Pembrolizumab (breast cancer, triple-negative, neoadjuvant and adjuvant)

Benefit assessment according to §35a SGB V[1] (expiry of the decision)

EXTRACT

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50679 Köln
Germany

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

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Medical and scientific advice

- Volker Heilmann, Günzburg, Germany

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

Patient and family involvement

No feedback of persons concerned was received within the framework of the present dossier assessment.

IQWiG employees involved in the dossier assessment

- Simon Bogner
- Tobias Effertz
- Tatjana Hermanns
- Simone Johner
- Michaela Florina Kerekes
- Philip Kranz
- Mattea Patt
- Kristina Schaubert

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

ACT	appropriate comparator therapy
AE	adverse event
CPS	combined positive score
ECOG PS	Eastern Cooperative Oncology Group – Performance Status
EFS	event-free survival
EORTC	European Organisation for Research and Treatment of Cancer
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
QLQ-BR23	Quality of Life Questionnaire Breast Cancer 23
QLQ-C30	Quality of Life Questionnaire – Core 30
RCT	randomized controlled trial
RR	Relatives Risiko
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
TNBC	triple-negative breast cancer
VAS	visuelle Analogskala

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] and then after surgery 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 30 September 2024.

The company had already submitted a dossier for a previous benefit assessment of the drug to be assessed. The dossier was sent to IQWiG on 23 June 2022. In this procedure, by decision of 15 December 2022, the G-BA limited its decision until 01 October 2024. The decision was limited since further data relevant for the assessment of the added benefit, in particular on overall survival, were to be expected from the KEYNOTE 522 study.

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

Table 2: Research question of the benefit assessment of pembrolizumab + 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; in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery	Taxane- and anthracycline[c]-based neoadjuvant chemotherapy according to physician's choice[d], choosing from: ▪ cyclophosphamide ▪ docetaxel ▪ doxorubicin ▪ epirubicin ▪ paclitaxel ▪ carboplatin 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. c. According to the G-BA, the implementation of an anthracycline-containing chemotherapy protocol must be weighed up in consideration of the cardiovascular risks. The cardiac functions must be closely monitored. d. According to the G-BA, a single-comparator study is generally insufficient for implementing treatment of physician's choice in a study of direct comparison. The investigators are expected to have a choice between several treatment options (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company deviates from the ACT specified by the G-BA. At first, it subdivided the therapeutic indication into two patient groups:

- Patients treated with pembrolizumab in combination with paclitaxel and carboplatin followed by pembrolizumab in combination with doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant)
- Patients treated with pembrolizumab in combination with a chemotherapy other than paclitaxel and carboplatin followed by pembrolizumab in combination with a chemotherapy other than doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant)

For the 1st patient group, the company then specified chemotherapy of physician's choice, operationalized as paclitaxel plus carboplatin followed by doxorubicin or epirubicin plus cyclophosphamide as neoadjuvant therapy before surgery as well as watchful waiting after surgery, operationalized as placebo as ACT. The company specified no ACT for the second patient group, but explained that no data were available for this patient group. The company's approach of determining the research question and the ACT according to the available

evidence is not appropriate. The present benefit assessment was conducted according to the research question stated in Table 2 and compared with the ACT specified by the G-BA.

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) were used to derive the added benefit.

Study pool and study design

The KEYNOTE 522 study, which compared pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) with placebo in combination with chemotherapy (neoadjuvant) followed by placebo (adjuvant) was included in the benefit assessment. The study was not designed for a comparison according to the research question, but it is nonetheless suitable for such a comparison with some limitations.

KEYNOTE 522 is an ongoing, randomized, double-blind RCT. It included adult patients with locally advanced, previously untreated, non-metastatic TNBC at high risk of recurrence. 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. If indicated, postoperative radiotherapy could be given in both treatment arms.

Treatment took place at most until the end of the adjuvant treatment phase or until disease progression in the neoadjuvant phase or until recurrence in the adjuvant phase, occurrence of unacceptable toxicity, decision by the investigator to discontinue the treatment or withdrawal of consent. The study did not provide for any switching between study arms.

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

Use of a uniform chemotherapy regimen in neoadjuvant treatment

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

Intervention

Unlike in KEYNOTE 522, the chemotherapy regimen for the combination is not firmly specified in the SPC for pembrolizumab. The study thus only allows conclusions for the combination of pembrolizumab with the chemotherapy regimen used in the study.

Implementation of the ACT

The G-BA specified the ACT to be taxane-based and anthracycline-based neoadjuvant chemotherapy of physician's choice, selecting from cyclophosphamide, docetaxel, doxorubicin, epirubicin, paclitaxel and carboplatin followed by watchful waiting after surgery.

The ACT's specification that the investigators are expected to have a choice of several treatment options (in the sense of a multi-comparator study) is therefore not implemented. It is unclear to what extent the specification of a uniform chemotherapy regimen for the patients in the study affects the results of patient-relevant outcomes.

The chemotherapy regimen used in the study represents one of the recommendations of current guidelines, but not the only standard of therapy for neoadjuvant chemotherapy in this therapeutic indication. It is unclear whether the different chemotherapy regimens recommended in the guidelines are equally suitable for all patients or what criteria are used to decide on a specific chemotherapy regimen. It is therefore unclear whether the chemotherapy regimen used in the study is the most suitable treatment for the patients included in KEYNOTE 522. In the commenting procedure of the initial assessment of pembrolizumab in the present therapeutic indication, clinical experts described the use of carboplatin as the standard of therapy, particularly in the curative situation of the younger high-risk group of patients. Overall, it is therefore assumed that sufficiently adequate treatment of the patients was ensured despite the lack of choice in the KEYNOTE 522 study.

Overall, the study was used for the benefit assessment in the present situation despite the uncertainties described. The uncertainties were taken into account in the assessment of the certainty of conclusions. Moreover, the study only permits conclusions on the added benefit for patients for whom paclitaxel + carboplatin followed by doxorubicin or epirubicin + cyclophosphamide is the suitable neoadjuvant chemotherapy of physician's choice. For

patients for whom paclitaxel + carboplatin followed by doxorubicin or epirubicin + cyclophosphamide is not the appropriate neoadjuvant chemotherapy according to physician's choice, no conclusions on added benefit can be drawn based on the KEYNOTE 522 study.

Implementation of watchful waiting in adjuvant treatment

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 reflect the recommendations of the German S3 guideline. However, the examination regimen in KEYNOTE 522 is overall considered a sufficient approximation of the ACT of watchful waiting.

Risk of bias

The risk of bias across outcomes is rated as low for the KEYNOTE 522 study. The risk of bias for the results on the outcomes "failure of the curative treatment approach" and “breast-conserving surgery” was also rated as low. The risk of bias for the results on overall survival is rated as high because the subsequent treatment of the patients failed to include a relevant number of treatment options recommended in current guidelines. No suitable data are available for the outcomes of symptoms (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 [EORTC QLQ-C30], European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Breast Cancer 23 [EORTC QLQ-BR23]), health status (visual analogue scale of the EQ-5D [EQ-5D VAS]), and health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR23). This is due to the rapid and differentially decreasing response rates as a result of the study design, the lack of an outcome recordings between the neoadjuvant and adjuvant treatment phases and the potentially different lengths of time between these phases. The risk of bias of the results for the outcomes of serious adverse events (SAEs), severe AEs as well as immune-related SAEs/severe AEs and further specific AEs is rated as high. Due to the follow-up period linked to the treatment duration, observations for the outcomes mentioned in the side effects category are incomplete for potentially informative reasons. Although the risk of bias is low for the outcome of discontinuation due to AEs, the certainty of results for this outcome is limited.

Irrespective of the aspects described under risk of bias, the certainty of conclusions of the results from the KEYNOTE 522 study is reduced across all outcomes. This is due to the lack of choice of the chemotherapy regimen, which was mandatory in both study arms. Overall, due to these uncertainties for the results on all outcomes of the KEYNOTE 522 study, no more than hints, for example of an added benefit, can be derived.

Results

Mortality

Overall survival

A statistically significant difference in favour of the intervention was shown for the outcome "overall survival". There was a hint of added benefit of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) versus chemotherapy (neoadjuvant) followed by watchful waiting (adjuvant).

Morbidity

Failure of the curative treatment approach

Operationalization

For the present benefit assessment, the outcome “failure of the curative treatment approach” is presented via EFS as time to event (effect measure hazard ratio [HR]) and as the occurrence of the event (effect measure relative risk (RR)). Each of the two analyses comprises the events of 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

A statistically significant difference in favour of the intervention was shown for the outcome "failure of the curative treatment approach". As a consequence, there is a hint of an added benefit of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) versus chemotherapy (neoadjuvant) followed by watchful waiting (adjuvant).

Breast-conserving surgery

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

Symptoms

No suitable data were available for the outcome “symptoms” (recorded using the EORTC QLQ-C30 and the EORTC QLQ-BR23). There is no hint of an added benefit of pembrolizumab in combination with chemotherapy (neoadjuvant), followed by pembrolizumab (adjuvant) versus chemotherapy (neoadjuvant) followed by watchful waiting (adjuvant); an added benefit is therefore not proven.

Health status

No suitable data are available for the outcome of health status (recorded using EQ-5D VAS). There is no hint of an added benefit of pembrolizumab in combination with chemotherapy (neoadjuvant), followed by pembrolizumab (adjuvant) versus chemotherapy (neoadjuvant) followed by watchful waiting (adjuvant); an added benefit is therefore not proven.

Health-related quality of life

No suitable data are available for the outcomes of health-related quality of life (recorded with the EORTC QLQ-C30 and EORTC QLQ-BR23). There is no hint of an added benefit of pembrolizumab in combination with chemotherapy (neoadjuvant), followed by pembrolizumab (adjuvant) versus chemotherapy (neoadjuvant) followed by watchful waiting (adjuvant); an added benefit is therefore not proven.

Side effects

SAEs and discontinuation due to AEs

A statistically significant difference to the disadvantage of the intervention was found for each of the outcomes of SAEs and discontinuation due to AEs. There is a hint of greater harm from pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) versus chemotherapy (neoadjuvant) followed by watchful waiting (adjuvant).

Severe AEs

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

Specific AEs

Immune-related SAEs, immune-related severe AEs

A statistically significant difference to the disadvantage of the intervention was found for each of the outcomes of immune-related SAEs and immune-related severe AEs. In each case, there was a hint of greater harm from pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) versus chemotherapy (neoadjuvant) followed by watchful waiting (adjuvant).

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 each of the outcomes of 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 to the disadvantage of the intervention. In each case, there was a hint of greater harm from pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) versus chemotherapy (neoadjuvant) followed by watchful waiting (adjuvant).

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

On the basis of the presented results, the probability and extent of the added benefit of the drug pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) in comparison with the ACT is assessed as follows:

Overall, both positive and negative effects of different extents were shown, each with the probability “hint”.

On the positive effects side, there is a hint of a considerable added benefit for both the outcome of overall survival and the outcome of failure of the curative treatment approach. On the negative effects side, in contrast, there are hints of greater harm of minor to major extent in the outcome category of serious/severe side effects, and a hint of greater harm with the extent “considerable” for the outcome category of non-serious/non-severe side effects. However, the effects observed regarding side effects are based exclusively on the shortened period (period of treatment plus a maximum of 90 days.

Suitable data are lacking for all patient-reported outcomes in the categories of morbidity and health-related quality of life.

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

The advantages in the outcomes of overall survival and failure of the curative treatment approach dominate in the assessment of the added benefit, but are outbalanced by the numerous disadvantages in the side effects, in particular SAEs, immune-related SAEs, immune-related severe AEs and discontinuations due to AEs.

In summary, for patients with locally advanced or early TNBC with a high risk of recurrence, for whom paclitaxel + carboplatin followed by doxorubicin or epirubicin + cyclophosphamide is the suitable neoadjuvant chemotherapy according to the physician's discretion, there is a hint of a minor added benefit of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) over the ACT.

For patients with locally advanced or early TNBC with a high risk of recurrence, for whom paclitaxel + carboplatin followed by doxorubicin or epirubicin + cyclophosphamide is not the suitable neoadjuvant chemotherapy according to the physician's discretion, an added benefit of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) versus the ACT has not been proven.

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

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[b] 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	Taxane- and anthracycline[c]-based neoadjuvant chemotherapy according to physician's choice[d], choosing from: ▪ cyclophosphamide ▪ docetaxel ▪ doxorubicin ▪ epirubicin ▪ paclitaxel ▪ carboplatin followed by watchful waiting after surgery	Patients for whom paclitaxel + carboplatin followed by doxorubicin or epirubicin + cyclophosphamide is the suitable neoadjuvant chemotherapy of physician's choice: ▪ hint of minor added benefit[e]
		Patients for whom paclitaxel + carboplatin followed by doxorubicin or epirubicin + cyclophosphamide is <u>not</u> the suitable neoadjuvant chemotherapy of physician's choice: ▪ added benefit not proven

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.
c. According to the G-BA, the implementation of an anthracycline-containing chemotherapy protocol must be weighed up in consideration of the cardiovascular risks. The cardiac functions have to be closely monitored.
d. According to the G-BA, a single-comparator study is generally insufficient for implementing treatment of physician's choice in a study of direct comparison. The investigators are expected to have a choice between several treatment options (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options.
e. 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.

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

The approach for the derivation of an overall conclusion on 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 research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of pembrolizumab + 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; in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery	Taxane- and anthracycline[c]-based neoadjuvant chemotherapy according to physician's choice[d], choosing from: ▪ cyclophosphamide ▪ docetaxel ▪ doxorubicin ▪ epirubicin ▪ paclitaxel ▪ carboplatin 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. c. According to the G-BA, the implementation of an anthracycline-containing chemotherapy protocol must be weighed up in consideration of the cardiovascular risks. The cardiac functions have to be closely monitored. d. According to the G-BA, a single-comparator study is generally insufficient for implementing treatment of physician's choice in a study of direct comparison. The investigators are expected to have a choice between several treatment options (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company deviates from the ACT specified by the G-BA. At first, it subdivided the therapeutic indication into two patient groups:

- Patients treated with pembrolizumab in combination with paclitaxel and carboplatin followed by pembrolizumab in combination with doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant)
- Patients treated with pembrolizumab in combination with a chemotherapy other than paclitaxel and carboplatin followed by pembrolizumab in combination with a

chemotherapy other than doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant)

For the 1st patient group, the company then specified chemotherapy of physician's choice, operationalized as paclitaxel plus carboplatin followed by doxorubicin or epirubicin plus cyclophosphamide as neoadjuvant therapy before surgery as well as watchful waiting after surgery, operationalized as placebo as ACT. The company specified no ACT for the second patient group, but explained that no data were available for this patient group. The company's approach of determining the research question and the ACT according to the available evidence is not appropriate. The present benefit assessment was conducted according to the research question stated in Table 4 and compared with the ACT specified by the G-BA.

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 to derive 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: 20 August 2024)
- bibliographical literature search on pembrolizumab (last search on 9 July 2024)
- search in trial registries / trial results databases for studies on pembrolizumab (last search on 09 July 2024)
- search on the G-BA website for pembrolizumab (last search on 12 July 2024)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 15 October 2024); for search strategies, see I Appendix A of the full dossier assessment.

The check did not identify any additional relevant study.

I 3.1 Studies included

The study presented in the following Table 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		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
KEYNOTE 522	Yes	Yes	No	Yes [3-5]	Yes [6,7]	Yes [8-12]

a. Study sponsored by the company.
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. The KEYNOTE 522 study compared pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) with placebo in combination with chemotherapy (neoadjuvant)

followed by placebo (adjuvant). The study was not designed for a comparison according to the research question of this benefit assessment (see Chapter I 2), but, with some limitations, the study is nonetheless suitable for such a comparison (see Section I 3.2).

The study pool is consistent with the study pool of the company.

I 3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: pembrolizumab + chemotherapy regimen of the study (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + chemotherapy of the study (neoadjuvant)/placebo (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 TNBC at high risk of recurrence[b] ▪ without prior treatment of the locally advanced TNBC ▪ with Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1	Pembrolizumab (N = 784) ▪ neoadjuvant: pembrolizumab + carboplatin + paclitaxel followed by pembrolizumab + epirubicin/doxorubicin + cyclophosphamide ▪ surgery ▪ adjuvant: pembrolizumab placebo (N = 390) ▪ neoadjuvant: placebo + carboplatin + paclitaxel followed by placebo + epirubicin/doxorubicin + cyclophosphamide ▪ Surgery ▪ adjuvant: placebo postoperative radiation according to local guidelines	Screening: up to 28 days treatment: ▪ neoadjuvant: (up to 8 cycles) ▪ surgery: 3 to 6 weeks after the last neoadjuvant therapy ▪ adjuvant: 30 to 60 days after surgery, up to 9 cycles ▪ or until disease progression (in the neoadjuvant phase) or relapse (in the adjuvant phase), occurrence of unacceptable toxicity, decision of the investigator, withdrawal of consent observation[c]: outcome-specific, until death, lost to follow-up, or withdrawal of consent	A total of 177 study centres in Australia, Brazil, Canada, Columbia, France, Germany, Ireland, Israel, Italy, Japan, Poland, Portugal, Russia, Singapore, Spain, South Korea, Sweden, Taiwan, Turkey, United Kingdom, United States 03/2017–ongoing data cut-offs[d]: 1st data cut-off: 24 September 2018 4th data cut-off: 23 March 2021 7nd data cut-off: 22 March 2024	Primary: pathological complete response, EFS secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: pembrolizumab + chemotherapy regimen of the study (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + chemotherapy of the study (neoadjuvant)/placebo (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. Defined based on tumour size and nodal status as T1c (1.0-2.0 cm) and N1-N2; or T2-T4 and N0-N2. c. Outcome-specific information is provided in Table 9. d. 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 took place 2 years after the randomization of the first patient. Thereafter, a new data cut-off was to be performed after each year up to 2024. The final data cut-off was planned for September 2026. For specific information on the data cut-offs see Table 8. 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 regimen of the study (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + chemotherapy regimen of the study (neoadjuvant) + placebo (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	8 cycles: placebo IV on Day 1 of a 3-week cycle + chemotherapy
	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	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 regimen of the study (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + chemotherapy regimen of the study (neoadjuvant) + placebo (adjuvant) (multipage table)

Study	Intervention	Comparison
	disallowed pretreatment ▪ chemotherapy, targeted therapy or radiation within 12 months before screening **allowed 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 treatmenta 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 **disallowed 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; CTCAE: Common Terminology Criteria for Adverse Events; 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. Adult patients with locally advanced, previously untreated, non-metastatic TNBC with a high risk of recurrence defined by tumour size and nodal status as T1c (1.0 to 2.0 cm) and N1-N2, or T2-T4 and N0-N2 were included. Patients had to be in good general health at study entry, according to an ECOG PS of 0 or 1, and have 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 specifications of the SPC [13]. Consistent with the marketing authorization, pembrolizumab dose adjustments were not allowed. If pembrolizumab/placebo was discontinued, chemotherapy could be continued.

Table 7 presents the chemotherapy regimen used in the KEYNOTE 522 study. 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. Due to the approval of pembrolizumab, it can be assumed for the intervention arm of the KEYNOTE 522 study that the therapy consisting of pembrolizumab + chemotherapy used in the neoadjuvant phase is approved as a whole, but a fixed chemotherapy regimen is not specified in the SPC for pembrolizumab. The chemotherapeutic agents used in the control arm are not fully approved for this therapeutic indication. Carboplatin is not approved for either adjuvant or neoadjuvant treatment of breast cancer [14], paclitaxel only for the adjuvant therapy situation [15] (for implementation of the ACT, see 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 either as concomitant treatment with the radiotherapy or 2 weeks after radiotherapy.

Treatment took place at most until the end of the adjuvant treatment phase or until disease progression in the neoadjuvant phase or until recurrence in the adjuvant phase, occurrence of unacceptable toxicity, decision by the investigator to discontinue the treatment or withdrawal of consent. The study did not provide for any switching between study arms.

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

Use of a uniform chemotherapy regimen in neoadjuvant treatment

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

Intervention

In contrast to the KEYNOTE 522 study, the chemotherapy regimen for the combination is not firmly specified in the SPC for pembrolizumab. The study thus only allows conclusions for the combination of pembrolizumab with the chemotherapy regimen used in the study.

Implementation of the ACT

The G-BA specified the ACT to be taxane-based and anthracycline-based neoadjuvant chemotherapy of physician's choice, selecting from cyclophosphamide, docetaxel, doxorubicin, epirubicin, paclitaxel and carboplatin followed by watchful waiting after surgery.

The ACT's specification that the investigators are expected to have a choice of several treatment options (in the sense of a multi-comparator study) is therefore not implemented. The company does not justify the selection of drugs used in the study. It is unclear to what extent the specification of a uniform chemotherapy regimen for the patients in the study affects the results of patient-relevant outcomes.

The chemotherapy regimen used in the study represents one of the recommendations of current guidelines, but not the sole standard of care for neoadjuvant chemotherapy in the present therapeutic indication [16-18]. It is unclear whether the different chemotherapy regimens recommended in the guidelines are equally suitable for all patients or what criteria are used to decide on a specific chemotherapy regimen. It is therefore unclear whether the chemotherapy regimen used in the study is the most suitable treatment for the patients included in KEYNOTE 522. In the commenting procedure to the first assessment of pembrolizumab in the present therapeutic indication, the clinical experts described the use of carboplatin as the standard of care, particularly in the curative setting of the younger high-risk group of patients (in Zusammenarbeit mit der [19]; Deutsche Gesellschaft für Senologie (DGS) [20]. Overall, it is therefore assumed that sufficiently adequate treatment of the patients was ensured despite the lack of choice in the KEYNOTE 522 study.

Overall, the study was used for the benefit assessment in the present situation despite the uncertainties described. The uncertainties were taken into account in the assessment of the certainty of conclusions of the results (see Section I 4.2). Beyond that, the study only allows statements on the added benefit for patients for whom paclitaxel + carboplatin followed by doxorubicin or epirubicin + cyclophosphamide is the suitable neoadjuvant chemotherapy of physician's choice. For patients for whom paclitaxel + carboplatin followed by doxorubicin or epirubicin + cyclophosphamide is not the appropriate neoadjuvant chemotherapy according to physician's choice, no conclusions on added benefit can be drawn based on the KEYNOTE 522 study.

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 had not started adjuvant treatment, who had 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 in the presence 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 [21,22]. The follow-up recommendations of the European guideline are unspecific [17], the currently valid German S3 guideline recommends follow-up examinations to be performed every three months in the first 3 years after primary therapy, every six months in the 4th and 5th year, and annually from the 6th year until at least the 10th year [21]. 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 recommendations of the German S3 Guideline. Overall, the examination regimen in the KEYNOTE 522 study is nevertheless considered to be a sufficient approximation to the ACT of watchful waiting for the present benefit assessment.

Use of postoperative radiotherapy

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 recommendations in guidelines [21-23].

It is not clear from the study documents how many patients received postoperative radiotherapy. However, the European Assessment Report (EPAR) [11] 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 51% 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 adjuvant treatment in the KEYNOTE 522 study is therefore accepted as indicated concomitant therapy and thus 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. 7 data cut-offs have been performed to date.

Table 8: Data cut-offs in the KEYNOTE 522 study

Data cut-off	**Originally planned primary target**	**Planned time**
1st 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
2nd data cut-off: 24 April 2019 (interim analysis 2)	▪ Final analysis pCR ▪ interim analysis EFS	About 2 years after randomization of the first patient
3rd 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 EFSb	**About 4 years after randomization of the first patient**
5th data cut-off: 23 March 2022 (interim analysis 5)	▪ Interim analysis EFSb	About 5 years after randomization of the first patient
6th data cut-off: 23 March 2023 (interim analysis 6)	▪ Interim analysis EFSb	One year after fifth data cut-off
Seventh data cut-off[a]: 22 March 2024 (interim analysis 7)	▪ Interim analysis EFSb	**One year after sixth data cut-off**
Final data cut-off: presumably September 2026	▪ Final analysis EFS	About 327 events of the outcome "EFS", unless the study was discontinued prematurely

a. Data sections relevant for the present benefit assessment are marked in bold, see text below.
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 5 onwards, no further confirmatory testing of EFS took place, but instead confirmatory testing of overall survival.

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

In Module 4 A, the company presents the analyses on the most recent, 7th data cut-off from 22 March 2024 for the outcomes of overall survival, EFS and the patient-reported outcomes on morbidity and health-related quality of life. For all other outcomes from the categories of morbidity and side effects, the company presents the analyses on the 4th data cut-off of 23 March 2021, as the observation period for these outcomes had already been completed at this time.

The company's approach is appropriate. New analyses are available for the outcomes of the side effects category in the study report on the 7th data cut-off from 22 March 2024. However, as expected, these differ only slightly from the analyses on the 4th data cut-off.

Concurring with the company's approach, the present benefit assessment uses the analyses on the 4th or on the 7th data cut-off.

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 regimen of the study (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + chemotherapy regimen of the study (neoadjuvant) + placebo (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
Symptoms (EORTC QLQ-C30, EORTC QLQ-BR23)	In the long-term follow-up up to 2 years after randomization or until disease progression or relapse, whichever occurred earlier[a]
Health status (EQ-5D VAS)	In the long-term follow-up up to 2 years after randomization or until disease progression or relapse, whichever occurred earlier[a]
Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR23)	In the long-term follow-up up to 2 years after randomization or until disease progression or relapse, whichever occurred earlier[a]
Side effects	
AEs/severe AEs[b]	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. As stated in the company's comments on the original project A22-63 [24]. The study protocol contains inconsistent information on whether the follow-up observation was to take place up to 2 years after randomization or up to 2 years after the end of treatment.
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; 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; VAS: visual analogue scale

According to the study documents, the follow-up observation of the outcomes “symptoms”, “health status” and “health-related quality of life” took place over a maximum period of up to 2 years after randomization and was thus systematically shortened.

The observation periods for the outcomes of the category of side effects were also 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).

Drawing a reliable conclusion on the total study period or the time to patient death, however, would require surveying these outcomes 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 study/treatment discontinuation – RCT, direct comparison: pembrolizumab + chemotherapy regimen of the study (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + chemotherapy regimen of the study (neoadjuvant) + placebo (adjuvant) (multipage table)

Study characteristic category	**Pembrolizumab + chemotherapy/pembrolizumab N[a] = 784**	**Placebo + chemotherapy/placebo N[a] = 390**
KEYNOTE 522		
Age [years], mean (SD)	49 (12)	49 (12)
Sex [F/M], %	> 99/< 1	100/0
Family origin n (%)		
Native American or Alaska Native	14 (2)	7 (2)
Asian	149 (19)	89 (23)
Black or African American	38 (5)	15 (4)
Native Hawaiian or native Pacific Islander	1 (0)	0 (0)
White	504 (64)	242 (62)
Multiple	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)

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

Study characteristic category	**Pembrolizumab + chemotherapy/pembrolizumab N[a] = 784**	**Placebo + chemotherapy/placebo N[a] = 390**
Menopausal status, n (%)		
Premenopause	438 (56)	221 (57)
Postmenopause	345 (44)	169 (43)
Missing	1 (0)	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 (0)	1 (0)
Disease stage, n (%)		
Stage I	0 (0)	1 (0)
Stage II	590 (75)	291 (75)
Stage III	194 (25)	98 (25)
PD-L1 CPS		
PD-L1 CPS ≥ 1	656 (84)	317 (81)
PD-L1 CPS ≥ 10	393 (50)	177 (45)
Missing	0	4 (1.0)
HER2 status		
0-1+ in IHC	595 (76)	286 (73)
2+ in IHC (but FISH-)	188 (24)	104 (27)
Missing	1 (< 1)	0
BRCA1/2 mutation		
BRCA1/2 mutation proven	40 (5)	14 (4)
BRCA1/2 mutation not proven	104 (13)	52 (13)
Missing	640 (82)	324 (83)
Treatment discontinuation, n (%)[b]	291 (37)	106 (27)
Until the adjuvant phase	190 (24)	58 (15)
In the adjuvant phase	101 (13)	48 (12)
Study discontinuation, n (%)[c]	127 (16)	91 (23)

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

Study characteristic category	Pembrolizumab + chemotherapy/pembrolizumab N[a] = 784	Placebo + chemotherapy/placebo N[a] = 390
a. Number of randomized patients. b. Data based on treatment discontinuation of all components. Common reasons for treatment discontinuation in the intervention vs. the control arm were: before the start of the adjuvant phase: 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%). c. The data include patients who died during the course of the study (intervention arm: 15% vs. control arm: 21%). Another reason for study discontinuation was the withdrawal of consent (1% vs. 2%). BRCA: breast cancer susceptibility gene; ECOG PS: Eastern Cooperative Oncology Group – Performance Status; f: female; FISH: fluorescence in situ hybridization; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; m: male; n: number of patients in the category; N: number of randomized patients; PD-L1 CPS: programmed cell death ligand 1 combined positive score; RCT: randomized controlled trial; SD: standard deviation		

The characteristics are largely comparable in the two treatment arms. The study population of KEYNOTE 522 consists almost exclusively of women (one man in the intervention arm). The average patient age was about 49 years. The majority of the patient population was 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%.

Before the start of the adjuvant phase, the most common reasons for treatment discontinuation for all components were AEs (intervention arm: 14% vs. control arm: 5%) and investigator's decision (4% vs. 4%), AEs in the adjuvant phase (5% vs. 3%) and relapse/recurrence (3% vs. 5%).

Information on the course of the study

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

Table 11: Information on the course of the study – RCT, direct comparison: pembrolizumab + chemotherapy regimen of the study (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + chemotherapy regimen of the study (neoadjuvant) + placebo (adjuvant)

Study **duration of the study phase** **outcome category/outcome**	**Pembrolizumab + chemotherapy/pembrolizumab** **N = 784**	**Placebo + chemotherapy/placebo** **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		
Median[a] [min; max]	73.5 [2.7; 83.9]	72.8 [3.4; 83.6]
Mean[a] (SD)	68.0 (18.2)	65.9 (19.5)
Event-free survival		
Median[b] [min; max]	72.4 [ND]	71.8 [ND]
Mean (SD)	ND	ND
Disease symptoms and health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR23)		
Median [min; max]	21.7 [ND]	21.4 [ND]
Mean (SD)	ND	ND
Health status (EQ-5D VAS)		
Median [min; max]	21.7 [ND]	21.6 [ND]
Mean (SD)	ND	ND
Side effects (AEs, severe AEs[c])		
Median [min; max]	14.3 [ND]	14.6 [ND]
Mean (SD)	ND	ND
Side effects (SAEs)		
Median [min; max]	16.2 [ND]	16.6 [ND]
Mean (SD)	ND	ND

a. Designated as follow-up duration in the study report, defined as the time from randomization until either death or the seventh data cut-off, if the patients are still alive.
b. Information provided by the company in Module 4 without information on the calculation method.
c. 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 mortality, morbidity, health-related quality of life, and side effects categories were also comparable between both treatment arms.

Information on subsequent therapies

Table 19 in I Appendix B shows the subsequent therapies patients received after discontinuing the study medication as first-line and second-line treatment. The information corresponds to the presentation of the company in Module 4 A Appendix 4G, which shows a very high level of detail. For the assessment of the subsequent therapies, an aggregated presentation of the various subsequent therapies would have been useful in the present situation.

In the intervention arm of the KEYNOTE 522 study, 18% of randomized patients had so far received at least one subsequent systemic therapy (including neoadjuvant and adjuvant treatments outside the study), compared with 25% in the comparator arm. Of these, 11% vs. 16% received first-line therapy in advanced stages of the disease, 6% vs. 12% received second-line therapy. The subsequent therapies used are almost exclusively chemotherapy combinations.

The comparison with the number of patients in whom distant recurrences were detected as the first recurrence (10 % vs. 14 %) and for whom there was therefore an indication for systemic treatment in the majority of cases, suggests that the use of an adequate extent of subsequent systemic therapies is appropriate. The therapies used are in line with the recommendations of older but still current guidelines such as the S3 guideline of 2021 [21]. Newer therapies, which have only been approved in recent years but were not available at the time the study was conducted, were only used minimally as subsequent treatment in the study. These include pembrolizumab in the first line (for patients with PD-L1-expressing tumours combined positive score [CPS] ≥ 10]) and sacituzumab govitecan and trastuzumab deruxtecan in the second line (for patients with human epidermal growth factor receptor 2 [HER2]-low breast cancer). These drugs are recommended in more recent or international guidelines for advanced disease [18,25,26]. The G-BA has assessed these treatment options with an added benefit [27-29].

The results of the outcome of overall survival are profoundly influenced by the subsequent antineoplastic therapies used after disease progression or relapse. It must be assumed that at least some of the patients would have benefited from the optimal use of new, targeted subsequent therapies (in particular pembrolizumab [in 1st line of therapy] and sacituzumab govitecan and trastuzumab deruxtecan [each in 2nd line of therapy]). This is taken into account in the assessment of the outcome-specific risk of bias (see Section I 4.2).

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 regimen of the study (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + chemotherapy regimen of the study (neoadjuvant) + placebo (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 is 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
  - failure of the curative treatment approach (represented via EFS)
  - breast-conserving surgery
  - symptoms, recorded with the EORTC QLQ-C30 and the EORTC QLQ-BR23
  - health status, recorded with 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 (CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - immune-related SAEs
  - immune-related severe AEs
  - other specific AEs, if any

The choice of patient-relevant outcomes deviates from that made 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 the outcomes – RCT, direct comparison: pembrolizumab + chemotherapy regimen of the study (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + chemotherapy regimen of the study (neoadjuvant) + placebo (adjuvant)

Study	Outcomes											
	Overall survival	Failure of the curative treatment approach	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 event-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 suitable data available; for justification, see text below.

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

Failure of the curative treatment approach

In this therapeutic indication, curative therapy is generally possible and the aim of treatment. The infeasibility of the planned surgery or recurrence after R0 remission means that the curative treatment approach in this line of therapy has failed. In the present treatment situation, failure of the curative treatment approach is a patient-relevant event because, albeit still possible in principle, later cure is clearly less likely to be achieved. Failure of the curative treatment approach is therefore considered a patient-relevant outcome in this assessment.

In the KEYNOTE 522 study, failure of the curative treatment approach was not directly recorded as an outcome. As an approximation, the present assessment considers the events that were recorded as part of the primary outcome of the KEYNOTE 522 study, i.e. the composite outcome of EFS, as operationalization for the outcome. The proportion of patients with event (referred to below as “event rate”) and also the time to the occurrence of an event (EFS) is used for the assessment. The operationalization of the outcome is explained below.

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 disease precluding definitive surgery
- local recurrence
- distal recurrence
- second primary tumour
- death from any cause

Thereby, detection of disease progression, local or distal recurrence or a second primary tumour was based on the investigator’s assessment.

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 was not classified as an EFS event.

In the presentation of results (both in Module 4 A and in the study documents), the event "progression of disease precluding definitive surgery" is divided into the sub-events "local progression of disease precluding definitive surgery", "local progression of disease precluding surgery", "positive resection margin at last surgery" and "distant metastasis" (in the neoadjuvant phase). This can be comprehended from the explanations in the study protocol from Amendment 2 onwards.

In the present data situation, the outcome of EFS is suitable for depicting the failure of curative treatment approach and is therefore used for the benefit assessment. In addition to the time to occurrence of an event (EFS, effect measure “HR”), the occurrence of the event (effect measure “RR”) is also relevant for the assessment.

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

In Module 4A, the company presented analyses on the 7th data cut-off for the EORTC QLQ-C30 and EORTC QLQ-BR23 scales as well as for the EQ-5D VAS for the outcomes on symptoms and health-related quality of life. Both treatment phases of the KEYNOTE 522 study

(neoadjuvant and adjuvant) were analysed using a cLDA model (constrained longitudinal data analysis) from the start of treatment to the long-term follow-up 12 months after randomization.

The analyses of the EORTC QLQ-C30 and the EORTC QLQ-BR23 presented by the company, as well as those of the EQ-5D VAS, are not suitable for the present benefit assessment. This is justified below.

The patient-reported outcomes (PROs) were assessed according to the study protocol at the beginning of Cycles 1, 5 and 8 of the neoadjuvant treatment phase and Cycles 1, 5 and 9 of the adjuvant treatment phase, provided that treatment had not been discontinued by then. In addition, recordings were planned 12 months and 24 months after randomization as part of the long-term follow-up. Patients transferred to this long-term follow-up when treatment was discontinued or after completion of adjuvant treatment. An exception was treatment discontinuation due to progression or recurrence, in which case there was no transfer to the long-term follow-up but the observation was terminated. The period directly after discontinuation of treatment is therefore not recorded in any of the recordings included in the analyses. An early discontinuation visit additionally described in the protocol is not mentioned in the present dossier.

The observed response rates of the questionnaires decrease sharply and differentially, especially at the beginning of adjuvant treatment (response rate at this time of the recording for all randomized patients: 64% in the intervention arm vs. 74% in the comparator arm). This is largely due to the lack of a PRO recording after treatment discontinuation as specified in the study protocol (according to the information provided by the company in Appendix 4G to Module 4A, 29% vs. 19% at this point in time). The values are therefore missing for potentially informative reasons. A discontinuation of observation immediately after discontinuation of therapy, as stipulated in the present study, is not appropriate, as this would not allow changes in symptoms and health-related quality of life timely associated with the treatment discontinuation to be recorded.

Secondly, the planning of the PRO recordings described above resulted in variable periods between the neoadjuvant and adjuvant treatment phases during which no patient-reported outcomes were recorded. The study protocol recommended an interval of 3 to 6 weeks before surgery and 30 to 60 days (i.e. approx. 4 to 8 weeks) after surgery between the last neoadjuvant and first adjuvant treatment. For patients who received radiotherapy, the recording-free periods were extended by a further approx. 7 weeks (5 weeks radiotherapy plus 2 weeks safety interval according to the study protocol) if radiotherapy was given sequentially to adjuvant therapy. This applied to 37% of the study participants. From a substantive perspective, this approach is not appropriate. The period between the neoadjuvant and adjuvant treatment phases is part of the study, so the PROs should be

continuously recorded. Furthermore, there is no information available on how long this period actually was and whether it differed between the study arms. In the cLDA analysis presented by the company, these variable intervals are not considered for an individual temporal allocation of the actual observation time points from randomization onwards.

In summary, the data on the patient-reported outcomes cannot be meaningfully interpreted due to the rapidly and differentially decreasing response rates caused by the study design, the lack of PRO recordings between the neoadjuvant and adjuvant treatment phases and the potentially different lengths of time between these phases and are therefore not used for the benefit assessment.

Analyses on the outcomes of the side effects category

AEs, SAEs, and severe AEs

In the analysis of side effects, the number of patients in whom an event occurred is primarily relevant. However, when analysing the time until occurrence of the event, effects may also result from an earlier or later occurrence of the event rather than on the basis of the proportions. Time-to-event analyses are of particular relevance in group comparisons with different mean observation periods [1]. The company presented time-to-event analyses for all side effects outcomes. In the present situation, however, the mean observation periods between the treatment arms are sufficiently similar (see Table 11) to use the RR as an effect measure to derive the added benefit for all outcomes in the side effects category.

Immune-related AEs

For the outcomes of immune-related AEs, immune-related severe AEs and immune-related SAEs, the operationalization of a predefined but regularly updated specific MedDRA PT collection (Medical Dictionary for Regulatory Activities, Preferred Term) of the outcome of adverse events of special interest (AEOSI) presented by the company is considered relevant. This is a selection of categories and PTs which count among the typical immune-related AEs and for which treatment with immunosuppressants (e.g. corticosteroids) of these AEs could be necessary, but did not have to be. This operationalization is deemed a sufficient approximation of 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 regimen of the study (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + chemotherapy regimen of the study (neoadjuvant) + placebo

Study		Outcomes											
	Study level	Overall survival	Failure of the curative treatment approach	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 event-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. Use of subsequent therapies to a relevant extent not in accordance with current guidelines, see Section I 3.2.
f. No suitable data available; for the reasoning, see Section I 4.1 of the present dossier assessment.
g. Incomplete observations for potentially informative reasons.
h. Despite the low risk of bias, the certainty of results is presumably limited for the outcome of discontinuation due to AEs.

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 "failure of the curative treatment approach" and “breast-conserving surgery” was rated as low.

The risk of bias for the results on overall survival is rated as high because the subsequent treatment of the patients failed to include a relevant number of treatment options recommended in current guidelines.

Suitable 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 for the outcomes of SAEs, severe AEs as well as immune-related SAEs/severe AEs and further specific AEs is 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 (see also Table 9).

Although the risk of bias is low for the outcome of discontinuation due to AEs, the certainty of results for this outcome is limited. Premature treatment discontinuation for reasons other than AEs represents a competing event for the outcome to be recorded, i.e. discontinuation due to AEs. 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 is impossible to estimate how many AEs are affected by this issue.

Summary assessment of the certainty of conclusions

Irrespective of the aspects described under risk of bias, the certainty of conclusions of the results from the KEYNOTE 522 study is reduced across all outcomes. This is due to the lack of choice of chemotherapy regimen described in Section I 3.1, which was firmly prescribed in both study arms. Overall, due to these uncertainties for the results on all outcomes of the KEYNOTE 522 study, no more than hints, for example of an added benefit, can be derived.

I 4.3 Results

Table 15 summarizes the results of the KEYNOTE 522 study on the comparison of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) versus chemotherapy (neoadjuvant) followed by placebo (adjuvant) in adult patients with locally advanced or early-stage TNBC at high risk of recurrence. Where necessary, IQWiG calculations are provided to supplement the data from the company’s dossier.

The Kaplan-Meier curves on the time-to-event analyses are presented in I Appendix C 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 D of the full dossier assessment. A list of the immune-related AEs that occurred is shown in I Appendix E. No such list is available for "immune-related SAEs” and "immune-related severe AEs" (CTCAE grade ≥ 3).

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab + chemotherapy regimen of the study (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + chemotherapy regimen of the study (neoadjuvant) + placebo (adjuvant) (multipage table)

Study **outcome category** **outcome**	**Pembrolizumab + chemotherapy/pembrolizumab**		**Placebo + chemotherapy/placebo**		**Pembrolizumab + chemotherapy/pembrolizumab vs. placebo + chemotherapy/placebo**
	N	**patients with event n (%)**	**N**	**patients with event n (%)**	**RR [95% CI]; p-value[a]**
KEYNOTE 522					
Mortality					
Overall survival[b]	784	115 (14.7) median time to event: NA	390	85 (21.8) median time to event: NA	HR 0.66 [0.50; 0.87]; 0.003[c]
Morbidity					
Failure of the curative treatment approach[b]					
Event rate	784	159 (20.3)	390	114 (29.2)	0.69 [0.56; 0.85]; < 0.001
Death	784	19 (2.4)	390	13 (3.3)	–
Distant metastases	784	4 (0.5)	390	1 (0.3)	–
Distant recurrence	784	77 (9.8)	390	56 (14.4)	–
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	33 (4.2)	390	20 (5.1)	–
Positive resection margin at last surgery	784	6 (0.8)	390	10 (2.6)	–
Second primary tumour	784	16 (2.0)	390	10 (2.6)	–
Event-free survival	784	Median time to event: NA	390	Median time to event: NA	HR 0.65 [0.51; 0.83]; 0.001[c]
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 suitable data[e]	
Symptoms (EORTC QLQ-BR23)				No suitable data[e]	
Health status (EQ-5D VAS)				No suitable data[e]	

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab + chemotherapy regimen of the study (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + chemotherapy regimen of the study (neoadjuvant) + placebo (adjuvant) (multipage table)

Study outcome category outcome	Pembrolizumab + chemotherapy/pembrolizumab		Placebo + chemotherapy/placebo		Pembrolizumab + chemotherapy/pembrolizumab vs. placebo + chemotherapy/placebo
	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 suitable data[e]	
EORTC QLQ-BR23				No suitable data[e]	
Side effects[f]					
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[g]	783	645 (82.4)	389	306 (78.7)	1.05 [0.99; 1.11]; 0.128
Discontinuation due to AEs[h]	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)	1.99 [1.63; 2.44]; < 0.001
Immune-related SAEs	783	83 (10.6)	389	5 (1.3)	8.25 [3.37; 20.17]; < 0.001
Immune-related severe AEs[g]	783	117 (14.9)	389	8 (2.1)	7.27 [3.59; 14.72]; < 0.001
Other 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[g])	783	25 (3.2)	389	0 (0)	25.37 [1.55; 415.62]; < 0.001
Gastrointestinal disorders (SOC, severe AEs[g])	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[g])	783	90 (11.5)	389	24 (6.2)	1.86 [1.21; 2.87]; 0.004
Hepatobiliary disorders (SOC, severe AEs[g])	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) – RCT, direct comparison: pembrolizumab + chemotherapy regimen of the study (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + chemotherapy regimen of the study (neoadjuvant) + placebo (adjuvant) (multipage table)

Study outcome category outcome	Pembrolizumab + chemotherapy/pembrolizumab		Placebo + chemotherapy/placebo		Pembrolizumab + chemotherapy/pembrolizumab vs. placebo + chemotherapy/placebo
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
Skin and subcutaneous tissue disorders (SOC, severe AEs[g])	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 [30].
b. Data cut-off: 22 March 2024.
c. 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).
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. Data cut-off 23 March 2021; the follow-up observation for AEs had already been completed at this data cut-off.
g. Operationalized as CTCAE grade ≥ 3.
h. Discontinuation of at least one component.

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 one) 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; VAS: visual analogue scale

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

A statistically significant difference in favour of the intervention was shown for the outcome "overall survival". Notably, the Kaplan-Meier curves on this outcome cross at baseline (see Figure 1). This is also discussed by the EMA in the EPAR [11]. Due to the very few events that have occurred up to this point, it is assumed that this is a coincidence. There was a hint of added benefit of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) versus chemotherapy (neoadjuvant) followed by watchful waiting (adjuvant).

Morbidity

Failure of the curative treatment approach

Operationalization

For the present benefit assessment, the outcome of failure of the curative treatment approach is presented via the time to event (effect measure HR) and the occurrence of the event (effect measure RR). Each of the two analyses comprises the events of 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

A statistically significant difference in favour of the intervention was shown for the outcome "failure of the curative treatment approach". As a consequence, there is a hint of an added benefit of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) versus chemotherapy (neoadjuvant) followed by watchful waiting (adjuvant).

Breast-conserving surgery

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

Symptoms

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

Health status

No suitable data are available for the outcome of health status (recorded using the EQ-5D VAS) (for reasons, see Section I 4.1). There is no hint of an added benefit of pembrolizumab in combination with chemotherapy (neoadjuvant), followed by pembrolizumab (adjuvant) versus chemotherapy (neoadjuvant) followed by watchful waiting (adjuvant); an added benefit is therefore not proven.

Health-related quality of life

There were no suitable data for the outcomes on health-related quality of life (recorded with the EORTC QLQ-C30 and the EORTC QLQ-BR23) (for reasons, see Section I 4.1). There is no hint of an added benefit of pembrolizumab in combination with chemotherapy (neoadjuvant), followed by pembrolizumab (adjuvant) versus chemotherapy (neoadjuvant) followed by watchful waiting (adjuvant); an added benefit is therefore not proven.

Side effects

SAEs and discontinuation due to AEs

A statistically significant difference to the disadvantage of the intervention was found for each of the outcomes of SAEs and discontinuation due to AEs. There is a hint of greater harm from pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) versus chemotherapy (neoadjuvant) followed by watchful waiting (adjuvant).

Severe AEs

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

Specific AEs

Immune-related SAEs, immune-related severe AEs

A statistically significant difference to the disadvantage of the intervention was found for each of the outcomes of immune-related SAEs and immune-related severe AEs. In each case, there was a hint of greater harm from pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) versus chemotherapy (neoadjuvant) followed by watchful waiting (adjuvant).

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 each of the outcomes of 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 to the disadvantage of the intervention. In

each case, there was a hint of greater harm from pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) versus chemotherapy (neoadjuvant) followed by watchful waiting (adjuvant).

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account for the present benefit assessment:

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

Of the characteristics mentioned, age was predefined as a subgroup characteristic. The characteristic of sex was disregarded because the study population only comprised one man.

For the outcomes “overall survival” and “failure of the curative treatment approach”, subgroup analyses are available for both selected characteristics. The version of the American Joint Committee on Cancer (AJCC) classification used to classify the stage of disease in the subgroup analyses is not specified in the study documents; presumably it is Version 7, which was used at the time of diagnosis before study inclusion. No interaction tests were available for the characteristic of tumour stage. They were calculated on the basis of the effect estimator “HR”. For the EFS rate as well as for the outcomes from the side effects category, the interaction test was performed using the Q-test on the basis of the RR. 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 [31].

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

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are 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 IQWiG *General Methods* [1].

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

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Chapter I 4 (Table 16).

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

It is impossible to infer from the dossier whether the below outcomes “failure of the curative treatment approach” and “discontinuation due to AEs” are serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Failure of the curative treatment approach

The outcome of failure of the curative treatment approach is deemed to be serious/severe. On the one hand, a recurrence of the cancer can be life-threatening, on the other hand, death from any cause (without prior recurrence) is included as a component in the outcome.

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 40% of the AEs that led to discontinuation of treatment in the intervention arm were serious AEs. Information on the proportion of severe AEs that led to discontinuation is not available. This outcome was assigned to the outcome category of non-serious/non-severe side effects.

Table 16: Extent of the added benefit at outcome level: pembrolizumab + chemotherapy (neoadjuvant)/pembrolizumab (adjuvant) versus the ACT (multipage table)

Outcome category **outcome**	**Intervention vs. comparison** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	NA vs. NA HR = 0.66 [0.50; 0.87]; 0.003 probability: "hint"	Outcome category: all-cause mortality $0.85 \leq CI_u < 0.95$ added benefit, extent: "considerable"
Morbidity		
Failure of the curative treatment approach		
Event rate	20.3% vs. 29.2% RR: 0.69 [0.56; 0.85]; < 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: 0.65 [0.51; 0.83]; < 0.001 probability: "hint"	
Outcomes with shortened observation period		
Morbidity		
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 suitable data[c]	Lesser/added benefit not proven
EORTC QLQ-BR23	No suitable data[c]	Lesser/added benefit not proven
Health status (EQ-5D VAS)	No suitable data[c]	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30	No suitable data[c]	Lesser/added benefit not proven
EORTC QLQ-BR23	No suitable data[c]	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][d] < 0.001 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"

Table 16: Extent of the added benefit at outcome level: pembrolizumab + chemotherapy (neoadjuvant)/pembrolizumab (adjuvant) versus the ACT (multipage table)

Outcome category **outcome**	**Intervention vs. comparison** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Severe AEs	82.4% vs. 78.7% RR: 1.05 [0.99; 1.11]; 0.128	Greater/lesser harm not proven
Discontinuation due to AEs	29.9% vs. 15.4% RR: 1.94 [1.50; 2.50]; RR: 0.52 [0.40; 0.67][d] < 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][d] < 0.001 probability: “hint”	Outcome category: serious/severe side effects $CI_o < 0.75$, 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][d] < 0.001 probability: “hint”	Outcome category: serious/severe side effects $CI_o < 0.75$, 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][d] 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][d] 0.041 probability: “hint”	Outcome category: serious/severe side effects greater harm, extent: “minor”[e]
Endocrine disorders (severe AEs)	3.2% vs. 0% RR: 25.37 [1.55; 415.62]; RR: 0.04 [0.002; 0.65][d] < 0.001 probability: “hint”	Outcome category: serious/severe side effects $CI_u < 0.75$; risk < 5% greater harm, extent: “considerable”

Table 16: Extent of the added benefit at outcome level: pembrolizumab + chemotherapy (neoadjuvant)/pembrolizumab (adjuvant) versus the ACT (multipage table)

Outcome category **outcome**	**Intervention vs. comparison** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Gastrointestinal disorders (severe AEs)	11.7% vs. 7.2% RR: 1.63 [1.09; 2.45]; RR: 0.61 [0.41; 0.92][d] 0.016 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"
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][d] 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][d] 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][d] < 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. See Section I 4.1 of the present dossier assessment for the reasoning.
d. Institute's calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit.
e. Discrepancy between CI and p-value; the extent is rated as minor.

AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; NA: not achieved; QLQ-BR23: Quality of Life Questionnaire – Breast Cancer 23; 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 taken into account 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) versus the ACT

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
Mortality ▪ overall survival: hint of an added benefit – extent: considerable	–
Morbidity serious/severe symptoms/late complications ▪ failure of the curative treatment approach: hint of added benefit – extent: “considerable”	
Outcomes with shortened observation period	
–	Serious/severe side effects ▪ SAEs: hint of greater harm – extent: "considerable" ▫ immune-related SAEs: hint of greater harm – extent: “major” ▫ blood and lymphatic system disorders; injury, poisoning and procedural complications; in each case hint of greater harm - extent: “minor” ▪ severe AEs ▫ immune-related severe AEs: hint of greater harm – extent: “major” ▫ skin and subcutaneous tissue disorders, hint of greater harm – extent: “major” ▫ endocrine disorders, general disorders and administration site conditions, hepatobiliary disorders; hint of greater harm in each case – extent: “considerable” ▫ gastrointestinal disorders (severe AEs), hint of greater harm – extent: “minor”
	Non-serious/non-severe side effects ▪ Discontinuation due to AEs: hint of greater harm – extent: considerable
No suitable data are available 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).	
AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-BR23: Quality of Life Questionnaire – Breast Cancer 23; QLQ-C30: Quality of Life Questionnaire– Core 30; SAE: serious adverse event; VAS: visual analogue scale	

Overall, both positive and negative effects of different extents were shown, each with the probability “hint”.

On the positive effects side, there is a hint of a considerable added benefit for both the outcome of overall survival and the outcome of failure of the curative treatment approach. On the negative effects side, in contrast, there are hints of greater harm of minor to major

extent in the outcome category of serious/severe side effects, and a hint of greater harm with the extent “considerable” for the outcome category of non-serious/non-severe side effects. However, the effects observed regarding side effects are based exclusively on the shortened period (period of treatment plus a maximum of 90 days.

Suitable data are lacking for all patient-reported outcomes in the categories of morbidity and health-related quality of life.

The advantages in the outcomes of overall survival and failure of the curative treatment approach dominate in the assessment of the added benefit, but are outbalanced by the numerous disadvantages in the side effects, in particular SAEs, immune-related SAEs, immune-related severe AEs and discontinuations due to AEs.

In summary, for patients with locally advanced or early TNBC with a high risk of recurrence, for whom paclitaxel + carboplatin followed by doxorubicin or epirubicin + cyclophosphamide is the suitable neoadjuvant chemotherapy according to the physician’s discretion, there is a hint of a minor added benefit of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) over the ACT.

For patients with locally advanced or early TNBC with a high risk of recurrence, for whom paclitaxel + carboplatin followed by doxorubicin or epirubicin + cyclophosphamide is not the suitable neoadjuvant chemotherapy according to the physician’s discretion, an added benefit of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) versus the ACT has not been proven.

Table 18 summarizes the result of the assessment of the added benefit of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) over the ACT.

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[b] 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	Taxane- and anthracycline[c]-based neoadjuvant chemotherapy according to physician's choice[d], choosing from: ▪ cyclophosphamide ▪ docetaxel ▪ doxorubicin ▪ epirubicin ▪ paclitaxel ▪ carboplatin followed by watchful waiting after surgery	Patients for whom paclitaxel + carboplatin followed by doxorubicin or epirubicin + cyclophosphamide is the suitable neoadjuvant chemotherapy of physician's choice: ▪ hint of minor added benefit[e]
		Patients for whom paclitaxel + carboplatin followed by doxorubicin or epirubicin + cyclophosphamide is <u>not</u> the suitable neoadjuvant chemotherapy of physician's choice: ▪ added benefit not proven

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.
c. According to the G-BA, the implementation of an anthracycline-containing chemotherapy protocol must be weighed up in consideration of the cardiovascular risks. Cardiac functions must be closely monitored.
d. According to the G-BA, a single-comparator study is generally insufficient for implementing treatment of physician's choice in a study of direct comparison. The investigators are expected to have a choice between several treatment options (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options.
e. 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.

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

The assessment described above deviates from that of the company, which derives an indication of a considerable added benefit for patients treated with pembrolizumab in combination with paclitaxel and carboplatin followed by pembrolizumab in combination with doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant). For patients treated with pembrolizumab in combination with a chemotherapy other than paclitaxel and carboplatin followed by pembrolizumab in combination with a chemotherapy other than doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant), the company did not derive any added benefit.

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

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

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