IQWiG Reports – Commission No. 19-81

Atezolizumab (breast cancer) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment Atezolizumab (Mammakarzinom) – Nutzenbewertung gemäß § 35a SGB V (Version 1.0; Status: 20 December 2019). 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.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Atezolizumab (breast cancer) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
20 September 2019

Internal Commission No.
A19-81

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Keywords: Atezolizumab, Triple Negative Breast Neoplasms, Benefit Assessment, NCT02425891

Table of contents

Page

List of tables ..... **iv**
List of abbreviations ..... **v**
2 Benefit assessment **1**
2.1 Executive summary of the benefit assessment **1**
2.2 Research question **4**
2.3 Information retrieval and study pool **3**
2.4 Results on added benefit **4**
2.5 Probability and extent of added benefit **4**
2.6 List of included studies **5**
References for English extract **5**

List of tables[2]

Page

Table 2: Research question of the benefit assessment of atezolizumab 1
Table 3: Atezolizumab – probability and extent of added benefit 3
Table 4: Research question of the benefit assessment of atezolizumab 4
Table 5: Approval and guideline recommendations of nab-paclitaxel (monotherapy) and paclitaxel (monotherapy) in the present therapeutic indication 6
Table 6: Overview on the studies on the comparison of nab-paclitaxel versus other taxanes included by the company (multipage table) 8
Table 7: Atezolizumab – probability and extent of added benefit 4

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
BSA	body surface area
CI	confidence interval
CI_u	upper limit of confidence interval
EMA	European Medicines Agency
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NVL	Nationale VersorgungsLeitlinie (National Care Guideline)
ORR	objective response rate
PFS	progression-free survival
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPCs	Summary of Product Characteristics
TNBC	metastatic triple-negative breast cancer

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 atezolizumab. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 20 September 2019.

Research question

The aim of the present report is the assessment of the added benefit of atezolizumab in combination with nab-paclitaxel (atezolizumab + nab-paclitaxel) in comparison with the appropriate comparator therapy (ACT) for the treatment of unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) in adult patients whose tumours have Programmed Cell Death-Ligand 1 (PD-L1) expression ≥ 1% and who have not received prior chemotherapy for the treatment of their metastatic disease.

The research question for the benefit assessment presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of atezolizumab

Subindication	**ACT**[a]
Atezolizumab in combination with nab-paclitaxel in adults with unresectable locally advanced or metastatic TNBC whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for the treatment of their metastatic disease	Anthracycline- and/or **taxane-containing systemic therapy** under consideration of the approval of the drugs[b]
a. Presentation of 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. The company chose the taxane "nab-paclitaxel". ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1; TNBC: triple-negative breast cancer	

The G-BA specified an anthracycline-containing and/or taxane-containing systemic therapy under consideration of the approval of the drugs. The company cited the ACT specified by the G-BA, but then it used the taxane "nab-paclitaxel" as comparator therapy. 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 nab-paclitaxel was sufficiently comparable to a paclitaxel approved in the present therapeutic indication by means of suitable

studies. For this purpose, the company presented data from different studies, which, however, are insufficient to demonstrate the comparability, particularly for the following reasons:

- In the majority of the studies, nab-paclitaxel was administered in other dosages or other dosing regimens than in the study presented by the company for the benefit assessment of atezolizumab;
- the remaining study with a similar nab-paclitaxel dosage provided no data on adverse events;
- moreover, it was a retrospective cohort study with the corresponding methodological limitations;
- also with regard to the efficacy outcomes, it was impossible to assess with sufficient certainty whether nab-paclitaxel is equal or non-inferior to other taxanes;
- depending on the respective study, the use of the applied taxanes (paclitaxel, docetaxel) deviated from the approval.

Due to the insufficiently demonstrated comparability of the benefit of nab-paclitaxel in comparison with a taxane approved for the therapeutic indication, nab-paclitaxel cannot be used as a comparator to prove an added benefit of atezolizumab + nab-paclitaxel.

The present assessment was conducted in comparison with the G-BA's ACT.

Moreover, the assessment was made by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

In its assessment, the company included the IMpassion130 study on the comparison of atezolizumab + nab-paclitaxel with nab-paclitaxel, which it considered relevant for his benefit assessment.

As explained above, the comparator nab-paclitaxel chosen by the company is not suitable to prove an added benefit of atezolizumab + nab-paclitaxel. Thus, the IMpassion130 study and the related data presented by the company are unsuitable for deriving conclusions on the added benefit of atezolizumab + nab-paclitaxel in comparison with the ACT specified by the G-BA.

The company presented no suitable data for the assessment of the added benefit of atezolizumab + nab-paclitaxel in comparison with the ACT in adult patients with TNBC who had not received prior chemotherapy for the treatment of their metastatic disease. This resulted in no hint of an added benefit of atezolizumab + nab-paclitaxel in comparison with the ACT; an added benefit is therefore not proven.

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

Table 3 presents a summary of the probability and extent of the added benefit of atezolizumab.

Table 3: Atezolizumab – probability and extent of added benefit

Subindication	ACT[a]	Probability and extent of added benefit
Atezolizumab in combination with nab-paclitaxel in adults with unresectable locally advanced or metastatic TNBC whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for the treatment of their metastatic disease.	Anthracycline- and/or **taxane-containing systemic therapy** under consideration of the approval of the drugs[b]	Added benefit not proven

a. Presentation of 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. The company chose the taxane "nab-paclitaxel".

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1; TNBC: triple-negative breast cancer

The G-BA decides on the added benefit.

[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].

2.2 Research question

The aim of the present report is the assessment of the added benefit of atezolizumab in combination with nab-paclitaxel (atezolizumab + nab-paclitaxel) in comparison with the ACT for the treatment of unresectable locally advanced or metastatic TNBC in adult patients whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for the treatment of their metastatic disease.

The research question for the benefit assessment presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of atezolizumab

Subindication	**ACT**[a]
Atezolizumab in combination with nab-paclitaxel in adults with unresectable locally advanced or metastatic TNBC whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for the treatment of their metastatic disease.	Anthracycline- and/or **taxane-containing systemic therapy** under consideration of the approval of the drugs[b]
a. Presentation of 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. The company chose the taxane "nab-paclitaxel". ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1; TNBC: triple-negative breast cancer	

The G-BA specified an anthracycline-containing and/or taxane-containing systemic therapy under consideration of the approval of the drugs. The company cited the ACT specified by the G-BA, but then it used the taxane "nab-paclitaxel" as comparator therapy. However, nab-paclitaxel is not approved for first-line therapy of 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 that nab-paclitaxel was sufficiently comparable to a paclitaxel approved in the present therapeutic indication by means of suitable studies [4]. For this purpose, the company presented data from different studies, which, however, are insufficient to demonstrate the comparability, particularly for the following reasons:

- In the majority of the studies, nab-paclitaxel was administered in other dosages or other dosing regimens than in the study presented by the company for the benefit assessment of atezolizumab;
- the remaining study with a similar nab-paclitaxel dosage provided no data on adverse events;
- moreover, it was a retrospective cohort study with the corresponding methodological limitations;

- also with regard to the efficacy outcomes, it was impossible to assess with sufficient certainty whether nab-paclitaxel is equal or non-inferior to other taxanes;
- depending on the respective study, the use of the applied taxanes (paclitaxel, docetaxel) deviated from the approval.

Hereinafter, the limitations of the presented studies will be addressed in detail.

The present assessment was conducted in comparison with the G-BA's ACT.

Moreover, the assessment was made by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Suitability of nab-paclitaxel as comparator for the present benefit assessment

As already described, the company specified nab-paclitaxel as comparator therapy. For the benefit assessment, it presented its study Impassion130 [5-14] that compares atezolizumab + nab-paclitaxel with nab-paclitaxel in the present therapeutic indication. In the IMpassion130 study, nab-paclitaxel was administered in doses of 100 mg/m² body surface area (BSA) on days 1, 8 and 15 of a 28-day cycle. As stated before, nab-paclitaxel was not approved for the present therapeutic indication of first-line therapy [3]. During the approval process of nab-paclitaxel at the European Medicines Agency (EMA), the company itself withdrew the application for approval for the first-line therapy. It did so before the background of a numerically shorter overall survival for patients under nab-paclitaxel in comparison with patients under paclitaxel [15].

The following Table 5 provides an overview on the approval and the application in accordance with the guidelines in the monotherapy of paclitaxel and nab-paclitaxel.

Table 5: Approval and guideline recommendations of nab-paclitaxel (monotherapy) and paclitaxel (monotherapy) in the present therapeutic indication

Drug	Approval[a]	Dosage	
		According to the Summary of Product Characteristics (SPC)	**According to guideline[b] (as far as indicated)**
Nab-paclitaxel (monotherapy)	Not approved [3]	▪ First-line treatment: not approved ▪ Second-line treatment - for patients in whom first-line therapy of the metastatic disease has failed and for whom standard anthracycline-containing therapy is not indicated: ▫ 260 mg/m² BSA, every 3 weeks [3]	▪ National S3 guideline [16]: ▫ 125 mg/m² BSA on days 1, 8 and 15 of a 28-day cycle ▪ NCCN guideline [17]: ▫ 100 or 125 mg/m² BSA weekly, on days 1, 8 and 15 of a 28-day cycle or ▫ 260 mg/m² BSA, every 21 days
Paclitaxel (monotherapy)	As monotherapy, paclitaxel is indicated for the treatment of metastatic breast cancer in patients who had not responded to anthracycline-containg standard therapy or for whom this therapy was not an option [18].	▪ First-line therapy: no dedicated information on the dosage for the monotherapy ▪ Second-line treatment: ▫ 175 mg/m² BSA, every 3 weeks [18]	▪ NCCN guideline [17]: ▫ 175 mg/m² on day 1 of a 21-day cycle ▫ 80 mg/m² BSA per week

a. With regard to the therapeutic indication of the treatment of unresectable, locally advanced or metastatic breast cancer in first-line therapy.

b. The following guidelines were searched for information on the dosage: S3 guideline published by the AWMF, DKG and DKH, version 4.2 2019 [16], guideline of the AGO, version 2019.1 [19], guideline of the DGHO/onkopedia 2018 [20], directive of the ESMO 2018 [21], guideline of the NCCN, version 1.2019 [17]. Concrete information on the dosage is found in the S3 and NCCN guidelines, without providing information on the treatment line. Moreover, AGO, DGHO and ESMO also recommend application of taxanes as monotherapy in the therapeutic indication.

AGO: German Gynaecological Oncology Working Group; AWMF: Association of the Scientific Medical Societies; DKG: German Cancer Society; DKH: German Cancer Aid; DKG: German Cancer Society; ESMO: European Society of Medical Oncology; DGHO: German Society of Haematology and Oncology; BSA: body surface area; NCCN: National Comprehensive Cancer Network

As described in Table 5, the SPCs and the guidelines provide heterogeneous data on the dosage of nab-paclitaxel and paclitaxel in the therapeutic indication of locally advanced or metastatic breast cancer, since the guidelines additionally recommend a weekly dosing regimen.

In order to use nab-paclitaxel as a comparator for deriving an added benefit, the company submitted clinical studies in its dossier, on the basis of which it concluded that the efficacy of nab-paclitaxel was at least comparable to paclitaxel and docetaxel and that nab-paclitaxel can therefore be used as a comparator for the present benefit assessment.

Data requirements for the comparison of nab-paclitaxel with other taxanes

Clinical studies considering patients with unresectable locally advanced or metastatic breast cancer in first-line treatment are suitable to demonstrate a benefit of nab-paclitaxel that is

comparable with other taxanes. Data on patients with TNBC would also be desirable in the narrower sense of the present therapeutic indication. The studies should also to compare treatment with nab-paclitaxel with a taxane approved for the present therapeutic indication. The studies submitted should also investigate both efficacy and adverse events. Furthermore, the dosage scheme of nab-paclitaxel should be comparable with that of the IMpassion130 study submitted by the company for the benefit assessment of atezolizumab + nab-paclitaxel. This is relevant because the 2009 and 2012 Gradishar studies [22,23] submitted by the company for the comparison of docetaxel with different doses of nab-paclitaxel showed that the dosage of nab-paclitaxel has effects on overall survival and on adverse events. In addition to the requirements on the study design described above, it should be possible to assess with sufficient certainty from the results whether there is equality or non-inferiority of nab-paclitaxel to other taxanes (e.g. by using non-inferiority limits or equivalence ranges recognized in the therapeutic indication).

Data presented by the company for the comparability of nab-paclitaxel with other taxanes

The company conducted an information retrieval for studies comparing nab-paclitaxel with paclitaxel and docetaxel in adults with advanced breast cancer in first-line therapy (for further information on information retrieval see Section 2.7.1 of the full dossier assessment). Within the framework of its information retrieval, the company identified 6 studies of direct comparison for the comparison of nab-paclitaxel with paclitaxel and one study of direct comparison for the comparison of nab-paclitaxel with docetaxel. The company also identified one meta-analysis whose results it used for a descriptive comparison of individual arms with its IMpassion130 study presented for the benefit assessment of atezolizumab + nab-paclitaxel.

Table 6 presents the studies identified by the company for the comparison of nab-paclitaxel with other taxanes with the respective limitations.

Table 6: Overview on the studies on the comparison of nab-paclitaxel versus other taxanes included by the company (multipage table)

Study; source	Study design	Population	Interventions (number of patients), dosage	Limitations
nab-paclitaxel vs. paclitaxel in the present therapeutic indication[a]				
CA0120-0 (approval study of nab-paclitaxel); Gradishar 2005 [24], EPAR 2015 [15]	RCT, open-label, parallel	▪ Adult patients (≥ 18 years) with metastatic breast cancer with and without pretreatment for the metastatic stage, who are candidates for monotherapy with paclitaxel ▪ ECOG PS of 0 or 1	▪ Nab-Paclitaxel (N = 233) ▪ Paclitaxel (N = 227) Interesting subpopulation thereof, patients in first-line treatment: ▪ Nab-paclitaxel (n = 97) ▪ Paclitaxel (n = 89) Dosage, treatment every 3 weeks: ▪ Nab-paclitaxel: 260 mg/m² BSA ▪ Paclitaxel: 175 mg/m² BSA	▪ Dosage regiment of nab-paclitaxel deviates from the one in the IMpassion130 study ▪ Missing data on adverse events for the first-line therapy ▪ On the basis of this study, the company withdrew the application for approval for the first-line treatment with nab-paclitaxel. ▪ A non-inferiority boundary or equivalence range for efficacy outcomes was not provided. ▪ No information on whether monotherapy with paclitaxel was indicated for the study population ▪ No information or analyses on the patient population with TNBC
CALGB 40502 (Study Alliance); Rugo 2015 [25]	RCT, open-label, parallel	▪ Adult patients (≥ 18 years) with stage IIIC or IV breast cancer ▪ No prior chemotherapy for the metastatic stage ▪ No treatment with bevacizumab ▪ ECOG PS of 0 or 1	▪ Nab-paclitaxel + bevacizumab (N = 271) ▪ Paclitaxel + bevacizumab (N = 283) ▪ Ixabepilon + bevacizumab (N = 245) Interesting subpopulation thereof, patients with TNBC: ▪ Nab-paclitaxel + bevacizumab (n = 65) ▪ Paclitaxel + bevacizumab (n = 73) Dosage, treatment in 28-day cycles: ▪ Nab-paclitaxel: 150 mg/m² BSA on days 1, 8 and 15 ▪ Paclitaxel: 90 mg/m² BSA on days 1, 8 and 15 ▪ Bevacizumab: 10 mg / kg on days 1 and 15	▪ The nab-paclitaxel dosage deviated notably from the one administered in the IMpassion130 study; moreover, nab-paclitaxel was administered in combination with bevacizumab. ▪ Subgroup analyses on the TNBC population are only available for the outcome “PFS” ▪ A non-inferiority boundary or equivalence range for efficacy outcomes was not provided.

Table 6: Overview on the studies on the comparison of nab-paclitaxel versus other taxanes included by the company (multipage table)

Study; source	Study design	Population	Interventions (number of patients), dosage	Limitations
US Flatiron Health Database (based on electronic patient records from 265 oncological clinics in the USA); Luhn 2019 [26]	Retrospective cohort study	▪ Adult patients (≥ 18 years) with confirmed TNBC ▪ Date of diagnosis between 1 January 2011 and 31 June 2016 ▪ Confirmed treatment with nab-paclitaxel or paclitaxel in first-line treatment within 90 days after diagnosis	▪ Nab-Paclitaxel (N = 105) ▪ Paclitaxel (N = 95) Dosage (n [%]): ▪ Nab-paclitaxel ▫ 100 mg/m² BSA; weekly: 81 (77.9) ▫ 125–150 mg/m² BSA, weekly: 8 (7.7) ▫ 260 mg/m² BSA, every 3 weeks 8 (7.7) ▪ Paclitaxel ▫ 80 mg/m² BSA; weekly: 69 (75.8) ▫ 90 mg/m² BSA; weekly: 5 (5.5) ▫ 175 mg/m² BSA, every 3 weeks 8 (8.8)	▪ Study design: retrospective cohort study ▪ No analyses on adverse events ▪ A non-inferiority boundary or equivalence range for efficacy outcomes was not provided. ▪ Deviating from the IMpassion130 study, nab-paclitaxel was administered as part of the weekly dosage without treatment pause. ▪ The approved dosage of paclitaxel in the present therapeutic indication is unclear (see Table 5) ▪ No information on whether monotherapy with paclitaxel was indicated for the study population
Further evidence presented by the company				
Gianni 2018 [27], Untch 2016 [28], Schneeweiß 2018 [29]	▪ The studies investigated nab-paclitaxel and paclitaxel within the framework of a neoadjuvant treatment of patients with non-metastatic breast cancer. Thus, the investigated patient population did not concur with the therapeutic indication[a].			
Gradishar 2009 [22], Gradishar 2012 [23]	RCT, open-label, parallel	▪ Adult patients (≥ 18 years) with pathologically confirmed stage IV breast cancer ▪ No prior chemotherapy for the metastatic stage ▪ ECOG PS of 0-2	▪ Nab-paclitaxel A (N = 76) ▪ Nab-paclitaxel B (N = 76) ▪ Nab-paclitaxel C (N = 74) ▪ Docetaxel (N = 74) Dosage: ▪ Nab-paclitaxel A: 300 mg/m² BSA, every 3 weeks ▪ Nab-paclitaxel B: 100 mg/m² BSA on days 1, 8 and 15 of a 28-day cycle ▪ Nab-paclitaxel C: 150 mg/m² BSA on days 1, 8 and 15 of a 28-day cycle ▪ Docetaxel: 100 mg/m² BSA, every 3 weeks	▪ According to the SPC, docetaxel is not approved for monotherapy in the present therapeutic indication [30]; thus, 2 unapproved therapies are compared.

Table 6: Overview on the studies on the comparison of nab-paclitaxel versus other taxanes included by the company (multipage table)

Study; source	Study design	Population	Interventions (number of patients), dosage	Limitations
Miles 2013 [31]	▪ The study is based on a meta-analysis of 3 RCTs, each of which investigates patients with HER2-negative metastatic breast cancer in first-line treatment: ▫ E2100: RCT (double-blind), comparison of paclitaxel + bevacizumab versus paclitaxel ▫ AVADO: RCT (open-label), comparison of docetaxel + bevacizumab versus docetaxel ▫ RIBBON-1: RCT (open-label), comparison of bevacizumab + chemotherapy (capecitabine, taxane- or anthracycline-containing chemotherapy) versus chemotherapy (capecitabine, taxane- or anthracycline-containing chemotherapy) ▪ In Module 3 A, the company presents a descriptive comparison of individual arms of the comparator arm of Miles 2013 summarized in a meta-analysis [31] and the comparator arm with nab-paclitaxel of the IMpassion130 study. ▪ The meta-analysis is based on a summary of different therapies, some of which are unapproved (e.g. docetaxel) or do not concur with the ACT specified by the G-BA (e.g. capecitabine).			

a. With regard to the therapeutic indication of the treatment of unresectable, locally advanced or metastatic breast cancer in first-line therapy.

BSA: body surface area; CI: confidence interval; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EPAR: European Public Assessment Report; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; n: subpopulation; N: number of randomized (included) patients; ORR: objective response rate; PFS: progression-free survival; RCT: randomized controlled trial; TNBC: triple-negative breast cancer; US: United States

Lack of suitability of the studies presented by the company for the comparability of nab-paclitaxel with paclitaxel

The company presented 6 studies for the comparison of nab-paclitaxel with paclitaxel (see Table 6). Only in 3 of these studies (Luhn 2019 [26], Gradishar 2005 [24], Rugo 2015 [25]), the comparison was made in the therapeutic indication of locally advanced or metastatic breast cancer in first-line therapy. These are discussed below:

Luhn 2019 (Flatiron Health Database)

Of the 3 studies in the therapeutic indication of locally advanced or metastatic breast cancer, only 1 study remained in which the dosage of nab-paclitaxel was similar to the IMpassion130 study (100 mg/m² KOF on days 1, 8 and 15 of a 28-day cycle) presented by the company for its benefit assessment. This study is a retrospective cohort study by Luhn 2019 [26], which is based on patient data from the US Flatiron Health Database. The data collected in the database come from electronic patient records from oncological clinics in the USA. In the study Luhn 2019 [26], 200 patients with metastatic TNBC were identified who received either nab-paclitaxel (N = 105) or paclitaxel (N = 95) as monotherapy in first-line treatment of the metastatic disease. Overall, however, the retrospective cohort study Luhn 2019 [26] is unsuitable to show sufficient comparability of nab-paclitaxel with paclitaxel. The reasons are as follows:

- Limitations of the study design (retrospective cohort study): The informative value of the study is very limited due to the retrospective study design and the lack of randomization.
- Missing data on adverse events: Irrespective of the problems caused by the retrospective study design, no data on adverse events were recorded in the study. In order to investigate the comparability of the benefit of nab-paclitaxel versus paclitaxel, data on adverse events are required in addition to those on efficacy. Analyses on adverse events were not planned within the framework of the study and were not reported.

For these two reasons alone, the Luhn 2019 study is unsuitable for providing sufficient data on the comparability of paclitaxel and nab-paclitaxel. There are further limitations:

- Limited conclusion on the comparable efficacy: Only results on overall survival and time to next treatment were reported. In a superiority test using adjusted Cox regression, the effect estimation was not statistically significant (hazard ratio [HR] [95% CI]; p-value: overall survival 0.98 [0.67; 1.44]; p = 0.82 and time to next therapy 0.89 [0.62; 1.29]; p = 0.44). Even if the company or the authors of the study publication do not state a non-inferiority boundary or equivalence range for this therapeutic indication, non-inferiority of nab-paclitaxel in comparison to paclitaxel cannot be assumed at a CI_u of 1.44. Overall, based on the available data, it cannot be assessed with sufficient certainty whether nab-paclitaxel is equal or non-inferior to paclitaxel.
- Differences in nab-paclitaxel administration: The majority of patients (n = 81 [77.9%]) received 100 mg/m² BSA nab-paclitaxel per week. In the IMpassion130 study presented by the company for its benefit assessment, nab-paclitaxel was also administered in weekly doses of 100 mg/m² BSA, but with a break after 3 weeks in a 28-day cycle.

- Administration of paclitaxel in accordance with the approval: There is no information on whether the included patients had not been candidates for anthracycline-containing standard therapy and thus monotherapy with paclitaxel had actually been indicated in accordance with the approval (see Table 5).
- Paclitaxel dosage: The Summary of Product Characteristics (SPCs) on paclitaxel provided no specific information on the dosage of paclitaxel as monotherapy in first-line treatment. According to the SPCs, paclitaxel is approved as combination therapy in a dosage of 175 or 220 mg/m² BSA for first-line treatment, or in a dosage of 175 mg/m² BSA for second-line treatment, in each case every 3 weeks [18]. In the study, paclitaxel was mostly administered at weekly doses of 80 or 90 mg/m² BSA. This deviates from the paclitaxel dosages described in the SPC. However, the guidelines also recommend weekly administration of 80 mg/m² BSA in addition to 3-week administration of 175 mg/m² BSA (see Table 5). It therefore remains unclear whether the dosage used in the study was adequate.

The other 2 studies presented by the company for the comparison of nab-paclitaxel with paclitaxel in the therapeutic indication of first-line treatment are also unsuitable to show sufficient comparability of nab-paclitaxel with paclitaxel:

Study CA0120-0 (Gradishar 2005)

In the study of Gradishar 2005 [24] (the approval study on nab-paclitaxel), nab-paclitaxel was administered in doses of 260 mg/m² BSA every 3 weeks. The applied dosage regimen of nab-paclitaxel thus deviates from the one in the Impassion130 study.

Moreover, only data on the efficacy are available for the relevant subpopulation of female patients in first-line treatment. Results on adverse events are only available for the total population (patients with and without pretreatment of their metastatic breast cancer), which, however, point to differences with regard to the adverse events of nab-paclitaxel and paclitaxel. A comparison of the adverse events (proportion of patients with event) showed differences both to the disadvantage of nab-paclitaxel versus paclitaxel (e.g. sensory neuropathy, nausea, vomiting and diarrhoea) and to the disadvantage of paclitaxel (neutropenias, skin reddening).

Analyses, for instance, on progression-free survival (PFS), on the objective response rate (ORR) and on overall survival were reported within the framework of the study for the relevant subpopulation of patients undergoing first-line treatment. A statistically significant difference in favour of nab-paclitaxel versus paclitaxel was shown for the outcome "ORR" (HR [95%- CI]; p-value: 1.57 [1.04; 2.37]; p = 0.029). No statistically significant effect (HR; p-value: 0.788; p = 0.173) was shown for the outcome "PFS" and for the outcome "overall survival" (HR; p-value: 0.90; p = 0.322). However, before the background of the numerically shorter overall survival of patients under nab-paclitaxel compared to patients under paclitaxel, the application for approval of first-line therapy was withdrawn within the approval process by the company [15].

Overall, the analyses on the cited outcomes were based on superiority tests. A non-inferiority boundary or equivalence range were not indicated by the company or by the authors of the study

publication. Moreover, data on the CI of the effect estimation are missing for several outcomes. Based on the available data, it can thus not be assessed with sufficient certainty whether nab-paclitaxel is equal or non-inferior to paclitaxel. Further, the study provides no information on whether the included patients had been candidates for anthracycline-containing standard therapy and whether monotherapy with paclitaxel had thus actually been indicated in accordance with the approval (see Table 5, [18]).

Study Rugo 2015

Among other things, the study of Rugo 2015 [25] compared nab-paclitaxel in combination with bevacizumab to paclitaxel in combination with bevacizumab. Nab-paclitaxel was administered in doses of 150 mg/m² BSA on days 1, 8 and 15 of a 28-day cycle. The dosage of nab-paclitaxel thus clearly deviates from the one in the IMpassion130 study. Statistically significant differences in the efficacy and harm of nab-paclitaxel at a dosage of 150 mg/m² BSA compared with a dosage of 100 mg/m² BSA (corresponding to the dose used in the IMpassion130 study) have already been reported [22,23]. In addition, monotherapy with nab-paclitaxel was used in the IMpassion130 study, while in the Rugo 2015 study paclitaxel and nab-paclitaxel were each administered in combination with bevacizumab.

Further studies

The 3 other studies presented by the company for the comparison of nab-paclitaxel with paclitaxel, (Gianni 2018 [27], Untch 2016 [28] and Schneeweiß 2018 [29]) investigated patients within the framework of a neoadjuvant treatment of the non-metastatic breast cancer. Therefore, these studies cannot be used to demonstrate a comparability of nab-paclitaxel versus paclitaxel in the therapeutic indication of locally advanced or metastatic breast cancer in first-line treatment.

For the comparison of nab-paclitaxel versus paclitaxel, the company presented 1 study (Gradishar 2009 and 2012 [22,23]), in which patients had received docetaxel as monotherapy. However, docetaxel monotherapy is not approved for patients in the therapeutic indication of first-line treatment [30]. Therefore, the study cannot be used to demonstrate a comparability of nab-paclitaxel versus a taxane approved in the therapeutic indication of first-line treatment.

Moreover, the company presented a descriptive comparison of individual arms from the meta-analysis of Miles 2013 [31] and the comparator arm of its IMpassion130 study. The study of Miles 2013 [31] summarizes results of randomized controlled trials (RCTs). The meta-analysis is based on a summary of different therapies, some of which are unapproved (e.g. docetaxel) or do not concur with the ACT specified by the G-BA (e.g. capecitabine). Therefore, the study of Miles 2013 [31] cannot be used to demonstrate a comparability of nab-paclitaxel in comparison with a taxane approved in the therapeutic indication.

Conclusion

Overall, the data presented by the company are insufficient to demonstrate that the benefit of nab-paclitaxel is sufficiently comparable with the taxane approved in the therapeutic indication of unresectable locally advanced or metastatic breast cancer in first-line treatment. Moreover,

within the framework of its search for studies on the adjusted indirect comparison on atezolizumab + nab-paclitaxel, the company itself identified no suitable study in Module 4 A for the comparison of anthracycline-containing and/or taxane-containing therapy in an approved dosage and suited for application with the common comparator "nab-paclitaxel". Due to the insufficiently demonstrated comparability of the benefit of nab-paclitaxel in comparison with a taxane approved for the therapeutic indication, nab-paclitaxel cannot be used as a comparator to prove an added benefit of atezolizumab + nab-paclitaxel.

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 atezolizumab (status: 16 July 2019)
- bibliographical literature search on atezolizumab (last search on 3 July 2019)
- search in trial registries for studies on atezolizumab (last search on 16 July 2019)
- bibliographical literature search on the ACT (last search on 4 July 2019)
- search in trial registries for studies on the ACT (last search on 17 July 2019)

To check the completeness of the study pool:

- search in trial registries for studies on atezolizumab (last search on 7 October 2019)

No study of direct comparison on atezolizumab + nab-paclitaxel in comparison with the ACT specified by the G-BA was identified from the check. This deviates from the company's assessment, which identified the IMpassion130 study.

The company also searched for studies for an adjusted indirect comparison of atezolizumab + nab-paclitaxel versus the ACT via the common comparator nab-paclitaxel, but identified no relevant studies for the comparator therapy.

Study pool of the company

For the direct comparison, the company identified the IMpassion130 study on the comparison of atezolizumab + nab-paclitaxel versus nab-paclitaxel in adult patients with unresectable locally advanced or metastatic TNBC who have not received prior chemotherapy or targeted systemic therapy for this stage. The company assessed this study to be relevant for its benefit assessment. Table 11 and Table 12 in Appendix A of the full dossier assessment describe the design of the IMpassion130 study.

While administration of atezolizumab + nab-paclitaxel is in compliance with the recommendations of the SPCs [32], nab-paclitaxel is not approved as monotherapy in the present therapeutic indication (see Table 5, [3]). In addition, the dosage used in the study is

neither the dosage recommended in the National Care Guideline (Nationale VersorgungsLeitlinie [NVL]) [16] nor the approved dosage for the treatment of patients in whom first-line treatment of the metastatic disease has failed and for whom standard anthracycline-containing therapy is not indicated (see Table 5, [3]).

As explained in Section 2.2, the comparator nab-paclitaxel chosen by the company is not suitable to prove an added benefit of atezolizumab + nab-paclitaxel. Thus, the IMpassion130 study and the related data presented by the company are unsuitable for deriving conclusions on the added benefit of atezolizumab + nab-paclitaxel in comparison with the ACT specified by the G-BA.

2.4 Results on added benefit

The company presented no suitable data for the assessment of the added benefit of atezolizumab + nab-paclitaxel in comparison with the ACT in adult patients with TNBC who had not received prior chemotherapy for the treatment of their metastatic disease. This resulted in no hint of an added benefit of atezolizumab + nab-paclitaxel in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

As the company presented no suitable data for the assessment of the added benefit of atezolizumab + nab-paclitaxel versus the ACT in adult patients with TNBC who have not received prior chemotherapy for the treatment of the metastatic disease, an added benefit of atezolizumab + nab-paclitaxel is not proven for the patients.

Table 7: Atezolizumab – probability and extent of added benefit

Subindication	**ACT**[a]	**Probability and extent of added benefit**
Atezolizumab in combination with nab-paclitaxel in adults with unresectable locally advanced or metastatic TNBC whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for the treatment of their metastatic disease.	Anthracycline- and/or **taxane-containing systemic therapy** under consideration of the approval of the drugs[b]	Added benefit not proven
a. Presentation of 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. The company chose the taxane "nab-paclitaxel". ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1; TNBC: triple-negative breast cancer		

The assessment described above deviates from that of the company, which derived an indication of considerable added benefit of atezolizumab + nab-paclitaxel on the basis of the data presented.

The G-BA decides on the added benefit.

2.6 List of included studies

Not applicable as the company did not present any relevant data for the benefit assessment.

References for English extract

Please see full dossier assessment for full reference list.

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

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