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Pembrolizumab (breast cancer) –

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 (Mammakarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 September 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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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 of persons concerned was received within the framework of the present dossier assessment.

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Part I: Benefit assessment

I Table of contents

I List of tables[2]

Page

[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
AGO	Arbeitsgemeinschaft Gynäkologische Onkologie
BSA	body surface area
CTCAE	Common Technology Criteria for Adverse Events
DGHO	Deutsche Gesellschaft für Hämatologie und. Medizinische Onkologie
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eDMC	external Data Monitoring Committee
EFS	event-free survival
EMA	European Medicines Agency
EORTC QLQ-30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-BR23	EORTC Quality of Life Questionnaire-Breast Cancer Module
EPAR	European Assessment Report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NCCN	National Comprehensive Cancer Network
pCR	pathological complete remission
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
TNBC	triple-negative breast cancer

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 (in combination with chemotherapy [neoadjuvant] followed by pembrolizumab as monotherapy [adjuvant]). 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 23 June 2022.

Research question

The aim of the present report is the assessment of the added benefit of pembrolizumab in combination with chemotherapy for neoadjuvant, and thereafter following surgery as monotherapy for adjuvant treatment, in comparison with the appropriate comparator therapy (ACT) in adult patients with locally advanced or early-stage triple-negative breast cancer (TNBC) at high risk of recurrence.

The G-BA's specification of the ACT results in the research question presented in Table 2.

Table 2: Research question of the benefit assessment of pembrolizumab + chemotherapy (neoadjuvant)/pembrolizumab (adjuvant)

Therapeutic indication	**ACT**[a]
Adult patients[b] with locally advanced, or early-stage triple-negative breast cancer at high risk of recurrence; combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery	Chemotherapy of physician's choice for the neoadjuvant treatment[c] followed by watchful waiting after surgery

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, the evidence on treatment options for men with breast cancer is extremely limited. According to the guidelines, the recommendations for the treatment of men are predominantly based on the recommendations for the treatment of women. Within the framework of the benefit assessment, separate consideration of men can be useful.
According to the G-BA, a sequential or combined chemotherapy regimen containing a taxane and an anthracycline is considered a suitable comparator in the neoadjuvant phase within the framework of a clinical study in the present therapeutic indication. The implementation of an anthracycline-containing chemotherapy protocol must be weighed up in consideration of the cardiovascular risks. There is a discrepancy between the drug therapies approved in the therapeutic indication and those recommended by the guidelines or used in health care. The drugs paclitaxel and cyclophosphamide are approved for adjuvant therapy but not explicitly for the neoadjuvant therapy situation, but are recommended in guidelines for neoadjuvant therapy. In the present therapeutic indication, the drug carboplatin is approved neither for the adjuvant nor for the neoadjuvant treatment situation. The approval and dosing information of the SPC of the drugs must be adhered to and deviations must be justified separately.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The G-BA initially specified chemotherapy of physician's choice as ACT, then updated this prior to dossier submission on 8 June 2022 and specified a chemotherapy of physician's choice for neoadjuvant treatment followed by watchful waiting after surgery. Based on the G-BA's

first definition of the ACT, the company operationalized this as neoadjuvant therapy with paclitaxel plus carboplatin followed by doxorubicin or epirubicin plus cyclophosphamide, as well as watchful waiting, operationalized as placebo, as ACT in adjuvant therapy.

The company named a uniform chemotherapy regimen for all patients in the target population without justifying the extent to which this chemotherapy regimen is equally suitable for all patients in the target population. The ACT specified by the G-BA was therefore used for the present benefit assessment.

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 study KEYNOTE 522 was used for the benefit assessment. This is an ongoing, double-blind RCT comparing pembrolizumab in combination with chemotherapy for neoadjuvant and then after surgery as monotherapy for adjuvant treatment versus placebo in combination with chemotherapy for neoadjuvant and then after surgery placebo for adjuvant treatment. Included were adult patients with locally advanced or early-stage, non-metastatic TNBC at high risk of recurrence, who had not received prior treatment in this TNBC stage.

Patients had to be in good general condition at study entry, corresponding to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 and had to have an adequate organ function. Patients with significant cardiovascular disease within the previous 6 months were excluded from the study.

The KEYNOTE 522 study included a total of 1174 patients who were randomized in a 2:1 ratio either to treatment with pembrolizumab + chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) (N = 784) or to treatment with placebo + chemotherapy (neoadjuvant) followed by placebo (adjuvant) (N = 390). Randomization was stratified by nodal status (positive versus negative), tumour size (T1/T2 versus T3/T4) and carboplatin treatment regimen (every 3 weeks vs. once weekly).

Treatment with pembrolizumab + chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) in the intervention arm corresponded to the recommendations of the Summary of Product Characteristics (SPC). Neoadjuvant treatment with chemotherapy in both study arms was initially 4 cycles of 3 weeks each with paclitaxel + carboplatin followed by a further 4 cycles of 3 weeks each with doxorubicin or epirubicin + cyclophosphamide.

While it can be assumed for the intervention arm of the KEYNOTE 522 study that the therapy of pembrolizumab + chemotherapy used in the neoadjuvant phase in this arm is approved as a whole due to the approval of pembrolizumab, this does not apply to the control arm. The chemotherapy regimen used in the control arm contained carboplatin, which is not approved in

the present therapeutic indication. Moreover, other drugs were used in chemotherapy that are not explicitly approved for neoadjuvant treatment. The assessment on the administration of carboplatin and paclitaxel and other uncertainties regarding treatment in the control arm are described in the following section.

Treatment of the study population took place until the completion of the 17th cycle or until disease progression in the neoadjuvant phase or recurrence in the adjuvant phase, occurrence of unacceptable toxicity, study discontinuation due to decision by the investigator, withdrawal of consent, lost to follow-up or death. Switching to the treatment of the other study arm was not planned.

Co-primary outcomes of the KEYNOTE 522 study were pathological complete response and event-free survival (EFS). Patient-relevant secondary outcomes comprise outcomes of the categories “mortality”, “morbidity”, “health-related quality of life” and “adverse events (AEs).

Implementation of the ACT

The G-BA specified chemotherapy of physician’s choice for neoadjuvant treatment followed by watchful waiting after surgery as ACT.

Use of a uniform chemotherapy regimen in neoadjuvant treatment

In the KEYNOTE 522 study, all patients received a uniform chemotherapy regimen.

In the various guidelines, however, no concrete/uniform chemotherapy regimen is named for neoadjuvant treatment of patients with TNBC, but there are various recommendations for sequential chemotherapy regimens - both in terms of the drugs to be used and the order and dosage of drug administration. In some cases, there are also significant differences in the therapy recommendations between the guidelines. It should be noted that the chemotherapy regimen used in the KEYNOTE 522 study is only listed in the guideline of the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) (with a deviating carboplatin dosage). Other guidelines (S3 guideline, guideline of Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie [DGHO], guideline of the National Comprehensive Cancer Network [NCCN]) do not mention this chemotherapy regimen.

It is unclear whether the different chemotherapy regimens recommended in the guidelines are equally suitable for all patients, or according to which criteria the therapy decision for a specific chemotherapy regimen is made. Thus, it is questionable whether the chemotherapy regimen used in the study is the most suitable treatment for the patients included in the KEYNOTE 522 study. If applicable, the investigator in the study should therefore have been given several possible chemotherapy regimens to choose from for the implementation of the ACT of a chemotherapy of physician's choice in the neoadjuvant treatment phase.

Administration of carboplatin

Carboplatin is approved neither for the adjuvant nor for the neoadjuvant treatment situation of breast cancer. The company argued, with reference to various randomized studies and guidelines on the neoadjuvant treatment of TNBC, that the improvement in pathological complete remission (pCR) rates, the prolongation of disease-free survival and overall survival would justify the addition of carboplatin to standard chemotherapy in TNBC patients, especially in TNBC patients who represent a high-risk population.

A carboplatin-containing chemotherapy regimen in the neoadjuvant treatment of TNBC is only recommended in the AGO guideline - with a carboplatin dosage deviating from the one used in the KEYNOTE 522 study. In other guidelines, the chemotherapy regimen used is not listed for the present therapeutic indication or it is listed, but the use of carboplatin is assessed as critically. The use of carboplatin is controversially discussed by the European Medicines Agency (EMA) and in the guidelines, because although an increased pCR rate was shown with carboplatin administration, there was no consistent improvement in EFS and overall survival and this was also at the cost of worse haematological toxicity.

Overall, there is no consensus yet on the inclusion of carboplatin in neoadjuvant treatment of TNBC. It is unclear to what extent the use of carboplatin affects the results of patient-relevant outcomes.

Dosing of paclitaxel

Although paclitaxel is not approved for the neoadjuvant therapy, the guidelines recommend that - if postoperative adjuvant chemotherapy is indicated - it should preferably be used neoadjuvantly.

According to the SPC, paclitaxel is approved for adjuvant combination therapy in a dosage of 175 mg/m^2 body surface area (BSA) every 3 weeks. In the KEYNOTE 522 study, paclitaxel (neoadjuvant) is used weekly at a dose of 80 mg/m^2 BSA in combination with carboplatin.

The company refers to everyday clinical practice as well as to the national and international guidelines, according to which the dose-dense, weekly administration with 80 mg/m^2 BSA used in KEYNOTE 522 is preferred over the 3-weekly dosing. According to the company, the weekly paclitaxel administration of 80 mg/m^2 BSA can achieve prolonged overall survival with lower toxicity.

The conclusions of the company cannot be found in the studies cited by it. In these, paclitaxel is used at a weekly dosage of 80 mg/m^2 BSA, but without a comparison to a dosage of 175 mg/m^2 BSA every 3 weeks. In the guidelines cited by the company (NCCN, AGO), there is no uniform recommendation that weekly administration of 80 mg/m^2 BSA is to be preferred or has an advantage in terms of disease-free survival and overall survival.

It is unclear to what extent weekly paclitaxel administration at a dose of 80 mg/m^2 BSA (compared with 3-weekly administration of 175 mg/m^2 BSA) affects the results of patient-relevant outcomes.

Limited certainty of conclusions

It is unclear to what extent the specification of a uniform chemotherapy regimen for the patients in the study as well as the administration of carboplatin and paclitaxel that is not compliant with the approval have an effect on the results of patient-relevant outcomes. Due to these uncertainties, the certainty of conclusions of the study is downgraded.

Implementation of watchful waiting in adjuvant treatment

Follow-up examinations

The adjuvant phase of the study was not designed for a comparison with watchful waiting, but the study is nonetheless suitable for such a comparison.

The examinations performed in the KEYNOTE 522 study do not fully represent the guideline recommendations. In particular, the study documents do not show that regular mammographies or supplementary ultrasounds of the breast were performed. As a result, recurrences may be detected later. Even though effects on the outcome of recurrence are not to be expected, this deviation is important for the interpretation of the results for the outcome of overall survival. If recurrences are recorded at a later point in time, patients may receive subsequent therapies at a later point in time. This is taken into account when interpreting the results for this outcome.

Apart from this uncertainty and despite the described deviations from the guideline recommendations, the examination regimen in the adjuvant phase of the KEYNOTE 522 study is overall considered to be a sufficient approximation to watchful waiting.

Use of postoperative radiotherapy

It should be noted that in the KEYNOTE 522 study - if indicated - postoperative radiotherapy could be given to patients in both treatment arms. This was permitted according to the treatment standard of the respective study centres, e.g. in the case of breast-conserving surgery, large primary tumour and patients with positive lymph nodes. This approach corresponds to the guidelines.

It is not clear from the study documents how many patients received postoperative radiotherapy. However, the European Assessment Report (EPAR) shows that this applied to 54% of patients in the intervention arm and 64% of patients in the comparator arm. In the KEYNOTE 522 study, approximately 45% of patients in both treatment arms underwent breast-conserving surgery, and over 50% of patients had lymph node involvement. There are therefore no signs suggesting that the use of radiotherapy in the patients was not carried out in accordance with the guidelines. The radiotherapy used in the KEYNOTE 522 study in the adjuvant treatment is therefore accepted as component of the ACT.

Data cut-offs and analyses

The KEYNOTE 522 study is still ongoing. To date, 5 of 8 planned data cut-offs have been conducted.

In Module 4 A, the company presents the results of the fourth data cut-off and thus not those of the most recent fifth data cut-off. In Module 4 A, the company justifies this with the fact that the significance threshold for overall survival was not undercut and this data cut-off was therefore not analysed. In the separate document submitted by the company as a reference for the study report of the fourth data cut-off, it is explained that an external Data Monitoring Committee (eDMC) reviewed the results of the fifth data cut-off on efficacy and safety on 23 May 2022. The eDMC had recommended to continue the study as planned until the next data cut-off. Since the null hypothesis for overall survival could not be rejected, the entire study team of the company should remain blinded to the results of this data cut-off. The study was to be continued in a blinded manner until the null hypothesis for overall survival could be rejected and the eDMC would therefore recommend unblinding or until the final data cut-off was made.

The missing representation of the results of the fifth data cut-off is not appropriate. The justification given by the company for this in Module 4 A, namely that the significance threshold for the outcome "overall survival" was not reached in the fifth data cut-off, is not valid. The aspect mentioned in the information document to the clinical study report to continue the study in a blinded manner is also not comprehensible, as there are already published analyses for all outcomes for the previous fourth data cut-off, i.e. also for overall survival. In principle, in accordance with the dossier template, complete analyses for all patient-relevant outcomes recorded must be conducted and provided for all of the data cut-offs relevant to the benefit assessment. Moreover, according to the data in the separate information document to the study report on the fifth data cut-off, such analyses are also already available.

Overall, the company does not sufficiently justify why the data for the fifth data cut-off are not presented. The dossier of the company is therefore incomplete in terms of content. For the present benefit assessment, the results of the fourth data cut-off presented by the company in Module 4 A are used as a substitute in the specific situation. In the present data constellation, it is not suspected that the fifth data cut-off will reveal relevantly different results. The lack of results for the fifth data cut-off was considered in the derivation of the added benefit.

Risk of bias

The risk of bias across outcomes was rated as low for the KEYNOTE 522 study. The outcome-specific risk of bias was also rated as low for the results of the outcomes "recurrence" and "breast-conserving surgery". For the results of the outcomes of overall survival, serious adverse events (SAEs), severe AEs, immune-related SAES, immune-related severe AEs and other specific AEs, the risk of bias was rated as high. Although the risk of bias for the outcome "discontinuation due to AEs" was low, the certainty of results for this outcome was limited. Usable data for the outcomes of symptoms (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30], EORTC QLQ-BR23),

health status (EQ-5D VAS) and health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR23) are not available.

Results

Mortality

Overall survival

There was no statistically significant difference between the treatment arms for the outcome "overall survival". This resulted in no hint of an added benefit of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) in comparison with the ACT; an added benefit is therefore not proven.

Morbidity

Recurrence

Operationalization

For the present benefit assessment, the outcome of recurrence is presented via the recurrence rate and EFS. Each of the two analyses comprises the events local progression preventing definitive surgery, local progression preventing surgery, positive resection margin at last surgery, local recurrence, distant recurrence, distant metastases, second primary tumour and death regardless of cause.

Result

For the outcome “recurrence”, there is a statistically significant difference between the treatment arms in favour of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) compared to the ACT. This resulted in a hint of added benefit of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) for this outcome.

Breast-conserving surgery

For the outcome "breast-conserving surgery", there was no statistically significant difference between the treatment arms. This resulted in no hint of an added benefit of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) in comparison with the ACT; an added benefit is therefore not proven.

Symptoms

No usable data were available for the outcome “symptoms” (recorded using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30] and the EORTC Quality of Life Questionnaire-Breast Cancer Module [EORTC QLQ-BR23]). This resulted in no hint of an added benefit of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) in comparison with the ACT; an added benefit is therefore not proven.

Health status

No usable data were available for the outcome "health status" (recorded using EQ-5D VAS). This resulted in no hint of an added benefit of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) in comparison with the ACT; an added benefit is therefore not proven.

Health-related quality of life

There were no usable data for the outcome "health-related quality of life" (recorded with the EORTC QLQ-C30 and the EORTC QLQ-BR23). This resulted in no hint of an added benefit of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) in comparison with the ACT; an added benefit is therefore not proven.

Side effects

SAEs and discontinuation due to AEs

For the outcomes "SAEs" and "discontinuation due to SAEs", there was a statistically significant difference to the disadvantage of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) compared to the ACT. In each case, this resulted in a hint of greater harm from pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant).

Severe AEs

There was no statistically significant difference between treatment arms for the outcome "severe AEs". This resulted in no hint of greater or lesser harm from pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) in comparison with the ACT; greater or lesser harm is therefore not proven.

Specific AEs

Immune-related SAEs, immune-related severe AEs , blood and lymphatic system disorders (SAEs), injury, poisoning and procedural complications (SAEs), endocrine disorders (severe AEs), gastrointestinal disorders (severe AEs), general disorders and administration site conditions (severe AEs), hepatobiliary disorders (severe AEs), skin and subcutaneous tissue disorders (severe AEs)

For the outcomes of immune-related SAEs, immune-related severe AEs, blood and lymphatic system disorders (SAEs), injury, poisoning and procedural complications (SAEs), endocrine disorders (severe AEs), gastrointestinal disorders (severe AEs), general disorders and administration site conditions (severe AEs), hepatobiliary disorders (severe AEs) as well as skin and subcutaneous tissue disorders (severe AEs), there is a statistically significant difference in each case to the disadvantage of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) versus the ACT. In each case, this resulted in a hint of greater harm from pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) versus the ACT.

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

On the basis of the results presented, the probability and extent of the added benefit of the drug pembrolizumab in combination with chemotherapy for neoadjuvant treatment, and thereafter following surgery as monotherapy in comparison with the ACT are assessed as follows:

On the side of the positive effects, there was a hint of considerable added benefit for the outcome "recurrence". In contrast, on the side of the negative effects, there are hints of greater harm with the extents "minor" to "considerable" for the outcome category of serious/severe side effects, and there is one hint of greater harm with the extent "considerable" for the outcome category of non-serious/non-severe side effects. However, the effects observed for side effects exclusively refer to the shortened period (treatment period plus a maximum of 90 days).

Suitable analyses of the patient-reported outcomes of the categories of morbidity and health-related quality of life are also lacking. In addition, the dossier submitted by the company is to be classified as incomplete in terms of content due to the missing presentation of the results on the most recent data cut-off of the KEYNOTE 522 study.

Overall, this means that the added benefit of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) compared to the ACT chemotherapy (neoadjuvant) followed by watchful waiting is not proven for patients with locally advanced or early-stage TNBC at high risk of recurrence.

Table 3 presents a summary of the probability and extent of the added benefit of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant).

[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].

Table 3: Pembrolizumab + chemotherapy (neoadjuvant)/pembrolizumab (adjuvant) – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with locally advanced, or early-stage triple-negative breast cancer at high risk of recurrence, in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery	Chemotherapy of physician's choice for the neoadjuvant treatment followed by watchful waiting after surgery	Added benefit not proven[b]

a. Presented is the respective ACT specified by the GBA.
b. The KEYNOTE 522 study only included patients with an ECOG PS of 0 or 1 and only one male patient. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 and to male patients.

ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee

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 combination with chemotherapy for neoadjuvant, and thereafter following surgery as monotherapy for adjuvant treatment, in comparison with the ACT in adult patients with locally advanced or early-stage TNBC at high risk of recurrence.

The G-BA's specification of the ACT results in the research question presented in Table 4.

Table 4: Research question of the benefit assessment of pembrolizumab + chemotherapy (neoadjuvant)/pembrolizumab (adjuvant)

Therapeutic indication	**ACT[a]**
Adult patients[b] with locally advanced, or early-stage triple-negative breast cancer at high risk of recurrence; combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery	Chemotherapy of physician's choice for the neoadjuvant treatment[c] followed by watchful waiting after surgery

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, the evidence on treatment options for men with breast cancer is extremely limited. According to the guidelines, the recommendations for the treatment of men are predominantly based on the recommendations for the treatment of women. Within the framework of the benefit assessment, separate consideration of men can be useful.
According to the G-BA, a sequential or combined chemotherapy regimen containing a taxane and an anthracycline is considered a suitable comparator in the neoadjuvant phase within the framework of a clinical study in the present therapeutic indication. The implementation of an anthracycline-containing chemotherapy protocol must be weighed up in consideration of the cardiovascular risks. There is a discrepancy between the drug therapies approved in the therapeutic indication and those recommended by the guidelines or used in health care. The drugs paclitaxel and cyclophosphamide are approved for adjuvant therapy but not explicitly for the neoadjuvant therapy situation, but are recommended in guidelines for neoadjuvant therapy. In the present therapeutic indication, the drug carboplatin is approved neither for the adjuvant nor for the neoadjuvant treatment situation. The approval and dosing information of the SPC of the drugs must be adhered to and deviations must be justified separately.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The G-BA initially specified chemotherapy of physician's choice as ACT, then updated this prior to dossier submission on 8 June 2022 and specified a chemotherapy of physician's choice for neoadjuvant treatment followed by watchful waiting after surgery. Based on the G-BA's first definition of the ACT, the company operationalized this as neoadjuvant therapy with paclitaxel plus carboplatin followed by doxorubicin or epirubicin plus cyclophosphamide, as well as watchful waiting, operationalized as placebo, as ACT in adjuvant therapy.

The company named a uniform chemotherapy regimen for all patients in the target population without justifying the extent to which this chemotherapy regimen is equally suitable for all patients in the target population. The ACT specified by the G-BA was therefore used for the present benefit assessment.

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: 23 May 2022)
- bibliographical literature search on pembrolizumab (last search on 20 April 2022)
- search in trial registries/trial results databases for studies on pembrolizumab (last search on 20 April 2022)
- search on the G-BA website for pembrolizumab (last search on 20 April 2022)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 04 July 2022); for search strategies, see I Appendix A of the full dossier assessment.

The check did not identify any additional relevant studies.

I 3.1 Studies included

The study presented in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: pembrolizumab + chemotherapy (neoadjuvant)/pembrolizumab (adjuvant) vs. chemotherapy (neoadjuvant)/watchful waiting (adjuvant)

Study	Study category			Available sources		
	Approval study for 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])
KEYNOTE 522	Yes	Yes	No	Yes [3,4]	Yes [5,6]	Yes [7-9]

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.
G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study KEYNOTE 522 was included in the present benefit assessment. In the KEYNOTE 522 study, placebo in combination with chemotherapy (neoadjuvant) followed by placebo (adjuvant) was used as ACT. The study was not designed for a comparison with chemotherapy (neoadjuvant) followed by watchful waiting (adjuvant), but the study is

nonetheless suitable for such a comparison (see Section I 3.2). 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 included studies – RCT, direct comparison: pembrolizumab + chemotherapy (neoadjuvant)/pembrolizumab (adjuvant) vs. chemotherapy (neoadjuvant)/watchful waiting (adjuvant) (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
KEYNOTE 522	RCT, double-blind, parallel	Adult patients with locally advanced[b] TNBC at high risk of recurrence ▪ without prior treatment of the locally advanced TNBC ▪ with Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1	Intervention arm[c] (N = 784) comparator arm[d] (N = 390)	Screening: up to 28 days treatment: 17 cycles or until progression of the disease in the neoadjuvant phase or recurrence in the adjuvant phase, occurrence of unacceptable toxicity, treatment discontinuation following the investigator's decision, withdrawal of consent, lost to follow-up or death observation[e]: outcome-specific, until death, lost to follow-up, or withdrawal of consent	177 study centres in Australia, Brazil, Canada, Columbia, France, Germany, Ireland, Israel, Italy, Japan, Poland, Portugal, Russia, Sweden, Singapore, South Korea, Spain, Taiwan, Turkey, United Kingdom, USA 03/2017 – ongoing data cut-offs[f]: first data cut-off: 24 September 2018 fourth data cut-off: 23 March 2021 fifth data cut-off[g]: 23 March 2022	Primary: pathological complete response, EFS secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the included studies – RCT, direct comparison: pembrolizumab + chemotherapy (neoadjuvant)/pembrolizumab (adjuvant) vs. chemotherapy (neoadjuvant)/watchful waiting (adjuvant) (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. According to the study documents, this also comprises patients with early-stage TNBC at high risk of recurrence (stage II and stage III). c. Pembrolizumab + chemotherapy (paclitaxel + carboplatin followed by doxorubicin or epirubicin + cyclophosphamide) neoadjuvant/pembrolizumab adjuvant. c. Placebo + chemotherapy (paclitaxel + carboplatin followed by doxorubicin or epirubicin + cyclophosphamide) neoadjuvant/placebo adjuvant. e. Outcome-specific information is described in Table 9. f. The first data cut-off was performed after the first 500 randomized patients had received neoadjuvant treatment for about 6 months and tumour resection had taken place. The second data cut-off was performed about 2 years after randomization of the first patient. Until 2024, a new data cut-off is to be carried out after every year. The final data cut-off is planned as soon as approx. 327 events of the outcome “event-free survival” will have occurred. g. In Module 4 A, the company presents the results of the fourth data cut-off and thus not those of the most recent fifth data cut-off. As justification, the company states that the significance threshold for overall survival was not undercut. According to a separate information document of the company to the clinical study report, an eDMC reviewed the results of the fifth data cut-off on efficacy and safety on 23 May 2022. The eDMC had recommended that the study be continued in a blinded manner until the null hypothesis for overall survival could be rejected (further explanation in the running text). AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EFS: event-free survival; N: number of randomized patients; RCT: randomized controlled trial; TNBC: triple-negative breast cancer						

Table 7: Characteristics of the intervention – RCT, direct comparison: pembrolizumab + chemotherapy (neoadjuvant)/pembrolizumab (adjuvant) vs. chemotherapy (neoadjuvant)/watchful waiting (adjuvant) (multipage table)

Study	Intervention	Comparison
KEYNOTE 522	**Neoadjuvant therapy:** 8 cycles: Pembrolizumab 200 mg, IV, on day 1 of a 3-week cycle + chemotherapy <u>chemotherapy in the intervention and the comparator arm:</u> ▪ 4 cycles: paclitaxel 80 mg/m² BSA IV on days 1, 8 and 15 of a 3-week cycle + carboplatin AUC 5 IV on day 1 or AUC 1.5 IV on days 1, 8 and 15 of a 3-week cycle followed by: ▪ 4 cycles: doxorubicin 60 mg/m² BSA or epirubicin 90 mg/m² BSA IV on day 1 of a 3-week cycle + cyclophosphamide 600 mg/m² BSA IV on day 1 of a 3-week cycle **surgery:** 3-6 weeks after the end of the neoadjuvant phase **adjuvant therapy** (9 cycles, start 30-60 days after surgery)**:** pembrolizumab 200 mg IV on day 1 of a 3-week cycle	8 cycles: Placebo IV on day 1 of a 3-week cycle + chemotherapy placebo IV on day 1 of a 3-week cycle
	Treatment adjustment: ▪ pembrolizumab/placebo: discontinuation for various immune-related AEs of CTCAE grade 2 (partly also CTCAE grade 3); treatment discontinuation in case of severe immune-related or infusion-related AEs; if pembrolizumab/placebo was discontinued, chemotherapy could be continued (no restart of pembrolizumab/placebo in the adjuvant phase) ▪ chemotherapy: dose adjustments depending on AE and severity, interruption or treatment discontinuation in case of toxicity; when discontinuing paclitaxel, carboplatin also had to be discontinued; when discontinuing doxorubicin/epirubicin or cyclophosphamide, pembrolizumab/placebo (neoadjuvant) also had to be discontinued (followed by surgery and adjuvant therapy); when discontinuing carboplatin, the remaining treatment could be continued as planned.	

Table 7: Characteristics of the intervention – RCT, direct comparison: pembrolizumab + chemotherapy (neoadjuvant)/pembrolizumab (adjuvant) vs. chemotherapy (neoadjuvant)/watchful waiting (adjuvant) (multipage table)

Study	Intervention	Comparison
	Non-permitted pretreatment ▪ chemotherapy, targeted therapy or radiation within 12 months before screening **permitted concomitant treatment** ▪ postoperative radiation in accordance with the treatment standard of the respective country, e.g. in case of larger primary tumour, after breast-conserving surgery or lymph node involvement ▪ corticosteroids orally or IV or other anti-inflammatory agents for the treatment of immune-related adverse events ▪ for the prevention of side effects of chemotherapy (neutropenia): granulocyte colony-stimulating factor (G-CSF) (filgrastim, pegfilgrastim) ▪ symptomatic treatment[a] for infusion reactions associated with pembrolizumab ▪ further therapies required for the wellbeing of the patients at the investigator's discretion and according to local standard **non-permitted concomitant treatment** ▪ immunotherapies and chemotherapies not predefined in the protocol ▪ other clinical investigational medication not predefined in the protocol ▪ radiotherapy (except postoperatively according to the standard treatment of the respective country) ▪ live vaccines within 30 days before the first dose of the study medication and during the study ▪ glucocorticoids (except for the treatment of immune-related AEs or as premedication of the chemotherapy drugs specified in the protocol)	
a. E.g. nonsteroidal anti-inflammatory drugs (NSAID), antihistamines, narcotics, acetaminophen. AE: adverse event; AUC: area under the concentration time curve; BSA: body surface area; G-CSF: granulocyte colony-stimulating factor; IV: intravenously; NSAID: nonsteroidal anti-inflammatory drug; RCT: randomized controlled trial		

KEYNOTE 522 is an ongoing, double-blind RCT comparing pembrolizumab in combination with chemotherapy for neoadjuvant and then after surgery as monotherapy for adjuvant treatment versus placebo in combination with chemotherapy for neoadjuvant and then after surgery placebo for adjuvant treatment. Included were adult patients with locally advanced, non-metastatic TNBC at high risk of recurrence, who had not received prior treatment in this TNBC stage. According to the study documents, patients with early-stage TNBC were also included in the study population. Patients had to be in good general condition at study entry, corresponding to an ECOG PS of 0 or 1 and had to have an adequate organ function. Patients with significant cardiovascular disease within the previous 6 months were excluded from the study.

The KEYNOTE 522 study included a total of 1174 patients who were randomized in a 2:1 ratio either to treatment with pembrolizumab + chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) (N = 784) or to treatment with placebo + chemotherapy (neoadjuvant) followed by placebo (adjuvant) (N = 390). Randomization was stratified by nodal

status (positive versus negative), tumour size (T1/T2 versus T3/T4) and carboplatin treatment regimen (every 3 weeks vs. once weekly).

Treatment with pembrolizumab + chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) in the intervention arm corresponded to the recommendations of the SPC [10]. Consistent with the marketing authorization, pembrolizumab dose adjustments were not allowed. If pembrolizumab/placebo was discontinued, chemotherapy could be continued.

Neoadjuvant treatment with chemotherapy in both study arms was initially 4 cycles of 3 weeks each with paclitaxel + carboplatin followed by a further 4 cycles of 3 weeks each with doxorubicin or epirubicin + cyclophosphamide. When paclitaxel was discontinued, carboplatin also had to be discontinued, whereas treatment could be continued as planned after discontinuation of carboplatin. If doxorubicin or epirubicin or cyclophosphamide was discontinued, treatment with pembrolizumab or placebo also had to be discontinued.

Table 7 presents the chemotherapy regimen used in the KEYNOTE 522 study. While it can be assumed for the intervention arm of the KEYNOTE 522 study that the therapy of pembrolizumab + chemotherapy used in the neoadjuvant phase in this arm is approved as a whole due to the approval of pembrolizumab [10], this does not apply to the control arm. The chemotherapy regimen used in the control arm contained carboplatin, which is not approved in the present therapeutic indication [11]. Moreover, other drugs were used in chemotherapy that are not explicitly approved for neoadjuvant treatment [12-15] (see Table 7). The assessment on the administration of carboplatin and paclitaxel and other uncertainties regarding treatment in the control arm are described in the following section.

If indicated, postoperative radiotherapy could be given in both treatment arms. In this case, adjuvant treatment with pembrolizumab or placebo was started at either the same time as radiotherapy or 2 weeks after radiotherapy.

Treatment of the study population took place until the completion of the 17th cycle or until disease progression in the neoadjuvant phase or recurrence in the adjuvant phase, occurrence of unacceptable toxicity, study discontinuation due to decision by the investigator, withdrawal of consent, lost to follow-up or death. Switching to the treatment of the other study arm was not planned.

Co-primary outcomes of the KEYNOTE 522 study were pathological complete response and EFS. Patient-relevant secondary outcomes comprise outcomes of the categories “mortality”, “morbidity”, “health-related quality of life” and “AEs”.

Implementation of the ACT

The G-BA specified chemotherapy of physician’s choice for neoadjuvant treatment followed by watchful waiting after surgery as ACT.

In the comparator arm (as well as in the intervention arm) of the KEYNOTE 522 study, the chemotherapy used in the neoadjuvant phase was paclitaxel + carboplatin over 4 cycles, followed by doxorubicin or epirubicin + cyclophosphamide over 4 cycles (see Table 7).

Use of a uniform chemotherapy regimen in neoadjuvant treatment

In the KEYNOTE 522 study, all patients received a uniform chemotherapy regimen.

In the various guidelines, however, no concrete/uniform chemotherapy regimen is named for neoadjuvant treatment of patients with TNBC [16-20], but there are various recommendations for sequential chemotherapy regimens - both in terms of the drugs to be used and the order and dosage of drug administration. In some cases, there are also significant differences in the therapy recommendations between the guidelines. It should be noted that the chemotherapy regimen used in the KEYNOTE 522 study is only listed in the AGO guideline (with a deviating carboplatin dosage) [18]. Other guidelines (S3 guideline, DGHO guideline, NCCN guideline) do not mention this chemotherapy regimen [16,17,20].

It is unclear whether the different chemotherapy regimens recommended in the guidelines are equally suitable for all patients, or according to which criteria the therapy decision for a specific chemotherapy regimen is made. Thus, it is questionable whether the chemotherapy regimen used in the study is the most suitable treatment for the patients included in the KEYNOTE 522 study. If applicable, the investigator in the study should therefore have been given several possible chemotherapy regimens to choose from for the implementation of the ACT of a chemotherapy of physician's choice in the neoadjuvant treatment phase.

It is unclear to what extent the specification of a uniform chemotherapy regimen for the patients in the study has an effect on the results of patient-relevant outcomes. Overall, the reliability of the study is downgraded given the further uncertainties mentioned below regarding the implementation of the ACT in the KEYNOTE 522 study.

Administration of carboplatin

Carboplatin is neither approved for the adjuvant nor for the neoadjuvant treatment situation of breast cancer [11]. The company argued, with reference to various randomized studies and guidelines on the neoadjuvant treatment of TNBC [18,21-27], that the improvement in pCR rates, the prolongation of disease-free survival and overall survival would justify the addition of carboplatin to standard chemotherapy in TNBC patients, especially in TNBC patients who represent a high-risk population.

A carboplatin-containing chemotherapy regimen in the neoadjuvant treatment of TNBC is only recommended in the AGO guideline [18] - with a different carboplatin dosage than that used in the KEYNOTE 522 study (area under the concentration time curve 6 [AUC 6] instead of AUC 5). In other guidelines, the chemotherapy regimen used is not listed for the present therapeutic indication [16,17] or it is listed, but the use of carboplatin assessed as critically [20].

The use of carboplatin is controversially discussed by the EMA [9] and in the guidelines [16,17,20,28], because although an increased pCR rate was shown with carboplatin administration, there was no consistent improvement in EFS and overall survival and this was also at the cost of worse haematological toxicity. EMA refers, among others, to 2 meta-analyses [29,30] examining platinum-based neoadjuvant chemotherapy in TNBC patients. Both studies conclude that due to the controversial results, further data - especially long-term data - are needed to clarify the relevance of carboplatin in the neoadjuvant therapy setting.

Overall, there is no consensus yet on the inclusion of carboplatin in neoadjuvant treatment of TNBC. It is unclear to what extent the use of carboplatin affects the results of patient-relevant outcomes. Overall, the reliability of the study is downgraded given the further uncertainties regarding the implementation of the ACT in the KEYNOTE 522 study.

Dosing of paclitaxel

Although paclitaxel is not approved for the neoadjuvant therapy, the guidelines recommend that - if postoperative adjuvant chemotherapy is indicated - it should preferably be used neoadjuvantly [16].

According to the SPC, paclitaxel is approved for adjuvant combination therapy in a dosage of 175 mg/m^2 BSA every 3 weeks [12]. In the KEYNOTE 522 study, paclitaxel (neoadjuvant) is used weekly at a dose of 80 mg/m^2 BSA in combination with carboplatin.

The company refers to everyday clinical practice as well as to the national and international guidelines [20,21,24-26,31], according to which the dose-dense, weekly administration with 80 mg/m^2 BSA used in KEYNOTE 522 is preferred over the 3-weekly dosing. According to the company, the weekly paclitaxel administration of 80 mg/m^2 BSA can achieve prolonged overall survival with lower toxicity.

The conclusions of the company cannot be found in the studies cited by it. In these, paclitaxel is used at a weekly dosage of 80 mg/m^2 BSA, but without a comparison to a dosage of 175 mg/m2 BSA every 3 weeks. In the guidelines cited by the company (NCCN, AGO [18,20]), there is no consistent recommendation that weekly administration of 80 mg/m^2 BSA is to be preferred or has an advantage in terms of disease-free survival and overall survival.

It is unclear to what extent weekly paclitaxel administration at a dose of 80 mg/m2 BSA (compared with 3-weekly administration of 175 mg/m^2 BSA) affects the results of patient-relevant outcomes. Overall, the reliability of the study is downgraded given the further uncertainties regarding the implementation of the ACT in the KEYNOTE 522 study.

Limited certainty of conclusions

It is unclear to what extent the specification of a uniform chemotherapy regimen for the patients in the study as well as the administration of carboplatin and paclitaxel that is not compliant with

the approval have an effect on the results of patient-relevant outcomes. Due to these uncertainties, the certainty of conclusions of the study is downgraded.

Implementation of watchful waiting in adjuvant treatment

Follow-up examinations

The adjuvant phase of the study was not designed for a comparison with watchful waiting, but the study is nonetheless suitable for such a comparison. This is explained below.

Targeted physical examinations were performed and laboratory parameters, ECOG PS and weight were recorded for all patients who did not start adjuvant treatment, who completed adjuvant treatment or who discontinued adjuvant treatment for reasons other than the occurrence of a recurrence. Moreover, the occurrence of a recurrence and the development of a second primary tumour (according to local or institutional guidelines of the respective study centres) should be recorded. Additional tests, examinations as well as imaging examinations for recurrent or metastatic disease (e.g. bone or liver scans) were to be performed at the discretion of the treating physician in accordance with the local treatment standards or at the time of symptoms. The study documents provide no information on which examination methods were to be used to assess the occurrence of these events.

The named examinations were carried out within the framework of follow-up visits (long-term follow-up). These visits were to take place at 3-month intervals for the first 2 years after the patient's randomization, every 6 months in years 3 to 5 after randomization, and then annually until the end of the study at the latest.

According to the guidelines, after-care in adjuvant treatment serves, among other things, the early detection of curatively treatable tumour recurrences, the detection of contralateral breast cancer, a second carcinoma, as well as the review of the success of the primary therapy and a psychological oncological support [16,17]. Follow-up should be quarterly for the first 3 years after primary therapy, half-yearly for the 4th and 5th year and annually from the 6th year until at least the 10th year. Patients should undergo physical examination at these intervals and laboratory values should be examined in case of clinical suspicion of recurrence and/or metastases. In addition, patients who have had the primary tumour surgically removed should have a mammography at least once a year, as well as a supplementary ultrasound of the affected breast.

The examinations performed in the KEYNOTE 522 study do not fully represent the guideline recommendations. In particular, the study documents do not show that regular mammographies or supplementary ultrasounds of the breast were performed. As a result, recurrences may be detected later. Even though effects on the outcome of recurrence are not to be expected, this deviation is important for the interpretation of the results for the outcome of overall survival. If recurrences are recorded at a later point in time, patients may receive subsequent therapies at a later point in time. This is taken into account when interpreting the results for this outcome.

Apart from this uncertainty and despite the described deviations from the guideline recommendations, the examination regimen in the adjuvant phase of the KEYNOTE 522 study is overall considered to be a sufficient approximation to watchful waiting.

Use of postoperative radiotherapy

It should be noted that in the KEYNOTE 522 study - if indicated - postoperative radiotherapy could be given to patients in both treatment arms. This was permitted according to the treatment standard of the respective study centres, e.g. in the case of breast-conserving surgery, large primary tumour and patients with positive lymph nodes. This approach corresponds to the guidelines [16,17,32].

It is not clear from the study documents how many patients received postoperative radiotherapy. However, the EPAR [9]) shows that this applied to 54% of patients in the intervention arm and 64% of patients in the comparator arm. In the KEYNOTE 522 study, approximately 45% of patients in both treatment arms underwent breast-conserving surgery, and over 50% of patients had lymph node involvement. There are therefore no signs suggesting that the use of radiotherapy in the patients was not carried out in accordance with the guidelines. The radiotherapy used in the KEYNOTE 522 study in the adjuvant treatment is therefore accepted as component of the ACT.

Data cut-offs and analyses

The KEYNOTE 522 study is still ongoing. Table 8 presents a total of 8 planned data cut-offs. 5 data cut-offs have been performed to date.

Table 8: Originally planned data cut-offs in the KEYNOTE 522 study

Data cut-off	Originally planned primary target	Planned time
First data cut-off: 24 September 2018 (interim analysis 1)	▪ Interim analysis pCR	After the first 500 randomized patients had received neoadjuvant treatment for about 6 months and tumour resection had taken place
Second data cut-off: 24 April 2019 (interim analysis 2)	▪ Final analysis pCR ▪ interim analysis EFS	About 2 years after randomization of the first patient
Third data cut-off: 23 March 2020 (interim analysis 3)	▪ Interim analysis EFS	About 3 years after randomization of the first patient
Fourth data cut-off[a]: 23 March 2021 (interim analysis 4)	▪ Interim analysis EFS[b]	About 4 years after randomization of the first patient
Fifth data cut-off: 23 March 2022 (interim analysis 5)	▪ Interim analysis EFS[b]	About 5 years after randomization of the first patient
Sixth data cut-off: 23 March 2023 (interim analysis 6)	▪ Interim analysis EFS[b]	One year after fifth data cut-off
Seventh data cut-off: 23 March 2024 (interim analysis 7)	▪ Interim analysis EFS[b]	One year after sixth data cut-off
Final data cut-off: presumably September 2026	▪ Final analysis EFS[b]	About 327 events of the outcome "EFS", unless the study was discontinued prematurely

a. Data cut-off presented by the company in Module 4 A.
b. Originally planned as interim analysis of the outcome "EFS". According to a separate information document on the study report submitted by the company, the null hypothesis for the EFS could be rejected for the fourth data cut-off. Therefore, from interim analysis 4 onwards, no further confirmatory testing of EFS took place, but instead confirmatory testing of overall survival.

EFS: event-free survival; pCR: pathological complete response

For the fourth data cut-off, the interim analysis of EFS was planned to be the primary objective in the study documents. A separate document submitted by the company as information for the clinical study report describes that the null hypothesis for the EFS could be rejected for the fourth data cut-off. For this reason, from interim analysis 4 onwards, confirmatory testing of overall survival should be carried out rather than confirmatory testing of EFS. According to the information document, the primary objective at the fifth data cut-off was the analysis of overall survival and not, as originally planned, an interim analysis of EFS.

In Module 4 A, the company presents the results of the fourth data cut-off and thus not those of the most recent fifth data cut-off. In Module 4 A, the company justifies this with the fact that the significance threshold for overall survival was not undercut and this data cut-off was therefore not analysed. In the separate document submitted by the company as a reference for the study report of the fourth data cut-off, it is explained that an eDMC reviewed the results of the fifth data cut-off on efficacy and safety on 23 May 2022. The eDMC had recommended to continue the study as planned until the next data cut-off. Since the null hypothesis for overall survival could not be rejected, the entire study team of the company should remain blinded to

the results of this data cut-off. The study was to be continued in a blinded manner until the null hypothesis for overall survival could be rejected and the eDMC would therefore recommend unblinding or until the final data cut-off was made.

The missing representation of the results of the fifth data cut-off is not appropriate. The justification given by the company for this in Module 4 A, namely that the significance threshold for the outcome "overall survival" was not reached in the fifth data cut-off, is not valid. The aspect mentioned in the information document to the clinical study report to continue the study in a blinded manner is also not comprehensible, as there are already published analyses for all outcomes for the previous fourth data cut-off, i.e. also for overall survival. In principle, in accordance with the dossier template, complete analyses for all patient-relevant outcomes recorded must be conducted and provided for all of the data cut-offs relevant to the benefit assessment [33]. Moreover, according to the data in the separate information document to the study report on the fifth data cut-off, such analyses are also already available.

Overall, the company does not sufficiently justify why the data for the fifth data cut-off are not presented. The dossier of the company is therefore incomplete in terms of content. For the present benefit assessment, the results of the fourth data cut-off presented by the company in Module 4 A are used as a substitute in the specific situation. In the present data constellation, it is not suspected that the fifth data cut-off will reveal relevantly different results. The lack of results for the fifth data cut-off was considered in the derivation of the added benefit.

Planned duration of 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 + chemotherapy (neoadjuvant)/pembrolizumab (adjuvant) vs. chemotherapy (neoadjuvant)/watchful waiting (adjuvant)

Study **outcome category** **outcome**	**Planned follow-up observation**
KEYNOTE 522	
Mortality	
Overall survival	Until death, withdrawal of consent or end of study
Morbidity	
Event-free survival	Until death, withdrawal of consent or end of study
Breast-conserving surgery	No follow-up observation[a]
Symptoms (EORTC QLQ-C30, EORTC QLQ-BR23)	In the long-term follow-up[b] during the first 2 years or until occurrence of disease progression or recurrence, whichever is earlier[c]
Health status (EQ-5D VAS)	In the long-term follow-up[b] during the first 2 years or until occurrence of disease progression or recurrence, whichever is earlier[c]
Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR23)	In the long-term follow-up[b] during the first 2 years or until occurrence of disease progression or recurrence, whichever is earlier[c]
Side effects	
AEs/severe AEs[d]	Up to 30 days after neoadjuvant therapy, after surgery and after adjuvant therapy respectively
SAEs	Up to 90 days after neoadjuvant therapy, after surgery and after adjuvant therapy, or up to 30 days after the end of study treatment if a new anticancer therapy was started

a. Information is based on the assessment of the investigator or before surgery.
b. Inconsistent information on the duration of the follow-up observations between the study documents and Module 4 A. According to the information in Module 4 A, follow-up observation was to be recorded during the long-term follow-up. Module 4 A does not mention limited recording until disease progression or recurrence.
c. The study documents show that as of Amendment 03 of the study protocol, it was specified that the long-term follow-up starts from randomization and not - as previously specified - only after the last study therapy. It is unclear what influence this has on the documentation time of the patient-reported outcomes.
d. Severe AEs are operationalized as CTCAE grade ≥ 3.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; ND: no data; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event

According to the study documents, the follow-up observation of the outcomes “health status” and “health-related quality of life” took place over a period of up to 2 years. This period was valid until amendment 02 of the protocol after the last study medication and was changed from amendment 03 of the protocol to the period from randomization. It is unclear what influence this has on the documentation time of the patient-reported outcomes.

The monitoring periods for the outcomes of the category of side effects were systematically shortened, because they were only recorded for the time of treatment with the study medication (plus 30 days or up to 90 days for SAEs).

However, to be able to draw a reliable conclusion on the total study period or the time to patient death, it would be necessary to record these outcomes as well for the total period, as was done for survival.

Characteristics of the study population

Table 10 shows the patient characteristics of the included study.

Table 10: Characteristics of the study population as well as discontinuation of study/treatment – RCT, direct comparison: pembrolizumab + chemotherapy (neoadjuvant)/pembrolizumab (adjuvant) vs. chemotherapy (neoadjuvant)/watchful waiting (adjuvant) (multipage table)

Study characteristic category	**Pembrolizumab + chemotherapy/pembrolizumab N[a] = 784**	**Chemotherapy/watchful waiting N[a] = 390**
KEYNOTE 522		
Age [years], mean (SD)	49 (12)	49 (12)
Sex [F/M], %	> 99/< 1	100/0
Family origin n (%)		
Native Americans or Alaskans	14 (2)	7 (2)
Asian	149 (19)	89 (23)
Black or African American	38 (5)	15 (4)
Native Hawaiians or Pacific Island natives	1 (< 1)	0 (0)
White	504 (64)	242 (62)
Several	13 (2)	6 (2)
Missing	65 (8)	31 (8)
Region, n (%)		
North America	166 (21)	78 (20)
Europe	388 (50)	180 (46)
Australia	23 (3)	16 (4)
Asia	166 (21)	91 (23)
Rest of the world	41 (5)	25 (6)
ECOG PS, n (%)		
0	678 (87)	341 (87)
1	106 (14)	49 (13)
Menopausal status, n (%)		
Premenopause	438 (56)	221 (57)
Postmenopause	345 (44)	169 (43)
Missing	1 (< 1)	0 (0)
Size of primary tumour, n (%)		
T1	53 (7)	24 (6)
T2	528 (67)	266 (68)
T3	145 (19)	73 (19)
T4	58 (7)	27 (7)
lymph node involvement, n (%)		
N0	376 (48)	194 (50)
N1	322 (41)	153 (39)
N2	85 (11)	42 (11)
N3	1 (< 1)	1 (< 1)
Disease stage[b], n (%)		
Stage I	0 (0)	1 (< 1)

Table 10: Characteristics of the study population as well as discontinuation of study/treatment – RCT, direct comparison: pembrolizumab + chemotherapy (neoadjuvant)/pembrolizumab (adjuvant) vs. chemotherapy (neoadjuvant)/watchful waiting (adjuvant) (multipage table)

Study characteristic category	**Pembrolizumab + chemotherapy/pembrolizumab N[a] = 784**	**Chemotherapy/watchful waiting N[a] = 390**
Stage II	590 (75)	291 (75)
Stage III	194 (25)	98 (25)
Treatment discontinuation, n (%)[c]	291 (37)	106 (27)
Study discontinuation, n (%)[d]	89 (11)	62 (16)

a. Number of randomized patients.
b. It can be assumed that this is the staging according to AJCC, as this was also used as inclusion criteria for the staging.
c. Data based on treatment discontinuation of all components. Common reasons for treatment discontinuation in the intervention vs. the control arm were: adverse event (14% vs. 5%), investigator's decision (4% vs. 4%), withdrawal of consent (4% vs. 3%) and in the adjuvant phase: adverse event (5% vs. 3%), withdrawal of consent (3% vs. 4%), relapse/recurrence (3% vs. 5%).
d. Common reasons for study discontinuation in the intervention vs. the control arm were: death (10% vs. 14%), withdrawal of consent (1% vs. 2%) and lost to follow-up (0.1% vs. 0%).

ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; M: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation

The characteristics are largely comparable between the two treatment arms. The study population of KEYNOTE 522 consists almost exclusively of women (one man in the intervention arm). The mean age of the patients was about 49 years. The majority of the patient population were of white family origin. The proportion of patients with an ECOG PS of 0 was about 87%, and the proportion of patients with stage II disease was about 75%.

In the neoadjuvant phase, the most common reasons for treatment discontinuation of all components were AEs (intervention arm: 14%, control arm: 5%); in the adjuvant phase, it were AEs (intervention arm: 5%, control arm: 3%) and relapse/recurrence (intervention arm: 3%, control arm: 5%).

Information on the course of the study

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 + chemotherapy (neoadjuvant)/pembrolizumab (adjuvant) vs. chemotherapy (neoadjuvant)/watchful waiting (adjuvant)

Study **duration of the study phase** **outcome category**	**Pembrolizumab + chemotherapy/pembrolizumab** **N = 784**	**Chemotherapy/watchful waiting** **N = 390**
KEYNOTE 522		
Treatment duration [months]		
Median [min; max]	13.3 [0; 21.9]	13.6 [0; 19.8]
Mean (SD)	11.2 (4.8)	12.3 (4.2)
Observation period [months]		
Overall survival[a]		
Median [min; max]	37.8 [2.7; 48.0]	37.6 [3.4; 47.6]
Mean (SD)	36.6 (8.0)	36.4 (7.9)
Disease symptoms, health status and health-related quality of life (EORTC QLQ-C30, EQ-5D VAS)		
Median [min; max]	19.7 [ND]	19.4 [ND]
Mean (SD)	ND	ND
Disease symptoms, health status and health-related quality of life (EORTC QLQ-BR23)		
Median [min; max]	19.6 [ND]	19.4 [ND]
Mean (SD)	ND	ND
AEs/severe AEs[b]		
Median [min; max]	14.3 [ND]	14.6 [ND]
Mean (SD)	ND	ND
SAEs		
Median [min; max]	16.2 [ND]	16.6 [ND]
Mean (SD)	ND	ND

a. The observation period is the time from randomization until either death or the fourth data cut-off, if the patients are still alive.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; max.: maximum; min: minimum; N: number of analysed patients; ND: no data; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; VAS: visual analogue scale

The median treatment durations were comparable in both treatment arms (intervention arm: 13.3 months; control arm: 13.6 months). The median observation periods for the outcomes of the categories “mortality”, “morbidity”, “health-related quality of life” and “side effects” were also comparable in both treatment arms.

Information on subsequent therapies

According to the information in the study documents, the subsequent therapies taken after the studies should be checked at regular intervals. However, the company did not present corresponding analyses of which subsequent therapy the patients in the intervention arm or in the comparator arm had received. Nor did the company describe the options available to the investigators in the study.

The results of the outcome "overall survival" are significantly influenced by the subsequent antineoplastic therapies used after a progression or relapse of the disease. The use of adequate subsequent therapies is thus of great importance for the assessment of the results on overall survival. For the KEYNOTE 522 study, it is not possible to assess whether the patients in both treatment arms received a guideline-compliant subsequent therapy due to the lack of information on the subsequent therapies used. This is taken into account when assessing the risk of bias for the results of the outcome "overall survival".

Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: pembrolizumab + chemotherapy (neoadjuvant)/pembrolizumab (adjuvant) vs. chemotherapy (neoadjuvant)/watchful waiting (adjuvant)

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 522	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the KEYNOTE 522 study.

Transferability of the study results to the German health care context

The company considers the results of KEYNOTE 522 to be transferable to the German health care context due to the characteristics of the investigated patient population, the study design and the approval-compliant use of pembrolizumab in combination with chemotherapy in the neoadjuvant setting followed by pembrolizumab as adjuvant monotherapy.

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
  - Breast-conserving surgery
  - Symptoms, recorded with the EORTC QLQ-C30 and EORTC QLQ-BR23
  - Health status, recorded using the EQ-5D VAS
- Health-related quality of life
  - Recorded with the EORTC QLQ-C30 and the EORTC QLQ-BR23
- Side effects
  - SAEs
  - Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - Discontinuation due to AEs
  - Immune-related SAEs
  - Immune-related severe AEs
  - Further specific AEs, if any

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

Table 13 shows the outcomes for which data were available in the included study.

Table 13: Matrix of outcomes – RCT, direct comparison: pembrolizumab + chemotherapy (neoadjuvant)/pembrolizumab (adjuvant) vs. chemotherapy (neoadjuvant)/watchful waiting (adjuvant)

Study	Outcomes											
	Overall survival	Recurrence[a]	Breast-conserving surgery	Symptoms (EORTC QLQ-C30, EORTC QLQ-BR23)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR23)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Immune-related SAEs[c]	Immune-related severe AEs[b, c]	Further specific AEs[b, d]
KEYNOTE 522	Yes	Yes	Yes	No[e]	No[e]	No[e]	Yes	Yes	Yes	Yes	Yes	Yes

a. Presented via the recurrence rate and disease-free survival; includes the events: local progression preventing definitive surgery, local progression preventing surgery, positive resection margin at last surgery, local recurrence, distant recurrence, distant metastases, second primary tumour and death regardless of cause.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. In each case, the operationalization of a specific MedDRA PT collection (outcome "adverse events" of special interest ["AEOSI"], Version 19.0) presented by the company is used.
d. The following events (MedDRA coding) are considered: "blood and lymphatic system disorders (SOC, SAEs), injury, poisoning and procedural complications (SOC, SAEs), endocrine disorders (SOC, severe AEs), gastrointestinal disorders (SOC, severe AEs), general disorders and administration site conditions (SOC, severe AEs), hepatobiliary disorders (SOC, severe AEs) and skin and subcutaneous tissue disorders (SOC, severe AEs).
e. No usable data available; see below for reasoning.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Notes on outcomes

Analyses on the outcome "recurrence"

According to the information in the study protocol, the outcome "EFS" was defined as time from randomization to the first occurrence of one of the following events:

- Progression of the disease that precludes definitive surgery
- Local recurrence
- Distal recurrence
- Second primary tumour

- positive resection margin at last surgery
- Death from any cause

Progression of the disease, local or distal recurrence and a second primary tumour are based on the investigator's decision.

From the further explanations in the study protocol on the operationalization of the outcome "EFS", it can be seen that, in addition, the following component is also counted as an EFS event:

- Distant metastasis

In patients who had locoregional progression (assessed radiologically) during the neoadjuvant treatment phase but underwent definitive surgery and did not have positive resection margins, this is not classified as an EFS event.

It should be noted that in Amendment 01 of the study protocol, "disease progression precluding surgery" was defined as a component of the outcome "EFS". From Amendment 02 of the study protocol, this component was renamed "disease progression precluding definitive surgery". In the presentation of results (both in Module 4 A and in the study documents), both components are listed separately. There is no justification for this procedure in Module 4 A or in the study documents. This remains without consequence, as, overall, only few events occurred for both components.

In addition, it should be noted that the outcome "recurrence" does not only include events that record the occurrence of recurrences after complete resection of the tumour, but also those that reflect progression events or the persistence of the tumour during the neoadjuvant phase (local progression that prevents definitive surgery, distant metastases). In the present therapeutic indication, both recurrence and progression events represent a failure of the curative treatment and are therefore relevant. For the two components of local progression, the uncertainty is that it is unclear what criteria were used to decide whether surgery was possible or not. Since, overall, only a few such events occurred, this is of no consequence for the present assessment.

For the outcome "recurrence", both the recurrence rate and the EFS are presented.

Analyses on patient-reported outcomes of the categories of morbidity and health-related quality of life

The analyses of the EORTC QLQ-C30 and the EORTC QLQ-BR23 for the categories "morbidity" and "health-related quality of life" as well as the analyses of the EQ-5D VAS for the category "morbidity" submitted by the company cannot be used for the present benefit assessment. In the analyses, the company considers the neoadjuvant and adjuvant treatment phases separately and presents the results of the change from baseline of the respective treatment phase, as well as the mean differences between the study arms. In addition, the values

for specific points in time during the course of the study are reported descriptively for each scale. The company did not present suitable analyses over the entire course of the study.

The company's approach is not appropriate. Only about 75% (pembrolizumab arm) and 85% (comparator arm) of all patients started the adjuvant treatment phase. The response rates for the PRO outcomes show that only about 62% and 73% of all patients completed the questionnaires on the PRO outcomes at the start of the adjuvant phase. Thus, only a greatly reduced proportion of patients in the ITT population, which varies between the treatment arms, is included in the analysis of the adjuvant phase. This proportion represents a subpopulation selected by the neoadjuvant treatment, so that a randomized comparison can no longer be assumed. However, a sole consideration of the neoadjuvant treatment phase is not meaningful for the derivation of the added benefit, as this does not allow a statement on the entire approved treatment period with pembrolizumab (neoadjuvant and adjuvant treatment) and thus the therapy concept of pembrolizumab in the present therapeutic indication.

Furthermore, it should be noted that the company calculated the analyses using constrained longitudinal data analysis (cLDA). Such analysis over the entire course of the study is considered suitable. Nevertheless, responder analyses of the time to (first or confirmed) deterioration according to IQWiG's General Methods would be preferable here [34].

Analyses on the outcomes of the category of side effects

For the outcomes of immune-related AEs, immune-related severe AEs and immune-related SAEs, the operationalization of a specific MedDRA PT collection of the outcome "adverse events of special interest" [AEOSI]) presented by the company is considered relevant. This is a selection of categories and PTs that belong to the typical immune-related AEs and for which treatment of the AEs with immunosuppression (e.g. with corticosteroids) could, but did not have to, be necessary. This operationalization is considered a sufficient approximation for immune-related AEs.

I 4.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: pembrolizumab + chemotherapy (neoadjuvant)/pembrolizumab (adjuvant) vs. chemotherapy (neoadjuvant)/watchful waiting (adjuvant)

Study	Study level	Outcomes											
		Overall survival	Recurrence[a]	Breast-conserving surgery	Symptoms (EORTC QLQ-C30, EORTC QLQ-BR23)	Health status (EQ-5D VAS)	health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR23)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Immune-related SAEs[c]	Immune-related severe AEs[b, c]	Further specific AEs[b, d]
KEYNOTE 522	L	H[e]	L	L	–[f]	–[f]	–[f]	H[g]	H[g]	L[h]	H[g]	H[g]	H[g]

a. Presented via the recurrence rate and disease-free survival; includes the events: local progression preventing definitive surgery, local progression preventing surgery, positive resection margin at last surgery, local recurrence, distant recurrence, distant metastases, second primary tumour and death regardless of cause.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. In each case, the operationalization of a specific MedDRA PT collection (outcome "adverse events of special interest" [AEOSI]) presented by the company is used.
d. The following events (MedDRA coding) are considered: "blood and lymphatic system disorders (SOC, SAEs), injury, poisoning and procedural complications (SOC, SAEs), endocrine disorders (SOC, severe AEs), gastrointestinal disorders (SOC, severe AEs), general disorders and administration site conditions (SOC, severe AEs), hepatobiliary disorders (SOC, severe AEs) and skin and subcutaneous tissue disorders (SOC, severe AEs).
e. Missing information on the subsequent antineoplastic therapies used in the patients (see further explanation in Section I 3.2).
f. No usable data available; see Section I 4.1 of the present dossier assessment for reasons.
g. Incomplete observations for potentially informative reasons.
h. Despite a low risk of bias, the certainty of results for the outcome of discontinuation due to AEs was assumed to be limited (see running text below).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high, L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module; 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 risk of bias for the results on the outcomes "recurrence" and "breast-conserving surgery" was rated as low. For the results on overall survival, the risk of bias was rated as high, since due to the lack of information on the subsequent therapies used, it cannot be assessed whether the patients in both treatment arms received guideline-compliant subsequent antineoplastic therapies.

Usable data for the outcomes of symptoms (EORTC QLQ-C30, EORTC QLQ-BR23), health status (EQ-5D VAS) and health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR23) are not available (see Section I 4.1).

The risk of bias of the results on the outcomes of SAEs, severe AEs as well as immune-related SAEs/severe AEs, and further specific AEs was rated as high. For the mentioned outcomes of the category of side effects, 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 (see also Table 9).

Although the risk of bias for the outcome “discontinuation due to AEs” was low, the certainty of results for this outcome was limited. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome of discontinuation due to AEs to be recorded. This means that, after discontinuation for other reasons, AEs that would have led to treatment discontinuation may have occurred, but that the criterion "discontinuation" can no longer be applied to them. It cannot be estimated how many AEs this concerns.

Summary assessment of the certainty of conclusions

Overall, the certainty of conclusions across all results of the KEYNOTE 522 study is reduced.

This results from the use of carboplatin in the comparator arm of the study, which was not in compliance with the approval. In addition, a uniform chemotherapy regimen was used for the patients in the study without allowing the investigators to choose between several possible chemotherapy regimens.

For the reasons mentioned above, at most hints of an added benefit can be derived for the results of the KEYNOTE 522 study based on the fourth data cut-off.

The effect of the incompleteness of the contents - due to the lack of the most current fifth data cut-off - is addressed in Section I 5.1 in the context of the overall conclusion on the added benefit.

I 4.3 Results

Table 15 summarizes the results for the comparison of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) versus chemotherapy (neoadjuvant) followed by watchful waiting (adjuvant) in adult patients with locally advanced or early-stage TNBC at high risk of recurrence. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company’s dossier.

The Kaplan-Meier curves on the event time analyses are presented in I Appendix B of the full dossier assessment, and the tables on common AEs, SAEs, severe AEs, and discontinuations due to AEs can be found in I Appendix C of the full dossier assessment. A list of the occurred categories of immune-related AEs, immune-related SAEs and immune-related severe AEs is provided in I Appendix D for information.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: pembrolizumab + chemotherapy (neoadjuvant)/pembrolizumab (adjuvant) vs. chemotherapy (neoadjuvant)/watchful waiting (adjuvant) (multipage table)

Study outcome category outcome	Pembrolizumab + chemotherapy/pembrolizumab		Chemotherapy/watchful waiting		Pembrolizumab + chemotherapy/pembrolizumab vs. chemotherapy/watchful waiting
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
KEYNOTE 522					
Mortality					
Overall survival	784	80 (10.2) median time to event: NA [NC; NC]	390	55 (14.1) median time to event: NA [NC; NC]	HR: 0.72 [0.51; 1.02]; 0.065[b]
Morbidity					
Recurrence[c]					
Recurrence rate	784	123 (15.7)	390	93 (23.8)	0.66 [0.52; 0.84]; < 0.001
Death	784	15 (1.9)	390	6 (1.5)	–
Distant metastases	784	4 (0.5)	390	1 (0.3)	–
Distant recurrence	784	60 (7.7)	390	51 (13.1)	–
Local progression preventing definitive surgery	784	1 (0.1)	390	0 (0)	–
Local progression preventing surgery	784	3 (0.4)	390	4 (1.0)	–
Local recurrence	784	28 (3.6)	390	17 (4.4)	–
Positive resection margin at last surgery	784	6 (0.8)	390	10 (2.6)	–
Second primary tumour	784	6 (0.8)	390	4 (1.0)	–
Event-free survival	784	Median time to event: NA [NC; NC]	390	Median time to event: NA [NC; NC]	HR: 0.63 [0.48; 0.82]; < 0.001[b]
Breast-conserving surgery	784	354 (45.2)	390	178 (45.6)	0.99 [0.87; 1.13]; 0.889[d]
Symptoms (EORTC QLQ-C30)				No usable data[e]	
Symptoms (EORTC QLQ-BR23)				No usable data[e]	
Health status (EQ-5D VAS)				No usable data[e]	

Table 15: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: pembrolizumab + chemotherapy (neoadjuvant)/pembrolizumab (adjuvant) vs. chemotherapy (neoadjuvant)/watchful waiting (adjuvant) (multipage table)

Study outcome category outcome	Pembrolizumab + chemotherapy/pembrolizumab		Chemotherapy/watchful waiting		Pembrolizumab + chemotherapy/pembrolizumab vs. chemotherapy/watchful waiting
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
Health-related quality of life					
EORTC QLQ-C30				No usable data[e]	
EORTC QLQ-BR23				No usable data[e]	
Side effects					
AEs (supplementary information)	783	777 (99.2)	389	389 (100)	–
SAEs	783	341 (43.6)	389	111 (28.5)	1.53 [1.28; 1.82]; < 0.001
Severe AEs[f]	783	645 (82.4)	389	306 (78.7)	1.05 [0.99; 1.11]; 0.128
Discontinuation due to AEs	783	234 (29.9)	389	60 (15.4)	1.94 [1.50; 2.50]; < 0.001
Immune-related AEs (supplementary information)	783	341 (43.6)	389	85 (21.9)	–
Immune-related SAEs	783	83 (10.6)	389	5 (1.3)	8.25 [3.37; 20.17]; < 0.001
Immune-related severe AEs[f]	783	117 (14.9)	389	8 (2.1)	7.27 [3.59; 14.72]; < 0.001
Further specific AEs					
Blood and lymphatic system disorders (SOC, SAEs)	783	154 (19.7)	389	58 (14.9)	1.32 [1.00; 1.74]; 0.047
Injury, poisoning and procedural complications (SOC, SAEs)	783	23 (2.9)	389	4 (1.0)	2.86 [0.99; 8.20]; 0.041
Endocrine disorders (SOC, severe AEs[f])	783	25 (3.2)	389	0 (0)	25.37 [1.55; 415.62]; < 0.001
Gastrointestinal disorders (SOC, severe AEs[f])	783	92 (11.7)	389	28 (7.2)	1.63 [1.09; 2.45]; 0.016
General disorders and administration site conditions (SOC, severe AEs[f])	783	90 (11.5)	389	24 (6.2)	1.86 [1.21; 2.87]; 0.004
Hepatobiliary disorders (SOC, severe AEs[f])	783	24 (3.1)	389	2 (0.5)	5.96 [1.42; 25.10]; 0.005

Table 15: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: pembrolizumab + chemotherapy (neoadjuvant)/pembrolizumab (adjuvant) vs. chemotherapy (neoadjuvant)/watchful waiting (adjuvant) (multipage table)

Study outcome category outcome	Pembrolizumab + chemotherapy/pembrolizumab		Chemotherapy/watchful waiting		Pembrolizumab + chemotherapy/pembrolizumab vs. chemotherapy/watchful waiting
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
Skin and subcutaneous tissue disorders (SOC, severe AEs[f])	783	49 (6.3)	389	3 (0.8)	8.11 [2.55; 25.87]; < 0.001

a. Institute's calculation of effect and CI (asymptotic). p-value: Institute's calculation (unconditional exact test, CSZ method according to [35].
b. HR, CI and p-value: Cox proportional hazards model stratified by nodal status (positive versus negative), tumour size (T1/T2 versus T3/T4) and choice of carboplatin (every 3 weeks vs. once weekly).
c. Proportion of patients, individual components are presented in the lines below (in each case, only with the qualifying events that are relevant for the formation of the composite outcome; calculation of effect estimates is therefore not meaningful).
d. Chochrane-Mantel-Haenszel method, stratified by nodal status (positive versus negative), tumour size (T1/T2 versus T3/T4) and choice of carboplatin (every 3 weeks vs. once weekly).
e. See Section I 4.1 of the present dossier assessment for the reasoning.
f. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; NA: not achieved; NC: not calculable; n: number of patients with (at least 1) event; N: number of analysed patients; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module; QLQ-C30: Quality of Life Questionnaire - Core 30; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class

On the basis of the available information, at most hints, e.g. of an added benefit, can be determined due to the uncertainties mentioned in Section I 3.2.

Mortality

Overall survival

There was no statistically significant difference between the treatment arms for the outcome "overall survival". This resulted in no hint of an added benefit of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) in comparison with the ACT; an added benefit is therefore not proven.

Morbidity

Recurrence

Operationalization

For the present benefit assessment, the outcome of recurrence is presented via the recurrence rate and EFS. Each of the two analyses comprises the events local progression preventing definitive surgery, local progression preventing surgery, positive resection margin at last surgery, local recurrence, distant recurrence, distant metastases, second primary tumour and death regardless of cause.

Result

For the outcome “recurrence”, there is a statistically significant difference between the treatment arms in favour of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) compared to the ACT. This resulted in a hint of added benefit of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) for this outcome.

Breast-conserving surgery

For the outcome "breast-conserving surgery", there was no statistically significant difference between the treatment arms. This resulted in no hint of an added benefit of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) in comparison with the ACT; an added benefit is therefore not proven.

Symptoms

There were no usable data for the outcome “symptoms” (recorded with the EORTC QLQ-C30 and the EORTC QLQ-BR23) (for reasons, see Section I 4.1). This resulted in no hint of an added benefit of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) in comparison with the ACT; an added benefit is therefore not proven.

Health status

There were no usable data for the outcome “health status” (recorded with the EQ-5D VAS) (for reasons, see Section I 4.1). This resulted in no hint of an added benefit of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) in comparison with the ACT; an added benefit is therefore not proven.

Health-related quality of life

There were no usable data for the outcome “health-related quality of life” (recorded with the EORTC QLQ-C30 and the EORTC QLQ-BR23) (for reasons, see Section I 4.1). This resulted in no hint of an added benefit of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) in comparison with the ACT; an added benefit is therefore not proven.

Side effects

SAEs and discontinuation due to AEs

For the outcomes "SAEs" and "discontinuation due to SAEs", there was a statistically significant difference to the disadvantage of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) compared to the ACT. In each case, this resulted in a hint of greater harm from pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant).

Severe AEs

There was no statistically significant difference between treatment arms for the outcome "severe AEs". This resulted in no hint of greater or lesser harm from pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) in comparison with the ACT; greater or lesser harm is therefore not proven.

Specific AEs

Immune-related SAEs, immune-related severe AEs , blood and lymphatic system disorders (SAEs), injury, poisoning and procedural complications (SAEs), endocrine disorders (severe AEs), gastrointestinal disorders (severe AEs), general disorders and administration site conditions (severe AEs), hepatobiliary disorders (severe AEs), skin and subcutaneous tissue disorders (severe AEs)

For the outcomes of immune-related SAEs, immune-related severe AEs, blood and lymphatic system disorders (SAEs), injury, poisoning and procedural complications (SAEs), endocrine disorders (severe AEs), gastrointestinal disorders (severe AEs), general disorders and administration site conditions (severe AEs), hepatobiliary disorders (severe AEs) as well as skin and subcutaneous tissue disorders (severe AEs), there is a statistically significant difference in each case to the disadvantage of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) versus the ACT. In each case, this resulted in a hint of greater harm from pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) versus the ACT.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics were considered for the present benefit assessment:

- age (< 65 years vs. ≥ 65 years)
- Tumour stage (stage II vs. stage III)

The mentioned characteristics were defined a priori. The characteristic of sex was disregarded because the study population only comprised one man.

For the outcomes "overall survival" and "recurrence" (EFS), subgroup analyses are available for both selected characteristics. For the other patient-relevant outcomes of the categories "morbidity", "health-related quality of life" and "AEs", analyses of the subgroup characteristics

used for the benefit assessment are only available for “age”. For the outcomes of the categories "morbidity" and "health-related quality of life", it should be noted that, overall, no usable data are available. For the outcomes “immune-related SAEs” and “immune-related severe AEs”, subgroup analyses are completely missing. According to the dossier template of the G-BA, the investigation of effect modifiers was required across all relevant outcomes [33].

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there had to be at least 10 events in at least 1 subgroup.

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

Using the methods described above, the available subgroup analyses do not reveal any effect modifications.

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 [34].

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 16).

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

It cannot be inferred from the dossier for the following outcomes of recurrence and discontinuation due to AEs whether they are serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Recurrence

The outcome of recurrence is considered to be serious/severe. On the one hand, recurrence of the cancer can be life-threatening, and a recurrence shows that the attempt to cure a potentially life-threatening disease with the curative therapy approach has not been successful. On the other hand, the event of death of any cause (without previous recurrence) is a component of the outcome of recurrence.

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, the study documents provide information on AEs and serious AEs that led to the discontinuation of treatment. This shows that < 50% of the AEs that led to discontinuation of treatment were serious AEs. Therefore, the outcome was assigned to the outcome category of non-serious/non-severe side effects.

Table 16: Extent of added benefit at outcome level: pembrolizumab + chemotherapy (neoadjuvant)/pembrolizumab (adjuvant) vs. chemotherapy (neoadjuvant)/watchful waiting (adjuvant) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Pembrolizumab + chemotherapy/pembrolizumab vs. chemotherapy/watchful waiting** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	NA vs. NA HR: 0.72 [0.51; 1.02]; 0.065	Lesser/added benefit not proven
Morbidity		
Recurrence[c]		
Recurrence rate	15.7% vs. 23.8% RR: 0.66 [0.52; 0.84]; < 0.001 probability: hint	Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_u < 0.90$ added benefit; extent: considerable
Event-free survival	NA vs. NA HR: 0.63 [0.48; 0.82]; < 0.001 probability: hint	
Breast-conserving surgery	45.2% vs. 45.6% RR: 0.99 [0.87; 1.13]; 0.889	Lesser/added benefit not proven
Symptoms		
EORTC QLQ-C30	No usable data[d]	Lesser/added benefit not proven
EORTC QLQ-BR23	No usable data[d]	Lesser/added benefit not proven
Health status (EQ-5D VAS)	No usable data[d]	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30	No usable data[d]	Lesser/added benefit not proven
EORTC QLQ-BR23	No usable data[d]	Lesser/added benefit not proven
Side effects		
SAEs	43.6% vs. 28.5% RR: 1.53 [1.28; 1.82]; RR: 0.65 [0.55; 0.78][e] < 0.001 probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: “considerable”
Severe AEs	82.4% vs. 78.7% RR: 1.05 [0.99; 1.11]; 0.128	Greater/lesser harm not proven

Table 16: Extent of added benefit at outcome level: pembrolizumab + chemotherapy (neoadjuvant)/pembrolizumab (adjuvant) vs. chemotherapy (neoadjuvant)/watchful waiting (adjuvant) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Pembrolizumab + chemotherapy/pembrolizumab vs. chemotherapy/watchful waiting** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Discontinuation due to AEs	29.9% vs. 15.4% RR: 1.94 [1.50; 2.50]; RR: 0.52 [0.40; 0.67][e] < 0.001 probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.8$ greater harm, extent: "considerable"
Immune-related SAEs	10.6% vs. 1.3% RR: 8.25 [3.37; 20.17]; RR: 0.12 [0.05; 0.30][e] < 0.001 probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"
Immune-related severe AEs	14.9% vs. 2.1% RR: 7.27 [3.59; 14.72]; RR: 0.14 [0.07; 0.28][e] < 0.001 probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"
Blood and lymphatic system disorders (SAEs)	19.7% vs. 14.9% RR: 1.32 [1.001; 1.74]; RR: 0.76 [0.57; 0.999][e] 0.047 probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"
Injury, poisoning and procedural complications (SAEs)	2.9% vs. 1.0% RR: 2.86 [0.99; 8.20]; RR: 0.35 [0.12; 1.01][e] 0.041 probability: hint	Outcome category: serious/severe side effects greater harm, extent: "minor"[f]
Endocrine disorders (severe AEs)	3.2% vs. 0% RR: 25.37 [1.55; 415.62]; RR: 0.04 [0.002; 0.65][e] < 0.001 probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$, risk < 5% greater harm, extent: "considerable"
Gastrointestinal disorders (severe AEs)	11.7% vs. 7.2% RR: 1.63 [1.09; 2.45]; RR: 0.61 [0.41; 0.92][e] 0.016 probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"

Table 16: Extent of added benefit at outcome level: pembrolizumab + chemotherapy (neoadjuvant)/pembrolizumab (adjuvant) vs. chemotherapy (neoadjuvant)/watchful waiting (adjuvant) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Pembrolizumab + chemotherapy/pembrolizumab vs. chemotherapy/watchful waiting** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
General disorders and administration site conditions (severe AEs)	11.5% vs. 6.2% RR: 1.86 [1.21; 2.87]; RR: 0.54 [0.35; 0.83][e] 0.004 probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
Hepatobiliary disorders (severe AEs)	3.1% vs. 0.5% RR: 5.96 [1.42; 25.10]; RR: 0.17 [0.04; 0.70][e] 0.005 probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$, risk < 5% greater harm, extent: "considerable"
Skin and subcutaneous tissue disorders (severe AEs)	6.3% vs. 0.8% RR: 8.11 [2.55; 25.87]; RR: 0.12 [0.04; 0.39][e] < 0.001 probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Presented via the recurrence rate and disease-free survival; includes the events: local progression preventing definitive surgery, local progression preventing surgery, positive resection margin at last surgery, local recurrence, distant recurrence, distant metastases, second primary tumour and death regardless of cause.
d. See Section I 4.1 of the present dossier assessment for the reasoning.
e. Institute's calculation, inverse direction of effect to enable use of limits to derive the extent of the added benefit.
f. Discrepancy between CI and p-value; the extent is rated as "minor".

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module; QLQ-C30: Quality of Life Questionnaire Core-30; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale

I 5.2 Overall conclusion on added benefit

Table 17 summarizes the results included in the overall conclusion on the extent of added benefit.

Table 17: Positive and negative effects from the assessment of pembrolizumab + chemotherapy (neoadjuvant)/pembrolizumab (adjuvant) compared with chemotherapy (neoadjuvant)/watchful waiting (adjuvant)

Positive effects	**Negative effects**
Total observation period	
Morbidity serious/severe symptoms/late complications ▪ recurrence[a]: hint of added benefit – extent: "considerable"	–
Shortened observation period	
–	Serious/severe side effects ▪ blood and lymphatic system disorders (SAEs); injury, poisoning and procedural complications (SAEs); gastrointestinal disorders (severe AEs) in each case hint of greater harm – extent: "minor" ▪ SAEs; endocrine disorders (severe AEs); general disorders and administration site conditions (severe AEs); hepatobiliary disorders (severe AEs): in each case, hint of greater harm - extent: "considerable" ▪ immune-related SAEs; immune-related severe AEs; skin and subcutaneous tissue disorders (severe AEs): in each case hint of greater harm – extent: "major"
–	Non-serious/non-severe side effects ▪ discontinuation due to AEs: hint of greater harm - extent: "considerable"
Usable data for the outcomes of symptoms (EORTC QLQ-C30, EORTC QLQ-BR23), health status (EQ-5D VAS) and health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR23) are not available.	
a. Presented via the recurrence rate and disease-free survival; includes the events: local progression preventing definitive surgery, local progression preventing surgery, positive resection margin at last surgery, local recurrence, distant recurrence, distant metastases, second primary tumour and death regardless of cause. AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module; QLQ-C30: Quality of Life Questionnaire Core-30; SAE: serious adverse event; VAS: visual analogue scale	

The overall consideration shows one positive and several negative effects of different extents with the probability "hint".

On the side of the positive effects, there was a hint of considerable added benefit for the outcome "recurrence". In contrast, on the side of the negative effects, there are hints of greater harm with the extents "minor" to "considerable" for the outcome category of serious/severe side effects, and there is one hint of greater harm with the extent "considerable" for the outcome category of non-serious/non-severe side effects. However, the effects observed for side effects exclusively refer to the shortened period (treatment period plus a maximum of 90 days).

Suitable analyses of the patient-reported outcomes of the categories of morbidity and health-related quality of life are also lacking. In addition, the dossier submitted by the company is to

be classified as incomplete in terms of content due to the missing presentation of the results on the most recent data cut-off of the KEYNOTE 522 study.

Overall, this means that the added benefit of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) compared to the ACT chemotherapy (neoadjuvant) followed by watchful waiting is not proven for patients with locally advanced or early-stage TNBC at high risk of recurrence.

The result of the assessment of the added benefit of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) in comparison with the ACT is summarized in Table 18.

Table 18: Pembrolizumab + chemotherapy (neoadjuvant)/pembrolizumab (adjuvant) – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with locally advanced, or early-stage triple-negative breast cancer at high risk of recurrence, in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery	Chemotherapy of physician's choice for the neoadjuvant treatment followed by watchful waiting after surgery	Added benefit not proven[b]
a. Presented is the respective ACT specified by the GBA. b. The KEYNOTE 522 study only included patients with an ECOG PS of 0 or 1 and only one male patient. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 and to male patients. ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company, which derived an indication of considerable 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.

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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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