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Pembrolizumab (renal cell carcinoma) –

Addendum to Commission A22-71 (dossier assessment)[1]

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
BICR	blinded independent central review
CTCAE	Common Terminology Criteria for Adverse Events
DFS	disease-free survival
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
FKSI-DRS	Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
NED	no evidence of disease
PT	Preferred Term
RR	relative risk
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
VAS	visual analogue scale
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor

1 Background

On 6 December 2022, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A22-71 (Pembrolizumab – Benefit assessment according to §35a Social Code Book V) [1].

To be able to decide on the added benefit, the G-BA needs further analyses in this procedure.

The commission comprises the assessment of the results of the second data cut-off of the KEYNOTE-564 study for the data on the first subsequent therapy as well as the outcome categories of morbidity (recurrence) and side effects on the basis of the analyses submitted by the pharmaceutical company (hereinafter referred to as the "company") in the commenting procedure [2], taking into account the corresponding information in the dossier [3]. In addition, the supplementary assessment is to examine the extent to which the analyses submitted by the company in the commenting procedure address the corresponding points of criticism in IQWiG's benefit assessment. Irrespective of this, a methodological review of the data in the dossier is to be carried out for the outcome of overall survival, taking into account the analyses submitted by the company in the commenting procedure, and the results are to be presented.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

The randomized clinical study KEYNOTE-564 was included for the benefit assessment of pembrolizumab in patients with clear-cell renal cell carcinoma at increased risk of recurrence after partial nephroprotective or complete nephrectomy. The KEYNOTE-564 study is an ongoing, double-blind, randomized, multicentre study on the comparison of pembrolizumab with placebo. A detailed description of the KEYNOTE-564 study can be found in the benefit assessment on commission A22-71 [1].

The benefit assessment was carried out on the basis of the results of the first data cut-off from 14 December 2020, as it was not clear why the second data cut-off submitted by the company was carried out. In the context of the commenting procedure, the company again referred to Amendment 5 to the KEYNOTE-564 study protocol, in which the performance of the second data cut-off was included.

Several interim analyses and one final analysis are planned for the study. As described in the dossier assessment, an additional interim analysis after approximately 100 deaths was included in Amendment 5 to the study protocol. In addition, according to Amendment 5, an additional analysis (Efficacy Update Report) was to be conducted if disease-free survival was not superior in the first interim analysis (corresponding to the first data cut-off of 14 December 2020) and current data were requested by the regulatory authority.

The criteria described in Amendment 5 for one of the 2 additional interim analyses were not met at the time of the second data cut-off on 14 June 2021: A total of 66 deaths had occurred at that time, and thus the specified threshold of approximately 100 deaths was not reached. Furthermore, for the results of the outcome of disease-free survival, the first interim analysis already showed superiority of pembrolizumab.

It therefore appears contradictory to perform the second data cut-off despite a statistically significant test result in favour of the intervention for the outcome of disease-free survival at the first data cut-off on 14 December 2020. However, there is contradictory information within the study documents as a whole. For example, the supplementary statistical analysis plan of 13 July 2021 states that the data cut-off for the Efficacy Update Report should be conducted 6 months after the first interim analysis, regardless of the result for the outcome of disease-free survival in this interim analysis.

In its comments and at the oral hearing, the company explained that the second data cut-off (14 June 2021) – regardless of the information in the study protocol – was carried out at the request of the regulatory authorities for the outcomes of disease-free survival, overall survival and adverse events (AEs). According to the company, the European Medicines Agency (EMA) had explicitly requested results on current data (especially on overall survival and disease-free survival) as part of the approval procedure. Taking into account the comments of the company in the commenting procedure, the available information is considered sufficient in the present

situation to use the second data cut-off of the KEYNOTE-564 study for the assessment of the added benefit of pembrolizumab.

2.1 Study characteristics

Detailed characteristics of the KEYNOTE-564 study and of the study population can be found in dossier assessment A22-71 [1].

At the second data cut-off, 38 (7.7%) of the patients in the intervention arm and 56 (11.2%) of the patients in the comparator arm had discontinued participation in the study. Compared with the first data cut-off, one more patient in the comparator arm had reached the maximum treatment duration.

Information on the course of the study

Table 1 shows the mean/median treatment duration of the patients and the mean/median observation period for individual outcomes at the second data cut-off.

Table 1: Information on the course of the study – RCT, direct comparison: pembrolizumab vs. watchful waiting

Study **Duration of the study phase** **Outcome category**	**Pembrolizumab** **N = 496**	**Placebo** **N = 498**
KEYNOTE-564		
Treatment duration[a] [months]		
Data cut-off 14 June 2021		
Median [min; max]	11.1 [ND; ND]	11.1 [ND; ND]
Mean (SD)	ND	ND
Observation period[b] [months]		
Overall survival		
Median [min; max]	29.4 [ND; ND]	28.9 [ND; ND]
Mean (SD)	ND	ND
Morbidity		
Recurrence		
Median [min; max]	25.7 [ND; ND]	22.9 [ND; ND]
Mean (SD)	ND	ND
Side effects		
Adverse events		
Median [min; max]	12.1 [ND; ND]	12.1 [ND; ND]
Mean (SD)	ND	ND
Serious adverse events		
Median [min; max]	14.0 [ND; ND]	14.0 [ND; ND]
Mean (SD)	ND	ND

a. The data refer to all patients who received at least one dose of the study medication (N = 488 versus N = 496).
b. In Module 5 A, the company did not provide any information on the determination of the observation period.
max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

In the KEYNOTE-564 study, the median treatment duration at the second data cut-off is approximately 11 months in both treatment arms.

With about 29 months at the second data cut-off, the median observation period for the outcome of overall survival is comparable in the intervention arm and the comparator arm.

The median observation period for the outcome of recurrence in the intervention arm is about 26 months at the second data cut-off and thus deviates from the comparator arm (23 months).

The observation period for the outcomes of the category of side effects was linked to the end of treatment (maximum 17 cycles or about 1 year plus 30 days for recordings of AEs, and 90 days for recordings of serious AEs [SAEs]); the median observation period in both treatment

arms is approximately 12 months for AEs and 14 months for SAEs. Hence, the observation periods for these outcomes are systematically shortened in comparison with overall survival.

Information on subsequent therapies

With its comments, the company subsequently submitted information on systemic therapies, surgical interventions and radiotherapies used as first subsequent therapies in patients with recurrence.

Table 2 shows the subsequent therapies patients received after discontinuing the study medication.

Table 2: Information on subsequent antineoplastic therapies (first subsequent therapy) – RCT, direct comparison: pembrolizumab vs. watchful waiting

Study Type of subsequent therapy	Patients with subsequent therapy n (%)	
	Pembrolizumab N = 496	Placebo N = 498
KEYNOTE-564 (data cut-off on 14 June 2021)		
Patients with recurrence	114 (23.0)[b]	169 (33.9)[c]
Subsequent antineoplastic therapies, total	84 (16.9[d])	123 (24.7[d])
Radiotherapy	9 (1.8[d])	12 (2.4[d])
Surgery	20 (4.0[d])	34 (6.8[d])
Systemic therapy[a]	55 (11.1)	77 (15.5)
Immune checkpoint inhibitor	10 (2.0)	30 (6.0)
Avelumab	ND	ND
Durvalumab	ND	ND
Ipilimumab	ND	ND
Nivolumab	ND	ND
Pembrolizumab	ND	ND
VEGF/VEGFR-targeted therapy	48 (9.7)	59 (11.8)
Other	6 (1.2)	21 (4.2)

a. Patients may have received more than one subsequent therapy and in this case are only counted once in the higher-level category of systemic therapy.
b. Including 6 deaths.
c. Including 3 deaths.
d. Institute's calculation.

n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor

Dossier assessment A22-71 described that the subsequent systemic therapies administered in the comparator arm of the KEYNOTE-564 study are not an adequate reflection of the current standard of therapy after recurrence. It was rated as unclear whether the effect in overall survival observed in the KEYNOTE-564 study would still exist with adequate use of immune checkpoint inhibitor-based therapy in subsequent therapy after recurrence. For this reason, the

results for the outcome of overall survival of the KEYNOTE-564 study were assessed as not interpretable.

For the data presented in Table 2, it should be noted that the company had already presented information on the first subsequent therapy after recurrence (second data cut-off) in Module 4 A of the dossier for this data cut-off. With the comments, it again submitted data on the first subsequent therapy (second data cut-off), which deviate from the previously presented data. Since in this subsequently submitted analysis, in some cases, fewer patients received a specific subsequent therapy, it is assumed that these are data for the first subsequent therapy and that the data in Module 4 A and in the dossier assessment (Table 12) are possibly the data for all subsequent therapies (across all lines).

In the comparator arm, 169 patients had a recurrence, including 3 deaths. At the second data cut-off, 77 patients in the comparator arm received systemic therapy as the first subsequent therapy. Of these, only 30 patients received an immune checkpoint inhibitor, 59 received vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR)-targeted therapy. This corresponds to 18.1% and 35.5% of patients with recurrence who had not died. It should be noted that patients may have received more than one first subsequent therapy.

In the commenting procedure, the commenters stated that, for patients with recurrence and a favourable risk profile, other options such as watchful waiting, radiation or surgery and, in particular, systemic therapy with VEGF inhibitors could be considered in addition to systemic therapy with immune checkpoint inhibitors (and combinations). For patients with a favourable risk profile, this VEGF therapy was to be considered equivalent to checkpoint inhibitor-based combination therapies, they added. National and international guidelines recommend immune checkpoint inhibitor-based therapies for first-line drug therapy of advanced/metastatic renal cell carcinoma [4-6]. According to the recommendations of the S3 guideline, the combinations of pembrolizumab or avelumab plus axitinib should be given to patients for first-line therapy of advanced or metastatic clear-cell renal cell carcinoma, regardless of the risk profile, and the combination of pembrolizumab plus ipilimumab should be given to patients with intermediate or poor risk. Other therapies, especially those targeted against VEGF/VEGFR should only be used if checkpoint inhibitor-based combination therapy cannot be used in the first line [4]. No further information on the classification of the patients to a risk group in the event of recurrence is available for the KEYNOTE-564 study. The company also did not provide any information that could be used to draw further conclusions about the criteria used in the study to decide which treatment option to use for the patients in the event of recurrence.

In addition, it was noted in the commenting procedure that all previous studies conducted on combination therapies with an immune checkpoint inhibitor and a tyrosine kinase inhibitor included mostly patients in the primary metastatic setting and that the transferability of the effects for overall survival shown in these studies to patients who have already undergone surgery was questionable. It should be noted that, for example, the KEYNOTE-426 study comparing pembrolizumab plus axitinib against sunitinib included a relevant proportion (61.2%

versus 57.6% with favourable/intermediate risk profile and 14% versus 27% with unfavourable risk profile) of patients with recurrent disease status at baseline [7]. Furthermore, it is unclear whether this characteristic (recurrent versus newly diagnosed) would lead to an effect modification, as corresponding subgroups were not investigated. The S3 guideline recommendation also does not differentiate between therapy recommendations for patients in the primary metastatic setting versus patients with recurrence.

The results in the outcome of overall survival are therefore not interpretable, even taking into account the information from the commenting procedure.

2.2 Results

2.2.1 Outcomes included

In compliance with the commission, the following outcomes for the second data cut-off are presented:

- Mortality
  - overall survival
- Morbidity
  - recurrence
- Side effects
  - SAEs
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - immune-related SAEs
  - immune-related severe AEs
  - further specific AEs

Notes on the outcome of recurrence and on the outcomes of the category of side effects can be found in dossier assessment A22-71 [1].

For the following patient-relevant outcomes of the categories of morbidity and health-related quality of life recorded by questionnaire, information is only available for the first data cut-off (see dossier assessment A22-71 [1]). An analysis of these outcomes was not planned for the second data cut-off. The data from the first data cut-off are still relevant to the benefit assessment, as no substantial gain in information is to be expected for the second data cut-off compared with the first data cut-off:

- Morbidity
  - symptoms recorded using the Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms (FKSI-DRS)
  - symptoms recorded using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)
  - health status recorded using the EQ-5D visual analogue scale (VAS)
- Health-related quality of life
  - recorded using the EORTC QLQ-C30

The data subsequently submitted by the company with the comments cannot eliminate the main uncertainties in the subsequent systemic therapies administered, so that the results for the outcome of overall survival are still rated as not interpretable.

2.3 Risk of bias

Table 3 describes the risk of bias for the results of the outcomes presented in compliance with the commission.

Table 3: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: pembrolizumab vs. watchful waiting

Study	Study level	Outcomes							
		Overall survival	Recurrence[a]	SAEs	Severe AEs[b]	Discontinuation due to AEs	Immune-related SAEs[c]	Immune-related severe AEs[b, c]	Further specific AEs[d]
KEYNOTE-564	L	-[e]	H[f]	H[g]	H[g]	L[h]	H[g]	H[g]	H[g]

a. Presented based on the recurrence rate and disease-free survival (includes the events of local recurrence, distant metastases, and death) as assessed by the investigator and additionally by the BICR (see benefit assessment A22-71 [1]).
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. In each case, the operationalization of a specific MedDRA PT collection from the outcome of adverse events of special interest ("AEOSI") presented by the company is used.
d. The following events are considered (MedDRA coding): endocrine disorders (SOC, severe AEs), gastrointestinal disorders (SOC, severe AEs), skin and subcutaneous tissue disorders (SOC, severe AEs), investigations (SOC, severe AEs) and metabolism and nutrition disorders (SOC, severe AEs).
e. No suitable data available.
f. As assessed by the investigator; due to the typical toxicity profile of pembrolizumab, a potential influence on the assessment of recurrence status is possible. For the additionally presented analyses according to BICR, there are in each case incomplete observations for potentially informative reasons, leading to a high risk of bias of the results (see also dossier assessment A22-71 [1]).
g. Incomplete observations for potentially informative reasons.
h. Despite the low risk of bias of the results, the certainty of results for the outcome of discontinuation due to AEs is assumed to be limited (see running text below).

AE: adverse event; AEOSI: adverse events of special interest; BICR: blinded independent central review; CTCAE: Common Terminology Criteria for Adverse Events; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

The outcome-specific risk of bias is rated as high for the results of the patient-relevant outcomes of recurrence and of the category of side effects, except the outcome of discontinuation due to AEs.

No suitable data are available for the outcome of overall survival (see Section 2.1 for reasons). Apart from the lack of suitable data, there are no potentially biasing aspects for this outcome. The results for the outcome of recurrence have a high risk of bias, as the typical toxicity profile of pembrolizumab may have a potential influence on the investigator's assessment of the recurrence status.

The risk of bias for the results of the outcome of discontinuation due to AEs is rated as low. Despite a low risk of bias of the results, the certainty of results is reduced for the outcome of

discontinuation due to AEs. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome to be recorded, discontinuation due to AEs. This means that, after discontinuation of therapy for other reasons, AEs that would have led to discontinuation may have occurred, but that the criterion of discontinuation can no longer be applied to them. It is impossible to estimate how many AEs are affected by this issue.

All results for other outcomes in the side effects category have a high risk of bias. For these outcomes, there are incomplete observations for potentially informative reasons due to the follow-up observation linked to the treatment duration and a possible association between outcome and reason for treatment discontinuation.

Assessment of the certainty of conclusions on immune-related AEs

Due to the size of the respective effect, there is a high certainty of results for the outcomes of immune-related SAEs and immune-related severe AEs from the KEYNOTE-564 study despite high risk of bias (see next section).

2.4 Results

Table 4 and Table 5 summarize the results of the second data cut-off on the comparison of pembrolizumab for the adjuvant treatment of adult patients with renal cell carcinoma at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Kaplan-Meier curves on the presented time-to-event analyses can be found in Appendix C. Results on common AEs, SAEs, severe AEs, and discontinuation due to AEs are presented in Appendix B. A list of the immune-related AEs, immune-related SAEs, and immune-related severe AEs (CTCAE grade ≥ 3) categories in which events occurred was not presented by the company for the second data cut-off.

Table 4: Results (mortality, morbidity, time to event) – RCT, direct comparison: pembrolizumab vs. watchful waiting (multipage table)

Study Outcome category Outcome	Pembrolizumab N	Pembrolizumab Median time to event in months [95% CI] Patients with event n (%)	Placebo N	Placebo Median time to event in months [95% CI] Patients with event n (%)	Pembrolizumab vs. placebo HR [95% CI]; p-value[a]
KEYNOTE-564 (data cut-off on 14 June 2021)					
Mortality					
Overall survival	496			No suitable data[b]	
Morbidity					
Recurrence					
Recurrence rate (investigator)[c]	496	– 114 (23.0)	498	– 169 (33.9)	RR: 0.68 [0.55; 0.83]; < 0.001[d]
Local recurrence	496	– 17 (3.4)	498	– 32 (6.4)	–
Distant metastases	496	– 91 (18.3)	498	– 134 (26.9)	–
Death	496	– 6 (1.2)	498	– 3 (0.6)	–
Disease-free survival (investigator)	496	NA 114 (23.0)	498	NA 169 (33.9)	0.63 [0.50; 0.80]; < 0.001
Supplementary information:					
Recurrence rate[e] (BICR)	477[f]	– 117 (24.5[f])	469[f]	– 141 (30.1[f])	RR: 0.82 [0.66; 1.01]; 0.058[d]
Disease-free survival[e] (BICR)	496	NA 117 (23.6)	498	NA 141 (28.3)	0.78 [0.61; 0.99]; 0.043
Event rate (BICR recurrence/progression rate)[g]	496	– 133 (26.8)	498	– 167 (33.5)	RR: 0.80 [0.66; 0.97]; 0.022[d]
Event-free survival (BICR)[g]	496	NA 133 (26.8)	498	NA 167 (33.5)	0.75 [0.60; 0.94]; 0.013

a. Unless otherwise stated, Cox proportional hazards model with associated 2-sided Wald test stratified by metastasis status (M1 NED vs. M0). Within M0, additional stratification is done according to ECOG PS (0 vs. 1) and region (USA vs. non-USA).
b. See Section 2.1 for reasons.
c. Individual components – if available – are shown in the lines below; since only the qualifying events are included in the recurrence rate (total), the effect estimates of the individual components are not shown.
d. RR, CI, p-value: Institute's calculations; CI asymptotic; p-value: unconditional exact test (CSZ method according to [8]).
e. Censoring at baseline of patients who were not tumour-free at baseline as assessed by the BICR.
f. Institute's calculations.
g. The outcome of event-free survival is based on the assessments of a BICR. It includes the events of recurrence (local recurrence or distant metastases) in patients who were tumour-free at baseline, or disease progression in patients who were assessed as tumour-free at baseline by the investigator but not by the BICR, or death of any cause. The assessment of disease status at baseline was based on baseline scans.

Table 4: Results (mortality, morbidity, time to event) – RCT, direct comparison: pembrolizumab vs. watchful waiting (multipage table)

Study Outcome category	Pembrolizumab		Placebo		Pembrolizumab vs. placebo
Outcome	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
BICR: blinded independent central review; CI: confidence interval; CSZ: convexity, symmetry, z-score; ECOG PS: Eastern Cooperative Oncology Performance Status; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NED: no evidence of disease; RCT: randomized controlled trial; RR: relative risk					

Table 5: Results (side effects) – RCT, direct comparison: pembrolizumab vs. watchful waiting

Study Outcome category Outcome	Pembrolizumab		Placebo		Pembrolizumab vs. placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
KEYNOTE-564 (data cut-off on 14 June 2021)					
Side effects					
AEs[b] (supplementary information)	488	470 (96.3)	496	453 (91.3)	–
SAEs[b]	488	101 (20.7)	496	57 (11.5)	1.80 [1.33; 2.43]; < 0.001
Severe AEs[b, c]	488	157 (32.2)	496	88 (17.7)	1.81 [1.44; 2.28]; < 0.001
Discontinuation due to AEs[b]	488	103 (21.1)	496	11 (2.2)	9.52 [5.18; 17.50]; < 0.001
Immune-related AEs (supplementary information)[d]	488	ND	496	ND	–
Immune-related SAEs[d]	488	42 (8.6)	496	1 (0.2)	42.69 [5.90; 308.94]; < 0.001
Immune-related severe AEs[c, d]	488	45 (9.2)	496	3 (0.6)	15.25 [4.77; 48.73]; < 0.001
Endocrine disorders (severe AEs, SOC)	488	12 (2.5)	496	1 (0.2)	12.20 [1.59; 93.44]; 0.002
Skin and subcutaneous tissue disorders (severe AEs, SOC)	488	10 (2.0)	496	2 (0.4)	5.08 [1.12; 23.07]; 0.019
Gastrointestinal disorders (severe AEs, SOC)	488	24 (4.9)	496	9 (1.8)	2.71 [1.27; 5.77]; 0.007
Investigations (severe AEs, SOC)[e]	488	27 (5.5)	496	4 (0.8)	6.86 [2.42; 19.46]; < 0.001
Metabolism and nutrition disorders (severe AEs, SOC)	488	26 (5.3)	496	14 (2.8)	1.89 [1.00; 3.57]; 0.047

a. RR, CI, p-value: Institute's calculations; CI asymptotic; p-value: unconditional exact test (CSZ method according to [8]).
b. Progression events of the underlying disease are not included (PTs "neoplasm progression", "malignant neoplasm progression" and "disease progression").
c. Operationalized as CTCAE grade ≥ 3.
d. In each case, the operationalization of a specific MedDRA PT collection from the outcome of adverse events of special interest ("AEOSI") presented by the company is used.
e. A major underlying event is alanine aminotransferase increased.

AE: adverse event; AEOSI: adverse events of special interest; CI: confidence interval; CSZ: convexity, symmetry, z-score; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class

As described in Section 2.3, due to the size of the respective effect of the outcomes of immune-related SAEs and immune-related severe AEs in the KEYNOTE-564 study, there is a high certainty of results despite the high risk of bias of the results. On the basis of the available information, at most indications, e.g. of an added benefit, can therefore be derived for these outcomes, and at most hints can be derived for all other outcomes due to the high risk of bias of the results or, for the outcome of discontinuation due to AEs, due to a limited certainty of results.

Mortality

No suitable data are available for the outcome of overall survival (see Section 2.1 for reasons).

This results in no hint of added benefit of pembrolizumab in comparison with watchful waiting; an added benefit is therefore not proven.

The results for the outcome of overall survival are presented in Appendix A.

Morbidity

Recurrence

For the outcome of recurrence (operationalized as recurrence rate and disease-free survival [DFS]), a statistically significant difference between the treatment groups in favour of pembrolizumab in comparison with watchful waiting is shown for both operationalizations. There is an effect modification by the characteristic of metastasis status (M0 versus M1 no evidence of disease [NED]) (see Section 2.5). For the operationalization of disease-free survival, a statistically significant difference in both patient groups is shown in favour of pembrolizumab. For the outcome of recurrence, operationalized via the recurrence rate, there is no effect modification (see C.2.2) but comparable estimates in both subgroups. For the outcome of recurrence, this results overall in a hint of an added benefit for both the M0 and the M1 NED groups, but with different extents. The operationalizations according to the blinded independent central review (BICR) presented as supplementary information – with the exception of the analysis on the recurrence rate according to the BICR – also show a statistically significant difference between the treatment groups in favour of pembrolizumab in comparison with watchful waiting.

This results in a hint of added benefit of pembrolizumab in comparison with watchful waiting for this outcome.

Side effects

SAEs, severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs

A statistically significant difference to the disadvantage of pembrolizumab in comparison with watchful waiting is shown between the treatment groups for the outcomes of SAEs, severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs. In each case, this results in a hint of greater harm of pembrolizumab in comparison with watchful waiting.

Specific AEs

Immune-related SAEs, immune-related severe AEs

A statistically significant difference to the disadvantage of pembrolizumab in comparison with watchful waiting is shown between the treatment groups for the outcomes of immune-related SAEs and immune-related severe AEs. Due to the size of the respective effect of these outcomes, there is a high certainty of results in the KEYNOTE-564 study despite the high risk of bias of the results. In each case, this results in an indication of greater harm of pembrolizumab in comparison with watchful waiting.

Endocrine disorders (severe AEs), skin and subcutaneous tissue disorders (severe AEs), gastrointestinal disorders (severe AEs), investigations (severe AEs) and metabolism and nutrition disorders (severe AEs)

For the outcomes of endocrine disorders (severe AEs), skin and subcutaneous tissue disorders (severe AEs), gastrointestinal disorders (severe AEs), investigations (severe AEs) and metabolism and nutrition disorders (severe AEs), there is a statistically significant difference between the treatment groups to the disadvantage of pembrolizumab in comparison with watchful waiting. In each case, this results in a hint of greater harm of pembrolizumab in comparison with watchful waiting.

2.5 Subgroups and other effect modifiers

The following potential effect modifiers were taken into account for the present benefit assessment:

- age (< 65 years versus ≥ 65 years)
- sex (male versus female)
- metastasis status (M0 vs. M1 NED)

The subgroup characteristics selected in the present benefit assessment had been defined a priori, but only for the outcome of disease-free survival.

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

For the second data cut-off, Module 4 A of the dossier still provides an incomplete picture due to missing subgroup analyses. The company did not submit any further subgroup analyses in the context of the commenting procedure. However, in comparison with the data for the first data cut-off, Module 4 A of the dossier contains additional subgroup analyses for the effect

modifiers of age and sex for the relevant outcome of overall survival for the second data cut-off. The available subgroup analyses for the second data cut-off are therefore used for the benefit assessment. Even after the oral hearing [9], there are still no subgroup analyses on the characteristic of metastasis status for the outcomes of overall survival, recurrence rate, the patient-relevant outcomes of the categories of morbidity and health-related quality of life collected by means of questionnaires, as well as for all outcomes of the side effects category. In addition, there are no subgroup analyses for the subgroup characteristics of age and sex for the recurrence rate, for the outcomes on overall rates of the side effects category (operationalized by the relative risk [RR]) and the specific outcomes of immune-related SAEs and immune-related severe AEs.

For the outcome category of side effects, the company considered the time to event, using the hazard ratio (HR) as effect measure. The subgroup analyses conducted by the company for this category are also based on the HR. In contrast to the approach of the company, the present assessment uses analyses of the number of patients with event with the RR effect measure for the side effect outcomes to derive the added benefit. Analyses based on the RR are therefore also preferable for the subgroup analyses.

Hence, the present benefit assessment checked whether a significant effect modification at the level of 0.2 was present using the HR. If this was the case, an interaction test was performed using the Q test, based on the RR.

An identical procedure was also chosen for the subgroup analyses of the outcome of recurrence rate.

The results of the subgroup analyses are presented in Table 6 and Table 7. The Kaplan-Meier curves on the subgroup results are presented in Appendix C.2.1.

Table 6: Subgroups (morbidity) – RCT, direct comparison: pembrolizumab vs. watchful waiting

Study Outcome Characteristic Subgroup	Pembrolizumab N	Pembrolizumab Median time to event in months [95% CI] Patients with event n (%)	Placebo N	Placebo Median time to event in months [95% CI] Patients with event n (%)	Pembrolizumab vs. placebo HR [95% CI][a]	Pembrolizumab vs. placebo p-value[a]
KEYNOTE-564 (data cut-off on 14 June 2021)						
Recurrence[b]						
Disease-free survival (investigator)						
Metastasis status						
M0	467	NA 107 (22.9)	469	NA [40.5; NC] 150 (32.0)	0.68 [0.53; 0.88]	0.003
M1 NED	29	NA [25.7; NC] 7 (24.1)	29	11.6 [5.6; NC] 19 (65.5)	0.28 [0.12; 0.66]	0.004
Total					Interaction[c]:	0.040

a. HR, CI and p-value: Cox proportional hazards model, unstratified.
b. There is no statistically significant effect modification for the recurrence rate, but comparable estimates in both subgroups (see calculations conducted by the Institute based on the RR in Appendix C.2.2).
c. Cox proportional hazards model with subgroup as covariable and corresponding interaction term; p-value based on likelihood ratio test.

CI: confidence interval; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; NED: no evidence of disease; RCT: randomized controlled trial; RR: relative risk

Table 7: Subgroups (side effects) – RCT, direct comparison: pembrolizumab vs. watchful waiting

Study Outcome Characteristic Subgroup	Pembrolizumab N	Pembrolizumab Patients with event n (%)	Placebo N	Placebo Patients with event n (%)	Pembrolizumab vs. placebo RR [95% CI][a]	Pembrolizumab vs. placebo p-value[a]
KEYNOTE-564 (data cut-off on 14 June 2021)						
Side effects						
Severe AEs[b]						
Age						
< 65	333	104 (31.2)	324	45 (13.9)	2.25 [1.64; 3.08]	< 0.001
≥ 65	155	53 (34.2)	172	43 (25.0)	1.37 [0.97; 1.92]	0.071
Total					Interaction[c]:	0.034

a. RR, CI, p-value: Institute's calculations; CI asymptotic; p-value: unconditional exact test (CSZ method according to [8]).
b. Operationalized as CTCAE grade ≥ 3.
c. Institute's calculation, Cochran's Q.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk

Morbidity

Recurrence

For the outcome of recurrence, there is an effect modification for the operationalization of disease-free survival by the characteristic of metastasis status (M0 vs. M1 NED). A statistically significant difference in favour of pembrolizumab was shown in both patient groups. For the outcome of recurrence, operationalized via the recurrence rate, there is no effect modification (see C.2.2) but comparable estimates in both subgroups. For the outcome of recurrence, this results overall in a hint of an added benefit for both the characteristic of metastasis status M0 and the characteristic of metastasis status M1 NED, but with different extents (see next section).

Side effects

Severe AEs (CTCAE ≥ 3)

There is an effect modification by the characteristic of age for the outcome of severe AEs (CTCAE ≥ 3).

A statistically significant difference to the disadvantage of pembrolizumab was shown for the age group < 65 years. This results in a hint of greater harm of pembrolizumab in comparison with watchful waiting for the outcome of severe AEs in patients < 65 years of age.

No statistically significant difference between treatment groups was found for patients ≥ 65 years. This results in no hint of greater harm of pembrolizumab in comparison with watchful waiting for patients ≥ 65 years of age; greater harm is therefore not proven.

2.6 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [10].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.6.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.2 (see Table 8).

Determination of the outcome category for outcomes on symptoms and side effects

It cannot be inferred from the dossier whether the outcome of discontinuation due to AEs is serious/severe or non-serious/non-severe. The classification of this outcome is explained below.

Discontinuation due to AEs

Information on the severity grades of the AEs due to which treatment was discontinued in the KEYNOTE-564 study is not available for the second data cut-off. For the first data cut-off of the study, the information in the study documents shows that a serious event was present in about 50% of the AEs that led to treatment discontinuation. For the second data cut-off, the information in Module 4 A shows that only individual further events occurred that led to treatment discontinuation. Therefore, this outcome is assigned to the outcome category of serious/severe side effects also in the assessment of the second data cut-off.

Table 8: Extent of added benefit at outcome level: pembrolizumab vs. watchful waiting (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pembrolizumab vs. placebo** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Total observation period		
Mortality		
Overall survival	No suitable data[c]	Lesser/added benefit not proven
Morbidity		
Recurrence[d]		Metastasis status M0: Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_u < 0.90$ Added benefit, extent: "considerable" metastasis status M1 NED: Outcome category: serious/severe symptoms/late complications $CI_u < 0.75$, risk ≥ 5% Added benefit, extent: "major"
Recurrence rate[e]	23% vs. 33.9% RR: 0.68 [0.55; 0.83]; p < 0.001 Probability: "hint"	
Disease-free survival (investigator)		
Metastasis status		
M0	NA vs. NA months HR: 0.68 [0.53; 0.88]; p = 0.003 Probability: "hint"	
M1 NED	NA vs. 11.6 months HR: 0.28 [0.12; 0.66] p = 0.004 Probability: "hint"	
Shortened observation period		
Morbidity (recorded using FKSI-DRS, EORTC QLQ-C30, EQ-5D-5L VAS)[f]		
Health-related quality of life (recorded using EORTC QLQ-C30)[f]		
Side effects		
SAEs	20.7% vs. 11.5% RR: 1.80 [1.33; 2.43] RR: 0.56 [0.41; 0.75][g]; p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm, extent: "considerable"
Severe AEs Age < 65 years	31.2% vs. 13.9% RR: 2.25 [1.64; 3.08] RR: 0.44 [0.32; 0.61][g]; p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: "major"
≥ 65 years	34.2% vs. 25.0% RR: 1.37 [0.97; 1.92] p = 0.071	Greater/lesser harm not proven

Table 8: Extent of added benefit at outcome level: pembrolizumab vs. watchful waiting (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pembrolizumab vs. placebo** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Discontinuation due to AEs	21.1% vs. 2.2% RR: 9.52 [5.18; 17.50] RR: 0.11 [0.06; 0.19][g]; p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: "major"
Immune-related SAEs	8.6% vs. 0.2% RR: 42.69 [5.90; 308.94] RR: 0.02 [0.003; 0.17][g]; p < 0.001 Probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: "major"
Immune-related severe AEs	9.2% vs. 0.6% RR: 15.25 [4.77; 48.73]; RR: 0.07 [0.02; 0.21][g]; p < 0.001 Probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"
Endocrine disorders (severe AEs)	2.5% vs. 0.2% RR: 12.20 [1.59; 93.44] RR: 0.08 [0.01; 0.63][g]; p = 0.002 Probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk < 5% Greater harm, extent: "considerable"
Skin and subcutaneous tissue disorders (severe AE)	2.0% vs. 0.4% RR: 5.08 [1.12; 23.07] RR: 0.20 [0.04; 0.89][g]; p = 0.019 Probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm, extent: "considerable"
Gastrointestinal disorders (severe AEs)	4.9% vs. 1.8% RR: 2.71 [1.27; 5.77] RR: 0.37 [0.17; 0.79][g]; p = 0.007 Probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm, extent: "considerable"
Investigations (severe AEs)	5.5% vs. 0.8% RR: 6.86 [2.42; 19.46] RR: 0.15 [0.05; 0.41][g]; p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: "major"

Table 8: Extent of added benefit at outcome level: pembrolizumab vs. watchful waiting (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pembrolizumab vs. placebo** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Metabolism and nutrition disorders (severe AEs)	5.3% vs. 2.8% RR: 1.89 [1.00; 3.57] RR: 0.53 [0.28; 1.00][g]; p = 0.047 Probability: "hint"	Outcome category: serious/severe side effects Greater harm, extent: "minor"

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size and the scale of the outcome are made with different limits based on the upper or lower limit of the confidence interval (CI_u or CI_L).
c. See Section 2.1 for reasons.
d. The outcome of recurrence was observed until recurrence, start of subsequent oncological therapy, pregnancy, withdrawal of consent, end of study, or death from any cause.
e. There is no statistically significant effect modification for the recurrence rate, but comparable estimates in both subgroups (see Section 2.5).
f. No data for the second data cut-off are available for the outcomes recorded using FKSI-DRS, EORTC QLQ-C30 and EQ-5D-5L VAS. Results for the first data cut-off can be found in dossier assessment A22-71 [1]. The data from the first data cut-off are still relevant to the benefit assessment, as no substantial gain in information is to be expected for the second data cut-off compared with the first data cut-off.
g. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CI_L: lower limit of confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; HR: hazard ratio; NED: no evidence of disease; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale

2.6.2 Overall conclusion on added benefit

Table 9 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 9: Positive and negative effects from the assessment of pembrolizumab in comparison with watchful waiting

Positive effects	Negative effects
Total observation period	
Morbidity Serious/severe symptoms/late complications ▪ Recurrence ▫ Metastasis status M0: hint of considerable added benefit ▫ Metastasis status M1 NED: hint of major added benefit	
Shortened observation period	
	Serious/severe side effects ▪ SAEs: hint of greater harm, extent: “considerable” ▫ Including: - Immune-related SAEs: indication of greater harm, extent: “major” ▪ Severe AEs ▫ Age (< 65 years): hint of greater harm – extent: “major” ▫ Included in the overall rate of severe AEs[a] - Immune-related severe AEs: indication of greater harm, extent: “major” - Investigations (severe AEs): hint of greater harm, extent: “major” - Endocrine disorders (severe AEs), gastrointestinal disorders (severe AEs), and skin and subcutaneous tissue disorders (severe AEs): each hint of greater harm, extent: “considerable” - Metabolism and nutrition disorders (severe AEs): each hint of greater harm, extent: “minor” ▪ Discontinuation due to AEs: hint of greater harm, extent: “major”
There are no suitable data for the outcome of overall survival and incomplete subgroup analyses, in particular, (except for the outcome of recurrence) no subgroup analyses are available for the subgroup characteristic of metastasis status (M0 vs. M1 NED). a. In each case no effect modification by the subgroup characteristic of age. AE: adverse event; NED: no evidence of disease; SAE: serious adverse event	

Overall, there are both positive and negative effects for pembrolizumab in comparison with watchful waiting.

On the side of positive effects, there is a hint of considerable added benefit for the outcome of recurrence for patients with metastasis status M0. For patients with metastasis status M1 NED, there is a hint of major added benefit.

Furthermore, there are hints and indications of greater harm with different, in some cases major extent for numerous outcomes in the side effects category.

The negative effects do not completely call into question the advantage in recurrence. However, except for the outcome of recurrence, no subgroup analyses are available for the subgroup

characteristic of metastasis status (M0 versus M1 NED). Therefore, it cannot be assessed whether and to what extent the presence of this characteristic also affects other patient-relevant outcomes.

In summary, there is a hint of a non-quantifiable added benefit of pembrolizumab in comparison with the appropriate comparator therapy of watchful waiting for the adjuvant treatment of adult patients with renal cell carcinoma at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

2.7 Summary

The data subsequently submitted by the company in the commenting procedure have changed the conclusion on the added benefit of pembrolizumab from dossier assessment A22-71.

Table 10 below shows the result of the benefit assessment of pembrolizumab, taking into account dossier assessment A22-71 and the present addendum.

Table 10: Pembrolizumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adjuvant treatment of adult patients with renal cell carcinoma[b] at increased[c] risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions	Watchful waiting	Hint of a non-quantifiable added benefit[d]

a. Presented is the ACT specified by the G-BA.
b. The KEYNOTE-564 study only included patients with renal cell carcinoma with clear cell component as well as with an ECOG PS of 0 or 1. It remains unclear whether the observed effects are transferable to patients without clear cell component and with an ECOG PS ≥ 2.
c. Defined as intermediate-high risk or high risk of recurrence, or M1 status with NED; the different risk categories were defined based on pathological tumour node metastasis and Fuhrman grading status. Intermediate-high risk was defined as pT2 with grade 4 or sarcomatoid features, or pT3 of any grade, each without lymph node involvement (N0) and without distant metastases (M0). High risk was defined as pT4 of any grade with N0 and M0 or pT of any stage, with any grade and with lymph node involvement (N1) and M0. M1 NED RCC status included patients who presented with solid, isolated soft tissue metastases that could be completely resected either at the time of nephrectomy (synchronous) or ≤ 1 year from nephrectomy (metachronous).
d. However, except for the outcome of recurrence, no subgroup analyses are available for the subgroup characteristic of metastasis status (M0 vs. M1 NED).

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; NED: no evidence of disease; pT: histopathologic primary tumour stage; RCC: renal cell carcinoma

The G-BA decides on the added benefit.

3 References

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Pembrolizumab (Nierenzellkarzinom) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2022 [Accessed: 02.11.2022]. URL: https://www.iqwig.de/download/a22-71_pembrolizumab_nutzenbewertung-35a-sgb-v_v1-0_neu.pdf.

2. MSD Sharp & Dohme. Stellungnahme zum IQWiG-Bericht Nr.1447: Pembrolizumab (Nierenzellkarzinom); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/865/#dossier in the document "Zusammenfassende Dokumentation"].

3. MSD Sharp & Dohme. Pembrolizumab (KEYTRUDA); Dossier zur Nutzenbewertung gemäß §35a SGB V [online]. 2022 [Accessed: 16.12.2022]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/865/#dossier.

4. Leitlinienprogramm Onkologie. S3-Leitlinie - Diagnostik, Therapie und Nachsorge des Nierenzellkarzinoms (Langversion 3.0) [online]. 2021 [Accessed: 03.05.2022]. URL: https://www.awmf.org/uploads/tx_szleitlinien/043-017OLl_S3_Diagnostik-Therapie-Nachsorge-Nierenzellkarzinom_2021-12.pdf.

5. Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie. Nierenzellkarzinom (Hypernephrom) - Leitlinie. Stand Mai 2022 [online]. [Accessed: 22.06.2022]. URL: https://www.onkopedia.com/de/onkopedia/guidelines#section2.

6. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidlines): Kidney Cancer (Version 4.2022). 2021.

7. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Pembrolizumab (Nierenzellkarzinom) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2020 [Accessed: 02.03.2020]. URL: https://www.iqwig.de/download/A19-99_Pembrolizumab_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

8. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574. https://dx.doi.org/10.1016/0167-9473(94)90148-1.

9. Gemeinsamer Bundesausschuss. Pembrolizumab (D-833): mündliche Anhörung gemäß § 35 a Abs. 2 SGB V - stenografisches Wortprotokoll [online]. 2022 [Accessed: 21.12.2022]. URL: https://www.g-ba.de/downloads/91-1031-865/2022-12-05_Wortprotokoll_Pembrolizumab_D-833.pdf.

10. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.1 [online]. 2022 [Accessed: 17.08.2022]. URL: https://www.iqwig.de/methoden/general-methods_version-6-1.pdf.

Appendix A – Results on the outcome of overall survival

Table 11: Results (mortality) – RCT, direct comparison: pembrolizumab vs. watchful waiting

Study Outcome category Outcome	Pembrolizumab N	Median time to event in months [95% CI] Patients with event n (%)	Placebo N	Median time to event in months [95% CI] Patients with event n (%)	Pembrolizumab vs. placebo HR [95% CI]; p-value[a]
KEYNOTE-564 (data cut-off on 14 June 2021)					
Mortality					
Overall survival	496	NA 23 (4.6)	498	NA 43 (8.6)	0.52 [0.31; 0.86]; 0.011

a. Unless otherwise stated, Cox proportional hazards model with associated 2-sided Wald test stratified by metastasis status (M1 NED vs. M0). Within M0, additional stratification is done according to ECOG PS (0 vs. 1) and region (USA vs. non-USA).

CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Performance Status; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NED: no evidence of disease; RCT: randomized controlled trial

Table 12: Subgroups (mortality) – RCT, direct comparison: pembrolizumab vs. watchful waiting

Study Outcome Characteristic Subgroup	Pembrolizumab N	Median time to event in months [95% CI] Patients with event n (%)	Placebo N	Median time to event in months [95% CI] Patients with event n (%)	Pembrolizumab vs. placebo HR [95% CI][a]	p-value[a]
KEYNOTE-564 (data cut-off on 14 June 2021)						
Mortality						
Overall survival						
Sex						
Female	149	NA [44.4; NC] 11 (7.4)	139	NA 8 (5.8)	1.32 [0.53; 3.28]	0.551
Male	347	NA 12 (3.5)	359	NA 35 (9.7)	0.34 [0.18; 0.66]	0.001
Total					Interaction[b]:	0.016

a. HR, CI and p-value: Cox proportional hazards model, unstratified.
b. Cox proportional hazards model with subgroup as covariable and corresponding interaction term; p-value based on likelihood ratio test.

CI: confidence interval; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial

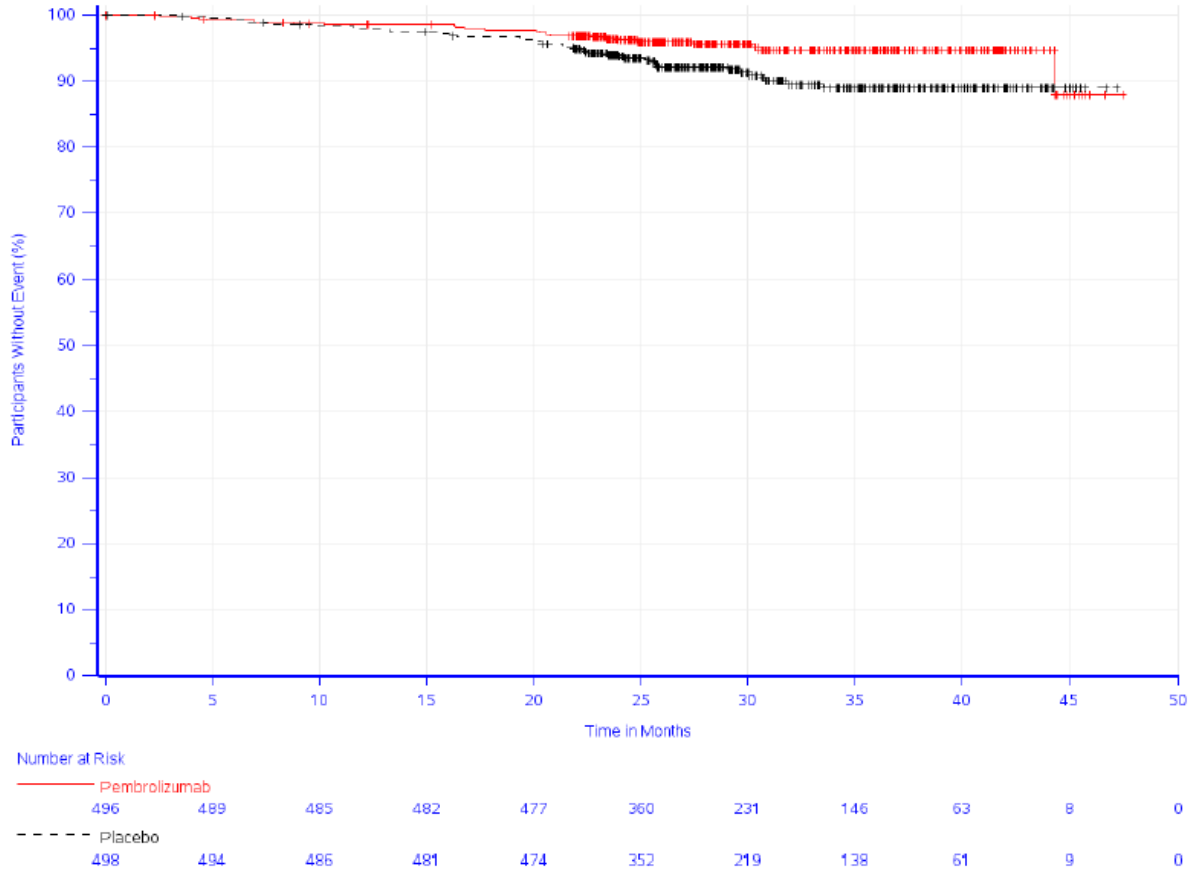

Figure 1: Kaplan-Meier curves for the outcome of overall survival – RCT, direct comparison: pembrolizumab vs. watchful waiting, KEYNOTE 564 study, second data cut-off (14 June 2021)

Appendix B – Results on side effects

For the overall rates of AEs, SAEs, and severe AEs (CTCAE grade ≥ 3), the following tables present events for System Organ Classes (SOCs) and Preferred Terms (PTs) according to the Medical Dictionary for Regulatory Activities (MedDRA), each on the basis of the following criteria:

- Overall rate of AEs (irrespective of severity grade): events that occurred in at least 10% of patients in one study arm
- Overall rates of severe AEs (e.g. CTCAE grade ≥ 3) and SAEs: events that occurred in at least 10 patients in one study arm
- In addition, for all events irrespective of severity grade: events that occurred in at least 10 patients and in at least 1% of patients in one study arm

For the outcome of discontinuation due to AEs, a complete presentation of all events (SOCs/PTs) that resulted in discontinuation is provided.

Table 13: Common AEs[a] – RCT, direct comparison: pembrolizumab vs. watchful waiting (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Pembrolizumab** **N = 488**	**Placebo** **N = 496**
KEYNOTE-564 (data cut-off on 14 June 2021)		
Overall rate of AEs[c]	470 (96.3)	453 (91.3)
Blood and lymphatic system disorders	38 (7.8)	31 (6.3)
Anaemia	20 (4.1)	18 (3.6)
Cardiac disorders	22 (4.5)	18 (3.6)
Ear and labyrinth disorders	23 (4.7)	20 (4.0)
Vertigo	9 (1.8)	11 (2.2)
Endocrine disorders	132 (27.0)	21 (4.2)
Adrenal insufficiency	10 (2.0)	1 (0.2)
Hyperthyroidism	62 (12.7)	1 (0.2)
Hypothyroidism	103 (21.1)	18 (3.6)
Eye disorders	40 (8.2)	36 (7.3)
Dry eye	10 (2.0)	3 (0.6)
Vision blurred	10 (2.0)	6 (1.2)

Table 13: Common AEs[a] – RCT, direct comparison: pembrolizumab vs. watchful waiting (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Pembrolizumab N = 488**	**Placebo N = 496**
Gastrointestinal disorders	262 (53.7)	228 (46.0)
Abdominal distension	10 (2.0)	5 (1.0)
Abdominal pain	38 (7.8)	40 (8.1)
Lower abdominal pain	6 (1.2)	10 (2.0)
Upper abdominal pain	14 (2.9)	18 (3.6)
Constipation	35 (7.2)	40 (8.1)
Diarrhoea	125 (25.6)	112 (22.6)
Dry mouth	33 (6.8)	5 (1.0)
Dyspepsia	22 (4.5)	12 (2.4)
Gastrooesophageal reflux disease	13 (2.7)	14 (2.8)
Nausea	80 (16.4)	48 (9.7)
Stomatitis	11 (2.3)	7 (1.4)
Vomiting	41 (8.4)	28 (5.6)
General disorders and administration site conditions	251 (51.4)	215 (43.3)
Asthenia	50 (10.2)	36 (7.3)
Chest pain	7 (1.4)	12 (2.4)
Chills	13 (2.7)	11 (2.2)
Fatigue	145 (29.7)	120 (24.2)
Influenza like illness	26 (5.3)	21 (4.2)
Oedema	11 (2.3)	1 (0.2)
Oedema peripheral	21 (4.3)	27 (5.4)
Pyrexia	31 (6.4)	23 (4.6)
Hepatobiliary disorders	25 (5.1)	10 (2.0)
Immune system disorders	14 (2.9)	10 (2.0)
Infections and infestations	215 (44.1)	182 (36.7)
Bronchitis	13 (2.7)	9 (1.8)
Influenza	18 (3.7)	11 (2.2)
Lower respiratory tract infection	12 (2.5)	5 (1.0)
Nasopharyngitis	28 (5.7)	42 (8.5)
Pneumonia	10 (2.0)	6 (1.2)
Rhinitis	11 (2.3)	10 (2.0)
Sinusitis	16 (3.3)	6 (1.2)
Upper respiratory tract infection	28 (5.7)	24 (4.8)
Urinary tract infection	31 (6.4)	22 (4.4)
Injury, poisoning and procedural complications	45 (9.2)	63 (12.7)
Investigations	162 (33.2)	116 (23.4)

Table 13: Common AEs[a] – RCT, direct comparison: pembrolizumab vs. watchful waiting (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Pembrolizumab N = 488**	**Placebo N = 496**
Alanine aminotransferase increased	35 (7.2)	17 (3.4)
Aspartate aminotransferase increased	36 (7.4)	10 (2.0)
Blood alkaline phosphatase increased	13 (2.7)	3 (0.6)
Blood creatinine increased	50 (10.2)	42 (8.5)
Blood thyroid stimulating hormone increased	11 (2.3)	5 (1.0)
Weight decreased	16 (3.3)	6 (1.2)
Weight increased	22 (4.5)	23 (4.6)
Metabolism and nutrition disorders	116 (23.8)	100 (20.2)
Decreased appetite	35 (7.2)	10 (2.0)
Hyperglycaemia	28 (5.7)	17 (3.4)
Hyperkalaemia	12 (2.5)	16 (3.2)
Hyperuricaemia	11 (2.3)	12 (2.4)
Hypophosphataemia	9 (1.8)	13 (2.6)
Musculoskeletal and connective tissue disorders	231 (47.3)	209 (42.1)
Arthralgia	108 (22.1)	94 (19.0)
Arthritis	10 (2.0)	7 (1.4)
Back pain	49 (10.0)	64 (12.9)
Flank pain	14 (2.9)	22 (4.4)
Muscle spasms	17 (3.5)	17 (3.4)
Musculoskeletal chest pain	5 (1.0)	13 (2.6)
Myalgia	46 (9.4)	32 (6.5)
Neck pain	3 (0.6)	22 (4.4)
Pain in extremity	35 (7.2)	25 (5.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	12 (2.5)	19 (3.8)
Nervous system disorders	153 (31.4)	123 (24.8)
Dizziness	39 (8.0)	27 (5.4)
Dysgeusia	13 (2.7)	6 (1.2)
Headache	69 (14.1)	62 (12.5)
Paraesthesia	17 (3.5)	8 (1.6)
Psychiatric disorders	53 (10.9)	56 (11.3)
Anxiety	12 (2.5)	15 (3.0)
Depression	13 (2.7)	11 (2.2)
Insomnia	26 (5.3)	30 (6.0)

Table 13: Common AEs[a] – RCT, direct comparison: pembrolizumab vs. watchful waiting (multipage table)

Study	Patients with event n (%)	
SOC[b] **PT[b]**	**Pembrolizumab** **N = 488**	**Placebo** **N = 496**
Renal and urinary disorders	65 (13.3)	52 (10.5)
Haematuria	14 (2.9)	11 (2.2)
Pollakiuria	8 (1.6)	10 (2.0)
Proteinuria	11 (2.3)	4 (0.8)
Reproductive system and breast disorders	26 (5.3)	16 (3.2)
Respiratory, thoracic and mediastinal disorders	159 (32.6)	124 (25.0)
Cough	76 (15.6)	50 (10.1)
Dyspnoea	31 (6.4)	27 (5.4)
Nasal congestion	11 (2.3)	16 (3.2)
Oropharyngeal pain	20 (4.1)	20 (4.0)
Productive cough	8 (1.6)	11 (2.2)
Rhinorrhoea	14 (2.9)	13 (2.6)
Skin and subcutaneous tissue disorders	251 (51.4)	163 (32.9)
Dermatitis	11 (2.3)	4 (0.8)
Dry skin	26 (5.3)	23 (4.6)
Itching	111 (22.7)	65 (13.1)
Rash	98 (20.1)	53 (10.7)
Rash maculo-papular	20 (4.1)	9 (1.8)
Rash pruritic	13 (2.7)	1 (0.2)
Vascular disorders	63 (12.9)	54 (10.9)
Hot flush	11 (2.3)	3 (0.6)
Hypertension	38 (7.8)	39 (7.9)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 24.0; SOCs and PTs used unmodified from Module 4 A.
c. Progression events of the underlying disease are not included (PTs “neoplasm progression”, “malignant neoplasm progression” and “disease progression”).

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 14: Common SAEs[a] – RCT, direct comparison: pembrolizumab vs. watchful waiting

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Pembrolizumab** **N = 488**	**Placebo** **N = 496**
KEYNOTE-564 (data cut-off on 14 June 2021)		
Overall rate of SAEs[c]	101 (20.7)	57 (11.5)
Cardiac disorders	10 (2.0)	5 (1.0)
Endocrine disorders	12 (2.5)	0 (0.0)
Gastrointestinal disorders	14 (2.9)	6 (1.2)
Infections and infestations	21 (4.3)	12 (2.4)
Metabolism and nutrition disorders	15 (3.1)	2 (0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (1.0)	10 (2.0)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 24.0; SOCs and PTs used unmodified from Module 4 A.
c. Progression events of the underlying disease are not included (PTs “neoplasm progression”, “malignant neoplasm progression” and “disease progression”).

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 15: Common severe AEs[a] (CTCAE grade ≥ 3) – RCT, direct comparison: pembrolizumab vs. watchful waiting

Study	Patients with event n (%)	
SOC[b] PT[b]	Pembrolizumab N = 488	Placebo N = 496
KEYNOTE-564 (data cut-off on 14 June 2021)		
Overall rate of severe AEs (CTCAE grade ≥ 3)[c]	157 (32.2)	88 (17.7)
Cardiac disorders	11 (2.3)	5 (1.0)
Endocrine disorders	12 (2.5)	1 (0.2)
Gastrointestinal disorders	24 (4.9)	9 (1.8)
Infections and infestations	22 (4.5)	15 (3.0)
Investigations	27 (5.5)	4 (0.8)
Alanine aminotransferase increased	11 (2.3)	1 (0.2)
Metabolism and nutrition disorders	26 (5.3)	14 (2.8)
Musculoskeletal and connective tissue disorders	10 (2.0)	5 (1.0)
Renal and urinary disorders	10 (2.0)	8 (1.6)
Respiratory, thoracic and mediastinal disorders	11 (2.3)	4 (0.8)
Skin and subcutaneous tissue disorders	10 (2.0)	2 (0.4)
Vascular disorders	18 (3.7)	15 (3.0)
Hypertension	14 (2.9)	13 (2.6)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 24.0; SOCs and PTs used unmodified from Module 4 A.
c. Progression events of the underlying disease are not included (PTs "neoplasm progression", "malignant neoplasm progression" and "disease progression").

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 16: Discontinuations due to AEs – RCT, direct comparison: pembrolizumab vs. watchful waiting (multipage table)

Study	Patients with event n (%)	
SOC[a] PT[a]	Pembrolizumab N = 488	Placebo N = 496
KEYNOTE-564 (second data cut-off: 14 June 2021)		
Overall rate of discontinuations due to AEs[b]	103 (21.1)	11 (2.2)
Blood and lymphatic system disorders	2 (0.4)	0 (0.0)
Immune thrombocytopenia	1 (0.2)	0 (0.0)
Thrombocytopenia	2 (0.4)	0 (0.0)
Cardiac disorders	6 (1.2)	0 (0.0)
Myocardial infarction	2 (0.4)	0 (0.0)
Atrial fibrillation	1 (0.2)	0 (0.0)
Cardiac failure	1 (0.2)	0 (0.0)
Myocarditis	1 (0.2)	0 (0.0)
Pleuropericarditis	1 (0.2)	0 (0.0)
Endocrine disorders	12 (2.5)	0 (0.0)
Adrenal insufficiency	6 (1.2)	0 (0.0)
Hypothyroidism	2 (0.4)	0 (0.0)
Thyroiditis	2 (0.4)	0 (0.0)
Autoimmune thyroiditis	1 (0.2)	0 (0.0)
Hypophysitis	1 (0.2)	0 (0.0)
Eye disorders	2 (0.4)	1 (0.2)
Eyelid ptosis	1 (0.2)	0 (0.0)
Retinal detachment	0 (0.0)	1 (0.2)
Visual impairment	1 (0.2)	0 (0.0)
Gastrointestinal disorders	13 (2.7)	0 (0.0)
Colitis	5 (1.0)	0 (0.0)
Diarrhoea	4 (0.8)	0 (0.0)
Diverticulum	1 (0.2)	0 (0.0)
Dry mouth	1 (0.2)	0 (0.0)
Enterocolitis	1 (0.2)	0 (0.0)
Gastritis	1 (0.2)	0 (0.0)
General disorders and administration site conditions	3 (0.6)	2 (0.4)
Fatigue	1 (0.2)	1 (0.2)
Asthenia	1 (0.2)	0 (0.0)
Multiorgan failure	1 (0.2)	0 (0.0)
Non-cardiac chest pain	0 (0.0)	1 (0.2)

Table 16: Discontinuations due to AEs – RCT, direct comparison: pembrolizumab vs. watchful waiting (multipage table)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Pembrolizumab** **N = 488**	**Placebo** **N = 496**
Hepatobiliary disorders	4 (0.8)	2 (0.4)
Drug-induced liver injury	1 (0.2)	0 (0.0)
Hepatitis	1 (0.2)	0 (0.0)
Hepatitis alcoholic	0 (0.0)	1 (0.2)
Hepatotoxicity	0 (0.0)	1 (0.2)
Immune-mediated hepatitis	1 (0.2)	0 (0.0)
Liver disorder	1 (0.2)	0 (0.0)
Immune system disorders	4 (0.8)	0 (0.0)
Sarcoidosis	3 (0.6)	0 (0.0)
Hypersensitivity	1 (0.2)	0 (0.0)
Infections and infestations	3 (0.6)	0 (0.0)
Pneumonia	2 (0.4)	0 (0.0)
Anorectal infection	1 (0.2)	0 (0.0)
Injury, poisoning and procedural complications	0 (0.0)	1 (0.2)
Multiple injuries	0 (0.0)	1 (0.2)
Investigations	16 (3.3)	1 (0.2)
Alanine aminotransferase increased	8 (1.6)	0 (0.0)
Blood creatinine increased	4 (0.8)	1 (0.2)
Aspartate aminotransferase increased	4 (0.8)	0 (0.0)
Amylase increased	1 (0.2)	0 (0.0)
Blood thyroid stimulating hormone decreased	1 (0.2)	0 (0.0)
Gamma-glutamyltransferase increased	1 (0.2)	0 (0.0)
Thyroxine increased	1 (0.2)	0 (0.0)
Transaminases increased	1 (0.2)	0 (0.0)
Tri-iodothyronine increased	1 (0.2)	0 (0.0)
Metabolism and nutrition disorders	7 (1.4)	0 (0.0)
Type 1 diabetes mellitus	3 (0.6)	0 (0.0)
Diabetes mellitus	2 (0.4)	0 (0.0)
Diabetic ketoacidosis	2 (0.4)	0 (0.0)
Glucose tolerance impaired	1 (0.2)	0 (0.0)
Musculoskeletal and connective tissue disorders	8 (1.6)	1 (0.2)
Arthralgia	2 (0.4)	1 (0.2)
Arthritis	3 (0.6)	0 (0.0)
Sjogren’s syndrome	2 (0.4)	0 (0.0)
Myositis	1 (0.2)	0 (0.0)

Table 16: Discontinuations due to AEs – RCT, direct comparison: pembrolizumab vs. watchful waiting (multipage table)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Pembrolizumab** **N = 488**	**Placebo** **N = 496**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.6)	2 (0.4)
Benign lung neoplasm	1 (0.2)	0 (0.0)
Choroid melanoma	0 (0.0)	1 (0.2)
Colon neoplasm	0 (0.0)	1 (0.2)
Neuroendocrine tumour	1 (0.2)	0 (0.0)
Papillary thyroid cancer	1 (0.2)	0 (0.0)
Nervous system disorders	5 (1.0)	1 (0.2)
Ataxia	0 (0.0)	1 (0.2)
Cerebellar syndrome	1 (0.2)	0 (0.0)
Cerebral ischaemia	1 (0.2)	0 (0.0)
Loss of consciousness	1 (0.2)	0 (0.0)
Myasthenia gravis	1 (0.2)	0 (0.0)
Polyneuropathy	1 (0.2)	0 (0.0)
Renal and urinary disorders	9 (1.8)	0 (0.0)
Acute kidney injury	4 (0.8)	0 (0.0)
Nephritis	2 (0.4)	0 (0.0)
Hydronephrosis	1 (0.2)	0 (0.0)
Renal impairment	1 (0.2)	0 (0.0)
Tubulointerstitial nephritis	1 (0.2)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	7 (1.4)	0 (0.0)
Immune-mediated lung disease	2 (0.4)	0 (0.0)
Pneumonitis	2 (0.4)	0 (0.0)
Pulmonary embolism	2 (0.4)	0 (0.0)
Asthma	1 (0.2)	0 (0.0)
Skin and subcutaneous tissue disorders	6 (1.2)	0 (0.0)
Rash	4 (0.8)	0 (0.0)
Lichen planus	1 (0.2)	0 (0.0)
Lichenification	1 (0.2)	0 (0.0)
Vascular disorders	1 (0.2)	0 (0.0)
Essential hypertension	1 (0.2)	0 (0.0)

a. MedDRA version 24.0; SOCs and PTs used unmodified from Module 4 A.
b. Progression events of the underlying disease are not included (PTs “neoplasm progression”, “malignant neoplasm progression” and “disease progression”).

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Appendix C – Kaplan-Meier curves

C.1 Recurrence

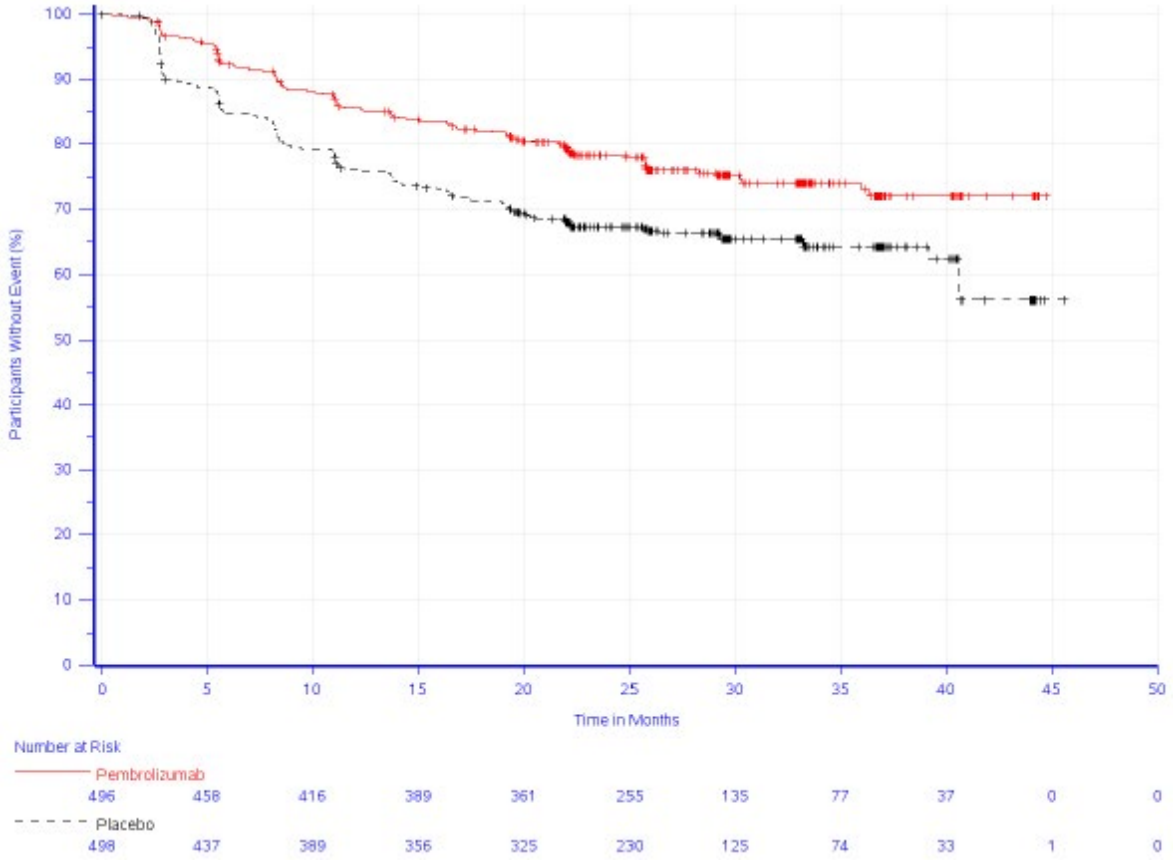

Figure 2: Kaplan-Meier curves for the outcome of disease-free survival (investigator) – RCT, direct comparison: pembrolizumab vs. watchful waiting, KEYNOTE-564 study, second data cut-off (14 June 2021)

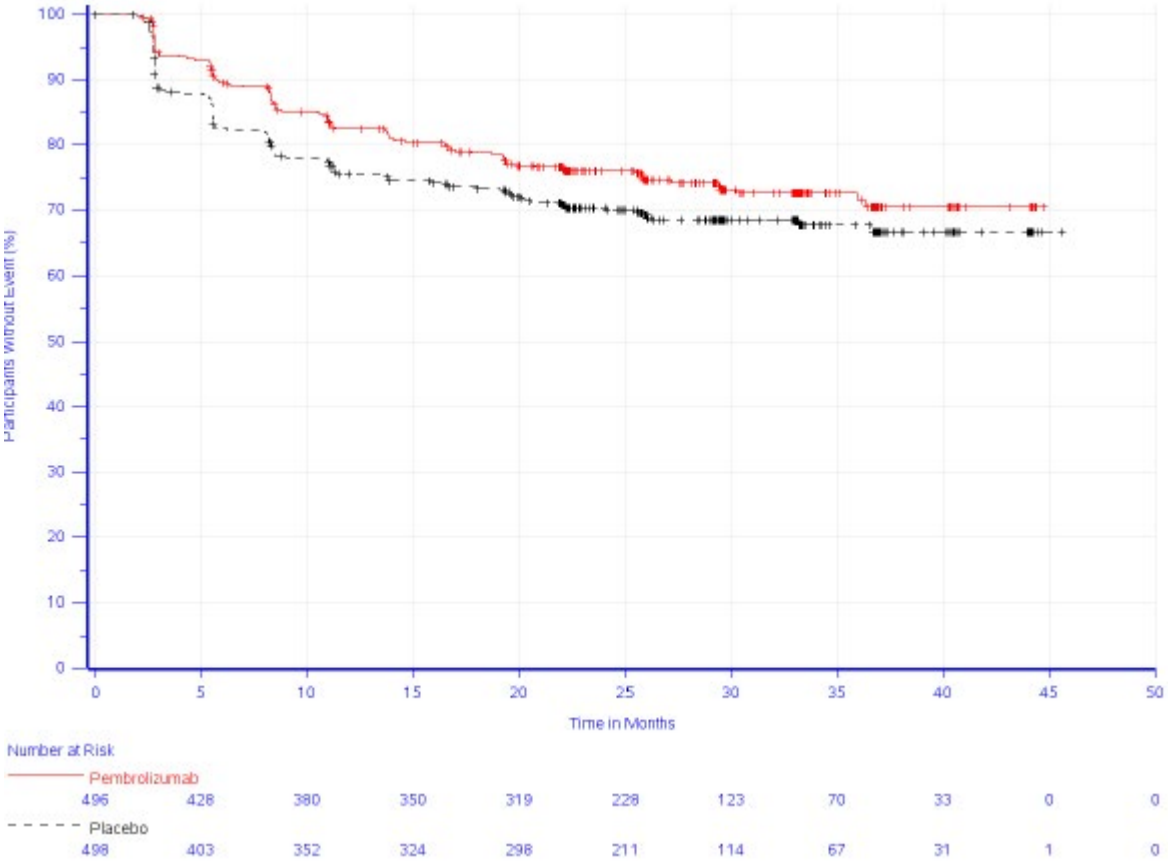

Figure 3: Kaplan-Meier curves for the outcome of disease-free survival (BICR) – RCT, direct comparison: pembrolizumab vs. watchful waiting, KEYNOTE-564 study, second data cut-off (14 June 2021)

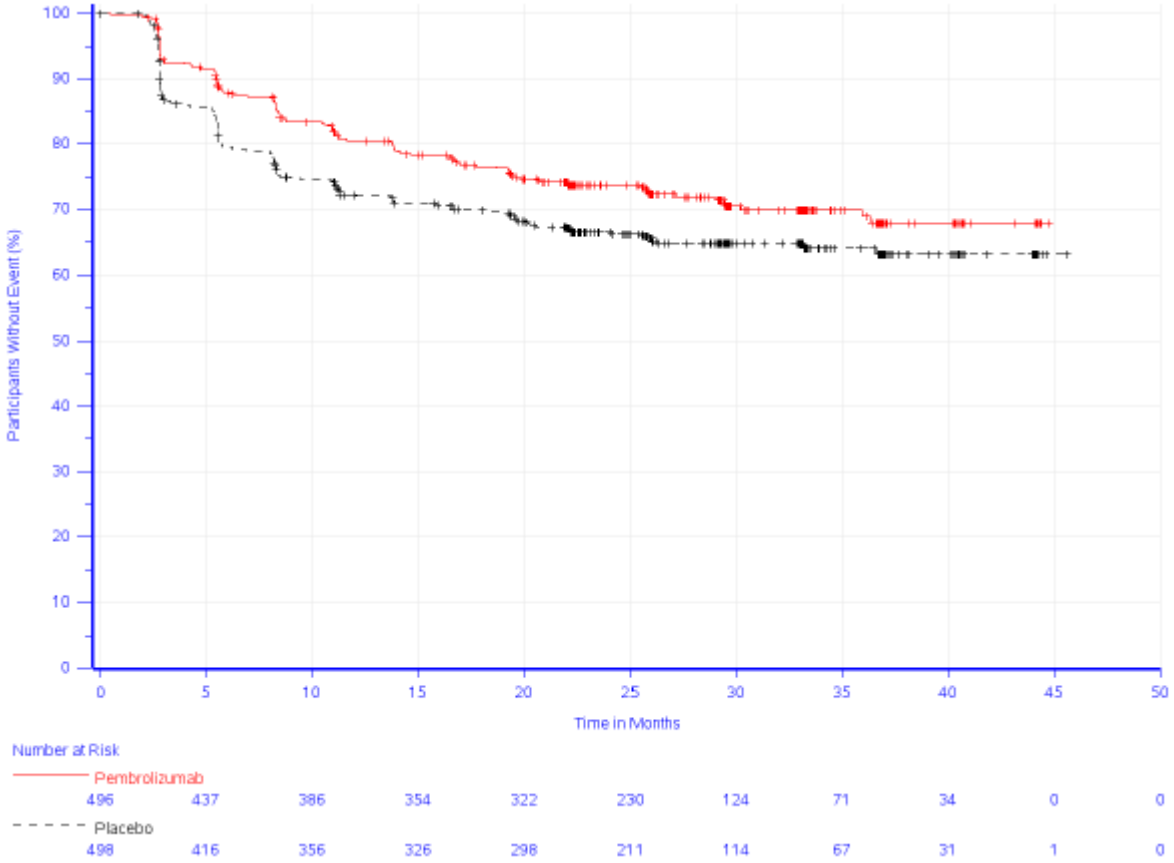

Figure 4: Kaplan-Meier curves for the outcome of event-free survival (BICR) – RCT, direct comparison: pembrolizumab vs. watchful waiting, KEYNOTE-564 study, second data cut-off (14 June 2021)

C.2 Subgroup analyses

C.2.1 Kaplan-Meier curves

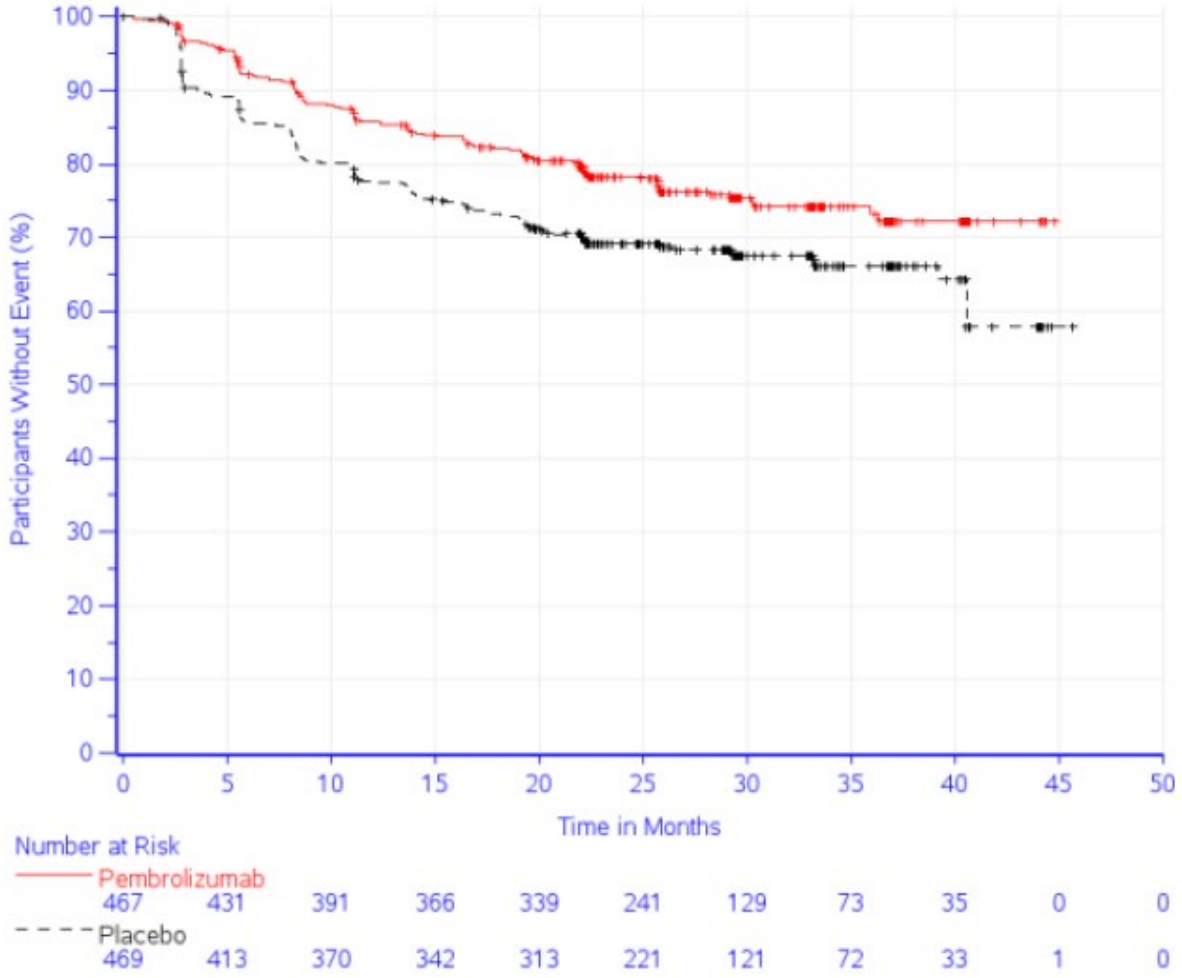

Figure 5: Kaplan-Meier curves for the outcome of disease-free survival, subgroup "metastasis status", category "M0" – RCT, direct comparison: pembrolizumab vs. watchful waiting, KEYNOTE-564 study, second data cut-off (14 June 2021)

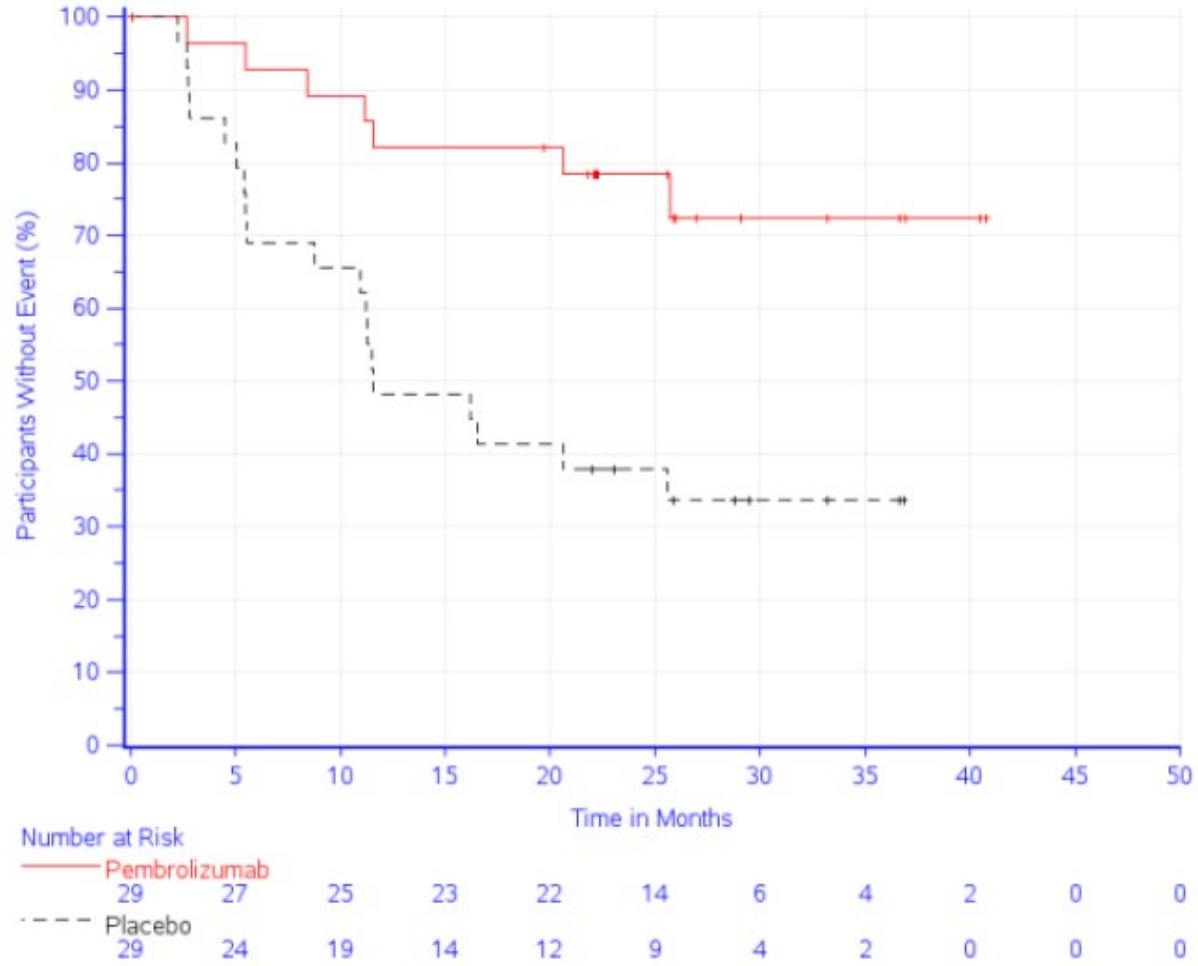

Figure 6: Kaplan-Meier curves for the outcome of disease-free survival, subgroup "metastasis status", category "M1 NED" – RCT, direct comparison: pembrolizumab vs. watchful waiting, KEYNOTE-564 study, second data cut-off (14 June 2021)

C.2.2 Recurrence rate

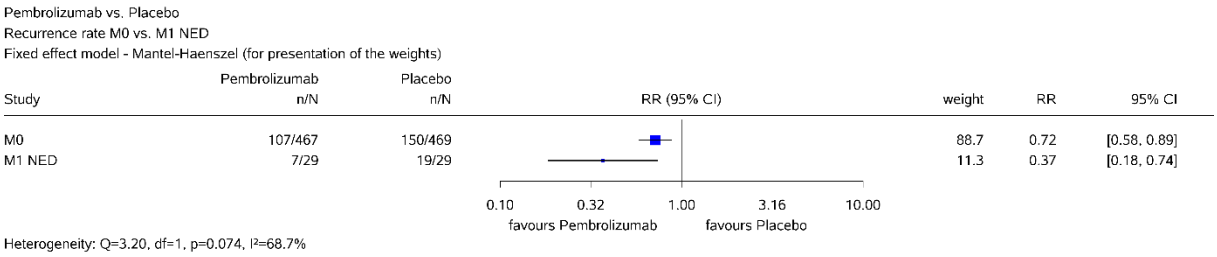

Figure 7: Subgroup analysis for the outcome of recurrence rate for the subgroups M0 vs. M1 NED (metastasis status) – RCT, direct comparison: pembrolizumab vs. watchful waiting, KEYNOTE-564 study, second data cut-off (14 June 2021)