IQWiG Reports – Commission No. A22-71

Pembrolizumab (renal cell carcinoma) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections I 1 to I 5 of the dossier assessment *Pembrolizumab (Nierenzellkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 October 2022). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Jochem Potenberg, Waldkrankenhaus Protestant Hospital, Berlin, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

IQWiG employees involved in the dossier assessment

- Annette Christoph
- Christiane Balg
- Tatjana Hermanns
- Katharina Hirsch
- Petra Kohlepp
- Regine Potthast
- Daniela Preukschat
- Min Ripoll

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Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BICR	blinded independent central review
CI	confidence interval
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DFS	disease-free survival
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EPAR	European Public Assessment Report
FKSI-DRS	Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MD	mean difference
MMRM	mixed-effects model with repeated measures
MRI	magnetic resonance imaging
NED	no evidence of disease
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMD	Standardized Mean Difference
VAS	visual analogue scale
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug pembrolizumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 21 July 2022.

Research question

The aim of the present report is the assessment of the added benefit of pembrolizumab in comparison with watchful waiting as appropriate comparator therapy (ACT) 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.

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of pembrolizumab

Therapeutic indication	ACT[a]
Adjuvant treatment of adult patients with renal cell carcinoma at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions	Watchful waiting
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) are used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

Study pool and study design

The KEYNOTE-564 study is included for the benefit assessment of pembrolizumab. The KEYNOTE-564 study is an ongoing, double-blind, randomized, multicentre study on the comparison of pembrolizumab with placebo. The study included adult patients with clear-cell renal cell carcinoma at increased risk of recurrence after partial nephroprotective or complete nephrectomy (and complete resection of metastatic lesions) with negative surgical margins. Increased risk of recurrence was defined as intermediate-high or high risk of recurrence, or M1 status with no evidence of disease (NED). Patients must have undergone the nephrectomy and/or metastasectomy at least 28 days prior to signing informed consent and no more than 12 weeks prior to randomization. Patients were also required to have computed tomography (CT) scan and/or magnetic resonance imaging (MRI) scan of the chest, abdomen, pelvis, brain

and bones within 28 days prior to randomization. Imaging results were sent to a blinded independent central review (BICR), which, according to the study protocol, checked before randomization that all scans were received and of diagnostic quality. The absence of tumours at the start of the study was confirmed by the investigator for inclusion in the study. Patients must not have received any systemic therapy for advanced renal cell carcinoma and had to be in good general condition according to the Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 1.

A total of 994 patients were enrolled in the KEYNOTE-564 study and randomized at a 1:1 ratio to treatment with either pembrolizumab (N = 496) or placebo (N = 498).

Pembrolizumab treatment was administered in 3-week cycles and was in line with the specifications of the Summary of Product Characteristics (SPC). Patients were treated for up to 1 year (maximum 17 cycles) or until confirmed recurrence, unacceptable toxicity, health reasons that prevented further administration of treatment, physician's or patient's decision to discontinue therapy, or withdrawal of consent.

Primary outcome of the KEYNOTE-564 study was disease-free survival (DFS) as assessed by the investigator. Patient-relevant secondary outcomes were outcomes on mortality, morbidity, health-related quality of life and adverse events (AEs).

The present benefit assessment uses the results from the first data cut-off of 14 December 2020.

Implementation of the appropriate comparator therapy

The G-BA specified watchful waiting as ACT. The KEYNOTE-564 study used placebo as comparator therapy. The study was not designed for a comparison with watchful waiting, but is nonetheless suitable for such a comparison. Despite minor deviations (e.g. no sonographic examinations, termination of clinical examinations and laboratory testing at the end of treatment, i.e. in the longest case after about 1 year) from the recommendations of the S3 guideline, the patients in the study received close and targeted examinations for the detection of local recurrences and distant metastases, so that the procedure in the KEYNOTE-564 study is rated as sufficient implementation of the ACT, and the study is used for the benefit assessment in comparison with watchful waiting.

Risk of bias and certainty of conclusions of the results

The risk of bias across outcomes is rated as low for the KEYNOTE-564 study. The outcome-specific risk of bias is rated as high for the results of all patient-relevant outcomes except the outcome of discontinuation due to AEs. Due to the size of the respective effect, there is a high certainty of results for the outcomes of immune-related serious AEs (SAEs) and immune-related severe AEs from the KEYNOTE-564 study despite high risk of bias. 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.

Results

Mortality

Overall survival

No suitable data are available for the outcome of overall survival, as 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 is not clear from the information in the dossier why only 41.1% or 30.9% (depending on the reference value: patients with subsequent therapy or with recurrence) of the patients received guideline-compliant treatment with immune checkpoint inhibitor-based therapy after recurrence. In the present situation, it is 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 cannot be interpreted.

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

Morbidity

Recurrence

For the outcome of recurrence (operationalized as recurrence rate and DFS), a statistically significant difference between the treatment groups in favour of pembrolizumab in comparison with watchful waiting is shown for both operationalizations. The operationalizations according to BICR presented as supplementary information 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.

Symptoms

FKSI-DRS

On the basis of mean differences, a statistically significant difference between treatment groups was found for the outcome of symptoms recorded with the Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms (FKSI-DRS). The standardized mean difference (SMD) was analysed to examine the relevance of the result. The 95% confidence interval (CI) of the SMD is not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the observed effect is relevant. This results in no hint of added benefit of pembrolizumab in comparison with watchful waiting; an added benefit is therefore not proven.

European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)

Fatigue, nausea and vomiting, dyspnoea and appetite loss

For the outcomes of fatigue, nausea and vomiting, dyspnoea and appetite loss, the analyses based on mean differences show statistically significant differences between the treatment groups. The SMD is analysed to examine the relevance of the result. The 95% CI of the SMD is not completely outside the irrelevance range of −0.2 to 0.2 for each of them. The observed effect can therefore not be inferred to be relevant. This results in no hint of added benefit of pembrolizumab in comparison with watchful waiting; an added benefit is therefore not proven in each case.

Pain, insomnia, constipation and diarrhoea

For the outcomes of pain, insomnia, constipation and diarrhoea, the analyses based on mean differences show no statistically significant differences between the treatment groups. This results in no hint of added benefit of pembrolizumab in comparison with watchful waiting; an added benefit is therefore not proven in each case.

Health status (EQ-5D VAS)

On the basis of mean differences, no statistically significant difference between treatment groups was found for the outcome of health status measured with the EQ-5D visual analogue scale (VAS). This results in no hint of added benefit of pembrolizumab in comparison with watchful waiting; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

Analyses based on mean differences show statistically significant differences between the treatment groups for each of the outcomes of global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning. The SMD is analysed to examine the relevance of the result. The 95% CI of the SMD is not completely outside the irrelevance range of −0.2 to 0.2 for each of them. The observed effect can therefore not be inferred to be relevant. This results in no hint of added benefit of pembrolizumab in comparison with watchful waiting; an added benefit is therefore not proven in each case.

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 (Common Terminology Criteria for Adverse Events [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), gastrointestinal disorders (severe AEs), skin and subcutaneous tissue disorders (severe AEs), investigations (severe AEs) and metabolism and nutrition disorders (severe AEs)

For the outcomes of endocrine disorders (severe AEs), gastrointestinal disorders (severe AEs), skin and subcutaneous tissue 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.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the extent and probability of the added benefit of the drug pembrolizumab compared with the ACT is assessed as follows:

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

For the other patient-reported outcomes of the outcome categories of morbidity and health-related quality of life, there are neither positive nor negative effects. It should be noted that no suitable data for the outcome of overall survival and overall no complete subgroup analyses for all relevant outcomes or relevant subgroup characteristics are available for the first data cut-off.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

The negative effects do not completely outweigh the advantage in recurrence, but result in a downgrading of the extent of the added benefit.

In summary, there is a hint of minor added benefit of pembrolizumab in comparison with the ACT 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.

Table 3 shows a summary of the probability and extent of added benefit of pembrolizumab.

Table 3: 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 minor added benefit

a. Presented is the respective ACT specified by the GBA.
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).

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 approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is the assessment of the added benefit of pembrolizumab in comparison with watchful waiting as ACT 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.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of pembrolizumab

Therapeutic indication	**ACT**[a]
Adjuvant treatment of adult patients with renal cell carcinoma at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions	Watchful waiting
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs are used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

I 3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on pembrolizumab (status: 11 May 2022)
- bibliographical literature search on pembrolizumab (last search on 4 May 2022)
- search in trial registries/trial results databases for studies on pembrolizumab (last search on 3 May 2022)
- search on the G-BA website for pembrolizumab (last search on 6 May 2022)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 29 July 2022); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 3.1 Studies included

The study presented in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: pembrolizumab vs. watchful waiting

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
MK-3475-564 (KEYNOTE-564[d])	Yes	Yes	No	Yes[e] [3]	Yes [4,5]	Yes [6,7]

a. Study for which the company was sponsor.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to by this acronym.
e. The CSR contains results only for the first data cut-off (14 December 2020). This is used for the assessment of all outcomes in the present benefit assessment. See Section I 3.2 for more details.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

For the benefit assessment of pembrolizumab, the procedure in the placebo-controlled KEYNOTE-564 study is rated as sufficient implementation of the ACT (see Section I 3.2) and the KEYNOTE-564 study is included. This concurs with the company's study pool.

I 3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.Table 6: Characteristics of the study included – RCT, direct comparison: pembrolizumab vs. watchful waiting (multipage table)

Study	Study design-	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
KEYNOTE-564	RCT, double-blind, parallel	Patients (≥ 18 years) ▪ with clear-cell renal cell carcinoma[b] ▪ at increased risk of recurrence[c] ▪ after partial nephroprotective or radical complete nephrectomy (and complete resection of metastatic lesions[d]) with negative surgical margins ▪ without prior systemic therapy for advanced renal cell carcinoma ▪ ECOG PS 0 or 1	▪ Pembrolizumab (N = 496) ▪ placebo (N = 498)	▪ Screening: ≤ 42 days ▪ Treatment: up to 1 year (maximum 17 cycles) or until confirmed recurrence, unacceptable toxicity, health reasons that prevent further administration of treatment, investigator's or patient's decision, or withdrawal of consent ▪ Observation[e]: outcome-specific, at most until death, withdrawal of consent, or end of the study	212 study centres in Argentina, Australia, Brazil, Canada, Chile, Colombia, Czech Republic, Finland, France, Germany, Ireland, Italy, Japan, Netherlands, Poland, Russia, South Korea, Spain, Taiwan, United Kingdom, and USA 06/2017–ongoing[f] Data cut-off: ▪ 14 December 2020[g] ▪ 14 June 2021[h]	▪ Primary: disease-free survival ▪ Secondary: mortality, morbidity, health-related quality of life, AEs

Table 6 and Table 7 describe the study used for the benefit assessment.Table 6: Characteristics of the study included – RCT, direct comparison: pembrolizumab vs. watchful waiting (multipage table)

Study	Study design-	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Histologically confirmed clear-cell renal cell carcinoma with or without sarcomatoid features.
c. Defined as intermediate-high 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. Patients must have undergone nephrectomy and/or metastasectomy ≥ 28 days prior to signing informed consent and ≤ 12 weeks prior to randomization, and be tumour-free as assessed by the investigator.
e. Outcome-specific information is described in Table 9.
f. Estimated duration of study: 102 months.
g. First interim analysis from 14 December 2020: prespecified first interim analysis of disease-free survival and interim analysis for overall survival.
h. Data cut-off from 14 June 2021: post-hoc.

AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; N: number of randomized patients; NED: no evidence of disease; pT: histopathologic primary tumour stage; RCC: renal cell carcinoma; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: pembrolizumab vs. watchful waiting

Study	Intervention	Comparison
KEYNOTE-564	Pembrolizumab 200 mg IV on day 1 of a 3-week cycle	Placebo IV on day 1 of a 3-week cycle
	Dose adjustments ▪ Dose delays or interruptions according to the SPC of pembrolizumab [8]	
	Non-permitted pretreatment ▪ therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another co-inhibitory T-cell receptor (i.e. CTLA-4, OX-40, CD137) ▪ prior anticancer therapy, monoclonal antibody[a], chemotherapy, or an investigational product within 4 weeks or 5 half-lives (whichever is longer) before first dose of study treatment ▪ chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study treatment ▪ systemic treatment (i.e. with disease-modifying agents, corticosteroids, or immunosuppressive drugs)[b] of an autoimmune disease in past 2 years ▪ radiotherapy **Permitted concomitant treatment** ▪ any treatments necessary for the patient's wellbeing **Non-permitted concomitant treatment** ▪ antineoplastic systemic chemotherapy or biological therapy ▪ immunotherapy other than pembrolizumab or chemotherapy ▪ radiotherapy ▪ live vaccines within 30 days prior to the first dose of study medication and during study treatment ▪ systemic glucocorticoids for any purpose other than to treat symptoms of immunological origin[c] ▪ investigational products other than pembrolizumab	

a. Excluding treatment with denosumab for bone-protective purposes if dosing was stable for ≥ 2 weeks before study start (screening).
b. Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
c. Except prophylactic corticosteroids to avoid allergic reactions (e.g. IV contrast dye or transfusions), inhaled steroids and intranasal or local injection of corticosteroids.

CD137: cluster of differentiation 137; CTLA-4: cytotoxic T-lymphocyte-associated antigen-4; IV: intravenous; PD-1: programmed cell death 1; PD-L: programmed cell death ligand 1; RCT: randomized controlled trial; SPC: Summary of Product Characteristics

The KEYNOTE-564 study is an ongoing, double-blind, randomized, multicentre study on the comparison of pembrolizumab with placebo. The study included adult patients with clear-cell renal cell carcinoma at increased risk of recurrence after partial nephroprotective or complete nephrectomy (and complete resection of metastatic lesions) with negative surgical margins. Increased risk of recurrence was defined as intermediate-high or high risk of recurrence, or M1 status with NED (see Table 6).

Patients must have undergone the nephrectomy and/or metastasectomy at least 28 days prior to signing informed consent and no more than 12 weeks prior to randomization.

Patients were also required to have CT scan and/or MRI scan of the chest, abdomen, pelvis, brain and bones within 28 days prior to randomization. Imaging results were sent to a BICR, which, according to the study protocol, checked before randomization that all scans were received and of diagnostic quality. The absence of tumours at the start of the study was confirmed by the investigator for inclusion in the study. Patients must not have received any systemic therapy for advanced renal cell carcinoma and had to be in good general condition according to the ECOG PS ≤ 1.

A total of 994 patients were enrolled in the KEYNOTE-564 study and randomized at a 1:1 ratio to treatment with either pembrolizumab (N = 496) or placebo (N = 498). Stratification was based on the characteristic of metastasis status (M1 NED versus M0). Within M0, additional stratification was done according to ECOG PS (0 versus 1) and region (USA versus non-USA).

Pembrolizumab treatment was administered in 3-week cycles and was in line with the specifications of the SPC [8]. Patients were treated for up to 1 year (maximum 17 cycles) or until confirmed recurrence, unacceptable toxicity, health reasons that prevented further administration of treatment, physician's or patient's decision to discontinue therapy, or withdrawal of consent. Consistent with the approval, pembrolizumab dose delays or interruptions due to toxicity were possible.

Primary outcome of the KEYNOTE-564 study was DFS as assessed by the investigator. Patient-relevant secondary outcomes were outcomes on mortality, morbidity, health-related quality of life and AEs.

Implementation of the appropriate comparator therapy

The G-BA specified watchful waiting as ACT.

The KEYNOTE-564 study used placebo as comparator therapy. The study was not designed for a comparison with watchful waiting, but is nonetheless suitable for such a comparison. This is explained below.

According to guidelines, the follow-up of patients at increased risk of recurrence after primary tumour therapy of renal cell carcinoma in the non-distant metastatic stage should be risk-adapted [9,10]. This includes clinical examinations, assessment of laboratory parameters and cross-sectional imaging (CT/MRI) of the abdomen/pelvis, and CT of the thorax as well as sonographic examinations of the abdomen in first 3-monthly, later annual check-ups.

Table 8: Follow-up schedule of routine diagnostics recommended in the S3 guideline[a] for patients at high risk of recurrence

	Time since resection of renal cell carcinoma			
Examination	**Year 1**	**Year 2**	**Years 3 to 4**	**Years 5 to 9**
Clinical examination	After 3, 6 and 12 months	Every 6 months	Every 12 months	Every 2 years
Laboratory testing	After 3, 6 and 12 months	Every 6 months	Every 12 months	Every 2 years
Abdominal sonography	After 3 months, additionally after 6 months (in case of partial nephrectomy)	After 18 months	Every 12 months	-[c]
CT thorax	Every 6 months	Every 6 months	Every 12 months	Every 2 years
CT abdomen	After 12 months, additionally after 3 and 6 months in case of partial nephrectomy[b]	After 24 months	-[c]	Every 2 years

a. See [10].
b. CT or MRI.
c. No general recommendation for routine performance provided.
CT: computed tomography; MRI: magnetic resonance imaging

The following examinations were performed for the assessment of the health status or the detection of recurrences in the KEYNOTE-564 study:

- Clinical examination: every 3 weeks until the end of treatment
- Laboratory testing: every 3 or 6 weeks and one further examination 30 days after the end of treatment
- Imaging (CT and/or MRI of the chest, abdomen and pelvis: every 3 months during treatment and in the first year after treatment, every 4 months in the 2nd to 4th year after treatment, every 6 months from the 5th year after treatment and until recurrence, start of new antineoplastic therapy, death, end of study, or withdrawal of consent; bone and brain examinations if clinically indicated)

In contrast to the recommendation in the S3 guideline (see Table 8), sonographic examinations were not planned. In addition, the end of clinical examinations and laboratory testing was linked to the end of treatment with the study medication and in the longest case ended after about 1 year.

Despite the deviations from the recommendations of the S3 guideline, the patients in the study received close and targeted examinations for the detection of local recurrences and distant metastases, so that the procedure in the KEYNOTE-564 study is rated as sufficient implementation of the ACT, and the study is used for the benefit assessment in comparison with watchful waiting.

Data cut-offs

The KEYNOTE-564 study is still ongoing. At the time of the benefit assessment, 2 data cut-offs were available:

- First data cut-off from 14 December 2020:

  Prespecified interim analysis of the primary outcome of DFS and interim analysis of the outcome of overall survival. The criteria defined according to the study documents were fulfilled at this point, as approximately 265 DFS events as assessed by the investigators had occurred, and at least 12 months of follow-up observation had elapsed since the inclusion of the last patient in the study.

- Data cut-off from 14 June 2021 (referred to as EMA data cut-off by the company):

  According to the information provided by the company in Module 4 A, this data cut-off was added as part of the approval procedure with the European Medicines Agency (EMA).

In Module 4 A, the company presented analyses of the data cut-off from 14 June 2021 for some of the outcomes and justified this with the longer observation period. The company did not submit a clinical study report (CSR) for the data cut-off from 14 June 2021. According to information provided by the company, no analyses were planned for the patient-reported outcomes for the outcome categories of morbidity and health-related quality of life for the data cut-off from 14 June 2021. For these outcomes, the company therefore used the results of the first data cut-off in Module 4 A.

For the data cut-off from 14 June 2021, there are uncertainties as to which concrete reason led to this analysis. According to information in Module 4 A, additional interim analyses were added with Amendment 5 (5 April 2022) of the study protocol. On the one hand, the US regulatory authority requested an additional interim analysis after approximately 100 deaths. On the other hand, an additional interim analysis 6 months after the first interim analysis was added for the European approval procedure if the outcome of DFS was not superior in the first interim analysis.

At the time of the data cut-off on 14 June 2021, a total of 66 deaths had occurred, and thus the threshold of 100 deaths set by the US regulatory authority had not been reached. Furthermore, the results of the outcome of DFS already fulfilled the predefined criteria (specified limit of $p < 0.0122$) for demonstrating the superiority of the intervention in the first interim analysis. The criteria for one of the 2 additional interim analyses described in Amendment 5 were thus not met.

Overall, it is therefore not clear from the available documents for what reason the data cut-off from 14 June 2021 was carried out. In particular, it is not evident that this is an a priori planned data cut-off or one required by regulatory authorities. The present benefit assessment therefore uses the results from the first data cut-off of 14 December 2020.

Follow-up observation

Table 9 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 9: Planned duration of follow-up observation – RCT, direct comparison: pembrolizumab vs. watchful waiting

Study Outcome category Outcome	Planned follow-up observation
KEYNOTE-564	
Mortality	
Overall survival	Until death, withdrawal of consent or end of study
Morbidity	
Recurrence[a]	Until recurrence, start of subsequent oncological therapy, pregnancy, withdrawal of consent, end of study, or death from any cause
Symptoms (EORTC QLQ-C30)	Until recurrence or start of subsequent oncological therapy[b]
Symptoms (FKSI-DRS)	Until recurrence or start of subsequent oncological therapy[b]
Health status (EQ-5D VAS)	Until recurrence or start of subsequent oncological therapy[b]
Health-related quality of life (EORTC QLQ-C30)	Until recurrence or start of subsequent oncological therapy[b]
Side effects	
AEs, severe AEs[c] and immune-related severe AEs[c], discontinuation due to AEs	30 days after the last dose of the study medication
SAEs and immune-related SAEs	90 days after the last dose of the study medication, or 30 days after the last dose of the study medication when switching to subsequent therapy

a. Presented based on the recurrence rate and disease-free survival, includes the events of local recurrence, distant metastases, and death from any cause.
b. After the end of treatment with the study medication, the recording was conducted annually until recurrence or the start of subsequent oncological therapy.
c. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The observation periods for the outcomes of the outcome category of side effects are systematically shortened because they were only recorded for the period of treatment with the study medication (plus 30 days or 90 days for SAEs and immune-related SAEs when there was no switch to subsequent therapy). Similarly, the observation periods for the outcomes of the category of morbidity and health-related quality of life recorded using the EORTC QLQ-C30, FKSI-DRS and EQ-5D VAS are systematically shortened, as they were only recorded until recurrence or the start of subsequent oncological therapy. Drawing a reliable conclusion on the

total study period or the time to patient death requires recording these outcomes for the total period, as was done for survival.

Table 10 shows the characteristics of the patients in the included study.

Table 10: Characteristics of the study population and of study/treatment discontinuation – RCT, direct comparison: pembrolizumab vs. watchful waiting (multipage table)

Study **Characteristic** **Category**	**Pembrolizumab** **N = 496**	**Placebo** **N = 498**
KEYNOTE-564		
Age [years], mean (SD)	58 (11)	59 (11)
Age category [years], n (%)		
< 65	338 (68)	326 (66)
≥ 65	158 (32)	172 (35)
Sex [F/M], %	30/70	28/72
Geographical region, n (%)		
North America	133 (27)	125 (25)
European Union	188 (38)	187 (38)
Rest of the world	175 (35)	186 (37)
ECOG PS, n (%)		
0	421 (85)	426 (86)
1	75 (15)	72 (15)
Type of nephrectomy, n (%)		
Partial	37 (8)	38 (8)
Radical	459 (93)	460 (92)
PD-L1 status, n (%)		
CPS < 1	124 (25)	113 (23)
CPS ≥ 1	365 (74)	383 (77)
Missing	7 (1)	2 (< 1)
Primary tumour, n (%)		
T1	11 (2)	15 (3)
T2	27 (5)	33 (7)
T3	444 (90)	437 (88)
T4	14 (3)	13 (3)
Tumour grading according to Fuhrman [11], n (%)		
Grade 1	19 (4)	16 (3)
Grade 2	153 (31)	150 (30)
Grade 3	219 (44)	213 (43)
Grade 4	103 (21)	119 (24)
Missing	2 (< 1)	0 (0)
Lymph node stage, n (%)		
N0	465 (94)	467 (94)
N1	31 (6)	31 (6)

Table 10: Characteristics of the study population and of study/treatment discontinuation – RCT, direct comparison: pembrolizumab vs. watchful waiting (multipage table)

Study **Characteristic** **Category**	**Pembrolizumab** **N = 496**	**Placebo** **N = 498**
Metastasis status, n (%)		
M0	467 (94)	469 (94)
M1 NED	29 (6)	29 (6)
Risk of recurrence[a]		
M0 – intermediate-high risk	422 (85)	433 (87)
M0 – high risk	40 (8)	36 (7)
M0 – other	5 (1)	0 (0)
M1 NED	29 (6)	29 (6)
Disease status at baseline according to BICR[b], n (%)		
Non-NED	19 (4)	29 (6)
NED	476 (96)	468 (94)
Missing	1 (< 1)	1 (< 1)
Treatment discontinuation, n (%)[c]	190 (39)	130 (26)
Maximum treatment duration reached	298 (61)	365 (74)
Study discontinuation, n (%)[d]	33 (7)	44 (9)

a. 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).
b. Disease status at baseline according to BICR was assessed by scans only.
c. Common reasons for treatment discontinuation in the intervention vs. the comparator arm were: AEs (21% vs. 2%), recurrence (11% vs. 20%), withdrawal of consent (4% vs. 2%).
d. Reasons for study discontinuation in the intervention vs. the comparator arm were: death (4% vs. 7%), withdrawal of consent (3% vs. 2%).

AE: adverse event; BICR: blinded independent central review; CPS: combined positive score; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; M: male; n: number of patients in the category; N: number of randomized patients; NED: no evidence of disease; PD-L1: programmed cell death ligand 1; pT: histopathologic primary tumour stage; RCT: randomized controlled trial; SD: standard deviation

The characteristics of the patients are balanced between the 2 treatment arms of the KEYNOTE-564 study. The patients were on average about 58 years old, predominantly male (70% versus 72%) and were enrolled in the study mainly in the European Union (38%) or North America (about 26%). About 85% of the patients had an ECOG PS of 0.

The majority of patients had undergone radical nephrectomy of a primary tumour extending beyond the kidney without lymph node involvement and distant metastases. The population comprised predominantly patients at intermediate-high risk of recurrence (approximately 86%)

as defined by the study protocol, and only a small proportion were included in the study after resection of metastatic lesions in an M1 NED status. However, according to the assessment of the radiological findings by a BICR, there were also a few patients in the population (around 4% versus 6%) who were not tumour-free at the start of the study, contrary to the assessment by the investigator.

The most common reasons for treatment discontinuation included the occurrence of AEs (pembrolizumab arm: 21%; comparator arm: 2%) and disease recurrence (pembrolizumab arm: 11%; comparator arm: 20%), with frequencies differing between treatment arms.

Table 11 shows the mean/median treatment duration of the patients and the mean/median observation period for individual outcomes.

Table 11: 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 December 2020		
Median [min; max]	11.1 [0.0; 14.3]	11.1 [0.0; 15.4]
Mean (SD)	9.0 (3.7)	9.8 (3.1)
Observation period [months]		
Overall survival[b]		
Median [min; max]	24.0 [2.5; 41.5]	23.8 [3.5; 41.4]
Mean (SD)	25.1 (7.0)	24.7 (7.0)
Morbidity		
Recurrence	ND	ND
Symptoms (EORTC QLQ-C30, FKSI-DRS, EQ-5D VAS)		
Median [min; max]	12.2 [ND; ND]	12.3 [ND; ND]
Mean (SD)	ND	ND
Health-related quality of life (EORTC QLQ-C30)		
Median [min; max]	12.2 [ND; ND]	12.3 [ND; ND]
Mean (SD)	ND	ND
Side effects	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. Time from randomization to death or the data-off date.

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; max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

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

With about 24 months at the first data cut-off, the median observation period for the outcome of overall survival is comparable in the intervention arm and the comparator arm.

With about 12 months at the first data cut-off, the median observation period for the patient-reported outcomes of symptoms (EORTC QLQ-C30, FKSI-DRS, EQ-5D VAS) and health-related quality of life (EORTC QLQ-C30) is also comparable in both treatment arms. Thus, compared with overall survival, data for the patient-reported outcomes on symptoms as well as for the outcome of health status are only available for a shortened observation period.

No data on the observation period are available for the outcome of recurrence and for the outcomes in the category of side effects. For the latter, the observation period is linked to the end of treatment (maximum 17 cycles or about 1 year plus 30 days for AE recordings or 90 days for SAE recordings). The median is therefore also estimated to be about 12 months and is systematically shortened for these outcomes in comparison with overall survival.

Table 12 shows the subsequent therapies patients received after discontinuing the study medication.

Table 12: Information on subsequent antineoplastic therapies[a] – RCT, direct comparison: pembrolizumab vs. watchful waiting (multipage table)

Study Type of subsequent therapy	Patients with subsequent therapy n (%)	
	Pembrolizumab N = 496	Placebo N = 498
KEYNOTE-564 (data cut-off: 14 December 2020)		
Patients with recurrence	103 (20.8)	149 (29.9)
Subsequent antineoplastic therapies, total	76 (15.3)	112 (22.5)
Radiotherapy	14 (2.8)	17 (3.4)
Surgery	19 (3.8)	32 (6.4)
Systemic therapy	63 (12.7)	86 (17.3)
Immune checkpoint inhibitor	14 (2.8)	46 (9.2)
Avelumab	2 (0.4)	2 (0.4)
Durvalumab	1 (0.2)	0 (0)
Ipilimumab	7 (1.4)	15 (3.0)
Nivolumab	9 (1.8)	33 (6.6)
Pembrolizumab	2 (0.4)	11 (2.2)
VEGF/VEGFR-targeted therapy	56 (11.3)	76 (15.3)
Sunitinib malate	21 (4.2)	28 (5.6)
Cabozantinib	14 (2.8)	15 (3.0)
Pazopanib	18 (3.6)	13 (2.6)
Axitinib	8 (1.6)	20 (4.0)
Pazopanib hydrochloride	7 (1.4)	13 (2.6)
Cabozantinib S-malate	4 (0.8)	6 (1.2)
Lenvatinib	1 (0.2)	3 (0.6)
Bevacizumab	1 (0.2)	3 (0.6)
Tivozanib	1 (0.2)	2 (0.4)
Sorafenib	0 (0)	2 (0.4)
Sorafenib tosylate	1 (0.2)	1 (0.2)
Temsirolimus	1 (0.2)	1 (0.2)
Epacadostat	0 (0)	1 (0.2)
Guadecitabine	1 (0.2)	0 (0)
Lenvatinib mesylate	1 (0.2)	0 (0)
Pan TIE2/VEGFR2 kinase inhibitors (unspecified)	0 (0)	1 (0.2)
Immunostimulants	1 (0.2)	4 (0.8)
Bempegaldesleukin	0 (0)	2 (0.4)
Interferon (unspecified)	0 (0)	1 (0.2)
Interferon alfa-2a	0 (0)	1 (0.2)
Interferon alfa-2b	1 (0.2)	0 (0)
Immunosuppressants	3 (0.6)	4 (0.8)
Everolimus	3 (0.6)	4 (0.8)
Urogenital system and sex hormones	0 (0)	1 (0.2)

Table 12: Information on subsequent antineoplastic therapies[a] – RCT, direct comparison: pembrolizumab vs. watchful waiting (multipage table)

Study Type of subsequent therapy	Patients with subsequent therapy n (%)	
	Pembrolizumab N = 496	Placebo N = 498
Medroxyprogesterone acetate	0 (0)	1 (0.2)
Various	0 (0)	1 (0.2)
Investigational preparation (unspecified)	0 (0)	1 (0.2)

a. Patients may have received more than one subsequent therapy and in this case are only counted once in higher-level categories (e.g. antineoplastic therapies).

n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial; TIE2: tyrosine kinase receptor Tie2; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor

In the KEYNOTE-564 study, subsequent therapies after recurrence of the disease were allowed without restrictions for patients in both study arms. The total subsequent antineoplastic therapies used in the 2 treatment arms of the KEYNOTE-564 study are shown in Table 12.

Overall, it should be noted that data on the first subsequent therapy after recurrence should be preferred to data on any subsequent therapy received after recurrence in order to assess whether patients with recurrence received guideline-compliant subsequent therapy in the 2 treatment arms. For the data provided by the company in Module 4 A for the data cut-off of 14 June 2021, it is clear that this is information on the first subsequent therapy after recurrence. For the first data cut-off considered in the present benefit assessment, this is not clear from the study documents. However, since the data in Module 4 A and the data from the study documents on individual subsequent therapies are partly identical, it can be assumed that the data presented in Table 12 also refer to the first subsequent therapy.

According to recommendations of national and international guidelines, there are different combination and monotherapies with immune checkpoint, tyrosine kinase or mTOR inhibitors for the first-line drug therapy of locally advanced and metastatic renal cell carcinoma depending on the risk group [9,10,12]. The S3 guideline recommends the immune checkpoint inhibitors pembrolizumab and avelumab, each in combination with the vascular endothelial growth factor receptor (VEGFR) inhibitor axitinib, for the treatment of advanced and/or metastatic clear-cell renal cell carcinoma [10]. In addition to the combination of pembrolizumab and axitinib, patients with intermediate or high risk are also recommended a combined therapy with ipilimumab plus nivolumab, which, among other things, achieved notable improvement in overall survival [13-15]. Other therapies, especially those targeted against vascular endothelial growth factor (VEGF)/VEGFR should be used if checkpoint inhibitor-based combination therapy cannot be used in the first line [10].

The subsequent systemic therapies administered in the comparator arm of the KEYNOTE-564 study are only an inadequate reflection of the current standard of therapy after recurrence:

A total of 112 (22.5%) patients in the comparator arm of the KEYNOTE-564 study (first data cut-off) received subsequent therapy. 46 (9.2%) patients received immune checkpoint inhibitor-based therapy and 76 (15.3%) patients received anti-VEGF/VEGFR-targeted therapy. This corresponds to 41.1% and 67.9% of patients treated with subsequent therapies [6].

Regarding patients with recurrence (149 patients in the comparator arm), this means that 46 (30.9%) patients with recurrence were treated with immune checkpoint inhibitor-based therapy. VEGF/VEGFR-targeted therapy was used in 76 (51%) patients. It should be noted that patients may have received more than one subsequent therapy or combined administration of an immune checkpoint inhibitor and a VEGF/R inhibitor.

It is not clear from the information in the dossier why only 41.1% or 30.9% (depending on the reference value: patients with subsequent therapy or with recurrence) of the patients received guideline-compliant treatment with immune checkpoint inhibitor-based therapy after recurrence.

On the basis of the available data, it is therefore questionable overall whether the patients in the comparator arm of the KEYNOTE-564 study received adequate subsequent therapy. This has consequences regarding the interpretability of the results of the outcome of overall survival (see Section I 4.2).

Risk of bias across outcomes (study level)

Table 13 shows the risk of bias across outcomes (risk of bias at study level).

Table 13: Risk of bias across outcomes (study level) – RCT, direct comparison: pembrolizumab vs. watchful waiting

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
KEYNOTE-564	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes is rated as low for the KEYNOTE-564 study.

Transferability of the study results to the German health care context

From the point of view of the company, the transferability of the results to the German health care context is given due to the characteristics, the investigated patient population, the study design and the use of pembrolizumab in compliance with the approval. The company added

that subgroups by region also showed no indication of deviating efficacy or safety of pembrolizumab.

The company did not provide any further information on the transferability of the study results to the German health care context.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - overall survival
- Morbidity
  - recurrence
  - symptoms, recorded with the EORTC QLQ-C30 symptom scales and the FKSI-DRS
  - health status, measured using the EQ-5D VAS
- Health-related quality of life
  - recorded with the global health status and the functional scales of the EORTC QLQ-C30
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - immune-related SAEs
  - immune-related severe AEs
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4).

Table 14 shows for which outcomes data are available in the included study.

Table 14: Matrix of outcomes – RCT, direct comparison: pembrolizumab vs. watchful waiting

Study	Outcomes											
	Overall survival	Recurrence[a]	Symptoms (EORTC QLQ-C30)	Symptoms (FKSI-DRS)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs[b]	Severe AEs[b, c]	Discontinuation due to AEs[b]	Immune-related SAEs[d]	Immune-related severe AEs[c, d]	Further specific AEs[e]
KEYNOTE-564	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

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.
b. Progression events of the underlying disease are not included (PTs "neoplasm progression", "malignant neoplasm progression" and "disease progression").
c. Severe AEs are 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. 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).

AE: adverse event; AEOSI: adverse events of special interest; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Overall survival

The overall survival of patients in the present therapeutic indication is composed of a phase of DFS until recurrence and the subsequent stage of advanced and/or metastatic RCC and lasts until the patients die of the consequences of the disease.

An observed effect in the outcome of overall survival is not only influenced by the initial study treatment, but also by the subsequent antineoplastic therapies used after disease progression or recurrence [16-18]. In order for an observed effect in the outcome of overall survival to be interpreted meaningfully, adequate guideline-compliant subsequent treatment of patients after progression or recurrence of the disease is necessary, especially in the adjuvant therapy situation.

The guideline recommendations for the advanced therapy stage of clear-cell renal cell carcinoma are decisive for the assessment of the subsequent therapies administered in the KEYNOTE-564 study. According to the S3 guideline Diagnostics, Therapy and Follow-up of Renal Cell Carcinoma and the guideline of the German Society for Haematology and Medical

Oncology, patients with advanced and/or metastatic clear-cell renal cell carcinoma should receive an immune checkpoint inhibitor-based therapy in the first line [9,10]. These recommendations are based on clear advantages in overall survival from immune checkpoint inhibitor-based therapy in comparison with sunitinib [13-15]. Several benefit assessments also showed advantages in overall survival for immune checkpoint inhibitor-based therapy over sunitinib [19-21]. In view of these findings and the guideline recommendations, it is not clear why only 41.1% or 30.9% (depending on the reference value: patients with subsequent therapy or with recurrence) of the patients received guideline-compliant treatment with immune checkpoint inhibitor-based therapy after recurrence.

In the KEYNOTE-564 study, subsequent therapies were allowed without restrictions after disease recurrence. However, the subsequent systemic therapies administered in the comparator arm of the KEYNOTE-564 study are only an inadequate reflection of the current standard of therapy after recurrence (see Section I 3.2). On the basis of the available data, it must be assumed that the systemic therapy of the patients after recurrence in the comparator arm was insufficient.

This is of particular importance in the present research question, the adjuvant treatment of renal cell carcinoma: Treatment with an immune checkpoint inhibitor-based therapy in advanced or metastatic disease is associated with a survival advantage. The research question to be answered is therefore whether overall survival is improved if patients who are considered disease-free receive adjuvant therapy with an immune checkpoint inhibitor, instead of immune checkpoint inhibitor-based therapy only being used after recurrence, as has been the case up to now [22]. Thus, treatment with an immune checkpoint inhibitor is advanced in the adjuvant treatment situation also in the KEYNOTE-564 study presented by the company. However, due to the insufficient treatment with an immune checkpoint inhibitor-based therapy after recurrence in the comparator arm of the KEYNOTE-564 study, this research question cannot be answered.

In the present situation, it is 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 cannot be interpreted.

Recurrence

The outcome of recurrence is a composite outcome and includes the components of local recurrence, distant metastases and death from any cause. For the outcome of recurrence, the results of the operationalizations are presented as the proportion of patients with recurrence (hereinafter referred to as “recurrence rate”) and as DFS.

For the operationalization of the outcome of DFS, the company defined different analyses. These differ, among other things, on whose assessment the absence of tumours at baseline and the occurrence of an event during the course of the study is based. The company presented

different analyses, including several sensitivity analyses. Of these, the following 3 analyses are presented in the present assessment.

- DFS as assessed by the investigator: This analysis considered all patients who were assessed to be tumour-free at baseline by the investigator. The assessment was based on clinical, pathological and radiological examinations, the latter being mandatory. Disease recurrence in the course of the study was determined in the same way. The assessment of the investigators was decisive for the decision to discontinue therapy (and thus determined the end of the imaging examinations); the assessment of the BICR was not awaited for this decision.
- DFS as assessed by the BICR: This analysis, referred to by the company as "sensitivity analysis 3", considered all patients who were assessed to be tumour-free by the BICR and who had recurrence during the course of the study. The assessment was based on the radiological examinations at baseline. Patients who, contrary to the investigator's assessment, were not tumour-free according to the imaging at baseline as assessed by the BICR were censored in the analysis at baseline. In the course of the study, the recording of recurrences (by means of imaging) was stopped as soon as the investigators detected a recurrence. In the event that the BICR subsequently came to the different assessment that, in their view, there was no recurrence yet, the BICR did not have any further scans to determine a recurrence (as assessed by the BICR). For the analysis of DFS as assessed by the BICR, these patients were censored at the time point of the last BICR assessment.
- Event-free survival as assessed by the BICR: This analysis considered all patients, i.e. also those patients who were assessed to be not tumour-free at baseline by the BICR and progressed during the course of the study. For the recording in the course of the study, the descriptions listed above apply (on DFS as assessed by the BICR).

The differences between the operationalizations concern the assessment of absence of tumour at baseline and recurrence during the course of the study.

The assessments by the investigator and the BICR differed in that the BICR classified 3.8% of the patients in the intervention arm and 5.8% in the comparator arm as not tumour-free at baseline, contrary to the investigator's assessment. Furthermore, there are differences in the assessment of whether recurrences occurred in the course of the study. The assessment by the investigator that recurrence had occurred did not agree with the assessment by the BICR in 18.4% of the patients in the intervention arm and in 13.4% of the patients in the comparator arm. The EMA guideline addresses the increased detection bias in the assessment by the investigator when it is known or (as in the present case), despite blinding, identifiable by the investigator due to the toxicity profile to which treatment group a patient is assigned and this influences the recording [23]. Methodologically, the BICR analysis is thus superior to the assessments by the investigator, but the implementation of this analysis in the KEYNOTE-564 study has weaknesses (see above): For example, the recording of recurrences by imaging was terminated as soon as the investigators detected a recurrence.

The EMA's European Public Assessment Report (EPAR) points out that the company had previously planned to use the BICR assessment as the primary outcome [12]. The typical toxicity profile of pembrolizumab could potentially influence the investigator in terms of their assessments.

The present benefit assessment presents the results for all 3 operationalizations, with the BICR analyses as supplementary information.

Notes on side effect outcomes

The company presented event time analyses for all side effect outcomes. Considering event time analyses is of particular relevance in group comparisons with different mean observation periods [1]. The company did not provide information on this. However, due to the comparable treatment durations in the 2 study arms (see Table 11), it is assumed in the present situation that the observation periods between the study arms are also comparable.

In the assessment of side effects, it is primarily relevant in how many patients an event occurred. In addition, when considering the time until occurrence of the event, effects can also result solely from an earlier or later occurrence of the event and not on the basis of the proportions. For this reason, the analyses of the relative risk are used in the present assessment to derive the added benefit.

I 4.2 Risk of bias

Table 15 describes the risk of bias for the results of the relevant outcomes.

Table 15: 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]	Symptoms (EORTC QLQ-C30)	Symptoms (FKSI-DRS)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	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[h]	H[h]	H[h]	H[h]	H[g]	H[g]	L[i]	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 Section I 4.1)
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 usable data available; see Section I 4.1 for the reasoning.
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 Section I 4.1).
g. Incomplete observations for potentially informative reasons.
h. High proportion of patients (> 10%) who were not included in the analysis, as well as a decreasing response rate to questionnaires over the course of the study.
i. 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; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

The outcome-specific risk of bias is rated as high for the results of all patient-relevant outcomes except the outcome of discontinuation due to AEs.

No suitable data are available for the outcome of overall survival (for reasons, see Section I 4.1); therefore, the risk of bias of the results is not assessed. 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 results of the patient-reported outcomes on symptoms, health status and health-related quality of life, recorded using the EORTC QLQ-C30, FKSI-DRS and EQ-5D VAS, have a high risk of bias due to a high

proportion of patients (> 10%) not included in the analysis, as well as a decreasing return of questionnaires over the course of the study.

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).

I 4.3 Results

Table 16, Table 17 and Table 18 summarize the results 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.

For assessing clinical relevance, an SMD is used, provided the mean difference (MD) is statistically significant. The company presented calculations for this, which it referred to as "Hedges' g". The company did not describe how the pooled standard deviation contained in the conventional Hedges' g formula was estimated. Thus, the results were checked with calculations conducted by the Instituted. For this purpose, SMD was determined using the MD estimated from the analysis of a mixed-effects model with repeated measures (MMRM), the associated 95% CI, and the respective sample size. The results depart from the company's calculation. Therefore, calculations conducted by the Institute are used for the assessment.

Kaplan-Meier curves on the presented event time analyses can be found in I Appendix B of the full dossier assessment. Results on common AEs, SAEs, severe AEs, and discontinuations due to AEs are presented in I Appendix C of the full dossier assessment. A list of the immune-related AEs, immune-related SAEs, and immune-related severe AEs (CTCAE grade ≥ 3) categories in which events occurred is presented as supplementary information in I Appendix D of the full dossier assessment.

Table 16: 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 (first data cut-off: 14 December 2020)					
Mortality					
Overall survival	No suitable data[b]				
Morbidity					
Recurrence					
Recurrence rate (investigator)[c]	496	– 109 (22.0)	498	– 151 (30.3)	RR: 0.72 [0.59; 0.897]; 0.003[d]
Local recurrence	496	– 16 (3.2)	498	– 30 (6.0)	–
Distant metastases	496	– 87 (17.5)	498	– 119 (23.9)	–
Death	496	– 6 (1.2)	498	– 2 (0.4)	–
Disease-free survival (investigator)	496	NA 109 (22.0)	498	NA 151 (30.3)	0.68 [0.53; 0.87]; 0.002
Supplementary information:					
Recurrence rate[c, e] (BICR)	477[f]	– 101 (21.2[f])	469[f]	– 129 (26.0[f])	RR: 0.77 [0.61; 0.97]; 0.024[d]
Disease-free survival[e] (BICR)	496	NA 101 (20.4)	498	NA 129 (25.9)	0.73 [0.56; 0.95]; 0.019[g]
Event rate (BICR recurrence/progression rate)[c, h]	496[f]	– 116 (23.4)	498[f]	– 155 (31.1)	RR: 0.75 [0.61; 0.92]; 0.006[d]
Recurrence		95 (19.2)		128 (25.7)	–
Progression		14 (2.8)		25 (5.0)	–
Death		7 (1.4)		2 (0.4)	–
Event-free survival (BICR)[h]	496	NA 116 (23.4)	498	NA 155 (31.1)	0.71 [0.55; 0.90]; 0.005[g]

Table 16: 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]

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 versus 1) and region (USA versus non-USA).
b. See Section I 4.1 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 [24]).
e. Censoring at baseline of patients who were not tumour-free at baseline as assessed by the BICR.
f. Institute's calculations.
g. p-value: Institute's calculations from information provided by the company on one-sided log-rank test
h. 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.

BICR: blinded independent central review; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; 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 17: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: pembrolizumab vs. watchful waiting (multipage table)

Study Outcome category Outcome	Pembrolizumab			Placebo			Pembrolizumab vs. placebo
	N[a]	Values at baseline mean (SD)	Mean change in the course of the study mean (SE)[b]	N[a]	Values at baseline mean (SD)	Mean change in the course of the study mean (SE)[b]	MD [95% CI][b]; p-value[c]
KEYNOTE-564 (first data cut-off: 14 December 2020)							
Morbidity							
FKSI-DRS[d]	423	32.86 (3.50)	−1.26 (0.18)	440	32.83 (3.46)	−0.58 (0.18)	−0.68 [−1.06; −0.30]; ND SMD[e]: −0.24 [−0.37; −0.10]
EORTC QLQ-C30 (symptoms)[f]							
Fatigue	426	18.70 (18.98)	6.45 (0.90)	443	18.76 (18.35)	3.86 (0.88)	2.59 [0.71; 4.47]; ND SMD[e]: 0.18 [0.05; 0.32]
Nausea and vomiting	426	2.03 (7.57)	2.12 (0.45)	443	2.14 (8.53)	0.90 (0.44)	1.23 [0.30; 2.15]; ND SMD[e]: 0.18 [0.04; 0.31]
Pain	426	15.85 (21.36)	3.48 (0.94)	443	13.96 (17.84)	2.24 (0.92)	1.24 [−0.71; 3.20]; ND
Dyspnoea	426	9.00 (18.43)	5.37 (0.89)	443	8.43 (16.91)	2.86 (0.88)	2.51 [0.65; 4.38]; ND SMD[e]: 0.18 [0.05; 0.31]
Insomnia	426	18.23 (24.92)	3.54 (1.12)	443	21.22 (26.17)	1.82 (1.11)	1.71 [−0.64; 4.06]; ND
Appetite loss	426	5.56 (15.10)	2.77 (0.74)	443	5.49 (14.27)	−0.28 (0.73)	3.05 [1.51; 4.60]; ND SMD[e]: 0.26 [0.13; 0.40]
Constipation	426	8.61 (17.68)	0.95 (0.84)	443	7.98 (16.68)	0.69 (0.82)	0.27 [−1.48; 2.01]; ND
Diarrhoea	426	4.30 (11.87)	3.97 (0.78)	443	3.99 (11.06)	3.37 (0.76)	0.60 [−1.01; 2.22]; ND

Table 17: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: pembrolizumab vs. watchful waiting (multipage table)

Study Outcome category Outcome	Pembrolizumab			Placebo			Pembrolizumab vs. placebo
	N[a]	Values at baseline mean (SD)	Mean change in the course of the study mean (SE)[b]	N[a]	Values at baseline mean (SD)	Mean change in the course of the study mean (SE)[b]	MD [95% CI][b]; p-value[c]
Health status							
EQ-5D-5L VAS[d]	436	84.07 (13.99)	−3.52 (0.66)	454	83.22 (14.48)	−2.44 (0.65)	−1.08 [−2.47; 0.30]; ND
Health-related quality of life							
EORTC QLQ-C30[d]							
Global health status	426	79.28 (18.56)	−5.52 (0.84)	443	77.29 (17.36)	−2.07 (0.83)	−3.45 [−5.20; −1.69]; ND SMD[e]: −0.26 [−0.39; −0.13]
Physical functioning	426	88.69 (14.89)	−2.91 (0.61)	443	88.88 (13.82)	−1.45 (0.60)	−1.46 [−2.73; −0.18]; ND SMD[e]: −0.15 [−0.29; −0.02]
Role functioning	426	87.95 (19.92)	−4.42 (0.92)	443	87.92 (19.07)	−2.11 (0.90)	−2.31 [−4.22; −0.39]; ND SMD[e]: −0.16 [−0.29; −0.03]
Emotional functioning	426	85.04 (17.60)	−3.10 (0.83)	443	84.41 (17.83)	−0.99 (0.82)	−2.11 [−3.86; −0.37]; ND SMD[e]: −0.16 [−0.29; −0.03]
Cognitive functioning	426	91.67 (13.44)	−4.55 (0.78)	443	90.44 (14.80)	−2.72 (0.77)	−1.83 [−3.46; −0.19]; ND SMD[e]: −0.15 [−0.28; −0.02]
Social functioning	426	90.26 (17.14)	−4.34 (0.88)	443	88.68 (18.90)	−1.01 (0.86)	−3.33 [−5.17; −1.50]; ND SMD[e]: −0.24 [−0.37; −0.11]

Table 17: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: pembrolizumab vs. watchful waiting (multipage table)

Study Outcome category Outcome	Pembrolizumab N[a]	Pembrolizumab Values at baseline mean (SD)	Pembrolizumab Mean change in the course of the study mean (SE)[b]	Placebo N[a]	Placebo Values at baseline mean (SD)	Placebo Mean change in the course of the study mean (SE)[b]	Pembrolizumab vs. placebo MD [95% CI][b]; p-value[c]
a Number of patients taken into account in the analysis for calculating the effect estimation; baseline values may be based on different patient numbers. b. MMRM with treatment group, metastasis status (M1 NED vs. M0), baseline value, and visits as covariables. Within M0, stratification is done according to ECOG (0 versus 1) and region (USA versus non-USA). c. According to the study documents, the company planned to analyse the PRO outcomes using the cLDA model. In its dossier assessment, the company presented results from an MMRM. Both models contain identical covariables. For the part of the analyses, a comparison of the results of the cLDA model and the MMRM was possible. There was no difference between the 2 types of analysis that was relevant for the derivation of the added benefit. This means that the approach of the company is of no consequence for the benefit assessment. d. Higher (increasing) values indicate improved symptoms/health-related quality of life; positive effects (intervention minus control) indicate an advantage for the intervention (scale range EORTC QLQ-C30 functional scales and global health status 0 to 100, EQ5D VAS 0 to 100, FKSI-DRS 0 to 36). e. Institute's calculation based on MD and CI of the MMRM. f. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus control) indicate an advantage for the intervention (scale range of 0 to 100). cDLA: constrained longitudinal data analysis; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; 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; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; ND: no data; NED: no evidence of disease; RCT: randomized controlled trial; SD: standard deviation; SMD: standardized mean difference; VAS: visual analogue scale							

Table 18: 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 (first data cut-off: 14 December 2020)					
Side effects					
AEs[b] (supplementary information)	488	470 (96.3)	496	452 (91.1)	–
SAEs[b]	488	100 (20.5)	496	56 (11.3)	1.81 [1.34; 2.46]; < 0.001
Severe AEs[b, c]	488	158 (32.4)	496	88 (17.7)	1.82 [1.45; 2.29]; < 0.001
Discontinuation due to AEs[b]	488	101 (20.7)	496	10 (2.0)	10.27 [5.43; 19.42]; < 0.001
Immune-related AEs (supplementary information)[d]	488	173 (35.5)	496	34 (6.9)	–
Immune-related SAEs[d]	488	41 (8.4)	496	1 (0.2)	41.67 [5.75; 301.75]; < 0.001
Immune-related severe AEs[d]	488	44 (9.0)	496	3 (0.6)	14.91 [4.66; 47.69]; < 0.001
Endocrine disorders (severe AE, SOC)	488	12 (2.5)	496	1 (0.2)	12.20 [1.59; 93.44]; 0.002
Skin and subcutaneous tissue disorders (severe AE, SOC)	488	10 (2.0)	496	2 (0.4)	5.08 [1.12; 23.07]; 0.019
Gastrointestinal disorders (severe AE, SOC)	488	23 (4.7)	496	9 (1.8)	2.60 [1.21; 5.56]; 0.010
Investigations (severe AE, SOC)[e]	488	27 (5.5)	496	4 (0.8)	6.86 [2.42; 19.46]; < 0.001
Metabolism and nutrition disorders (severe AE, 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 [24]).
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; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class

As described in Section I 4.2, 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 I 4.1 for reasons).

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

Morbidity

Recurrence

For the outcome of recurrence (operationalized as recurrence rate and DFS), a statistically significant difference between the treatment groups in favour of pembrolizumab in comparison with watchful waiting is shown for both operationalizations. The operationalizations according to BICR presented as supplementary information 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.

Symptoms

FKSI-DRS

On the basis of mean differences, a statistically significant difference between treatment groups was found for the outcome of symptoms recorded with the FKSI-DRS. The SMD is analysed to examine the relevance of the result. In each case, the 95% CI of the SMD is not completely outside the irrelevance range of −0.2 to 0.2. The observed effect can therefore not be inferred to be relevant. This results in no hint of added benefit of pembrolizumab in comparison with watchful waiting; an added benefit is therefore not proven.

EORTC QLQ-C30

Fatigue, nausea and vomiting, dyspnoea and appetite loss

For the outcomes of fatigue, nausea and vomiting, dyspnoea and appetite loss, the analyses based on mean differences show statistically significant differences between the treatment groups. The SMD is analysed to examine the relevance of the result. The 95% CI of the SMD is not completely outside the irrelevance range of −0.2 to 0.2 for each of them. The observed effect can therefore not be inferred to be relevant. This results in no hint of added benefit of

pembrolizumab in comparison with watchful waiting; an added benefit is therefore not proven in each case.

Pain, insomnia, constipation and diarrhoea

For the outcomes of pain, insomnia, constipation and diarrhoea, the analyses based on mean differences show no statistically significant differences between the treatment groups. This results in no hint of added benefit of pembrolizumab in comparison with watchful waiting; an added benefit is therefore not proven in each case.

Health status (EQ-5D VAS)

On the basis of mean differences, no statistically significant difference between treatment groups was found for the outcome of health status measured with the EQ-5D VAS. This results in no hint of added benefit of pembrolizumab in comparison with watchful waiting; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

Analyses based on mean differences show statistically significant differences between the treatment groups for each of the outcomes of global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning. The SMD is analysed to examine the relevance of the result. The 95% CI of the SMD is not completely outside the irrelevance range of −0.2 to 0.2 for each of them. The observed effect can therefore not be inferred to be relevant. This results in no hint of added benefit of pembrolizumab in comparison with watchful waiting; an added benefit is therefore not proven in each case.

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

For the outcomes of endocrine disorders (severe AEs), gastrointestinal disorders (severe AEs), skin and subcutaneous tissue 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.

I 4.4 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 versus M1 NED)

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

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.

Overall, the study documents do not contain complete subgroup analyses for all relevant outcomes or relevant subgroup characteristics (age, sex and disease severity [M0 versus M1 NED]) for the first data cut-off. Hence, no subgroup analyses overall are used for the benefit assessment.

I 5 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 [1].

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.

I 5.1 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 I 4 (see Table 19).

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

For the relevant subpopulation of the KEYNOTE-564 study, information is available on the severities of the AEs due to which treatment was discontinued. This shows that there was a serious event in about 50% of the AEs that led to treatment discontinuation. Therefore, this outcome is assigned to the outcome category of serious/severe side effects.

Table 19: Extent of added benefit at outcome level: pembrolizumab vs. watchful waiting (multipage table)

Outcome category **Outcome**	**Pembrolizumab vs. placebo** **Median time to event (months) or proportion of events (%) or MD** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Total observation period[c]		
Mortality		
Overall survival	No suitable data[d]	Lesser benefit/added benefit not proven
Morbidity		
Recurrence		Outcome category: serious/severe symptoms/late complications added benefit, extent: "considerable"
Recurrence rate	22% vs. 30.3% RR: 0.72 [0.59; 0.897]; p = 0.003 probability: "hint"	
Disease-free survival (investigator)	NA vs. NA months HR: 0.68 [0.53; 0.87]; p = 0.002 probability: "hint"	
Shortened observation period		
Symptoms		
FKSI-DRS	Mean change: −1.26 vs. −0.58 MD: −0.68 [−1.06; −0.30]; p-value: ND SMD: −0.24 [−0.37; −0.10][e]	Lesser benefit/added benefit not proven
EORTC QLQ-C30 symptom scales		
Fatigue	Mean change: 6.45 vs. 3.86 MD: 2.59 [0.71; 4.47]; p-value: ND SMD: 0.18 [0.05; 0.32][e]	Lesser benefit/added benefit not proven
Nausea and vomiting	Mean change: 2.12 vs. 0.90 MD: 1.23 [0.30; 2.15]; p-value: ND SMD: 0.18 [0.04; 0.31][e]	Lesser benefit/added benefit not proven
Pain	Mean change: 3.48 vs. 2.24 MD: 1.24 [−0.71; 3.20] p-value: ND	Lesser benefit/added benefit not proven
Dyspnoea	Mean change: 5.37 vs. 2.86 MD: 2.51 [0.65; 4.38]; p-value: ND SMD: 0.18 [0.05; 0.31][e]	Lesser benefit/added benefit not proven

Table 19: Extent of added benefit at outcome level: pembrolizumab vs. watchful waiting (multipage table)

Outcome category **Outcome**	**Pembrolizumab vs. placebo** **Median time to event (months) or proportion of events (%) or MD** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Insomnia	Mean change: 3.54 vs. 1.82 MD: 1.71 [−0.64; 4.06]; p-value: ND	Lesser benefit/added benefit not proven
Appetite loss	Mean change: 2.77 vs. −0.28 MD: 3.05 [1.51; 4.60]; p-value: ND SMD: 0.26 [0.13; 0.40][e]	Lesser benefit/added benefit not proven
Constipation	Mean change: 0.95 vs. 0.69 MD: 0.27 [−1.48; 2.01]; p-value: ND	Lesser benefit/added benefit not proven
Diarrhoea	Mean change: 3.97 vs. 3.37 MD: 0.60 [−1.01; 2.22] p-value: ND	Lesser benefit/added benefit not proven
Health status		
EQ-5D VAS	Mean change: −3.52 vs. −2.44 MD: −1.08 [−2.47; 0.30]; p-value: ND	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 functional scales		
Global health status	Mean change: −5.52 vs. −2.07 MD: −3.45 [−5.20; −1.69]; p-value: ND SMD: −0.26 [−0.39; −0.13][e]	Lesser benefit/added benefit not proven
Physical functioning	Mean change: −2.91 vs. −1.45 MD: −1.46 [−2.73; −0.18]; p-value: ND SMD: −0.15 [−0.29; −0.02][e]	Lesser benefit/added benefit not proven
Role functioning	Mean change: −4.42 vs. −2.11 MD: −2.31 [−4.22; −0.39]; p-value: ND SMD: −0.16 [−0.29; −0.03][e]	Lesser benefit/added benefit not proven
Emotional functioning	Mean change: −3.10 vs. −0.99 MD: −2.11 [−3.86; −0.37]; p-value: ND SMD: −0.16 [−0.29; −0.03][e]	Lesser benefit/added benefit not proven
Cognitive functioning	Mean change: −4.55 vs. −2.72 MD: −1.83 [−3.46; −0.19]; p-value: ND SMD: −0.15 [−0.28; −0.02][e]	Lesser benefit/added benefit not proven

Table 19: Extent of added benefit at outcome level: pembrolizumab vs. watchful waiting (multipage table)

Outcome category **Outcome**	**Pembrolizumab vs. placebo** **Median time to event (months) or proportion of events (%) or MD** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Social functioning	Mean change: −4.34 vs. −1.01 MD: −3.33 [−5.17; −1.50]; p-value: ND SMD: −0.24 [−0.37; −0.11][e]	Lesser benefit/added benefit not proven
Side effects		
SAEs	20.5% vs. 11.3% RR: 1.81 [1.342; 2.46] RR: 0.55 [0.41; 0.745][f]; p < 0.001 probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% greater harm, extent: “major”
Severe AEs	32.4% vs. 17.7% RR: 1.82 [1.45; 2.29] RR: 0.55 [0.44; 0.69][f]; p < 0.001 probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% greater harm, extent: “major”
Discontinuation due to AEs	20.7% vs. 2.0% RR: 10.27 [5.43; 19.42] RR: 0.10 [0.05; 0.18][f]; p < 0.001 probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% greater harm, extent: “major”
Immune-related SAEs	8.4% vs. 0.2% RR: 41.67 [5.75; 301.75] RR: 0.02 [0.003; 0.17][f]; 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	9.0% vs. 0.6% RR: 14.91 [4.66; 47.69]; RR: 0.07 [0.02; 0.21][f]; 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][f]; p = 0.002 probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75, risk < 5% greater harm, extent: “considerable”

Table 19: Extent of added benefit at outcome level: pembrolizumab vs. watchful waiting (multipage table)

Outcome category **Outcome**	**Pembrolizumab vs. placebo** **Median time to event (months) or proportion of events (%) or MD** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
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][f]; 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)	4.7% vs. 1.8% RR: 2.60 [1.21; 5.56] RR: 0.38 [0.18; 0.83][f]; p = 0.010 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][f]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"
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][f]; 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. 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.
d. See Section I 4.1 for reasons.
e. If the CI for the SMD is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.
f. 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; MD: mean difference; RR: relative risk; SAE: serious adverse event; SMD: standardized mean difference; VAS: visual analogue scale

I 5.2 Overall conclusion on added benefit

Table 20 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 20: 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: hint of considerable added benefit	
Shortened observation period	
▪	Serious/severe side effects ▪ SAEs: hint of greater harm, extent: “major” ▫ Including: - Immune-related SAEs: indication of greater harm, extent: “major” ▪ Severe AEs: hint of greater harm, extent: “considerable” ▫ Including: - 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”
No suitable data for the outcome of overall survival and no complete subgroup analyses for all relevant outcomes or relevant subgroup characteristics are available.	
AE: adverse event; 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 considerable added benefit for the outcome of recurrence.

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

For the other patient-reported outcomes of the outcome categories of morbidity and health-related quality of life, there are neither positive nor negative effects. It should be noted that no suitable data for the outcome of overall survival and overall no complete subgroup analyses for all relevant outcomes or relevant subgroup characteristics are available for the first data cut-off. The negative effects do not completely outweigh the advantage in recurrence, but result in a downgrading of the extent of the added benefit.

In summary, there is a hint of minor added benefit of pembrolizumab in comparison with the ACT 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.

The result of the assessment of the added benefit of pembrolizumab in comparison with the ACT is summarized in Table 21.

Table 21: 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 minor added benefit

a. Presented is the respective ACT specified by the GBA.
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).

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 assessment described above deviates from that of the company, which claimed an indication of major added benefit.

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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

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