastases (yes versus no), haemoglobin concentration (<10 g per decilitre versus ≥10 g per decilitre), and time since the last dose of chemotherapy (<3 months versus ≥3 months). Of the 542 randomised patients, 266 patients in the pembrolizumab group and 255 in the chemotherapy group received assigned treatment.

early termination after the second interim analysis

The study consisted of two pre-specified interim analyses and was prematurely terminated after the second interim analysis (October 2016), because pembrolizumab met the superiority thresholds for overall survival (OS) in the co-primary populations. The second interim analysis was performed after 334 deaths had occurred in the total population and 104 deaths had occurred in the population of patients with a tumour PD-L1 combined positive score of ≥10% (PD-L1 ≥10% population) assessed by the PD-L1 IHC 22C3 pharmDx assay (Dako North America).

median age of 67 years in the pembrolizumab group

ECOG performance status of 0–2

Enrolled patients had a median age of 67 (29–88) and 65 (26–84) years in the pembrolizumab and chemotherapy group, respectively. The study population had an ECOG performance status of 0–2 and had at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1. Detailed patient characteristics, including inclusion and exclusion criteria, are reported in Table 4.

co-primary endpoints: OS & PFS

The co-primary outcomes of KEYNOTE-045 were OS and progression-free survival (PFS); secondary outcomes included objective response rate (ORR), the duration of confirmed response (DOR), and safety (total population). Adverse events (AEs) were assessed in conformity with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 4.0).

7.1.1 Clinical efficacy

D0001: What is the expected beneficial effect of pembrolizumab on mortality?

median OS gain: 2.9 months

At the time of second interim analysis (7 September 2016), 334 deaths had occurred in the intention-to-treat population. In the total population the median OS was 10.3 months (95% CI 8.0–11.8) in the pembrolizumab group and 7.4 months (95% CI 6.1–8.3) in the chemotherapy group. OS was statistically significantly longer in the pembrolizumab group (hazard ratio [HR] for death, 0.73; 95% CI 0.59-0.91; p = 0.002). The estimated overall survival rate at 12 months was 43.9% (95% CI 37.8–49.9) and 30.7% (95% CI 25.0-36.7) in the pembrolizumab and chemotherapy group, respectively.

statistically significantly longer OS in the PD-L1 ≥10% population

In the PD-L1 ≥10% population OS was statistically significantly longer in the pembrolizumab group (HR for death, 0.57; 95% CI 0.37–0.88; p = 0.005). The median OS was 8.0 months (95% CI 5.0–12.3) in the pembrolizumab group compared to 5.2 months (95% CI 4.0–7.4) in the chemotherapy group.

D0006: How does pembrolizumab affect progression (or recurrence) of urothelial carcinoma?

no statistically significant difference in the duration of PFS

437 events of disease progression or death have occurred in the intention-to-treat population at the time of the second interim analysis. The median PFS was 2.1 months (95% CI 2.0–2.2) and 3.3 months (95% CI 2.3–3.5) in the pembrolizumab and chemotherapy group, respectively. There was no statistically significant difference in the duration of PFS between the two study groups, neither in the total population (HR for death or disease progression, 0.98; 95% CI 0.81–1.19; p = 0.42) nor in the PD-L1 ≥10% population (HR, 0.89; 95% CI 0.61–1.28; p = 0.24). The estimated PFS rate at 12 months was 16.8% (95% CI 12.3-22.0) in the pembrolizumab group compared to 6.2% (95% CI 3.3-10.2) in the chemotherapy group.

D0005: How does pembrolizumab affect symptoms and findings (severity, frequency) of urothelial carcinoma?

statistically significant difference in ORR

ORR gain: 9.7%

The ORR was statistically significantly higher in the pembrolizumab group compared to the chemotherapy group, 21.1% (95% CI 16.4–26.5) versus 11.4% (95% CI 7.9–15.8), (p = 0.001). In both study groups the median time to response was 2.1 months. At the time of the second interim analysis, 41 of 57 patients (72.0%) showed a continued response in the pembrolizumab group and 11 of 31 patients (35.0%) had a continued response in the chemotherapy group. In the pembrolizumab group the median duration of response (DOR) was not reached, while in the chemotherapy group it was 4.3 months. The estimated DOR of at least 12 months was 68.0% of patients in the pembrolizumab group and 35.0% in the chemotherapy group.

D0011: What is the effect of pembrolizumab on patients'body functions?

immune-mediated AEs, potential immunogenicity

Pembrolizumab may affect body functions by causing immune-mediated AEs including pneumonitis, hepatitis, colitis, endocrinopathies, nephritis and renal dysfunction. In addition, since pembrolizumab is a therapeutic protein, there is a potential for immunogenicity [7].

D0012: What is the effect of pembrolizumab on generic health-related quality of life?

D0013: What is the effect of pembrolizumab on disease-specific quality of life?

results on QoL only available in abstract form

Currently, quality of life (QoL) data is only available in abstract form [24]. Pembrolizumab was associated with a consistently better health-related quality of life compared to the investigator's choice of paclitaxel, docetaxel, or vinflunine. The global health status was similar between the arms. Regarding time to deterioration in the global health status, a prolonged score with pembrolizumab compared to chemotherapy was shown (HR 0.70, p = 0.002).

Table 1: Efficacy results of the KEYNOTE-045 trial

Descriptive statistics and estimated variability	**Treatment group**	**Pembrolizumab**	**Chemotherapy**
	Number of subjects	270	272
	Median OS, months (95% CI)	10.3 (8.0–11.8)	7.4 (6.1–8.3)
	Median OS (PD-L1 ≥10%), months (95% CI)	8.0 (5.0–12.3)	5.2 (4.0–7.4)
	Median PFS, months (95% CI)	2.1 (2.0–2.2)	3.3 (2.3–3.5)
	ORR, % (95% CI)	21.1 (16.4–26.5)	11.4 (7.9–15.8)
	Median DOR, months	NR	4.3
	QoL	NA	NA
Effect estimate per comparison	**Comparison groups**		**Pembrolizumab vs. Chemotherapy**
	OS	HR	0.73
		95% CI	0.59–0.91
		Log-rank test p value	0.002
	OS (PD-L1 ≥10%)	HR	0.57
		95% CI	0.37–0.88
		Log-rank test p value	0.005
	PFS	HR	0.98
		95% CI	0.81–1.19
		Log-rank test p value	0.42

Abbreviations: CI = confidence interval, HR = hazard ratio, DOR = duration of response, NA = not available, NR = not reached, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, QoL = quality of life

7.1.2 Safety

C0008: How safe is pembrolizumab in relation to the comparator(s)?

any grade AEs

pembrolizumab: 60.9%
chemotherapy: 90.2%

AEs of any grade related to treatment were reported from 60.9% (pembrolizumab) and 90.2% (chemotherapy) of the patients. The most frequent treatment-related AEs of any grade were pruritus (19.5%), fatigue (13.9%) and nausea (10.9%) in the pembrolizumab group and alopecia (37.6%), fatigue (27.8%) and anaemia (24.7%) in the chemotherapy group.

grade 3-5 AEs

pembrolizumab: 15.0%
chemotherapy: 49.4%

Grade ≥3 treatment-related events occurred less frequently in the pembrolizumab group compared to the chemotherapy group (15.0% versus 49.4% of patients), as well as treatment-related discontinuation, 5.6% versus 11.0%. In the pembrolizumab group, no treatment-related AEs of grade 3 or higher have occurred with an incidence of ≥5%. The most common treatment-related grade ≥3 AEs, with an incidence of ≥5% in the chemotherapy group, were neutropenia (13.3%), decreased neutrophil count (12.2%), anaemia (7.8%), febrile neutropenia (7.1%), and decreased white-cell count (5.1%).

4 treatment-related deaths in the pembrolizumab group

In total, eight deaths were attributed to either chemotherapy or pembrolizumab. Out of those eight deaths, four occurred in the pembrolizumab group either due to pneumonitis, a urinary tract obstruction, a malignant neoplasm progression, or an unspecified cause.

C0002: Are the harms related to dosage or frequency of applying pembrolizumab?

No evidence was found to answer this research question.

C0005: What are the susceptible patient groups that are more likely to be harmed through the use of pembrolizumab?

pregnant or breast-feeding women susceptible, due to potential foetal harm and impaired fertility

Pembrolizumab may impair fertility and cause foetal harm, resulting in major birth defects or miscarriages, due to its mechanism of action. It is advised that females use effective contraception during the treatment with pembrolizumab and discontinue breast feeding for at least four months following the final dosage [7].

Table 2: Most frequent treatment-related adverse events[1]

Adverse event (according to NCI-CTC version 4.0)	**Pembrolizumab** (n = 266)		**Chemotherapy group** (n = 255)	
	Any grade n (%)	Grade ≥3 n (%)	Any grade n (%)	Grade ≥3 n (%)
Treatment-related event				
Any event	162 (60.9)	40 (15.0)	230 (90.2)	126 (49.4)
Event leading to discontinuation of treatment	15 (5.6)	12 (4.5)	28 (11.0)	16 (6.3)
Event leading to death	4 (1.5)	4 (1.5)	4 (1.6)	4 (1.6)
Event occurring in ≥10% of patients in either group				
Pruritus	52 (19.5)	0 (0)	7 (2.7)	1 (0.4)
Fatigue	37 (13.9)	3 (1.1)	71 (27.8)	11 (4.3)
Nausea	29 (10.9)	1 (0.4)	62 (24.3)	4 (1.6)
Diarrhoea	24 (9.0)	3 (1.1)	33 (12.9)	2 (0.8)
Decreased appetite	23 (8.6)	0 (0)	41 (16.1)	3 (1.2)
Asthenia	15 (5.6)	1 (0.4)	36 (14.1)	7 (2.7)
Anaemia	9 (3.4)	2 (0.8)	63 (24.7)	20 (7.8)
Constipation	6 (2.3)	0 (0)	52 (20.4)	8 (3.1)
Peripheral sensory neuropathy	2 (0.8)	0 (0)	28 (11.0)	5 (2.0)
Neutrophil count decreased	1 (0.4)	1 (0.4)	36 (14.1)	31 (12.2)
Peripheral neuropathy	1 (0.4)	0 (0)	27 (10.6)	2 (0.8)
Neutropenia	0 (0)	0 (0)	39 (15.3)	34 (13.3)
Alopecia	0 (0)	0 (0)	96 (37.6)	2 (0.8)
Event of interest				
Any event	45 (16.9)	12 (4.5)	19 (7.5)	4 (1.6)
Hypothyroidism	17 (6.4)	0 (0)	3 (1.2)	0 (0)
Hyperthyroidism	10 (3.8)	0 (0)	1 (0.4)	0 (0)
Pneumonitis	11 (4.1)	6 (2.3)	1 (0.4)	0 (0)
Colitis	6 (2.3)	3 (1.1)	1 (0.4)	0 (0)
Infusion reaction	2 (0.8)	0 (0)	10 (3.9)	0 (0)
Nephritis	2 (0.8)	2 (0.8)	0 (0)	0 (0)
Severe skin reaction	2 (0.8)	1 (0.4)	3 (1.2)	3 (1.2)
Thyroiditis	2 (0.8)	0 (0)	0 (0)	0 (0)
Adrenal insufficiency	1 (0.4)	1 (0.4)	0 (0)	0 (0)
Myositis	0 (0)	0 (0)	1 (0.4)	1 (0.4)

Abbreviations: AEs = adverse events, NCI-CTC = National Cancer Institute Common Terminology Criteria for Adverse Events

[1] All patients who received at least one dose of study treatment are included.

7.2 Clinical effectiveness and safety – Further studies

KEYNOTE-012: safety and activity in locally advanced or metastatic PD-L1 positive UC patients

A non-randomised, multi-cohort, open-label phase Ib trial [20] was conducted to assess the safety and activity of pembrolizumab in patients with locally advanced or metastatic UC. All patients (115) were pre-screened and were required to have at least 1.0% PD-L1 expression detected on the tumour cells or in tumour stroma, as determined by immunohistochemistry. 61 (53.0%) were PD-L1 positive, of whom 33 were enrolled in the study and 27 comprised the full analysis set. Every two weeks patients received a dose of 10 mg/kg of intravenous pembrolizumab. The primary endpoints were safety and overall response (OR, defined by RECIST, version 1.1) assessed by a masked, independent central review.

most common AEs: fatigue & peripheral oedema

OR in 26.0% of patients

The most frequent treatment-related AEs of any grade were fatigue (six [18.0%] of 33 patients) and peripheral oedema (four [12.0%]). Treatment-related grade 3 AEs occurred in five (15.0%) patients and serious treatment-related AEs were experienced in three (9.0%) patients. An OR was achieved in seven patients (26.0%), of whom three showed a complete response and four a partial response after a median follow-up of 13 months. In total, four deaths occurred during the study, due to cardiac arrest, pneumonia, sepsis and subarachnoid haemorrhage; none of those were considered as treatment-related.

8 Estimated costs

A0021: What is the reimbursement status of pembrolizumab?

estimated costs per treatment cycle: € 6,856

In Austria, pembrolizumab is available as 25 mg and 50 mg concentrated infusion solutions. The ex-factory price of 100 mg is € 3,428; therefore, based on a dose of 200 mg every three weeks, costs of € 6,856 per treatment cycle would incur [25].

9 Ongoing research

1 ongoing phase III study investigating pembrolizumab in UC

In June 2017, a search in databases www.clinicaltrials.gov and https://www.clinicaltrialsregister.eu/ was conducted. One ongoing phase III trial investigating pembrolizumab in UC was identified:

- **NCT02853305:** A phase III randomised controlled clinical trial of pembrolizumab with or without platinum-based combination chemotherapy versus chemotherapy in subjects with advanced or

metastatic urothelial carcinoma. Estimated study completion date is March 2020.

numerous ongoing phase I and II trials in different indications and treatment lines

Various phase I and II studies are currently ongoing in different treatment lines in patients with UC, either using pembrolizumab monotherapy or combination treatment (e.g., NCT02351739, NCT02335424, NCT02717156, NCT02621151, and NCT02437370). In addition, pembrolizumab is also currently being investigated in other indications, like hepatocellular carcinoma, colon cancer, breast cancer, pancreatic cancer and renal cell cancer.

10 Discussion

indication approved by the FDA, but not yet by the EMA

Since May 2017, pembrolizumab has been approved by the FDA for the treatment of locally advanced or metastatic UC patients, who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy [7]. In Europe pembrolizumab has not yet received marketing authorisation for the treatment of UC, but for several other indications [3].

KEYNOTE-045: early termination after second interim analysis

statistically significant prolonged OS in the total as well as in the PD-L1 ≥10% population

The FDA approval was based on an open-label, international, randomised phase III study, the KEYNOTE-045 trial [6, 19]. The study was conducted to assess the efficacy and safety of pembrolizumab in 542 patients with UC that have recurred or progressed following platinum-based chemotherapy. After the early termination of the trial (second interim analysis), OS was statistically significantly longer in the total as well as in the PD-L1 ≥10% population, with a gain in median OS of 2.9 and 2.8 months in the total and PD-L1 ≥10% population, respectively. There was no statistically significant difference in the duration of PFS between the two study groups, neither in the total nor in the PD-L1 ≥10% population. However, the ORR in the total population was statistically significantly higher in the pembrolizumab group compared to the chemotherapy group (+9.7%).

further investigation of the subgroup: never smokers

A statistically significantly prolonged OS was shown across all subgroups analyses, except for patients who had no smoking history. Therefore, additional investigations are necessary in order to exclude any disadvantages for the non-smoking patient population – especially since similar trends for this patient population are available in trials investigating immune checkpoint inhibitors in NSCLC [26-28].

treatment-related AEs of any grade & grade 3–5 less common in the pembrolizumab group

In terms of safety, treatment-related AEs of any grade, as well as of grades 3–5, were more common in the chemotherapy group than in the pembrolizumab group. The most frequent treatment-related AEs of any grade in the pembrolizumab arm were pruritus, fatigue and nausea. The discontinuation rate was also higher in the chemotherapy group compared to the pembrolizumab group (5.6% versus 11.0%). Patient-reported outcomes, like QoL, were only available in abstract form.

sparse evidence about QoL is available

Although data regarding QoL is currently available in abstract form [24] and pembrolizumab causes fewer side effects than the investigator's choice of

chemotherapy (paclitaxel, docetaxel, or vinflunine), more evidence is needed to ensure a favourable benefit for patients treated with pembrolizumab.

high risk of bias: unclear allocation concealment &generation of randomisation sequence, open-label, early termination

Besides that, the early termination of the KEYNOTE-045 can lead to a systematic overestimation of the treatment effect of pembrolizumab [29]. Therefore, a low level of evidence of the benefit of pembrolizumab exists, which cannot be translated into clinical practice without further confirmative trials [30]. In general, there are several methodological limitations of the KEYNOTE-045 study. No evidence was available on the generation of randomisation sequence as well as on the allocation concealment, which may lead to a selection bias. Furthermore, since it is an open-label study – patients and treating physicians are aware of the treatment a patient receives - the probability of a performance as well as a detection bias is given. However, an external data and safety monitoring committee assessed efficacy and safety at the time of pre-specified interim analyses and subsequently may act against these biases.

ESMO-MCBS

original: grade 4
adapted: grade 3

Given the non-curative treatment setting of pembrolizumab and the statistically significant co-primary endpoint OS, we applied Form 2a of the ESMO-MCBS in order to assess whether pembrolizumab satisfies the criteria for a "meaningful clinical benefit" (score 4 or 5). Both the original as well as the adapted version of the MCBS were applied [22, 23]. The application of the ESMO-MCBS to the KEYNOTE-045 study resulted in a grade 4 and 3 in the original and the adapted version of the ESMO-MCBS, respectively. Therefore, pembrolizumab only leads to a meaningful clinical benefit in the original scale, but not in the adapted framework. This difference occurs due to the use of the point estimate of the HR in the adapted framework instead of the lower limit of the HR in the original version.

age of the study population was not representative for the actual patient population

Since 230 (42.4%) patients of the study were younger than 65 years and the median age at diagnosis of bladder cancer is 69 years in men and 71 in women, the study population reflected younger patients than those common in clinical practice. In addition, only 6 (1.1%) patients had an ECOG performance-status score of 2. A gain of 2.9 months in median OS was observed not only in a younger, but also in a less diseased population (ECOG 0–1), and might not be reached in the general patient population. Therefore, this patient population should be further analysed in future trials to identify any advantages or disadvantages for less fit patients when treated with pembrolizumab.

robust biomarker is needed for a better patient selection

Moreover, there is no standard value that is termed as a positive PD-L1 status. Consequently, the cut-off levels of the PD-L1 status may have an influence on response rates and limit comparability of trial results investigating PD-L1 inhibitors [31]. In the KEYNOTE-045 trial, OS was statistically significantly prolonged in both investigated study populations (total and PD-L1 ≥10% population). Since the PD-L1 status had no major effect on the results of the study, it would be crucial to identify a more reliable predictive biomarker to select those patients who benefit most from pembrolizumab [31-33].

direct comparisons of pembrolizumab to nivolumab & atezolizumab

Two other PD-L1 inhibitors (nivolumab and atezolizumab) are already approved in the US for the treatment of patients with UC [34, 35]. In addition, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending nivolumab for the treatment of UC in Europe [36]. Direct comparisons of pembrolizumab to these immune checkpoint inhibitors would therefore be important in order to identify the best

treatment option for UC patients after failure of prior platinum-containing therapy.

costs per one treatment cycle: € 6,850

The costs of one pembrolizumab (200 mg every three weeks) treatment cycle are approximately € 6,850; for a treatment duration of six weeks (two treatment cycles) costs of about € 13,700 would occur. On the other hand, the cost per six weeks for the treatment of UC with nivolumab is about € 12,700 [25]. Since atezolizumab has not been approved yet in Europe, no price estimates are available. Thus, one treatment cycle of nivolumab would be slightly less expensive than one treatment cycle of pembrolizumab. However, additional costs for the treatment of side effects, possible future biomarkers and in the in/outpatient sector will incur. For that reason, a direct comparison of nivolumab and pembrolizumab is recommended to identify the costs in relation to the efficacy.

significant OS improvement, fewer toxicities

lack of a reliable biomarker

direct comparison to nivolumab & atezolizumab

In conclusion, the treatment with pembrolizumab offers a statistically significant improvement in OS of 2.9 months, independent of the PD-L1 status, with a superior safety profile compared to chemotherapy at high costs. Due to the early termination of the trial, though, a systematic overestimation of the treatment effect of pembrolizumab is possible, leading to a need of long-term data. In addition, the identification of a robust predictive biomarker to identify the most suitable patients will be crucial in the future. Finally, the direct comparison of pembrolizumab to nivolumab and atezolizumab is essential to investigate which treatment option UC patients benefit the most from.

Table 3: Benefit assessment based on original ESMO-MCBS and adapted benefit assessment based on adapted ESMO-MCBS

ESMO-MCBS	Active substance	Indication	Intention	PE	Form	MG standard treatment	Efficacy				Safety		AJ	FM
							MG months	*HR (95% CI)*	*Score calculation*	*PM*	*Toxicity*	*QoL*		
Adapted ESMO-MCBS	Pembrolizumab	UC (2nd-line)	Not curative	OS	2a	≤1 year	+2.9	0.73 0.59–0.91	HR >0.65-0.70 OR Gain 1.5–2.4 months	2	-34.4% grade 3–4 AEs (+1)	-	+1[A]	**3**
Original ESMO-MCBS	Pembrolizumab	UC (2nd-line)	Not curative	OS	2a	≤1 year	+2.9	0.73 0.59–0.91	HR ≤0.65 AND Gain 2.5–2.9 months	4	x	-	x	**4**

Abbreviations: AJ = Adjustments, CI = confidence interval, FM = final adjusted magnitude of clinical benefit grade, HR = hazard ratio, m = months, MG = median gain, ND = no difference, OS = overall survival, PE = primary endpoint, PM = preliminary magnitude of clinical benefit grade, QoL = quality of life, UC = urothelial cancer

DISCLAIMER

The scores achieved with the ESMO Magnitude of Clinical Benefit Scale are influenced by several factors: by the specific evaluation form used, by the confidence interval (CI) of the endpoint of interest, and by score adjustments due to safety issues. Ad form: Every individual form measures a different outcome. The meaning of a score generated by form 2a is not comparable to the exact same score resulting from the use of form 2c. To ensure comparability, we report the form that was used for the assessment. Ad CI: The use of the lower limit of the CI systematically favours drugs with a higher degree of uncertainty (broad CI). Hence, we decided to avoid this systematic bias and use the mean estimate of effect. Ad score adjustments: Cut-off values and outcomes that lead to an up- or downgrading seem to be arbitrary. In addition, they are independent of the primary outcome and, therefore, a reason for confounding. Hence, we report the adjustments separately.

[A] Downgrade due to a negative difference of at least 10% in grade ≥3 AEs

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12 Appendix

Table 4: Characteristics of the KEYNOTE-045 trial

Title: Pembrolizumab as second-line therapy for advanced urothelial carcinoma [6, 19]			
Study identifier	NCT02256436, EudraCT number 2014-002009-40, KEYNOTE-045		
Design	Phase III, randomised, international, open-label trial		
	Duration		Two pre-specified interim analyses. Termination (October 2016) after the second interim analysis, cut-off date 7 September 2016.
Hypothesis	Superiority The study was designed to show a prolonged OS (HR 0.781) in patients treated with pembrolizumab compared to those who received investigator´s choice of chemotherapy. The planned sample size of the study was 470 patients to provide 88% power at a one-sided 2.5% significance level in the total population and 86% power to show a HR of 0.625 in the PD-L1 ≥10% population.		
Funding	Merck Sharp & Dohme Corp.		
Treatments groups	Intervention (n = 270)		200 mg pembrolizumab IV every three weeks
	Control (n = 272)		Investigator's choice of chemotherapy, every three weeks either paclitaxel: 175 mg/m², docetaxel: 75 mg/m² or vinflunine: 320 mg/m².
Endpoints and definitions	Overall survival (co-primary outcome)	OS	time from randomisation to death from any cause
	Progression-free survival (co-primary outcome)	PFS	time from randomisation to disease progression or death from any cause per RECIST 1.1
	Objective response rate	ORR	percentage of patients who had a confirmed response defined as the time from the first documented complete or partial response to disease progression or death, per RECIST 1.1
	Duration of confirmed response	DOR	time from the first documented complete or partial response to disease progression or death
Database lock	Last updated: 6 April 2017		
Results and Analysis			
Analysis description	**Primary Analysis** Efficacy analyses were performed in the intention-to-treat population (all patients who were assigned to a treatment group); safety was assessed in the as-treated population (all patients who received at least one dose of study treatment). OS and PFS were analysed by a stratified log-rank test; HRs and associated 95% CIs were calculated with the use of a stratified Cox proportional-hazards model and Ephron's method of handling ties.		

Title: Pembrolizumab as second-line therapy for advanced urothelial carcinoma [6, 19]		
Study identifier	NCT02256436, EudraCT number 2014-002009-40, KEYNOTE-045	
Analysis population	Inclusion	❁ Age ≥ 18 years ❁ Histologically or cytologically confirmed diagnosis of UC of the renal pelvis, ureter, bladder, or urethra, that is a transitional cell or mixed transitional/non-transitional (predominantly transitional) cell type ❁ Progression or recurrence of UC following a first-line platinum-containing regimen (e.g., cisplatin, carboplatin) for metastatic or inoperable locally advanced disease; or adjuvant platinum-based therapy following cystectomy for localised muscle-invasive UC with recurrence/progression ≤12 months following completion of therapy; or neoadjuvant platinum-containing therapy prior to cystectomy for localised muscle-invasive UC with recurrence ≤12 months following completion of therapy ❁ No more than 2 prior lines of systemic chemotherapy for metastatic UC ❁ Availability of tissue for biomarker analysis from an archival tissue sample or newly obtained core or excisional biopsy of a tumour lesion not previously irradiated ❁ Measureable disease ❁ ECOG performance status of 0, 1, or 2 ❁ Adequate organ function ❁ Female participants of childbearing potential have a negative urine or serum pregnancy test; or are surgically sterile, or willing to use two acceptable methods of birth control, or abstain from heterosexual activity for the course of the study. ❁ Male participants must be willing to use an adequate method of contraception starting with the first dose of study medication.
	Exclusion	❁ UC that is suitable for local therapy administered with curative intent ❁ Currently participating in or has participated in a study of an investigational agent or using an investigational device (4 weeks prior to the first dose) ❁ Diagnosis of immunodeficiency or receiving systemic steroid therapy or any other form of immunosuppressive therapy (7 days prior to the first dose) ❁ Anti-cancer mAb within 4 weeks prior to study day 1 or not recovered from AEs due to agents administered more than 4 weeks earlier ❁ Prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks of study day 1 or not recovered from prior AEs ❁ Prior therapy with all choices of active comparator ❁ Known additional malignancy that is progressing or requires active treatment (exceptions: BCC of the skin, SCC of the skin that has undergone potentially curative therapy or in situ cancer; or prostate cancer that was identified following cystoprostatectomy for bladder cancer that is Stage T2N0M0 or lower) ❁ Known active CNS metastases and/or carcinomatous meningitis ❁ Active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic or immunosuppressive agents ❁ Active cardiac disease ❁ Evidence of interstitial lung disease or active non-infectious pneumonitis ❁ Active infection requiring systemic therapy ❁ History of severe hypersensitivity reaction to paclitaxel, docetaxel, or to other drugs formulated with polysorbate 80 or polyoxyethylated castor oil, or to vinflunine or other vinca alkaloids ❁ Requires ongoing therapy with a medication that is a strong inhibitor or inducer of the cytochrome 3A4 (CYP3A4) enzymes ❁ Pregnant, breastfeeding, or expecting to conceive or father children within the projected duration of the trial ❁ Prior therapy with a PD-1 or anti-PD-Ligand 1 agent, or with an agent directed to another co-inhibitory T-cell receptor ❁ HIV ❁ Active hepatitis B or hepatitis C ❁ Received a live virus vaccine within 30 days of planned start of trial treatment

Title: Pembrolizumab as second-line therapy for advanced urothelial carcinoma [6, 19]			
Study identifier	NCT02256436, EudraCT number 2014-002009-40, KEYNOTE-045		
Analysis population *(continuation)*	Characteristics	Intervention (n = 270)	Control (n = 272)
	Median age years, (range)	67 (29–88)	65 (26–84)
	Gender, n (%)	♂ 200 (74.1) ♀ 70 (25.9)	♂ 202 (74.3) ♀ 70 (25.7)
	ECOG performance-status score, n (%) 0 1 2 Missing data	 119 (44.1) 143 (53.0) 2 (0.7) 6 (2.2)	 106 (39.0) 158 (58.1) 4 (1.5) 4 (1.5)
	Current or former smoker, n/total n (%)	165/269 (61.3)	186/269 (69.1)
	Pure transitional-cell features in histologic testing, n/total n (%)	186/270 (68.9)	197/270 (73.0)
	Tumour PD-L1 combined positive score ≥10%, n/total n (%)	74/260 (28.5)	90/266 (33.8)
	Site of primary tumour in bladder or urethra, n/total n (%)	232/270 (85.9)	234/271 (86.3)
	Visceral disease, n/total n (%)	240/269 (89.2)	233/271 (86.0)
	Liver metastases, n/total n (%)	91/270 (33.7)	95/271 (35.1)
	Haemoglobin concentration <10 g/dl, n/total n (%)	43/262 (16.4)	44/267 (16.5)
	Number of risk factors, n (%) 0 1 2 3 or 4 Missing data	 54 (20.0) 96 (35.6) 66 (24.4) 45 (16.7) 9 (3.3)	 44 (16.2) 97 (35.7) 80 (29.4) 45 (16.5) 6 (2.2)
	Completion or discontinuation of most recent therapy <3 months previously, n/total n (%)	103/269 (38.3)	104/271 (38.4)

Abbreviations: AEs = adverse events, BCC = basal cell carcinoma, CI = confidence interval, CNS = central nervous system, ECOG = Eastern Cooperative Oncology Group, HIV = human immunodeficiency virus, HR = hazard ratio, mAb = monoclonal antibody, PD-1 = anti-programmed cell death 1, SSC = squamous cell carcinoma, UC = urothelial carcinoma

Table 5: Risk of bias assessment on study level is based on EUnetHTA (Internal validity of randomised controlled trials) [21]

Criteria for judging risk of bias		Risk of bias
Adequate generation of randomisation sequence: randomisation stratified according to ECOG performance-status score, presence of liver metastases, haemoglobin concentration, and time since the last dose of chemotherapy. No evidence was found for the generation of randomisation sequence.		unclear
Adequate allocation concealment: Treatment assignment was not blinded.		unclear
Blinding: open-label	**Patient**	no
	Treating physician	no
Selective outcome reporting unlikely		yes
No other aspects which increase the risk of bias: industry funded the study, provided study drugs, and was involved in study design, data collection, analysis, interpretation, writing of the report; early termination of the study after the second interim analysis		high
Risk of bias – study level		high

Abbreviations: ECOG = Eastern Cooperative Oncology Group