IQWiG Reports – Commission No. A21-145

Pembrolizumab (breast cancer) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Pembrolizumab (Mammakarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 Februar 2022). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSA	body surface are
CPS	combined positive score
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
TNBC	triple-negative breast cancer
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug pembrolizumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 16 November 2021.

Research question

The aim of the present report is the assessment of the added benefit of pembrolizumab in combination with chemotherapy (hereinafter referred to as "pembrolizumab + chemotherapy") in comparison with the appropriate comparator therapy (ACT) in adult patients with locally recurrent, unresectable or metastatic triple-negative breast cancer (TNBC) whose tumours express programmed cell death ligand 1 (PD-L1) (combined positive score [CPS] ≥ 10) and who have not received prior chemotherapy for metastatic disease.

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

Therapeutic indication	**ACT**[a]
Adult patients with locally recurrent, unresectable or metastatic triple-negative breast cancer whose tumours express PD-L1 (CPS ≥ 10) and who have not received prior chemotherapy for metastatic disease[b]	Anthracycline- and/or **taxane-containing systemic therapy** under consideration of the approval of the drugs[c]
a. Presented is the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b. For the present therapeutic indication, it is assumed that on the one hand, radiotherapy is not considered a possible curative option and, on the other hand, measures aimed at achieving operability, e.g. neoadjuvant therapy, if such is indicated, have been exhausted in patients with locally recurrent unresectable disease that is isolated, i.e. without evidence of distant metastases. c. The company chose paclitaxel and nab-paclitaxel. ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1	

The G-BA specified an anthracycline- and/or taxane-containing systemic therapy as ACT, taking into account the approval of the drugs. Although the company named the ACT of the G-BA, it also used nab-paclitaxel as a comparator therapy in addition to paclitaxel. However, nab-paclitaxel is not approved for the present therapeutic indication. The approval of nab-paclitaxel only covers the treatment of metastatic breast cancer in adults in whom first-line therapy of the metastatic disease has failed and for whom standard anthracycline-containing therapy is not indicated. The G-BA pointed out that nab-paclitaxel could only be used as a comparator for the

proof of added benefit if the dossier demonstrated that the therapeutic benefit of nab-paclitaxel was sufficiently comparable to a paclitaxel approved in the present therapeutic indication by means of suitable clinical studies. For this purpose, the company refers to data from studies that were already presented in a previous benefit assessment of atezolizumab. Moreover, the company did not present any new evidence for the comparability of nab-paclitaxel with a taxane approved in the therapeutic indication. As explained in detail in the benefit assessment of atezolizumab, the studies presented are insufficient to demonstrate that the benefit of nab-paclitaxel is sufficiently comparable with a taxane approved in the therapeutic indication of unresectable locally advanced or metastatic breast cancer in first-line treatment. In contrast to the benefit assessment of atezolizumab, in which only nab-paclitaxel was used as a comparator, both paclitaxel and nab-paclitaxel were used as comparators in the present situation in the KEYNOTE 355 study submitted by the company. Based on subgroup analyses on the characteristic "chemotherapy (paclitaxel vs. nab-paclitaxel)", it can be estimated that the results for the comparison of pembrolizumab with nab-paclitaxel are sufficiently applicable to a comparison of pembrolizumab with paclitaxel. The resulting uncertainty, however, was considered in the derivation of the added benefit.

The assessment was 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 for the derivation of added benefit.

Study pool and study design

The study KEYNOTE 355 was used for the benefit assessment. This is a double-blind RCT comparing pembrolizumab in combination with chemotherapy versus placebo in combination with chemotherapy. In each case, the chemotherapy was a chemotherapy of physician's choice using paclitaxel, nab-paclitaxel or gemcitabine/carboplatin. Only a subpopulation is considered, because gemcitabine/carboplatin is not comprised by the ACT. Therefore, for the intervention arm, no data are available for the combination of pembrolizumab with other approved chemotherapy combination partners.

Adult patients with locally recurrent unresectable or metastatic TNBC who had not yet received chemotherapy for this disease stage could be included in the study. 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 should only be included in the study if they had already received (neo)adjuvant treatment with anthracyclines, unless there was a contraindication to anthracyclines or anthracyclines were not suitable as a treatment option according to the physician's assessment. Patients with de novo metastatic TNBC could be included if there was a contraindication or if anthracyclines were not suitable as a treatment option according to medical assessment.

Before randomization, the PD-L1 expression of the tumour tissue had to be determined. However, patients were included in the study regardless of their PD-L1 expression.

The KEYNOTE 355 study included a total of 847 patients, randomized in a 2:1 ratio either to treatment with pembrolizumab + chemotherapy (N = 566) or placebo + chemotherapy (N = 281).

Treatment with pembrolizumab in the intervention arm was largely in compliance with the specifications of the Summary of Product Characteristics (SPC). In both, the intervention and the comparator arm, paclitaxel or nab-paclitaxel were applied in doses of 90 or 100 mg/m^2 body surface area (BSA) on days 1, 8 and 15 of a 28-day cycle. For a combination therapy, these dosages largely comply with the guideline recommendations. Uncertainties resulting from the paclitaxel and nab-paclitaxel doses used in monotherapy are described further below in the section on the relevant subpopulation.

Co-primary outcomes of the KEYNOTE 355 study were "overall survival" and "progression-free survival (PFS)". Patient-relevant secondary outcomes were outcomes on morbidity, health-related quality of life and adverse events (AEs).

Relevant subpopulation of the KEYNOTE 355 study

For the benefit assessment, the company presented data and analyses on a subpopulation of the KEYNOTE 355 study. This subpopulation comprised all patients whose tumours expressed PD-L1 with a CPS ≥ 10 and who had been assigned to chemotherapy with paclitaxel or nab-paclitaxel prior to randomization. The company's approach is accepted for the present benefit assessment, but is associated with various uncertainties. These uncertainties as well as their effects for the present benefit assessment are described in more detail below.

PD-L1 status

In accordance with the approved therapeutic indication of pembrolizumab + chemotherapy, only patients whose tumours express PD-L1 with a CPS ≥ 10 are relevant for the research question. The restriction of the population to patients whose tumours express PD-L1 with a CPS ≥ 10 is therefore appropriate.

Implementation of the ACT

Comparability of nab-paclitaxel and paclitaxel

The G-BA specified an anthracycline- and/or taxane-containing systemic therapy as ACT, taking into account the approval of the drugs.

The company chose paclitaxel and nab-paclitaxel as ACT. The G-BA pointed out that nab-paclitaxel could only be used as a comparator for the proof of added benefit if the dossier demonstrated by means of suitable clinical studies that the therapeutic benefit of nab-paclitaxel was sufficiently comparable to a paclitaxel approved in the present therapeutic indication. The company did not provide sufficient evidence for this. Nevertheless, nab-paclitaxel was accepted as a sufficiently suitable comparator. In contrast to the benefit assessment of atezolizumab, this is due to the fact that in the KEYNOTE 355 study presented by the company, both paclitaxel and nab-paclitaxel were used as comparators and that in the subpopulation presented by the

company in the subgroup analyses for the characteristic "chemotherapy (paclitaxel vs. nab-paclitaxel)", there are essentially no relevant effect modifications, so that in this case it can be assumed that nab-paclitaxel is comparable to the taxane paclitaxel approved for this indication. The subpopulation presented by the company was thus used for the benefit assessment. The remaining uncertainty, however, was considered in the derivation of the added benefit.

Uncertainties regarding the dosage of paclitaxel and nab-paclitaxel in monotherapy

The SPC on paclitaxel provides no specific information on the dosage of paclitaxel as monotherapy in first-line treatment. In the studies referenced in the guidelines, 175 mg/m² BSA paclitaxel every 3 weeks or 80 to 90 mg/m² BSA paclitaxel weekly were the most commonly used dosing regimens. The dosing regimen of 90 mg/m² BSA on days 1, 8, 15 of a 28-day cycle used in the KEYNOTE 355 study is only found as a dosing regimen in a combination therapy. Based on the available information, the dosing regimen with 3 applications used in the KEYNOTE 355 study, followed by a 1-week break, does not appear appropriate and suggests an undersupply of patients in the comparator arm. However, it cannot be assumed that the pronounced effect shown for the outcome "overall survival" is solely due to an undersupply in the comparator arm.

The dosing regimen of 100 mg/m² BSA nab-paclitaxel on days 1, 8, 15 of a 28-day cycle used in the KEYNOTE 355 study also appears to be low for the monotherapy. The guidelines predominantly refer to a nab-paclitaxel dosage of 125 mg/m² BSA on days 1, 8 and 15 of a 28-day cycle.

Overall, the data are used for the assessment, but due to the uncertainties regarding an undersupply of patients in the comparator arm and how large the impact of this undersupply would be, the extent of, for example, an added benefit cannot be quantified.

Lack of suitability of patients for anthracycline therapy unclear

Paclitaxel is approved as monotherapy for the treatment of metastatic breast cancer in patients who have not responded to standard anthracycline-containing therapy or for whom such therapy is not an option. However, there are no data available that can be used to verify whether anthracyclines were actually no longer an option for any patient. Based on the characteristics of the relevant subpopulation, this question cannot be answered. Furthermore, based on the patient characteristics, it remains unclear to what extent an anthracycline- and taxane-containing combination therapy would also have been indicated for patients. The resulting uncertainty was considered in the derivation of the added benefit.

Summary

Overall, the subpopulation presented by the company (patients whose tumours express PD-L1 with a CPS ≥ 10 and who had been assigned to chemotherapy with paclitaxel or nab-paclitaxel prior to randomization) was used for the benefit assessment. However, due to the uncertainties described with regard to the comparability of nab-paclitaxel and paclitaxel, the undersupply in the comparator arm and a lack of patient suitability for therapy with anthracyclines, the certainty

of conclusions of the information is limited. Therefore, on the one hand, at most hints, e.g. of an added benefit, can be determined for all outcomes irrespective of bias aspects and, on the other hand, the extent, e.g. of an added benefit, cannot be quantified.

Risk of bias

The risk of bias across outcomes was rated as low for the KEYNOTE 355 study. The outcome-specific risk of bias was also rated as low for the results of the outcome "overall survival", and as high for the results of all other patient-relevant outcomes.

Results

Mortality

Overall survival

For the outcome "overall survival", a statistically significant difference was found in favour of pembrolizumab + chemotherapy in comparison with placebo + chemotherapy. This results in a hint of added benefit of pembrolizumab + chemotherapy in comparison with the ACT for this outcome.

Morbidity

Symptoms (EORTC Quality of Life Questionnaire-Core 30 [QLQ-C30] and EORTC Quality of Life Questionnaire-Breast Cancer Module [QLQ-BR23])

Outcome on symptoms were recorded using EORTC QLQ-C30 and the EORTC QLQ-BR23. In each case, the time to first deterioration by ≥ 10 points (scale range from 0 to 100) was considered.

Fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation (EORTC QLQ-C30), side effects of the systemic therapy, symptoms in the arm region and "upset by hair loss (EORTC QLQ-BR23)

No statistically significant difference between the treatment groups was shown for each of the following scales: fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation (EORTC QLQ-C30), side effects of systemic treatment, symptoms in the arm region (EORTC QLQ-BR23) and upset by hair loss. This resulted in no hint of an added benefit of pembrolizumab + chemotherapy in comparison with the ACT; an added benefit is therefore not proven in each case.

Diarrhoea (EORTC QLQ-C30)

A statistically significant difference to the disadvantage of pembrolizumab + chemotherapy in comparison with placebo + chemotherapy was shown for the "diarrhoea" scale. This difference was no more than marginal, however. This resulted in no hint of an added benefit of pembrolizumab + chemotherapy in comparison with the ACT; an added benefit is therefore not proven.

Symptoms in chest region (EORTC QLQ-BR23)

A statistically significant difference in favour of pembrolizumab + chemotherapy in comparison with placebo + chemotherapy was shown for the scale "symptoms in chest region". This difference was no more than marginal, however. This resulted in no hint of an added benefit of pembrolizumab + chemotherapy in comparison with the ACT; an added benefit is therefore not proven.

Health status (EQ-5D visual analogue scale [VAS])

There were no usable data for the outcome "health status", recorded with the EQ-5D VAS. This resulted in no hint of an added benefit of pembrolizumab + chemotherapy in comparison with the ACT; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30 and EORTC QLQ-BR23

"Health-related quality of life" was recorded using the EORTC QLQ-C30 and the EORTC QLQ-BR23. In each case, the time to first deterioration by ≥ 10 points (scale range from 0 to 100) was considered.

Global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning (EORTC QLQ-C30), body image, sexual activity and future perspective (EORTC QLQ-BR23)

No statistically significant differences between the treatment groups were shown for each of the following scales: global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning (EORTC QLQ-C30), body image, sexual activity and future perspective (EORTC QLQ-BR23). This resulted in no hint of an added benefit of pembrolizumab + chemotherapy in comparison with the ACT; an added benefit is therefore not proven in each case.

Sexual enjoyment (EORTC QLQ-BR23)

No usable data were available for the EORTC QLQ-BR23 scale "sexual enjoyment". Since patients who had not been sexually active at the beginning of the study were censored, the company's approach does not ensure that the burden of patients who became sexually active during the course of treatment was recorded. This resulted in no hint of an added benefit of pembrolizumab + chemotherapy in comparison with the ACT; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs) and severe AEs

No statistically significant difference between the treatment groups was shown for the outcomes "SAEs" and "severe AEs". In each case, this resulted in no hint of greater or lesser harm from pembrolizumab + chemotherapy in comparison with the ACT; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

There were no usable data for the outcome "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from pembrolizumab + chemotherapy in comparison with the ACT; greater or lesser harm is therefore not proven.

Specific AEs

Immune-related SAEs and immune-related severe AEs

There was no statistically significant difference between the treatment groups for the outcomes of immune-related SAEs and immune-related severe AEs. In each case, this resulted in no hint of greater or lesser harm from pembrolizumab + chemotherapy in comparison with the ACT; greater or lesser harm is therefore not proven.

Diarrhoea (AEs), dysgeusia (AEs) and "gastrointestinal disorders (SAEs)

A statistically significant difference to the disadvantage of pembrolizumab + chemotherapy versus placebo + chemotherapy was shown for each of the outcomes "diarrhoea (AEs)", "dysgeusia (AEs)" and "gastrointestinal disorders (SAEs)". In each case, this resulted in a hint of greater harm from pembrolizumab + chemotherapy in comparison with the ACT.

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

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

Overall, there are positive and negative effects, each with the probability "hint" and the extent "non-quantifiable".

The advantage for pembrolizumab + chemotherapy over the ACT is shown for the outcome "overall survival". In contrast, there are negative effects in the category of serious/severe side effects for the outcome "gastrointestinal disorders" and in the category of non-serious/non-severe side effects for the outcomes "diarrhoea" and "dysgeusia". However, these negative effects do not completely call into question the positive effect.

Overall, this results in a hint of non-quantifiable added benefit of pembrolizumab + chemotherapy versus the ACT for adult patients with locally recurrent unresectable or

[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].

metastatic TNBC whose tumours express PD-L1 (CPS ≥ 10) and who have not received prior chemotherapy for metastatic disease.

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

Table 3: Pembrolizumab + chemotherapy – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with locally recurrent, unresectable or metastatic triple-negative breast cancer whose tumours express PD-L1 (CPS ≥ 10) and who have not received prior chemotherapy for metastatic disease[b]	Anthracycline- and/or **taxane-containing systemic therapy** under consideration of the approval of the drugs[c]	Hint of a non-quantifiable added benefit[d]

a. Presented is the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. For the present therapeutic indication, it is assumed that on the one hand, radiotherapy is not considered a possible curative option and, on the other hand, measures aimed at achieving operability, e.g. neoadjuvant therapy, if such is indicated, have been exhausted in patients with locally recurrent unresectable disease that is isolated, i.e. without evidence of distant metastases.
c. The company chose paclitaxel and nab-paclitaxel.
d. The KEYNOTE 355 study only included patients with an ECOG PS of 0 or 1. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2.

ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1

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

2.2 Research question

The aim of the present report is the assessment of the added benefit of pembrolizumab in combination with chemotherapy (hereinafter referred to as “pembrolizumab + chemotherapy”) in comparison with the ACT in adult patients with locally recurrent, unresectable or metastatic TNBC whose tumours express PD-L1 (CPS ≥ 10) and who have not received prior chemotherapy for metastatic disease.

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:

Therapeutic indication	**ACT**[a]
Adult patients with locally recurrent, unresectable or metastatic TNBC whose tumours express PD-L1 (CPS ≥ 10) and who have not received prior chemotherapy for metastatic disease[b]	Anthracycline- and/or **taxane-containing systemic therapy** under consideration of the approval of the drugs[c]
a. Presented is the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b. For the present therapeutic indication, it is assumed that on the one hand, radiotherapy is not considered a possible curative option and, on the other hand, measures aimed at achieving operability, e.g. neoadjuvant therapy, if such is indicated, have been exhausted in patients with locally recurrent unresectable disease that is isolated, i.e. without evidence of distant metastases. c. The company chose paclitaxel and nab-paclitaxel. ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1	

The G-BA specified an anthracycline- and/or taxane-containing systemic therapy as ACT, taking into account the approval of the drugs. Although the company named the ACT of the G-BA, it also used nab-paclitaxel as a comparator therapy in addition to paclitaxel. However, nab-paclitaxel is not approved for the present therapeutic indication. The approval of nab-paclitaxel only covers the treatment of metastatic breast cancer in adults in whom first-line therapy of the metastatic disease has failed and for whom standard anthracycline-containing therapy is not indicated [3]. The G-BA pointed out that nab-paclitaxel could only be used as a comparator for the proof of added benefit if the dossier demonstrated by means of suitable clinical studies that the therapeutic benefit of nab-paclitaxel was sufficiently comparable to a paclitaxel approved in the present therapeutic indication [4]. For this purpose, the company refers to data from studies that were already presented in a previous benefit assessment of atezolizumab [5]. Moreover, the company did not present any new evidence for the comparability of nab-paclitaxel with a taxane approved in the therapeutic indication. As explained in detail in the benefit assessment of atezolizumab, the studies presented are insufficient to demonstrate that the benefit of nab-paclitaxel is sufficiently comparable with a taxane approved in the therapeutic indication of unresectable locally advanced or metastatic breast cancer in first-line treatment [5]. In contrast to the benefit assessment of atezolizumab, in which only nab-paclitaxel was used as a comparator, both paclitaxel and nab-paclitaxel were used as comparators in the present situation in the KEYNOTE 355 study submitted by the company. Based on subgroup analyses on the characteristic “chemotherapy (paclitaxel vs. nab-paclitaxel)”, it can be estimated that the results for the comparison of pembrolizumab with nab-paclitaxel are sufficiently applicable to a comparison of pembrolizumab with paclitaxel. The resulting uncertainty, however, was considered in the derivation of the added benefit (see Section 2.3.2).

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

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on pembrolizumab (status: 23 September 2021)
- bibliographical literature search on pembrolizumab (last search on 21 September 2021)
- search in trial registries/trial results databases for studies on pembrolizumab (last search on 23 September 2021)
- search on the G-BA website for pembrolizumab (last search on 21 September 2021)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 24 November 2021); for search strategies, see Appendix A of the full dossier assessment.

The check did not identify any additional relevant study.

2.3.1 Studies included

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

Table 5: Study pool of the company – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a]

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[b] (yes/no)	Third-party study (yes/no)	Clinical study report (CSR) (yes/no [citation])	Registry entries[c] (yes/no [citation])	Publication and other sources[d] (yes/no [citation])
KEYNOTE 355	Yes	Yes	No	Yes [6]	Yes [7,8]	Yes [9]

a. Paclitaxel or nab-paclitaxel or gemcitabine/carboplatin.
b. Study for which the company was sponsor.
c. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
d. 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 355 was used for the benefit assessment. Thereby, a subpopulation was considered because the study also allowed the administration of therapies going beyond the ACT (see Section 2.3.2). This concurs with the company's approach. Due to the implementation of the ACT, only the agents paclitaxel and nab-paclitaxel are therefore considered as chemotherapy in both the control arm and the intervention arm. Therefore, for the intervention arm, no data are available for the combination of pembrolizumab with other approved chemotherapy combination partners.

2.3.2 Study characteristics

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

Table 6: Characteristics of the studies included by the company – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a] (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
KEYNOTE 355	RCT, double-blind, parallel	▪ Adult patients (≥ 18 years) with locally recurrent unresectable or metastatic breast cancer ▪ triple negative: (hormone receptor-negative and HER2-negative) ▪ no prior chemotherapy[c] ▪ ECOG PS ≤ 1	Pembrolizumab + chemotherapy[a] (N = 566) placebo + chemotherapy[a] (N = 281) relevant subpopulation thereof[d]: pembrolizumab + chemotherapy[e] (n = 96) placebo + chemotherapy[e] (N = 47)	Screening: 28 days prior to the start of treatment treatment: ▪ until confirmed disease progression (RECIST version 1.1), unacceptable toxicity, occurrence of intercurrent diseases requiring the discontinuation of the study medication, treatment discontinuation following the decision by the physician or the patient, death or end of study ▪ pembrolizumab/placebo: at most 24 months[f] observation[g]: outcome-specific, at most until death or end of study	251 study centres in Argentina, Australia, Belgium, Brazil, Canada, Chile, Colombia, Czech Republic, Denmark, France, Germany, Hong Kong, Hungary, Ireland, Italy, Japan, Malaysia, Mexico, Netherlands, New Zealand, Poland, Russia, South Korea, Spain, Taiwan, Turkey, Ukraine, United Kingdom, USA 08/2016–ongoing data cut-offs: ▪ 18 October 2018[h] ▪ 11 December 2019[h] ▪ 15 June 2020[h] ▪ 15 June 2021 (final)	Primary: overall survival, PFS secondary: morbidity, health-related quality of life, AEs

Table 6: Characteristics of the studies included by the company – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a] (multipage table)

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

a. Paclitaxel or nab-paclitaxel or gemcitabine/carboplatin.
b. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
c. Either patients with locally recurrent breast cancer were not previously treated with chemotherapy or curative treatment was not possible or, in patients with metastatic breast cancer, the breast cancer was not previously treated with chemotherapy (treatment with curative intent was allowed with a history of locally recurrent breast cancer).
d. The subpopulation includes patients whose tumours express PD-L1 (CPS ≥ 10) and who had been assigned to taxane chemotherapy prior to randomization.
e. Paclitaxel or nab-paclitaxel.
f. Patients who achieved a confirmed complete response according to RECIST 1.1 after at least 8 cycles of treatment with pembrolizumab and received at least 2 further cycles of treatment with pembrolizumab after complete response were allowed to interrupt the treatment. In the event of subsequent confirmed disease progression, treatment could be continued for up to 17 further cycles ("second course phase"). Moreover, patients with stable disease, complete or partial response after 24 months of treatment with pembrolizumab were also allowed to start treatment with up to 17 further cycles of pembrolizumab in the event of subsequent confirmed disease progression, if they had not received any other subsequent therapy by then. At the time of the final data cut-off, 2 patients in the intervention arm were in the second phase of treatment in the relevant subpopulation.
g. Outcome-specific information is provided in Table 8.
h. Interim analyses.

AE: adverse event; CPS: combined positive score; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HER2: human epidermal growth factor receptor 2; n: relevant subpopulation; N: number of randomized patients; PD-L1: programmed cell death ligand 1; PFS: progression-free survival; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria In Solid Tumours

Table 7: Characteristics of the intervention – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a]

Study	Intervention	Comparison
KEYNOTE 355	Pembrolizumab 200 mg IV as infusion administered over 30 minutes every 21 days + on days 1, 8 and 15, all 28 days: ▪ paclitaxel[b] 90 mg/m² IV or ▪ nab-paclitaxel[b] 100 mg/m² IV	Placebo, IV as infusion administered over 30 minutes every 21 days + on days 1, 8 and 15, all 28 days: ▪ paclitaxel[b] 90 mg/m² IV or ▪ nab-paclitaxel[b] 100 mg/m² IV
	Dose adjustment ▪ pembrolizumab/placebo: no dose adjustment allowed; treatment interruption[c]/discontinuation due to toxicity was allowed ▪ paclitaxel/nab-paclitaxel: at most 2 dose reductions[d] by 20% of the current dose and treatment interruptions[c]/discontinuations in case of toxicity allowed ▪ if pembrolizumab/placebo was discontinued, chemotherapy could be continued, or if chemotherapy was discontinued, administration of pembrolizumab/placebo could be continued.	
	Permitted pretreatment ▪ treatment of the stage I-III breast cancer[e] with curative intent ▪ systemic (neo)adjuvant therapy with anthracyclines, unless anthracyclines were contraindicated or not the best option according to the investigator **non-permitted pretreatment** ▪ anti-PD-1, anti-PD-L1, anti PD-L2 drugs and drugs that are directed against another co-inhibitory T-cell receptor (such as CTLA-4, OX-40, CD137) ▪ ≤ 7 days before randomization: ▫ systemic steroids or immunosuppressants ▫ all drugs that are prohibited in combination with paclitaxel/nab-paclitaxel according to the SPC **permitted concomitant treatment** ▪ corticosteroids and appropriate standard therapy for immune-related AEs associated with pembrolizumab ▪ symptomatic treatment[f] for infusion reactions associated with pembrolizumab ▪ symptomatic radiotherapy of individual lesions or the brain **non-permitted concomitant treatment** ▪ other antineoplastic systemic chemotherapies or biologic treatments ▪ drugs that were not allowed even as pretreatment	

a. For the analysed subpopulation: paclitaxel or nab-paclitaxel.
b. Paclitaxel/nab-paclitaxel was administered after pembrolizumab/placebo and, if applicable, after premedication for chemotherapy according to local guidelines.
c. Treatment interruptions due to AEs were allowed for a maximum of 12 weeks for pembrolizumab/placebo and for at most 4 weeks for paclitaxel/nab-paclitaxel.
d. Subsequent dose re-escalation not allowed.
e. There had to be ≥ 6 months between curative treatment and the first documented disease progression (adjuvant radiotherapy was not considered curative treatment for this time calculation). If taxanes, gemcitabine or platinum agents had been given (neo)adjuvantly, the same drug class could be given again if there were ≥ 12 months between the curative treatment and the first documented disease progression.
f. e.g. antihistamines, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, narcotics

AE: adverse event; CD137: cluster of differentiation 137; CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; IV: intravenous; NSAIDs: nonsteroidal anti-inflammatory drugs; OX-40: corresponds to cluster of differentiation 134; PD-L1/2: programmed cell death-ligand 1/2; RCT: randomized controlled trial

KEYNOTE 355 is a double-blind RCT comparing pembrolizumab in combination with chemotherapy versus placebo in combination with chemotherapy. In each case, the chemotherapy was a chemotherapy of physician's choice using paclitaxel, nab-paclitaxel or gemcitabine/carboplatin.

Adult patients with locally recurrent unresectable or metastatic TNBC who had not yet received chemotherapy for this disease stage could be included in the study. In fact, however, the KEYNOTE 355 study included very few patients with inoperable local recurrence (3.5% of the patients in the relevant subpopulation; for the relevant subpopulation, see section below). Patients had to be in good general condition at study entry, corresponding to an ECOG PS of 0 or 1 and had to have an adequate organ function. Patients with active CNS metastases or carcinomatous meningitis were excluded from participation in the study; hence, no data are available for them.

In the case of previous treatment of the (stage I-III) breast cancer with curative intent, at least 6 months had to elapse between the completion of this treatment and the first documented disease progression.

If taxanes, gemcitabine or platinum agents were given (neo)adjuvantly, the same drug class could be re-administered in the KEYNOTE 355 study if at least 12 months had elapsed between completion of the treatment with curative intent and the first documented disease progression. Patients should only be included in the study if they had already received (neo)adjuvant treatment with anthracyclines, unless there was a contraindication to anthracyclines or anthracyclines were not suitable as a treatment option according to the physician’s assessment. Patients with de novo metastatic TNBC could be included if there was a contraindication to anthracyclines or if anthracyclines were not suitable as a treatment option according to medical assessment.

Before randomization, the PD-L1 expression of the tumour tissue had to be determined. This test had to be performed in a central laboratory and the tumour tissue had to be obtained from a new biopsy or one taken shortly before study inclusion. However, patients were included in the study regardless of their PD-L1 expression. The PD-L1 expression was determined using the PD-L1 IHC 22C3 pharmDx Kit.

A total of 847 patients were included in the KEYNOTE 355 study. Prior to randomization, the physician determined which of the named chemotherapies (nab-paclitaxel, paclitaxel or gemcitabine/carboplatin) the respective patient should receive on the basis of criteria not described in more detail by the company. Patients were then randomized in a 2:1 ratio either to treatment with pembrolizumab + chemotherapy (N = 566) or placebo + chemotherapy (N = 281). Randomization was stratified by chemotherapy (taxanes vs. gemcitabine/carboplatin), tumour PD-L1 status (CPS ≥ 1 vs. CPS < 1) and prior therapy with the same chemotherapy substance class in the (neo)adjuvant setting (yes vs. no).

Treatment with pembrolizumab in the intervention arm was largely in compliance with the specifications of the SPC [10]. Correspondingly, dose adjustment was not allowed; treatment interruptions due to toxicity were possible and were largely in compliance with the SPC [10]. Deviating from the requirements of the SPC, treatment with pembrolizumab was limited to a maximum treatment duration of 35 cycles (approx. 2 years). However, according to the SPC, treatment with pembrolizumab should be continued until progression of the cancer or the occurrence of unacceptable toxicity [10]. In the relevant subpopulation of the KEYNOTE 355 study (see the section below on the relevant subpopulation), 10 (10.5%) patients in the intervention arm reached the 35 treatment cycles. There is no information on when these patients showed a progression of the disease. It is therefore unclear how long the further treatment should have been continued according to the SPC. Overall, treatment with pembrolizumab was thus not performed in accordance with the approval for a small proportion of the study population.

In both, the intervention and the comparator arm, paclitaxel or nab-paclitaxel were applied in doses of 90 or 100 mg/m^2 BSA on days 1, 8 and 15 of a 28-day cycle. For a combination therapy, these dosages largely comply with the guideline recommendations [11-13]. Uncertainties resulting from the paclitaxel and nab-paclitaxel doses used in monotherapy are described further below in the section on the relevant subpopulation. The administration of the necessary premedications listed in the SPC of paclitaxel was adequately implemented in the KEYNOTE 355 study. The use of the drugs gemcitabine/carboplatin is not discussed further, as these are not relevant due to the specification of the ACT.

Moreover, the study population was treated until disease progression (determined using RECIST criteria version 1.1), occurrence of unacceptable toxicity or intercurrent diseases requiring the discontinuation of the study medication or decision by the investigator or the patient. A switch to the treatment of the respective other study arm was not planned.

Co-primary outcomes of the KEYNOTE 355 study were “overall survival” and “PFS”. Patient-relevant secondary outcomes were outcomes on morbidity, health-related quality of life and AEs.

Relevant subpopulation of the KEYNOTE 355 study

For the benefit assessment, the company presented data and analyses on a subpopulation of the KEYNOTE 355 study. This subpopulation comprised all patients whose tumours expressed PD-L1 with a CPS ≥ 10 and who had been assigned to chemotherapy with paclitaxel or nab-paclitaxel prior to randomization. The company’s approach is accepted for the present benefit assessment, but is associated with various uncertainties. These uncertainties as well as their effects for the present benefit assessment are described in more detail below.

PD-L1 status

In accordance with the approved therapeutic indication of pembrolizumab + chemotherapy, only patients whose tumours express PD-L1 with a CPS ≥ 10 are relevant for the research

question. However, the KEYNOTE 355 study included patients irrespective of the PD-L1 expression. The restriction of the population to patients whose tumours express PD-L1 with a CPS ≥ 10 is therefore appropriate.

Implementation of the ACT

Comparability of nab-paclitaxel and paclitaxel

The G-BA specified an anthracycline- and/or taxane-containing systemic therapy as ACT, taking into account the approval of the drugs.

In the KEYNOTE 355 study, the physician could choose between the following chemotherapy options for each patient before randomization: paclitaxel, nab-paclitaxel or gemcitabine/carboplatin. Gemcitabine/carboplatin is not approved in the present therapeutic indication and is no treatment option of the ACT specified by the G-BA. The exclusion of patients treated with gemcitabine/carboplatin from the relevant subpopulation is therefore appropriate.

The G-BA pointed out that nab-paclitaxel could only be used as a comparator for the proof of added benefit if the dossier demonstrated by means of suitable clinical studies that the therapeutic benefit of nab-paclitaxel was sufficiently comparable to a paclitaxel approved in the present therapeutic indication [4]. To show the comparability of nab-paclitaxel and paclitaxel, the company referred to various studies [14-18] that have already been presented in a previous benefit assessment on atezolizumab. However, these were not considered sufficient to show the comparability in the benefit assessment on atezolizumab [5] (see Section 2.2). Nevertheless, the approach of the company to use the subpopulation of patients treated with paclitaxel and nab-paclitaxel for the assessment is accepted in the present situation. In contrast to the benefit assessment of atezolizumab, in which only nab-paclitaxel was used as a comparator, both paclitaxel and nab-paclitaxel were used as comparators in the present situation in the KEYNOTE 355 study submitted by the company. The company formed a subpopulation from the KEYNOTE 355 study in which both paclitaxel and nab-paclitaxel were used as comparators.

Based on subgroup analyses on the characteristic “chemotherapy (paclitaxel vs. nab-paclitaxel)” in this subpopulation, it was investigated whether the results for the comparison of pembrolizumab with nab-paclitaxel were sufficiently applicable to a comparison with paclitaxel. In doing so, there were essentially no relevant effect modifications for patient-relevant outcomes. In the two subgroups, different effects were shown for the outcome "overall survival” (p-value of the interaction test: p = 0.18). However, the subgroup of patients treated with nab-paclitaxel showed a smaller effect than the subgroup of patients treated with paclitaxel (HR 95% CI: nab-paclitaxel: 0.63 [0.39; 1.03] vs. paclitaxel 0.34 [0.16; 0.72]). Otherwise, only 2 scales of the EORTC showed a statistically significant effect modification (for the scale "insomnia" and for the scale "sexual activity"). These effect modifications are not considered sufficient to fundamentally question the applicability of the results of pembrolizumab with nab-paclitaxel to the comparison with the taxane paclitaxel approved in this indication. The

subpopulation presented by the company was thus used for the benefit assessment. The remaining uncertainty, however, was considered in the derivation of the added benefit.

Uncertainties regarding the dosage of paclitaxel and nab-paclitaxel in monotherapy

As described above, paclitaxel was used in doses of 90 mg/m^2 BSA on days 1, 8 and 15 of a 28-day cycle in the KEYNOTE 355 study. The SPC on provides no specific information on the dosage of paclitaxel as monotherapy in first-line treatment [19]. The guidelines do not provide consistent information [11-13,20-22]. In the studies referenced in the guidelines, 175 mg/m² BSA paclitaxel every 3 weeks or 80 to 90 mg/m² BSA paclitaxel weekly were the most commonly used dosing regimens. The dosing regimen of 90 mg/m² BSA on days 1, 8, 15 of a 28-day cycle used in the KEYNOTE 355 study is only found as a dosing regimen in a combination therapy [11-13]. Based on the available information, the dosing regimen with 3 applications used in the KEYNOTE 355 study, followed by a 1-week break, does not appear appropriate and suggests an undersupply of patients in the comparator arm. However, it cannot be assumed that the pronounced effect shown for the outcome "overall survival" is solely due to an undersupply in the comparator arm. However, it is questionable to what extent the dosage of paclitaxel represents the actual health care setting in Germany.

The company argues that there was no undersupply because a dosing regimen of 175 mg/m² BSA paclitaxel every 3 weeks corresponded to an average dose of 446.6 mg paclitaxel per month and in the dosing regimen used in the KEYNOTE 355 study, an average of 514.8 mg of paclitaxel was administered per month. However, the company presented no data that could be used to check whether the therapeutic benefit of the average dose of paclitaxel per month in the different dosing regimens was comparable.

As already explained, nab-paclitaxel is not approved for the present therapeutic indication. The dosing regimen of 100 mg/m² BSA nab-paclitaxel on days 1, 8, 15 of a 28-day cycle used in the KEYNOTE 355 study also appears to be low for the monotherapy. The guidelines predominantly refer to a nab-paclitaxel dosage of 125 mg/m² BSA on days 1, 8 and 15 of a 28-day cycle [11,12]. It is therefore questionable to what extent the used dosage of paclitaxel represents the actual health care setting in Germany. In the justification for the benefit assessment procedure of atezolizumab for the first-line treatment of unresectable locally advanced or metastatic TNBC, in which nab-paclitaxel was used at the same dosage in the comparator arm in the submitted IMpassion 130 study, the uncertainties regarding the dosage of nab-paclitaxel were also described. However, this was accepted with the comment that a reduced dose could also be acceptable in view of toxicities and associated treatment discontinuations [23]. The dose of nab-paclitaxel used is therefore also accepted with uncertainty in the present situation.

Overall, the data are used for the assessment, but due to the uncertainties regarding an undersupply of patients in the comparator arm and how large the impact of this undersupply would be, the extent of, for example, an added benefit cannot be quantified.

Lack of suitability of patients for anthracycline therapy unclear

In the subpopulation of the KEYNOTE 355 study submitted by the company, paclitaxel or nab-paclitaxel was used as chemotherapy in the control arm.

Paclitaxel is approved as monotherapy for the treatment of metastatic breast cancer in patients who have not responded to standard anthracycline-containing therapy or for whom such therapy is not an option [24]. According to the inclusion criteria of KEYNOTE 355, (neo)adjuvant treatment with anthracyclines had to have taken place, contraindication to anthracyclines had to be present or anthracyclines were not to be the best treatment option in the treating physician's assessment. However, there are no data available that can be used to verify whether anthracyclines were actually no longer an option for any patient. Based on the characteristics of the relevant subpopulation, this question cannot be answered. Especially since, according to the guidelines, anthracyclines can also be used again in patients with at least 12 months of disease-free interval after completion of (neo)adjuvant chemotherapy [20,22]. Furthermore, based on the patient characteristics, it remains unclear to what extent an anthracycline- and taxane-containing combination therapy would also have been indicated for patients. According to the guidelines, combination therapy is indicated in cases of severe symptoms, rapid tumour growth and aggressive tumour behaviour [11,12,20,22]. The resulting uncertainty was considered in the derivation of the added benefit.

Summary

Overall, the subpopulation presented by the company (patients whose tumours express PD-L1 with a CPS ≥ 10 and who had been assigned to chemotherapy with paclitaxel or nab-paclitaxel prior to randomization) was used for the benefit assessment. However, due to the uncertainties described with regard to the comparability of nab-paclitaxel and paclitaxel, the undersupply in the comparator arm and a lack of patient suitability for therapy with anthracyclines, the certainty of conclusions of the information is limited. Therefore, on the one hand, at most hints, e.g. of an added benefit, can be determined for all outcomes irrespective of bias aspects and, on the other hand, the extent, e.g. of an added benefit, cannot be quantified.

Data cut-offs

KEYNOTE 355 is still ongoing. 4 data cut-offs have been performed to date:

- 18 October 2018: prespecified interim analysis 1 for "overall survival" and "PFS", as well as final analysis for the objective response rate, planned after completed recruitment and approx. 9 months after randomization of the first 640 patients
- 11 December 2019: prespecified interim analysis 2, planned after approx. 185 results in the outcome "overall survival" in patients whose tumours express PD-L1 (CPS ≥ 10) or final PFS analysis
- 15 June 2020: prespecified interim analysis 3, planned after approx. 210 results in the outcome "overall survival" in patients whose tumours express PD-L1 (CPS ≥ 10)

- 15 June 2021: prespecified final analysis, planned after approx. 240 results in the outcome "overall survival" in patients whose tumours express PD-L1 (CPS ≥ 10)

In the present benefit assessment, the results of the prespecified, final analysis of the KEYNOTE 355 study presented by the company were used (data cut-off: 15 June 2021).

Planned duration of follow-up observation

Table 8 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a]

Study outcome category outcome	Planned follow-up observation
KEYNOTE 355	
Mortality	
Overall survival	Until death, end of study or withdrawal of consent
Morbidity	
Symptoms (EORTC QLQ-C30, EORTC QLQ-BR23)	Until 30 days after the last dose of the study medication
Health status (EQ-5D VAS)	Until 30 days after the last dose of the study medication
Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR23)	Until 30 days after the last dose of the study medication
Side effects	
AEs/severe AEs[b]	Until 30 days after the last dose of the study medication
SAEs	Until 90 days after the last dose of the study medication or until initiation of a new anticancer therapy, however, at least 30 days after the last dose of study medication

a. For the analysed subpopulation: paclitaxel or nab-paclitaxel.
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; 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

The monitoring periods for the outcomes of the categories "morbidity", "health-related quality of life" and "side effects" were systematically shortened, because they were only recorded for the time of treatment with the study medication (plus 30 days or up to 90 days for SAEs). However, to be able to draw a reliable conclusion on the total study period or the time to patient death, it would be necessary to record these outcomes as well for the total period, as was done for survival.

Characteristics of the relevant subpopulation

Table 9 shows the characteristics of the patients of the relevant subpopulation in the study included.

Table 9: Characteristics of the study population – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a] (multipage table)

Study characteristic category	Pembrolizumab + chemotherapy[a] N[b] = 96	Placebo + chemotherapy[a] N[b] = 47
KEYNOTE 355		
Age [years], mean (SD)	54 (12)	56 (12)
Sex [F/M], %	100/0	100/0
Family origin, n (%)		
Native Americans or Native Alaskans	2 (2.1)	0 (0)
Asian	14 (14.6)	11 (23.4)
Black or African American	5 (5.2)	4 (8.5)
White	70 (72.9)	30 (63.8)
Several	2 (2.1)	1 (2.1)
Missing	3 (3.1)	1 (2.1)
Disease status, n (%)		
Metastatic, de novo	36 (37.5)	23 (48.9)
Metastatic, recurrence	57 (59.4)	21 (44.7)
Locally recurrent, unresectable	2 (2.1)	3 (6.4)
Missing	1 (1.0)	0 (0)
Disease-free interval, n (%)		
Metastatic, de novo	36 (37.5)	23 (48.9)
< 12 months	7 (7.3)	5 (10.6)
≥ 12 months	52 (54.2)	19 (40.4)
Number of metastases, n (%)		
0	2 (2.1)	3 (6.4)
1	21 (21.9)	9 (19.1)
2	33 (34.4)	17 (36.2)
≥ 3	39 (40.6)	18 (38.3)
Missing	1 (1.0)	0 (0)

Table 9: Characteristics of the study population – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a] (multipage table)

Study characteristic category	Pembrolizumab + chemotherapy[a] N[b] = 96	Placebo + chemotherapy[a] N[b] = 47
Location of metastases[c], n (%)		
Total, patients with metastatic disease	93 (96.9)	44 (93.6)
Bones	20 (20.8)	11 (23.4)
Brain	2 (2.1)	3 (6.4)
Chest	6 (6.3)	3 (6.4)
Chest wall	28 (29.2)	4 (8.5)
Liver	30 (31.3)	15 (31.9)
Lungs	52 (54.2)	26 (55.3)
Lymph nodes	73 (76.0)	36 (76.6)
Other metastases	18 (18.8)	6 (12.8)
ECOG PS, n (%)		
0	61 (63.5)	29 (61.7)
1	35 (36.5)	18 (38.3)
Chemotherapy (IVRS)[d], n (%)		
Nab-paclitaxel	63 (65.6)	36 (76.6)
Paclitaxel	33 (34.4)	11 (23.4)
Prior (neo)adjuvant chemotherapy, n (%)		
Yes	47 (49.0)	21 (44.7)
Taxanes	38 (39.6)	15 (31.9)
Platinum-containing	7 (7.3)	4 (8.5)
Anthracyclines	44 (45.8)	19 (40.4)
Other	44 (45.8)	19 (40.4)
No	49 (51.0)	26 (55.3)
Treatment discontinuation, n (%)[e]	83 (87.4)	43 (91.5)
Study discontinuation, n (%)[f]	66 (68.8)	39 (83.0)

a. For the analysed subpopulation: paclitaxel or nab-paclitaxel.
b. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
c. Breast, chest wall and lymph nodes also include locally recurrent lesions.
d. The chemotherapy actually received during the course of the study deviates from the chemotherapy assigned before randomization for 2 patients in the intervention arm. Actually received in the intervention arm n (%): nab-paclitaxel: 61 (63.5); paclitaxel 33 (34.4); gemcitabine/carboplatin: 1 (1.0); missing data: 1 (1.0).
e. Common reasons for treatment discontinuation in the intervention versus the control arm were disease progression (53 [55.8%] vs. 36 [76.6%]) and AEs (10 [10.5%] vs. 2 [4.3%]).
f. Common reasons for study discontinuation in the intervention versus the control arm were death (59 [61.5%] vs. 38 [80.9%]) and withdrawal of consent (7 [7.3%] vs. 1 [2.1%]).

AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; IVRS: interactive voice response system; F: female; M: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation

The characteristics of the relevant subpopulation were predominantly comparable between the two treatment arms. The study population of the KEYNOTE 355 study consisted exclusively of women. The mean age of the patients was about 55 years, about 70% were of white family origin and about 96% had metastatic disease. Approx. 63% of the patients had an ECOG PS of 0.

49% of the patients in the intervention arm and 45% of those in the control arm had received (neo)adjuvant chemotherapy. Of the named agents, anthracyclines were used most frequently in both treatment arms in 46% and 40% of patients, followed by taxanes in 40% and 32% of patients. In the relevant subpopulation, 66% of patients in the intervention arm and 77% in the control arm received nab-paclitaxel as chemotherapy. In both treatment arms, the most common reasons for treatment discontinuation were disease progression (intervention arm: 56 %; control arm: 77 %), followed by side effects (intervention arm: 11%; control arm: 4 %), with frequencies differing between the arms.

Information on the course of the study

Table 10 shows the mean/median treatment duration of the patients and the mean/median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a]

Study **duration of the study phase** **outcome category**	**Pembrolizumab + chemotherapy[a]** **N = 96**	**Placebo + chemotherapy[a]** **N = 47**
KEYNOTE 355		
Treatment duration [months]		
Median [min; max]	9.4 [ND]	4.4 [ND]
Mean (SD)	ND	ND
Observation period [months]		
Overall survival[b]		
Median [min; max]	28.4 [ND]	16.1 [ND] A.]
Mean (SD)	ND	ND
Morbidity (EORTC QLQ-C30, EORTC QLQ-BR23, EQ-5D VAS)		
Median [min; max]	9.7 [ND] A.]	5.9 [ND] A.]
Mean (SD)	ND	ND
Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR23)		
Median [min; max]	9.7 [ND] A.]	5.9 [ND] A.]
Mean (SD)	ND	ND
Side effects (AEs, severe AEs[c])		
Median [min; max]	10.4 [ND] A.]	5.3 [ND] A.]
Mean (SD)	ND	ND
Side effects (SAEs)		
Median [min; max]	12.0 [ND] A.]	6.9 [ND] A.]
Mean (SD)	ND	ND

a. For the analysed subpopulation: paclitaxel or nab-paclitaxel.
b. Information on how the observation period was calculated is not available.
c. Severe AEs are operationalized as CTCAE grade ≥ 3.

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

With 9.4 months, the median treatment duration was more than twice as long in the intervention arm than in the control arm (4.4 months). The median observation period for the outcome "overall survival" is also significantly longer in the intervention arm (28.4 months) compared to 16.1 months in the control arm, although it is unclear how this was calculated. The clear differences in the median observation period are also shown in the outcomes on morbidity and health-related quality of life (both 9.7 months vs. 5.9 months), as well as in the outcomes on side effects (10.4 months vs. 5.3 months for AEs/severe AEs and 12.0 months vs. 6.9 months for SAEs).

Information on subsequent therapies

Table 11 shows which subsequent therapies patients received after discontinuing the study medication.

Table 11: Information on subsequent oncological systemic therapies – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a]

Study drug class[b, c] drug	Patients with subsequent therapy n (%)	
	pembrolizumab + chemotherapy[a] N = 96	placebo + chemotherapy[a] N = 47
KEYNOTE 355		
Total	46 (47.9)	27 (57.4)
Antineoplastic treatments	46 (47.9)	27 (57.4)
Capecitabine	17 (17.7)	8 (17.0)
Cyclophosphamide	6 (6.3)	9 (19.1)
Carboplatin	9 (9.4)	5 (10.6)
Gemcitabine	8 (8.3)	5 (10.6)
Doxorubicin	5 (5.2)	5 (10.6)
Cisplatin	4 (4.2)	3 (6.4)
Paclitaxel	3 (3.1)	3 (6.4)
Vinorelbine	3 (3.1)	3 (6.4)
Eribulin mesylate	5 (5.2)	1 (2.1)
Bevacizumab	2 (2.1)	2 (4.3)
Docetaxel	2 (2.1)	2 (4.3)
Fluorouracil	0 (0.0)	3 (6.4)
Pembrolizumab	2 (2.1)	1 (2.1)
Doxorubicin hydrochloride	1 (1.0)	1 (2.1)
Epirubicin hydrochloride	0 (0.0)	1 (2.1)
Olaparib	2 (2.1)	0 (0.0)
Palbociclib	0 (0.0)	1 (2.1)
Glembatumumab	1 (1.0)	0 (0.0)
Ixabepilone	1 (1.0)	0 (0.0)
Leramilimab	1 (1.0)	0 (0.0)
Spartalizumab	1 (1.0)	0 (0.0)
Endocrine therapy	0 (0.0)	1 (2.1)
Bicalutamide	0 (0.0)	1 (2.1)

a. For the analysed subpopulation: paclitaxel or nab-paclitaxel.
b. Each patient was categorized only once in the category of systemic therapies in which he had an event.
c. Including the patients who had been randomly assigned to the pembrolizumab arm and who discontinued treatment with pembrolizumab (second course phase).

n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

Subsequent therapy following disease progression was allowed without restrictions in both study arms. Overall, 47.9% of the patients in the intervention arm and 57.4% of the patients in the control arm received subsequent systemic antineoplastic therapy. The drugs used in the subsequent therapy are comparable between the treatment arms. The patients most frequently received subsequent therapy with capecitabine (17.7% vs. 17.0%) and with cyclophosphamide (6.3% vs. 19.1%).

Overall, the subsequent therapies used in the CA209-577 study are in line with guideline recommendations are in line with guideline recommendations [20,22].

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[a] vs. placebo + chemotherapy[a]

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
KEYNOTE 355	Yes	Yes	Yes	Yes	Yes	Yes	Low

a. For the analysed subpopulation: paclitaxel or nab-paclitaxel.
RCT: randomized controlled trial

The risk of bias across outcomes was rated as low for the KEYNOTE 355 study.

Transferability of the study results to the German health care context

The company considers the results of KEYNOTE 355 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.

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

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality

  Overall survival

- Morbidity

  Symptoms, recorded with the EORTC QLQ-C30 and EORTC QLQ-BR23

  Health status, recorded using the EQ-5D VAS

- Health-related quality of life

  EORTC QLQ-C30 and EORTC QLQ-BR23

- Side effects

  SAEs

  severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)

  Discontinuation due to AEs

  Immune-related SAEs and severe AEs

  further specific AEs, if any

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

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

Table 13: Matrix of outcomes – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a]

Study	Outcomes											
	Overall survival	**Symptoms (EORTC QLQ-C30, EORTC QLQ-BR23)**	**Health status (EQ-5D VAS)**	**Health-related quality of life (EORTC C30, EORTC QLQ-BR23)**	**SAEs**	**Severe AEs[b]**	**Discontinuation due to AEs**	**Immune-related SAEs[c]**	**Immune-related severe AEs[b,c]**	**Diarrhoea (PT, AEs)**	**Dysgeusia (PT, AEs)**	**Gastrointestinal disorders (SOC, SAEs)**
KEYNOTE 355	Yes	Yes	No[d]	Yes	Yes	Yes	No[d]	Yes	Yes	Yes	Yes	Yes

a. For the analysed subpopulation: paclitaxel or nab-paclitaxel.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome of adverse events of special interest ("AEOSI") is used.
d. No usable data available; see following text for reasons.

AE: adverse event; AEOSI: adverse events of special interest; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; 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 analyses of the outcome categories "morbidity" and "health-related quality of life"

- Symptoms and health-related quality of life: In its dossier, the company presented responder analyses for EORTC QLQ-C30 and the EORTC QLQ-BR23 for the time to first deterioration by ≥ 10 points (respective scale range 0-100). As explained in the *General Methods* of the Institute [1,25], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to a predefined value of at least 15% of the scale range of an instrument (in post-hoc analyses exactly 15 % of the scale range). For the EORTC QLQ-C30 and its additional modules, the analysis with a previously accepted response threshold of 10 points is considered a sufficient approximation to an analysis with a 15% threshold (15 points) in certain constellations and is used for the benefit assessment (for an explanation, see [26]). Regardless of this, for a transitional period until the adjusted module templates for the dossier come into

force (see FAQs of the G-BA [27]), analyses with the previously accepted response threshold of 10 points for the EORTC QLQ-C30 as well as all additional modules of the EORTC will be used primarily.

- Health status recorded using the EQ-5D VAS: In its dossier, the company presented responder analyses for the health status on the time to first deterioration by ≥ 7 or ≥ 10 points (respective scale range 0-100). These were not used for the dossier assessment. As explained in the *General Methods* of the Institute [1,25], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to a predefined value of at least 15% of the scale range of an instrument (in post-hoc analyses exactly 15 % of the scale range). The responder analyses on "health status" presented by the company are provided as supplementary information in Appendix D of the full dossier assessment.

Notes on side effect outcomes

- Discontinuation due to AEs": The company did not specify whether at least one or all of the drug(s) were discontinued. According to the information in the study protocol, chemotherapy could be continued if pembrolizumab or placebo was discontinued and, conversely, pembrolizumab or placebo could be continued if chemotherapy was discontinued. In the context of the benefit assessment, the operationalization "discontinuation of ≥ 1 drug component" is to be preferred, as every AE that leads to a discontinuation of the therapy is relevant.
  Data on discontinuations separated by drugs are not available for the relevant subpopulation. The results on the outcome "discontinuation due to AEs" are thus not usable for the present benefit assessment.

2.4.2 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[a] vs. placebo + chemotherapy[a]

Study	Study level	Outcomes												
		Overall survival	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]	Diarrhoea (PT, AEs)	Dysgeusia (PT, AEs)	Gastrointestinal disorders (SOC, SAEs)
KEYNOTE 355	L	L	H[d]	–[e]	H[d]	H[f]	H[f]	–[e]	H[f]	H[f]	H[f]	H[f]	H[f]

a. For the analysed subpopulation: paclitaxel or nab-paclitaxel.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome of adverse events of special interest ("AEOSI") is used.
d. Strongly decreasing and highly differential returns in the course of the study.
e. No usable data available; for reasons, see Section 2.4.1 of the present benefit assessment.
f. Incomplete observations for potentially informative reasons.

AE: adverse event; AEOSI: adverse events of special interest; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; 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 of the result on the outcome "overall survival" was rated as low. For each of the outcomes on symptoms (symptom scales of the EORTC QLQ-C30 and EORTC QLQ-BR23) and health-related quality of life (functional scales of the EORTC QLQ-C30 and EORTC QLQ-BR23), the risk of bias of the results was rated as high. In the patients included in the analysis, there was a strongly decreasing response rate to the respective questionnaires in both treatment arms and a strongly differentiated response rate between the treatment arms.

No usable data are available for the outcomes "health status (EQ-5D VAS)" and "discontinuation due to AEs"; therefore, the risk of bias was not assessed.

The risk of bias of the results of the outcomes of SAEs, severe AEs as well as immune-related SAEs/severe AEs, diarrhoea (AEs), dyspnoea (AEs) and gastrointestinal disorders (SAEs) 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 and a possible association between outcome and reason for treatment discontinuation (see also Table 8).

Summary assessment of the certainty of conclusions

Due to the uncertainties described in Section 2.3.2 regarding the comparability of nab-paclitaxel and paclitaxel, the undersupply in the comparator arm and a lack of patient suitability for treatment with anthracyclines, the certainty of conclusions of the KEYNOTE 355 study is deemed limited. Hence, irrespective of the partially low outcome-specific risk of bias, at most hints, e.g. of added benefit, can be derived on the basis of the available information for all outcomes. The assumed underdosage in the comparator arm and the uncertainty as to what effect this has, also means that the extent, e.g. of an added benefit, cannot be quantified.

2.4.3 Results

Table 15 summarizes the results on the comparison of pembrolizumab + chemotherapy with placebo + chemotherapy in adult patients with locally recurrent unresectable or metastatic TNBC whose tumours express PD-L1 (CPS ≥ 10) and who have not received prior chemotherapy for metastatic disease. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The Kaplan-Meier curves on the event time analyses are presented in Appendix B, the results on common AEs, SAEs and severe AEs in Appendix C of the full dossier assessment. Event time analyses for the outcome of EQ-5D VAS with the response criteria of ≥ 7 and ≥ 10 points are presented as supplementary information in Appendix D of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a] (multipage table)

Study outcome category outcome	Pembrolizumab + chemotherapy[a]		Placebo + chemotherapy[a]		Pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a]
	L	median time to event in months [95% CI] patients with event n (%)	L	median time to event in months [95% CI] patients with event n (%)	HR [95% CI][b]; p-value[b]
KEYNOTE 355					
Mortality					
Overall survival	96	29.7 [22.8; 38.3] 61 (63.5)	47	16.1 [10.5; 20.8] 39 (83.0)	0.56 [0.37; 0.84]; 0.005
Morbidity					
Symptoms (EORTC QLQ-C30) – time to deterioration[c]					
Fatigue	94	1.4 [1.0; 2.6] 75 (79.8)	45	2.1 [1.4; 4.9] 31 (68.9)	1.14 [0.75; 1.73]; 0.552
Nausea and vomiting	94	3.5 [1.5; 7.6] 56 (59.6)	45	5.3 [1.4; 11.8] 22 (48.9)	1.12 [0.68; 1.84]; 0.658
Pain	94	3.9 [3.0; 7.6] 57 (60.6)	45	3.5 [1.4; 3.9] 32 (71.1)	0.72 [0.46; 1.11]; 0.136
Dyspnoea	94	7.4 [5.5; 18.7] 44 (46.8)	45	17.7 [9.0; NC] 12 (26.7)	1.57 [0.83; 2.98]; 0.169
Insomnia	94	8.3 [3.7; 22.1] 44 (46.8)	45	18.4 [5.6; NC] 14 (31.1)	1.49 [0.81; 2.72]; 0.199
Appetite loss	94	5.2 [3.5; 9.7] 56 (59.6)	45	3.9 [3.0; 11.8] 24 (53.3)	1.02 [0.63; 1.65]; 0.935
Constipation	94	8.0 [4.9; 11.9] 48 (51.1)	45	7.7 [4.9; NC] 16 (35.6)	1.33 [0.75; 2.36]; 0.325
Diarrhoea	94	4.0 [3.5; 8.3] 55 (58.5)	45	18.4 [5.6; NC] 14 (31.1)	1.98 [1.10; 3.58]; 0.023
Symptoms (EORTC QLQ-BR23) – time to deterioration[c]					
Side effects of systemic therapy	94	1.4 [0.8; 1.4] 75 (79.8)	45	1.4 [0.8; 2.1] 34 (75.6)	1.07 [0.71; 1.61]; 0.753
Symptoms in chest region	94	NA [12.6; NC] 26 (27.7)	45	7.7 [3.5; NC] 18 (40.0)	0.49 [0.27; 0.91]; 0.023
Symptoms in arm region	94	7.6 [5.5; 12.0] 50 (53.2)	45	3.9 [1.5; 7.7] 26 (57.8)	0.83 [0.51; 1.33]; 0.432
Upset by hair loss	94	0.8 [0.8; 1.4] 70 (74.5)	45	0.8 [0.7; 2.1] 34 (75.6)	1.05 [0.69; 1.58]; 0.826
Health status (EQ-5D VAS)				No usable data available[d]	

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a] (multipage table)

Study outcome category outcome	Pembrolizumab + chemotherapy[a]		Placebo + chemotherapy[a]		Pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a]
	L	median time to event in months [95% CI] patients with event n (%)	L	median time to event in months [95% CI] patients with event n (%)	HR [95% CI][b]; p-value[b]
Health-related quality of life					
EORTC QLQ-C30, time to deterioration[e]					
Global health status	94	5.8 [3.6; 9.9] 55 (58.5)	45	5.6 [3.5; 14.5] 22 (48.9)	0.99 [0.60; 1.63]; 0.969
Physical functioning	94	6.4 [3.8; 7.7] 63 (67.0)	45	5.6 [3.4; 14.5] 23 (51.1)	1.12 [0.69; 1.82]; 0.651
Role functioning	94	3.4 [1.4; 5.6] 62 (66.0)	45	4.9 [1.4; 9.7] 26 (57.8)	1.21 [0.76; 1.92]; 0.418
Emotional functioning	94	9.7 [5.8; 12.0] 47 (50.0)	45	9.7 [4.5; NC] 19 (42.2)	1.20 [0.70; 2.06]; 0.505
Cognitive functioning	94	3.5 [2.6; 5.5] 66 (70.2)	45	3.9 [1.4; 7.6] 27 (60.0)	1.11 [0.71; 1.74]; 0.646
Social functioning	94	3.5 [1.6; 3.8] 65 (69.1)	45	3.5 [1.4; 11.8] 27 (60.0)	1.03 [0.65; 1.61]; 0.906
EORTC QLQ-BR23, time to deterioration[e]					
Body image	94	5.6 [3.5; 8.9] 50 (53.2)	45	3.5 [1.4; 5.6] 27 (60.0)	0.71 [0.44; 1.14]; 0.160
Sexual activity	94	NA [5.6; NC] 34 (36.2)	45	22.7 [3.6; NC] 17 (37.8)	0.80 [0.44; 1.44]; 0.460
Sexual enjoyment	No usable data available[f]				
Future perspective	94	11.3 [6.3; NC] 38 (40.4)	45	25.3 [4.9; NC] 17 (37.8)	1.07 [0.60; 1.91]; 0.815
Side effects					
AEs (presented as supplementary information)[g]	95	0.3 [0.1; 0.3][h] 93 (97.9)	47	0.3 [0.1; 0.4][h] 45 (95.7)	-
SAEs[g]	95	29.5 [20.5; NC][h] 28 (29.5)	47	NA [19.3; NC][a] 7 (14.9)	1.86 [0.81; 4.26]; 0.144
Severe AEs[g,i]	95	5.7 [4.2; 10.3][h] 61 (64.2)	47	6.5 [2.8; NC][h] 23 (48.9)	1.20 [0.74; 1.94]; 0.459
Discontinuation due to AEs	No usable data available[d]				

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a] (multipage table)

Study outcome category outcome	Pembrolizumab + chemotherapy[a]		Placebo + chemotherapy[a]		Pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a]
	L	median time to event in months [95% CI] patients with event n (%)	L	median time to event in months [95% CI] patients with event n (%)	HR [95% CI][b]; p-value[b]
Immune-related SAEs[g,j]	95	NA 4 (4.2)	47	NA 0 (0.0)	NC; 0.165
Immune-related severe AEs[g,i,j]	95	NA 8 (8.4)	47	NA 0 (0)	NC; 0.067
Diarrhoea (PT, AEs)	95	13.3 [7.6; NC][h] 41 (43.2)	47	21.2 [17.3; NC][h] 7 (14.9)	2.81 [1.26; 6.28]; 0.012
Dysgeusia (PT, AEs)	95	NA 12 (12.6)	47	NA 0 (0.0)	NC; 0.017
Gastrointestinal disorders (SOC, SAEs)	95	NA 8 (8.4)	47	NA 0 (0.0)	NC; 0.044

a. For the analysed subpopulation: paclitaxel or nab-paclitaxel.
b. Cox proportional hazards model with treatment as covariate, stratified by pretreatment with the same chemotherapy substance class in the (neo)adjuvant setting (yes vs. no); 2-sided p-value (Wald test, score test in case of zero events in one of the study arms).
c. Time to first deterioration. A score increase by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0-100).
d. See Section 2.4.1 for reasons.
e. Time to first deterioration. A score decrease by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0-100).
f. At baseline, information on the sexual enjoyment was not available for about 55% and 51% of the patients. These patients were therefore not considered in the analysis. The approach of the company does not ensure that the burden of patients who become sexually active in the course of the treatment is recorded.
g. Without recording of progression of the underlying disease.
h. Institute's calculation (conversion from weeks to months).
i. Operationalized as CTCAE grade ≥ 3.
j. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome of adverse events of special interest ("AEOSI") is used.

AE: adverse event; AEOSI: adverse events of special interest; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Based on the available information, due to the uncertainties described with regard to the comparability of nab-paclitaxel and paclitaxel, the extent of undersupply in the comparator arm

and a lack of patient suitability for therapy with anthracyclines (see Section 2.3.2 and Section 2.4.2), at most hints, e.g. of an added benefit, can be determined for all outcomes.

Mortality

Overall survival

For the outcome “overall survival”, a statistically significant difference was found in favour of pembrolizumab + chemotherapy in comparison with placebo + chemotherapy. This resulted in a hint of added benefit of pembrolizumab + chemotherapy in comparison with the ACT for this outcome.

Morbidity

Symptoms (EORTC QLQ-C30 and EORTC QLQ-BR23)

Outcome on symptoms were recorded using EORTC QLQ-C30 and the EORTC QLQ-BR23. In each case, the time to first deterioration by ≥ 10 points (scale range from 0 to 100) was considered.

Fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation (EORTC QLQ-C30), side effects of the systemic therapy, symptoms in the arm region and “upset by hair loss (EORTC QLQ-BR23)

No statistically significant difference between the treatment groups was shown for each of the following scales: fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation (EORTC QLQ-C30), side effects of systemic treatment, symptoms in the arm region (EORTC QLQ-BR23) and upset by hair loss.

This resulted in no hint of an added benefit of pembrolizumab + chemotherapy in comparison with the ACT; an added benefit is therefore not proven in each case.

Diarrhoea (EORTC QLQ-C30)

A statistically significant difference to the disadvantage of pembrolizumab + chemotherapy in comparison with placebo + chemotherapy was shown for the "diarrhoea” scale. This difference was no more than marginal, however (see Section 2.5.1). This resulted in no hint of an added benefit of pembrolizumab + chemotherapy in comparison with the ACT; an added benefit is therefore not proven.

Symptoms in chest region (EORTC QLQ-BR23)

A statistically significant difference in favour of pembrolizumab + chemotherapy in comparison with placebo + chemotherapy was shown for the scale "symptoms in chest region”. This difference was no more than marginal, however (see Section 2.5.1). This resulted in no hint of an added benefit of pembrolizumab + chemotherapy in comparison with the ACT; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

There were no usable data for the outcome "health status", recorded with the EQ-5D VAS (for reasons, see Section 2.4.1). This resulted in no hint of an added benefit of pembrolizumab + chemotherapy in comparison with the ACT; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30 and EORTC QLQ-BR23

"Health-related quality of life" was recorded using the EORTC QLQ-C30 and the EORTC QLQ-BR23. In each case, the time to first deterioration by ≥ 10 points (scale range from 0 to 100) was considered.

Global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning (EORTC QLQ-C30), body image, sexual activity and future perspective (EORTC QLQ-BR23)

No statistically significant differences between the treatment groups were shown for each of the following scales: global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning (EORTC QLQ-C30), body image, sexual activity and future perspective (EORTC QLQ-BR23). This resulted in no hint of an added benefit of pembrolizumab + chemotherapy in comparison with the ACT; an added benefit is therefore not proven in each case.

Sexual enjoyment (EORTC QLQ-BR23)

No usable data were available for the EORTC QLQ-BR23 scale "sexual enjoyment". Since patients who had not been sexually active at the beginning of the study were censored, the company's approach does not ensure that the burden of patients who became sexually active during the course of treatment was recorded. This resulted in no hint of an added benefit of pembrolizumab + chemotherapy in comparison with the ACT; an added benefit is therefore not proven.

Side effects

SAEs and severe AEs

No statistically significant difference between the treatment groups was shown for the outcomes "SAEs" and "severe AEs". In each case, this resulted in no hint of greater or lesser harm from pembrolizumab + chemotherapy in comparison with the ACT; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

No usable data are available for discontinuation due to AEs (see Section 2.4.1 for reasons). This resulted in no hint of greater or lesser harm from pembrolizumab + chemotherapy in comparison with the ACT; greater or lesser harm is therefore not proven.

Specific AEs

Immune-related SAEs and immune-related severe AEs

There was no statistically significant difference between the treatment groups for the outcomes of immune-related SAEs and immune-related severe AEs. In each case, this resulted in no hint of greater or lesser harm from pembrolizumab + chemotherapy in comparison with the ACT; greater or lesser harm is therefore not proven.

Diarrhoea (AEs), dysgeusia (AEs) and "gastrointestinal disorders (SAEs)

A statistically significant difference to the disadvantage of pembrolizumab + chemotherapy versus placebo + chemotherapy was shown for each of the outcomes "diarrhoea (AEs)", "dysgeusia (AEs)" and "gastrointestinal disorders (SAEs)" In each case, this resulted in a hint of greater harm from pembrolizumab + chemotherapy in comparison with the ACT.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics are relevant for the present benefit assessment:

- age (< 65 years versus ≥ 65 years)
- visceral disease (yes versus no)

The mentioned characteristics were defined a priori. The characteristic of sex was disregarded because the relevant subpopulation did not comprise any men.

However, the company only presented subgroup analyses for both chosen characteristics for the outcome "overall survival". For the other patient-relevant outcomes of the categories "morbidity", "health-related quality of life" and "adverse events", analyses of the subgroup characteristics used for the benefit assessment are only available for "age". 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 [28].

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. For binary data, there must also be at least 10 events in at least 1 subgroup.

Presented are only the results showing an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05). 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 results did not show any effect modifications.

2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

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

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 16).

Determination of the outcome category for symptom outcomes

It cannot be inferred from the dossier whether the following outcomes were serious/severe or non-serious/non-severe. The classification of these outcomes is justified.

There is insufficient information to classify the severity category for the outcomes “diarrhoea” and “chest symptoms”, assessed with the EORTC QLQ-C30 and the EORTC QLQ-BR23, respectively. Therefore, the outcomes were assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Table 16: Extent of added benefit at outcome level: pembrolizumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Outcome category **outcome**	**Pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a]** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability[b]**	**Derivation of extent[c]**
Mortality		
Overall survival	29.7 vs. 16.1 HR: 0.56 [0.37; 0.84] p = 0.005 probability: "hint"	Outcome category: mortality added benefit, extent: "non-quantifiable"
Morbidity		
Symptoms (EORTC QLQ-C30) - symptom scales		
Fatigue	1.4 vs. 2.1 HR: 1.14 [0.75; 1.73] p = 0.552	Lesser benefit/added benefit not proven
Nausea and vomiting	3.5 vs. 5.3 HR: 1.12 [0.68; 1.84] p = 0.658	Lesser benefit/added benefit not proven
Pain	3.9 vs. 3.5 HR: 0.72 [0.46; 1.11] p = 0.136	Lesser benefit/added benefit not proven
Dyspnoea	7.4 vs. 17.7 HR: 1.57 [0.83; 2.98] p = 0.169	Lesser benefit/added benefit not proven
Insomnia	8.3 vs. 18.4 HR: 1.49 [0.81; 2.72] p = 0.199	Lesser benefit/added benefit not proven
Appetite loss	5.2 vs. 3.9 HR: 1.02 [0.63; 1.65] p = 0.935	Lesser benefit/added benefit not proven
Constipation	8.0 vs. 7.7 HR: 1.33 [0.75; 2.36] p = 0.325	Lesser benefit/added benefit not proven
Diarrhoea	4.0 vs. 18.4 HR: 1.98 [1.10; 3.58] HR: 0.51 [0.28; 0.91][d] p = 0.023	Outcome category: non-serious/non-severe symptoms / late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[e]
Symptoms (EORTC QLQ-BR23) - symptom scales		
Side effects of systemic therapy	1.4 vs. 1.4 HR: 1.07 [0.71; 1.61] p = 0.753	Lesser benefit/added benefit not proven

Table 16: Extent of added benefit at outcome level: pembrolizumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Outcome category **outcome**	**Pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a]** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability[b]**	**Derivation of extent[c]**
Symptoms in chest region	NA vs. 7.7 HR: 0.49 [0.27; 0.91] p = 0.023	Outcome category: non-serious/non-severe symptoms / late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[e]
Symptoms in arm region	7.6 vs. 3.9 HR: 0.83 [0.51; 1.33] p = 0.432	Lesser benefit/added benefit not proven
Upset by hair loss	0.8 vs. 0.8 HR: 1.05 [0.69; 1.58] p = 0.826	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	No usable data available[f]	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 global health status and functional scales		
Global health status	5.8 vs. 5.6 HR: 0.99 [0.60; 1.63] p = 0.969	Lesser benefit/added benefit not proven
Physical functioning	6.4 vs. 5.6 HR: 1.12 [0.69; 1.82] p = 0.651	Lesser benefit/added benefit not proven
Role functioning	3.4 vs. 4.9 HR: 1.21 [0.76; 1.92] p = 0.418	Lesser benefit/added benefit not proven
Emotional functioning	9.7 vs. 9.7 HR: 1.20 [0.70; 2.06] p = 0.505	Lesser benefit/added benefit not proven
Cognitive functioning	3.5 vs. 3.9 HR: 1.11 [0.71; 1.74] p = 0.646	Lesser benefit/added benefit not proven
Social functioning	3.5 vs. 3.5 HR: 1.03 [0.65; 1.61] p = 0.906	Lesser benefit/added benefit not proven
EORTC QLQ-BR23		

Table 16: Extent of added benefit at outcome level: pembrolizumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Outcome category **outcome**	**Pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a]** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability[b]**	**Derivation of extent[c]**
Body image	5.6 vs. 3.5 HR: 0.71 [0.44; 1.14] p = 0.160	Lesser benefit/added benefit not proven
Sexual activity	NA vs. 22.7 HR: 0.80 [0.44; 1.44] p = 0.460	Lesser benefit/added benefit not proven
Sexual enjoyment	No usable data available[g]	Lesser benefit/added benefit not proven
Future perspective	11.3 vs. 25.3 HR: 1.07 [0.60; 1.91] p = 0.815	Lesser benefit/added benefit not proven
Side effects		
SAEs	29.5 vs. NA HR: 1.86 [0.81; 4.26] p = 0.144	Greater/lesser harm not proven
Severe AEs	5.7 vs. 6.5 HR: 1.20 [0.74; 1.94] p = 0.459	Greater/lesser harm not proven
Discontinuation due to AEs	No usable data available[f]	Greater/lesser harm not proven
Immune-related SAEs	NA vs. NA HR: NC p = 0.165	Greater/lesser harm not proven
Immune-related severe AEs	NA vs. NA HR: NC p = 0.067	Greater/lesser harm not proven
Diarrhoea (AEs)	13.3 vs. 21.2 HR: 2.81 [1.26; 6.28] HR: 0.36 [0.16; 0.79][d] p = 0.012 probability: "hint"	Outcome category: non-serious/non-severe side effects greater harm, extent: "non-quantifiable"
Dysgeusia (AEs)	NA vs. NA HR: NC p = 0.017 probability: "hint"	Outcome category: non-serious/non-severe side effects greater harm, extent: "non-quantifiable"
Gastrointestinal disorders (SAEs)	NA vs. NA HR: NC p = 0.044 probability: "hint"	Outcome category: serious/severe side effects greater harm, extent: "non-quantifiable"

Table 16: Extent of added benefit at outcome level: pembrolizumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Outcome category **outcome**	**Pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a]** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability[b]**	**Derivation of extent[c]**
a. Paclitaxel or nab-paclitaxel. b. Probability provided if a statistically significant and relevant effect is present. c. 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). d. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit. e. The extent of the effect in this non-serious/non-severe outcome was no more than marginal. f. See Section 2.4.1 of the present benefit assessment for reasons. g. At baseline, information on the sexual enjoyment was not available for about 55% and 51% of the patients. These patients were censored by the company at month 0. The approach of the company does not ensure that the burden of patients who only become sexually active in the course of the treatment is recorded. AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module; QLQ-C30: Quality of Life Questionnaire Core-30; NC: not calculable: SAE: serious adverse event; VAS: visual analogue scale		

2.5.2 Overall conclusion on added benefit

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

Table 17: Positive and negative effects from the assessment of pembrolizumab + chemotherapy[a] in comparison with the ACT

Positive effects	**Negative effects**
Mortality ▪ overall survival: hint of added benefit – extent: “non-quantifiable”	-
-	Serious/severe side effects ▪ gastrointestinal disorders (SAEs): hint of greater harm – extent: "non-quantifiable"
▪ -	Non-serious/non-severe side effects ▪ diarrhoea (AEs): hint of greater harm – extent: “non-quantifiable” ▪ dysgeusia (AEs): hint of greater harm – extent: “non-quantifiable”
There were no usable data for the outcome "health status".	
a. Paclitaxel or nab-paclitaxel. AEs: adverse events; SAE: serious adverse event	

Overall, there are positive and negative effects, each with the probability "hint" and the extent "non-quantifiable".

The advantage for pembrolizumab + chemotherapy over the ACT is shown for the outcome "overall survival". In contrast, there are negative effects in the category of serious/severe side effects for the outcome "gastrointestinal disorders" and in the category of non-serious/non-severe side effects for the outcomes "diarrhoea" and "dysgeusia". However, these negative effects do not completely call into question the positive effect.

Overall, this results in a hint of non-quantifiable added benefit of pembrolizumab + chemotherapy versus the ACT for adult patients with locally recurrent unresectable or metastatic TNBC whose tumours express PD-L1 (CPS ≥ 10) and who have not received prior chemotherapy for metastatic disease.

The result of the assessment of the added benefit of pembrolizumab + chemotherapy in comparison with the ACT is summarized in Table 18.

Table 18: Pembrolizumab + chemotherapy – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with locally recurrent unresectable or metastatic TNBC whose tumours express PD-L1 (CPS ≥ 10) and who have not received prior chemotherapy for metastatic disease[b]	Anthracycline- and/or **taxane-containing systemic therapy** under consideration of the approval of the drugs[c]	Hint of a non-quantifiable added benefit[d]

a. Presented is the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. For the present therapeutic indication, it is assumed that on the one hand, radiotherapy is not considered a possible curative option and, on the other hand, measures aimed at achieving operability, e.g. neoadjuvant therapy, if such is indicated, have been exhausted in patients with locally recurrent unresectable disease that is isolated, i.e. without evidence of distant metastases.
c. The company chose paclitaxel and nab-paclitaxel.
d. The KEYNOTE 355 study only included patients with an ECOG PS of 0 or 1. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2.

ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1

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

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

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Please see full dossier assessment for full reference list.

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

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