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Atezolizumab (breast cancer) –

Addendum to Commission A19-81[1]

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common-Terminology-Criteria-for-Adverse-Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HLT	High Level Term
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
PD-L1	programmed death ligand 1
PFS	progression-free survival
PT	Preferred Term
QLQ-BR23	Quality of Life Questionnaire-Breast Cancer 23
QLQ-C30	Quality of Life Questionnaire – Core 30
RCT	randomized controlled trial
SAE	serious adverse event
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SPC	Summary of Product Characteristics
TNBC	triple-negative breast cancer
VAS	visual analogue scale

1 Background

On 10 February 2020, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A19-81 (Atezolizumab – Benefit assessment according to §35a Social Code Book V) [1].

Aim of the benefit assessment is to assess the added benefit of atezolizumab in combination with nab-paclitaxel (atezolizumab + nab-paclitaxel) compared to the appropriate comparator therapy (ACT) in adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC), whose tumours have a programmed death ligand 1 (PD-L1) expression ≥ 1% and who have not received prior chemotherapy for the treatment of the metastatic disease. For this purpose, the pharmaceutical company (hereinafter referred to as "the company") submitted the IMpassion130 study with its dossier [2]. The dossier assessment concluded that this study was unsuitable to assess the added benefit of atezolizumab [1]. This is due to the fact that nab-paclitaxel used in the comparator arm of the study is not approved for the present therapeutic indication of first-line treatment and is thus not part of the ACT. In its dossier, the company did also not show that the therapeutic benefit of nab-paclitaxel is sufficiently comparable to a taxane approved in the therapeutic indication.

The G-BA commissioned IQWiG with the assessment of the data of the IMpassion130 study presented in the dossier under consideration of the information provided in the commenting procedure [3].

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment of the IMpassion130 study

2.1 IMpassion130 study

Detailed characteristics of the IMpassion130 study are presented in Table 11 and Table 12 of benefit assessment A19-81 [1].

IMpassion130 is a randomized controlled trial (RCT) on the comparison of atezolizumab + nab-paclitaxel versus placebo + nab-paclitaxel in adult patients with unresectable locally advanced or metastatic TNBC, who have not yet received prior chemotherapy or targeted systemic therapy for this stage. A total of 902 patients stratified by previous taxane therapy (yes vs. no), the presence of liver metastases (yes vs. no) and programmed cell death ligand 1 (PD-L1) status (PD-L1 status of tumour-infiltrating immune cells ≥ 1%: yes vs. no) in a ratio of 1:1 were randomly assigned to both study arms. While administration of atezolizumab + nab-paclitaxel is in compliance with the recommendations of the Summary of Product Characteristics (SPC) [4], nab-paclitaxel is not approved as monotherapy in the present therapeutic indication [5]. Moreover, the dosage of nab-paclitaxel used in the study does not correspond to the dosage recommended in the national health care guidelines [6], nor to the approved dosage for the treatment of patients in whom first-line therapy of the metastatic disease has failed and for whom standard anthracycline-containing therapy is not indicated.

For the benefit assessment, the company used the data of a subpopulation of patients whose tumours had PD-L1 expressions ≥ 1% of the tumour-infiltrating immune cells and who thus corresponded to the approval population. The subpopulation comprised 185 patients in the atezolizumab + nab-paclitaxel arm and 184 patients in the placebo + nab-paclitaxel arm.

As described in dossier assessment A19-81, the IMPassion130 study is not suitable for assessing the added benefit of atezolizumab in comparison with the ACT. The G-BA defined an anthracycline- and/or taxane-containing systemic therapy as ACT under consideration of the approval of the drugs [7]. The G-BA also pointed out that nab-paclitaxel applied in the study can only be used as a comparator for the proof of added benefit if the dossier can demonstrate on the basis of suitable studies that the therapeutic benefit of nab-paclitaxel is sufficiently comparable to that of a paclitaxel approved for the present therapeutic indication. For this purpose, the company presented data from several studies with its dossier, which, however, are insufficient to show the comparability [1]. Neither did the company's comments reveal any new aspects that would justify sufficient comparability, nor did they yield any relevant new data [3].

In compliance with the commission, the results of the IMpassion130 study are presented hereinafter.

Planned duration of follow-up observation

Table 1 shows the planned duration of follow-up observation of the patients for the individual outcomes in the IMpassion130 study.

Table 1: Planned duration of follow-up observation – RCT, direct comparison: atezolizumab + nab-paclitaxel versus placebo + nab-paclitaxel

Study **Outcome category** **Outcome**	**Planned follow-up observation**
IMpassion130	
Mortality	
Overall survival	Until death, lost to follow-up or termination of study
Morbidity	
Symptoms (EORTC QLQ-C30 and EORTC QLQ-BR23[a])	Until 1 year after treatment discontinuation
Health status (EQ-5D VAS)	Until 1 year after treatment discontinuation
Health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-BR23[a])	Until 1 year after treatment discontinuation
Side effects	
All outcomes in the category "side effects"	Until 30 days after the last dose of the study medication or until initiation of a new antineoplastic treatment (whichever occurred first)

a. The questionnaire was only filled in by female participants.

EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module; QLQ-C30: Quality of Life Questionnaire Core30; RCT: randomized controlled trial; VAS: visual analogue scale

The observation periods for the outcomes of the outcome categories "morbidity", "health-related quality of life" and "side effects" were systematically shortened. Thus, outcomes of the category "side effects" were recorded only for the period of treatment with the study medication plus 30 days. Although the outcomes on morbidity and health-related quality of life were to be monitored up to a maximum of 12 months after treatment discontinuation, the documents show that less than 40% of patients eligible for recordings of patient-reported outcomes in the follow-up period completed a questionnaire within the recordings after treatment discontinuation.

To be able to draw a reliable conclusion on the entire study period or the time until death of the patients, it would be necessary to record all outcomes - such as overall survival - over the entire period.

Characteristics of the subpopulation analysed by the company

Table 2 shows the characteristics of the subpopulation of patients in the IMpassion130 study analysed by the company whose tumours had PD-L1 expression ≥ 1%.

Table 2: Characteristics of the study population – RCT, direct comparison: atezolizumab + nab-paclitaxel versus placebo + nab-paclitaxel (multipage table)

Study Characteristics Category	**Atezolizumab + nab-paclitaxel**	**Placebo + nab-paclitaxel**
IMpassion130	N[a] = 185	N[a] = 184
Age [years], mean (SD)	54 (13)	54 (12)
Sex [F/M], %	99/1	100/0
Family origin, n (%)		
White	125 (67.6)	129 (70.1)
Asian	38 (20.5)	28 (15.2)
Black/African American	9 (4.9)	14 (7.6)
Native American/Alaskan	8 (4.3)	9 (4.9)
Other	5 (2.7)	4 (2.2)
ECOG PS, n (%)		
0	107 (57.8)	112 (60.9)
1	77 (41.6)	72 (39.1)
2	1 (0.5)	0 (0)
Disease stage, n (%)		
Locally advanced, non-resectable	23 (12.4)	24 (13.1)
Metastatic	162 (87.6)	159 (86.9)
Disease duration: time between first diagnosis and randomization [years], mean (SD)	2.53 (2.9)	2.53 (3.1)
Number of locations of the disease, n (%)		
0-3	149 (80.5)	140 (76.5)
> 3	36 (19.5)	43 (23.5)
Location of metastases, n (%)		
Brain	15 (8.1)	11 (6.0)
Liver	42 (22.7)	41 (22.3)
Lungs	86 (46.5)	98 (53.3)
Bones	54 (29.2)	49 (26.6)
Neoadjuvant/adjuvant chemotherapies, n (%)	125 (67.6)	117 (63.6)
Taxane-based therapy	96 (51.9)	97 (52.7)
Anthracycline-based therapy	109 (58.9)	101 (54.9)
Treatment discontinuation[b], n (%)		
Atezolizumab/placebo	161 (87.0)	183 (99.5)
Nab-paclitaxel	173 (93.5)	177 (96.2)
Study discontinuation[b], n (%)	102 (55.1)	123 (66.8)

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Data cut-off: 2 January 2019.

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

The demographic and clinical characteristics are balanced between the study arms. The mean age of the female patients and 1 male patient was 54 years; most of them had metastatic stage of disease (87%).

A total of 114 (61.6%) patients in the intervention arm and 119 (64.7%) patients in the control arm received subsequent antineoplastic therapy (data cut-off: 2 January 2019). The most common subsequent therapies included antimetabolites (e.g. capecitabine and gemcitabine), platinum-containing combinations (carboplatin and cisplatin), cytotoxic antibiotics (e.g. doxorubicin, epirubicin), eribulin, cyclophosphamide and taxane. Except for taxanes and cyclophosphamide, which were administered much more frequently in the control arm, the follow-up therapies between the two study arms were largely balanced.

Study course and data cut-offs

The company presented analyses on different data cut-offs in its dossier.

- Analysis on morbidity and health-related quality of life: data cut-off: 17 April 2018.
  - The data cut-off corresponds to the prespecified final analysis on the outcome "progression-free survival (PFS)" and the first interim analysis on "overall survival" (scheduled after 600 PFS events, performed after 736 PFS events in the total population).
- Analyses on side effects: data cut-off: 3 September 2018
  - The analysis was performed within the framework of a „safety update" report for the U.S. Food and Drug Administration.
- Analyses on mortality: data cut-off: 2 January 2019
  - The data cut-off corresponds to the prespecified second interim analysis on overall survival (performed after 534 deaths in the total population).

The company presented no analyses on the outcomes "morbidity", "health-related quality of life" and "adverse events" for the last submitted data cut-off of 2 January 2019. Since at the time the analyses on side effects in the total population were submitted (3 September 2018), there were no patients in the comparator arm and only 45 (10.0%) patients in the intervention arm undergoing treatment, the earlier data cut-off of 3 September 2018 could be used for the consideration of adverse events (AEs), because follow-up observation was planned to end 30 days after treatment discontinuation.

In the analysed subpopulation, only 33 (17.8%) patients in the intervention arm and 21 (11.4%) patients in the control arm were still under treatment with atezolizumab or placebo at the time the analyses on "morbidity" and "health-related quality of life" were presented (17 April 2018). Moreover, despite the planned follow-up observation of 12 months, less than 40% of the patients eligible for recordings of patient-reported outcomes in the follow-up observation period completed a questionnaire after treatment discontinuation. Moreover, the median observation

period after treatment discontinuation at this data cut-off showed that the planned follow-up observation period of 12 months had already been completed in the majority of the patients (median [Q1; Q3]: 12.2 months [8.7; 15.8]). Overall, it cannot be assumed that analyses on "morbidity" and "health-related quality of life" at a later data cut-off will deviate significantly from the analyses presented in the addendum.

Treatment switching from the comparator intervention to the experimental intervention was possible after unblinding of the study (at the data cut-off of 17 April 2018). At the last data cut-off of 2 January 2019, no patient of the analysis population presented by the company had switched from the placebo + nab-paclitaxel arm to treatment with atezolizumab + nab-paclitaxel. The final data cut-off for "overall survival" is still pending.

Table 3 shows the mean and median treatment and observation periods of the subpopulation analysed by the company for individual outcomes and the respective data cut-offs, if available.

Table 3: Information on the study course – RCT, direct comparison: atezolizumab + nab-paclitaxel versus placebo + nab-paclitaxel

Study **Duration of the study phase** **Data cut-off** **Outcome category**	**Atezolizumab + nab-paclitaxel**	**Placebo + nab-paclitaxel**
IMpassion130		
Treatment duration [months]	N = 185	N = 181
Data cut-off: 17 April 2018		
Atezolizumab/placebo		
Median [Q1; Q3]	6.1 [3.2; 11.1]	3.7 [1.8; 7.2]
Mean (SD)	7.7 (6.0)	5.6 (5.0)
Nab-paclitaxel		
Median [Q1; Q3]	5.2 [3.3; 8.9]	3.7 [1.8; 6.9]
Mean (SD)	6.7 (5.1)	5.0 (4.3)
Data cut-off: 3 September 2018		
Atezolizumab/placebo		
Median [Q1; Q3]	6.1 [3.3; 11.1]	3.7 [1.8; 7.2]
Mean (SD)	8.4 (7.1)	5.8 (5.5)
Nab-paclitaxel		
Median [Q1; Q3]	5.2 [3.3; 8.9]	3.7 [1.8; 6.9]
Mean (SD)	7.1 (5.9)	5.2 (4.9)
Data cut-off: 2 January 2019	ND	ND
Observation period [months]	N = 185	N = 184
Overall survival[a]	ND	ND
Morbidity	ND	ND
Health-related quality of life	ND	ND
Side effects	ND	ND

a. For "overall survival", the company only provided data on the observation period after treatment discontinuation; data cut-off: 2 January 2019 – median in months [Q1; Q3]: atezolizumab + nab-paclitaxel 19.4 [10.4; 23.8]; placebo + nab-paclitaxel 15.7 [8.1; 21.1]; mean value in months (SD): atezolizumab + nab-paclitaxel 18.2 (9.3); placebo + nab-paclitaxel 15.5 (9.1).

N: number of analysed patients; ND: no data; Q1: 25% quantile; Q3: 75% quantile; RCT: randomized controlled trial; SD: standard deviation

At the data cut-offs 17 April 2018 and 3 September 2018, median treatment duration with the study medication was clearly longer in the intervention arm than in the control arm (atezolizumab/placebo: 6.1 vs. 3.7 months; nab-paclitaxel: 5.2 vs. 3.7 months). Information on the observation periods are not available for any of the outcomes.

Risk of bias across outcomes (study level)

Table 4 shows the risk of bias across outcomes (risk of bias at study level).

Table 4: Risk of bias across outcomes (study level) – RCT, direct comparison: atezolizumab + nab-paclitaxel versus placebo + nab-paclitaxel

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
IMpassion130	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

For the IMpower130 study, the risk of bias across outcomes was rated as low.

2.2 Results of the IMpassion130 study

According to the G-BA's commission, the following sections present the results of the IMpassion130 study. The reporting of results is based on the subpopulation of patients analysed by the company whose tumours had PD-L1 expression ≥ 1% (approval population).

2.2.1 Considered outcomes

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

- Mortality
  - Overall survival
- Morbidity
  - symptoms measured with of the instruments European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Core 30 (QLQ-C30) and Quality of Life Questionnaire-Breast Cancer 23 (QLQ-BR23)
  - health status measured with the European Quality of Life-5 Dimensions (EQ-5D) visual analogue scale (VAS)
- Health-related quality of life
  - Measured with EORTC QLQ-C30 and QLQ-BR23
- Side effects
  - Serious adverse events (SAEs)
  - Severe AEs (Common-Terminology-Criteria-for-Adverse-Events[CTCAE] grade 3–4)
  - Discontinuation due to AEs
  - Immune-related AEs, SAEs and severe AEs (CTCAE grade 3–4)
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier on the benefit assessment of atezolizumab (Module 4 A) [2].

Table 5 shows for which outcomes data were available in the IMpassion130 study.

Table 5: Matrix of the outcomes – RCT, direct comparison: atezolizumab + nab-paclitaxel versus placebo + nab-paclitaxel

Study	Outcomes										
	Overall survival	**Symptoms (EORTC QLQ-C30 and QLQ-BR23)**	**Health status (EQ-5D VAS)**	**Health-related quality of life (EORTC QLQ-C30 and QLQ-BR23)**	**SAEs**	**Discontinuation due to AEs**	**Severe AEs (CTCAE grade 3–4)**	**Immune-related AEs[b]**	**Immune-related SAEs[b]**	**Immune-related severe AEs (CTCAE grade 3–4)[b]**	**Investigations (SOC, severe AEs with [CTCAE grade 3–4]) Studies**
IMpassion130	Yes	Yes	No[a]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. No usable data since the validity of the response criterion of 10 points is not met (see benefit assessment A18-33 [8]).
b. A list of PTs, HLTs and SMQs considered in the analysis can be found in the clinical study report.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life5 Dimensions; HLT: High Level Term; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module; QLQ-C30: Quality of Life Questionnaire Core30; RCT: randomized controlled trial; SMQ: standardized MedDRA Query; SOC: System Organ Class; SAE: serious adverse event; VAS: visual analogue scale

2.2.2 Risk of bias

Table 6 describes the risk of bias for the relevant outcomes.

Table 6: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: atezolizumab + nab-paclitaxel versus placebo + nab-paclitaxel

Study	Study level	Outcomes										
		Overall survival	Symptoms (EORTC QLQ-C30 and QLQ-BR23)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30 and QLQ-BR23)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade 3–4)	Immune-related AEs	Immune-related SAEs	Immune-related severe AEs (CTCAE grade 3–4)	Investigations (SOC, severe AEs [CTCAE grade 3–4])
IMpassion130	L	L	H[a]	–[b]	H[a]	H[c]	N[d]	H[c]	H[c]	H[c]	H[c]	H[c]

a. Large proportion of patients (> 10%) who were not considered in the analysis.
b. No usable data since the validity of the response criterion of 10 points is not met (for more information see benefit assessment A18-33 [8]).
c. Incomplete observations for potentially informative reasons.
d. Despite the low risk of bias, the certainty of results for the outcome "discontinuation due to AEs" was assumed to be restricted (see below).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life5 Dimensions; H: high; L: low; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module; QLQ-C30: Quality of Life Questionnaire Core30; RCT: randomized controlled trial; SOC: System Organ Class; SAE: serious adverse event; VAS: visual analogue scale

The outcome-specific risk of bias in the IMpassion130 study was only low for the outcomes "overall survival" and "discontinuation due to AEs". The risk of bias of the results on the outcomes "symptoms" and "health-related quality of life" is potentially high, which is particularly due to the large proportion of patients (> 10%) not considered in the analysis.

Except for the outcome "discontinuation due to AEs", the risk of bias is high for all results of the AE-related outcomes. The planned follow-up observation period after end of treatment was 30 days for these outcomes. The observation period thus depends decisively on the reason for treatment discontinuation "disease progression". At the data cut-off of 2 January 2019, 82.6% of the patients with treatment discontinuation in the intervention arm and 78.1% in the control arm had discontinued treatment due to disease progression. Due to a possible correlation between disease progression and the AE-related outcomes, there are incomplete observations for potentially informative reasons. The differing treatment discontinuation behaviour is also associated with different median treatment durations (atezolizumab/placebo: 6.1 vs. 3.7 months, data cut-off: 3 September 2018).

The risk of bias for the outcome "discontinuation due to AEs" is low; however, the certainty of results for this outcome is limited. Premature treatment discontinuation for reasons other than

AEs is a competing event for the outcome “discontinuation due to UEs” to be recorded. This means that after discontinuation for other reasons, AEs that would have led to treatment discontinuation may have occurred, but the criterion “discontinuation” was no longer recordable for them. The number of relevant AEs cannot be assessed.

2.2.3 Results

Table 7 summarizes the results on the comparison of atezolizumab + nab-paclitaxel versus placebo + nab-paclitaxel in the subpopulation of patients whose tumours had PD-L1 expressions ≥ 1% (approval population) in the IMpassion130 study. As far as available, the Kaplan-Meier curves on the considered outcomes are presented in Appendix A; the common AEs, SAEs, severe SAEs (CTCAE grade 3–4) and all AEs that resulted in treatment discontinuation are listed in Appendix B.

Table 7: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: atezolizumab + nab-paclitaxel versus placebo + nab-paclitaxel (multipage table)

Study Outcome category Outcome	Atezolizumab + nab-paclitaxel		Placebo + nab-paclitaxel		Atezolizumab + nab-paclitaxel vs. placebo + nab-paclitaxel
	N	Median time to event in months [95% CI] patients with event n (%)	N	Median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value[a]
IMpassion130					
Mortality (data cut-off 2 January 2019)					
Overall survival	185	25.0 [19.6; 30.7] 94 (50.8)	184	18.0 [13.6; 20.1] 110 (59.8)	0.71 [0.54; 0.93]; 0.013
Morbidity[b] (data cut-off: 17 April 2018)					
EORTC QLQ-C30 (symptom scales)[c]					
Fatigue	164	1.8 [1.1; 1.9] 142 (86.6)	158	1.9 [1.1; 2.7] 126 (79.7)	1.06 [0.83; 1.35]; 0.613
Nausea and vomiting	164	3.8 [2.8; 6.0] 115 (70.1)	158	4.3 [2.8; 5.6] 102 (64.6)	1.01 [0.77; 1.33]; 0.934
Pain	164	3.1 [2.0; 4.6] 123 (75.0)	158	5.1 [3.5; 7.4] 100 (63.3)	1.34 [1.03; 1.76]; 0.031
Dyspnoea	164	3.9 [3.2; 5.6] 103 (62.8)	158	4.8 [2.9; 7.4] 90 (57.0)	1.03 [0.78; 1.37]; 0.821
Insomnia	164	6.6 [4.4; 12.2] 90 (54.9)	158	7.3 [4.0; 15.6] 76 (48.1)	1.03 [0.75; 1.39]; 0.863
Appetite loss	164	4.9 [3.8; 8.4] 97 (59.1)	158	4.3 [3.5; 6.1] 93 (58.9)	0.94 [0.70; 1.25]; 0.661
Constipation	164	4.8 [3.7; 7.8] 102 (62.2)	158	5.7 [3.4; 7.6] 93 (58.9)	0.95 [0.72; 1.26]; 0.744
Diarrhoea	164	4.9 [3.7; 8.3] 100 (61.0)	158	6.0 [4.7; 9.3] 87 (55.1)	1.12 [0.84; 1.49]; 0.432
EORTC QLQ-BR23 (symptom scales)[c]					
Side effects of the systemic therapy	164	1.1 [1.0; 1.2] 139 (84.8)	158	1.9 [1.1; 1.9] 124 (78.5)	1.18 [0.92; 1.51]; 0.205
Symptoms in chest region	164	17.4 [9.8; 24.8] 67 (40.9)	158	12.0 [8.2; NA] 60 (38.0)	0.96 [0.67; 1.37]; 0.813
Symptoms in arm region	164	4.6 [2.8; 5.6] 103 (62.8)	158	4.1 [2.8; 7.4] 93 (58.9)	0.99 [0.75; 1.31]; 0.945
Upset by hair loss	no usable data[d]				
Health status (EQ-5D VAS)	no usable data[e]				

Table 7: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: atezolizumab + nab-paclitaxel versus placebo + nab-paclitaxel (multipage table)

Study Outcome category Outcome	Atezolizumab + nab-paclitaxel		Placebo + nab-paclitaxel		Atezolizumab + nab-paclitaxel vs. placebo + nab-paclitaxel
	N	Median time to event in months [95% CI] patients with event n (%)	N	Median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value[a]
Health-related quality of life (data cut-off: 17 April 2018)[b]					
EORTC QLQ-C30 (functional scales)[f]					
Global health status	164	2.9 [2.1; 3.7] 121 (73.8)	158	2.8 [2.4; 3.8] 104 (65.8)	1.00 [0.77; 1.31]; 0.982
Role functioning	164	2.8 [1.9; 3.7] 122 (74.4)	158	2.8 [2.4; 3.8] 119 (75.3)	0.91 [0.71; 1.18]; 0.493
Physical functioning	164	3.1 [2.5; 4.4] 120 (73.2)	158	3.8 [3.1; 5.2] 116 (73.4)	0.97 [0.75; 1.25]; 0.798
Emotional functioning	164	6.5 [5.0; 9.5] 90 (54.9)	158	6.0 [3.8; 9.6] 86 (54.4)	0.91 [0.67; 1.22]; 0.512
Cognitive functioning	164	3.0 [2.8; 3.9] 117 (71.3)	158	3.5 [2.8; 4.4] 108 (68.4)	0.96 [0.74; 1.26]; 0.792
Social functioning	164	2.8 [2.1; 4.7] 120 (73.2)	158	2.9 [2.8; 3.8] 110 (69.6)	0.96 [0.74; 1.25]; 0.793
EORTC QLQ-BR23 (functional scales)[f]					
Body image	164	NA 38 (23.2)	158	NA 29 (18.4)	1.19 [0.73; 1.93]; 0.479
Future perspective	164	3.8 [2.7; 7.4] 93 (56.7)	158	4.7 [2.8; 14.3] 78 (49.4)	1.04 [0.77; 1.40]; 0.777
Sexual activity	164	23.7 [14.7; NA] 56 (34.1)	158	NA [12.0; NA] 54 (34.2)	0.88 [0.60; 1.28]; 0.495
Enjoyment of sex				no usable data[d]	
Side effects (data cut-off 3 September 2018)					
AEs (supplementary information)	185	ND 185 (100.0)	181	ND 177 (97.8)	–
SAEs	185	ND 43 (23.2)	181	ND 31 (17.1)	1.17 [0.74; 1.87]; 0.501[g]
Severe AEs (CTCAE grade 3–4)	185	ND 97 (52.4)	181	ND 73 (40.3)	1.20 [0.89; 1.63]; 0.234[g]
Discontinuation due to AEs	185	ND 37 (20.0)	181	ND 13 (7.2)	2.34 [1.24; 4.41]; 0.007[g]
Immune-related AEs[h]	185	ND 107 (57.8)	181	ND 66 (36.5)	1.63 [1.20; 2.22]; 0.002[g]
Immune-related SAEs[h]	185	ND 3 (1.6)	181	ND 3 (1.7)	0.80 [0.16; 3.96]; 0.778[g]

Table 7: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: atezolizumab + nab-paclitaxel versus placebo + nab-paclitaxel (multipage table)

Study Outcome category Outcome	Atezolizumab + nab-paclitaxel		Placebo + nab-paclitaxel		Atezolizumab + nab-paclitaxel vs. placebo + nab-paclitaxel
	N	Median time to event in months [95% CI] patients with event n (%)	N	Median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value[a]
Immune-related severe AEs (CTCAE grade 3–4)[h]	185	ND 10 (5.4)	181	ND 7 (3.9)	1.20 [0.46; 3.17]; 0.710[g]
Studies (SOC, severe AEs, CTCAE grade 3–4)	185	ND 26 (14.1)	181	ND 11 (6.1)	2.06 [1.02; 4.18]; 0.041[g]

a. Cox regression model and log-rank test, each stratified by presence of liver metastases (yes vs. no) and prior taxane therapy (yes vs. no).
b. Results of all patients for whom an analysis at baseline and at least one analysis after the start of the study was available.
c. Time to first deterioration; defined as an increase of the score by ≥ 10 points compared with baseline.
d. Unclear proportion of patients with missing values at baseline and in the course of the study.
e. No usable analyses, since the validity of the response criterion of 10 points was not met (for a supplementary presentation of results see Appendix C) and steady analyses are not available.
f. Time to first deterioration; defined as decrease of the score by ≥ 10 points compared to baseline.
g. Unstratified Cox regression model; unstratified log-rank test.
h. A list of PTs, HLTs and SMQs considered in the analysis can be found in the study report.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organization for Research and Treatment of Cancer; EQ-5D: European Quality of Life5 Dimensions; HLT: High Level Term; HR: Hazard Ratio; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; ND: no data; PT: Preferred Term; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module; QLQ-C30: Quality of Life Questionnaire Core30; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

Mortality

Overall survival

A statistically significant difference in favour of atezolizumab + nab-paclitaxel in comparison with placebo + nab-paclitaxel was shown for the outcome “overall survival”.

Morbidity

Health status (EQ-5D VAS)

Usable analyses are not available for the outcome “health status” (EQ-5D VAS), since the validity of the response criterion of 10 points was not met [8]. Continuous analyses are lacking. The analyses presented by the company are provided as supplementary information in Appendix C.

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

The company operationalized the outcomes on symptoms as time to first deterioration by 10 points on the respective scale.

11 of a total of 12 scales showed no statistically significant differences between the treatment groups for the symptom scales of the EORTC QLQ-C30 and the additional module QLQ-BR23. A statistically significant difference to the disadvantage of atezolizumab + nab-paclitaxel in comparison with placebo + nab-paclitaxel was shown for the "pain" scale. Usable data for the scale "upset by hair loss" are not available.

Health-related quality of life

Health-related quality of life (functional scales EORTC QLQ-C30 and QLQ-BR23)

The company operationalized the outcomes on health-related quality of life as time to first deterioration by 10 points on the respective scale.

None of the 10 scales showed statistically significant differences between the treatment groups for the symptom scales of the EORTC QLQ-C30 and the additional module QLQ-BR23. Usable data for the scale "pleasure in sex" are not available.

Side effects

SAEs, severe AEs (CTCAE grade 3–4)

No statistically significant differences between the treatment groups were shown for the outcomes "SAEs" and "severe AEs (CTCAE grade 3–4)".

Discontinuation due to AEs

A statistically significant difference to the disadvantage of atezolizumab + nab-paclitaxel in comparison with placebo + nab-paclitaxel was shown for the outcome "discontinuation due to AEs".

Immune-related AEs, SAEs and severe AEs (CTCAE grade 3–4)

Immune-related AEs were operationalized by the company via a list of Preferred Terms (PTs), High Level Terms (HLTs) and standardized Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQs) that were considered in the analysis. This list can be found in the study report.

A statistically significant difference to the disadvantage of atezolizumab + nab-paclitaxel in comparison with placebo + nab-paclitaxel was shown for the outcome "immune-related AEs". This outcome largely includes "immune-related rash" (64.5% vs. 69.7% based on all patients with immune-related AEs in the respective study arm).

No statistically significant differences between the treatment groups were shown for the outcomes "immune-related SAEs" and "immune-related severe AEs (CTCAE grade 3–4)".

Further specific AEs

Further specific AEs were selected on the basis of the events that had occurred in the study, based on the frequency and the differences between the treatment arms and under consideration of the patient relevance.

Studies (System Organ Class [SOC], severe AEs, [CTCAE grade 3–4])

A statistically significant difference to the disadvantage of atezolizumab + nab-paclitaxel in comparison with placebo + nab-paclitaxel was shown for the outcome "studies (SOC, severe AEs [CTCAE grade 3–4])".

Subgroups

Neither the study protocol nor the statistical analysis plan prespecified subgroup analyses on specific subgroup characteristics. In the study report, the company presented subgroup analyses for overall survival and the PFS for a variety of subgroup characteristics defined post hoc. In Module 4 of its dossier, the company presented analyses for selected subgroups on some, but not on all outcomes. For all outcomes, the company presented subgroup analyses for the characteristics "age (18–40, 41–64, ≥ 65)", "Eastern Cooperative Oncology Group Performance Status (ECOG PS) (0, 1)", "number of tumour localisations (0–3, > 3)" and "geographical region" (Europe, North America, Latin America, Asia/Australia). Moreover, the company presented subgroup analyses for the prespecified stratification characteristics "liver metastases" (yes, no) and "previous taxane therapy" (yes, no), but not for outcomes of the category "adverse events".

In general, the company justified its selection by referring to the requirements of the dossier template. The company did not give reasons why, for instance, it did not present analyses for all relevant outcomes for all subgroup characteristics selected by it. Therefore, the present addendum considers no subgroup analyses, because a results-driven reporting cannot be ruled out.

Summary

Overall, a statistically significant difference in favour of atezolizumab + nab-paclitaxel in comparison with nab-paclitaxel is shown for the outcome "overall survival" on the positive side. On the negative side, in contrast, there are statistically significant differences to the disadvantage of atezolizumab + nab-paclitaxel versus nab-paclitaxel for the outcomes "pain", "discontinuation due to AEs", "immune-related AEs" and "studies" (SOC, severe AEs [CTCAE grade 3–4]).

2.3 Summary

The conclusion on the added benefit of atezolizumab from dossier assessment A19-81 is not changed by the present addendum, since the IMpassion130 study presented by the company is not suitable to draw conclusions on the added benefit of atezolizumab + nab-paclitaxel versus the ACT.

The following Table 8 shows the result of the benefit assessment of atezolizumab under consideration of dossier assessment A19-81 and the present addendum.

Table 8: Atezolizumab – probability and extent of added benefit

Subindication	**ACT**[a]	**Probability and extent of added benefit**[b]
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-containing 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 References

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

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8. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Bosutinib (chronische myeloische Leukämie): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A18-33 [online]. 29.08.2018 [Accessed: 05.09.2018]. (IQWiG-Berichte; Volume 660). URL: https://www.iqwig.de/download/A18-33_Bosutinib_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

Appendix A – Kaplan-Meier curves in the subpopulation of patients with PD-L1 expression ≥ 1% (approval population)

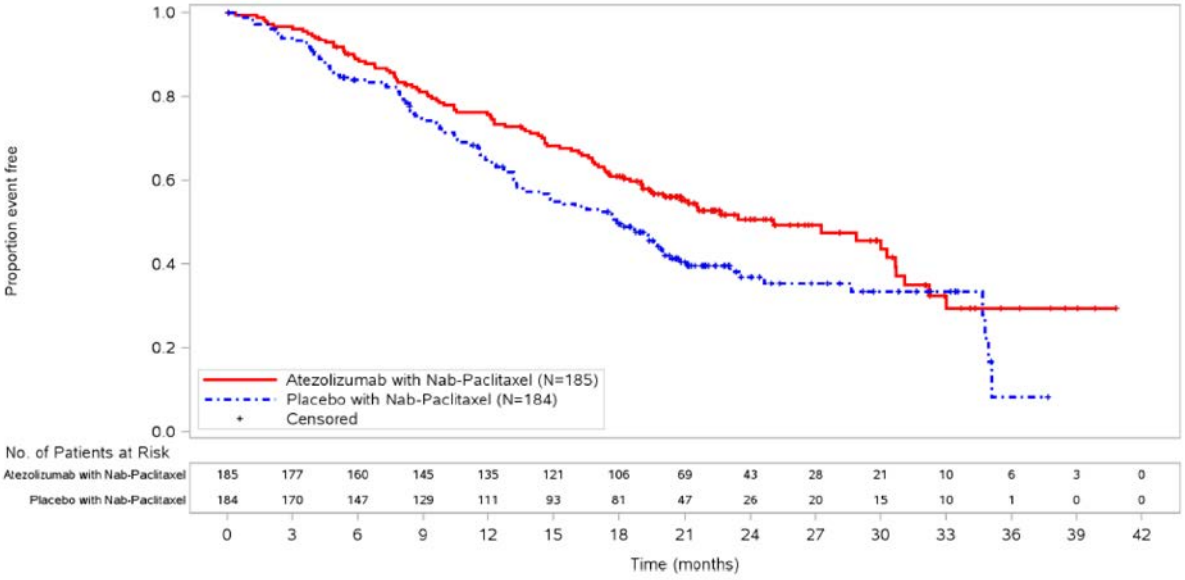

Figure 1: Kaplan-Meier curve for the outcome "overall survival" (data cut-off: 2 January 2019)

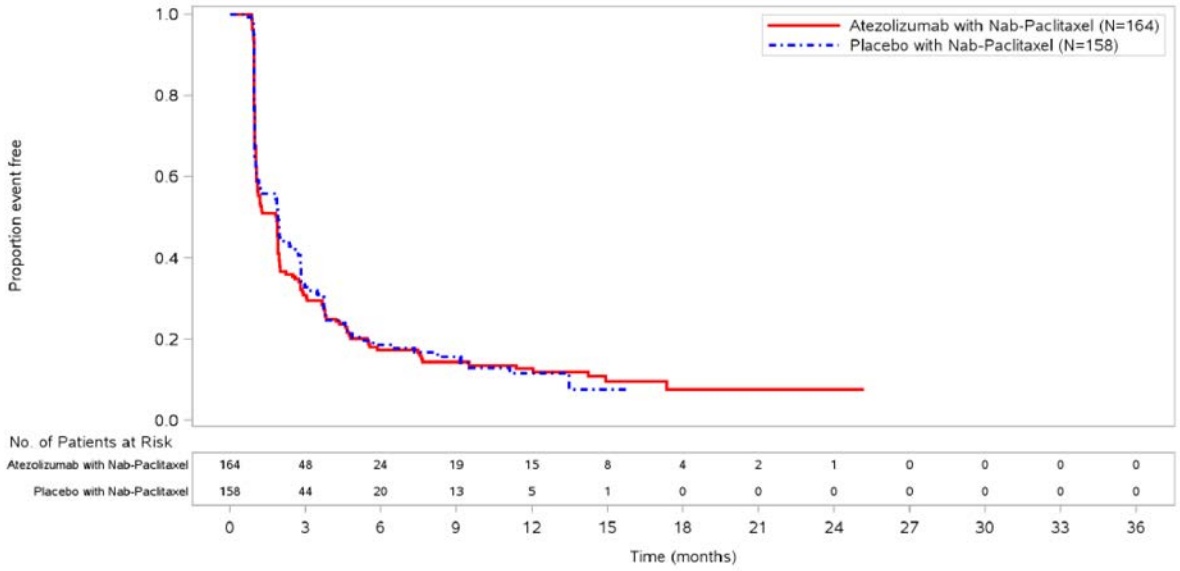

Figure 2: Kaplan-Meier curve for the outcome "time to deterioration: fatigue" (EORTC QLQ-C30) (data cut-off: 17 April 2018)

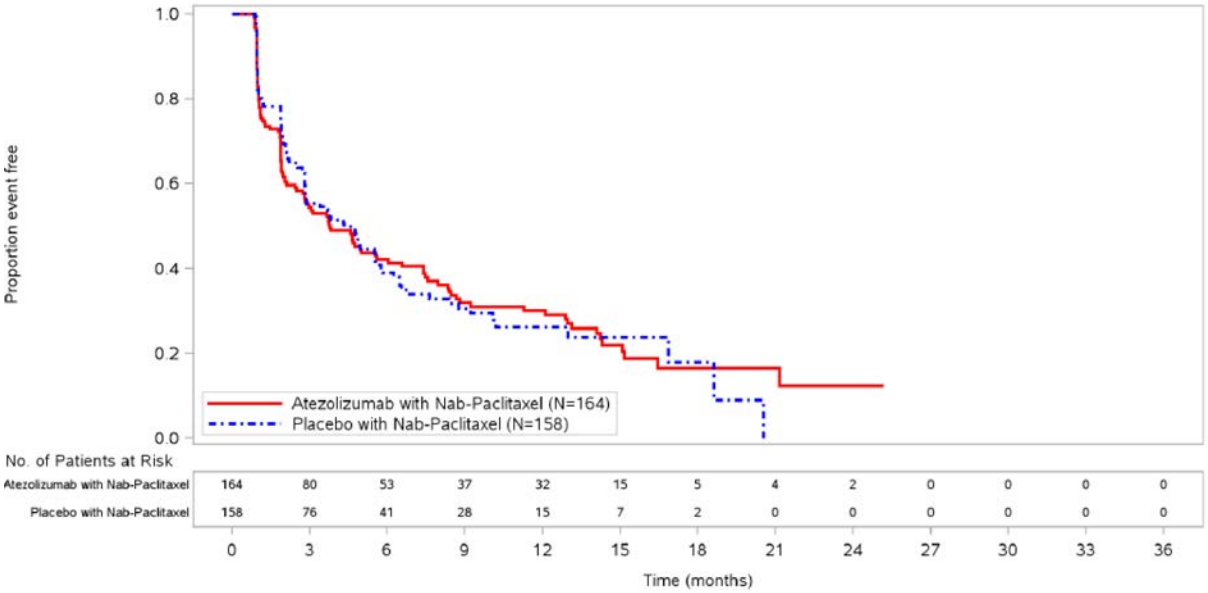

Figure 3: Kaplan-Meier curve for the outcome "time to deterioration: nausea and vomiting" (EORTC QLQ-C30) (data cut-off: 17 April 2018)

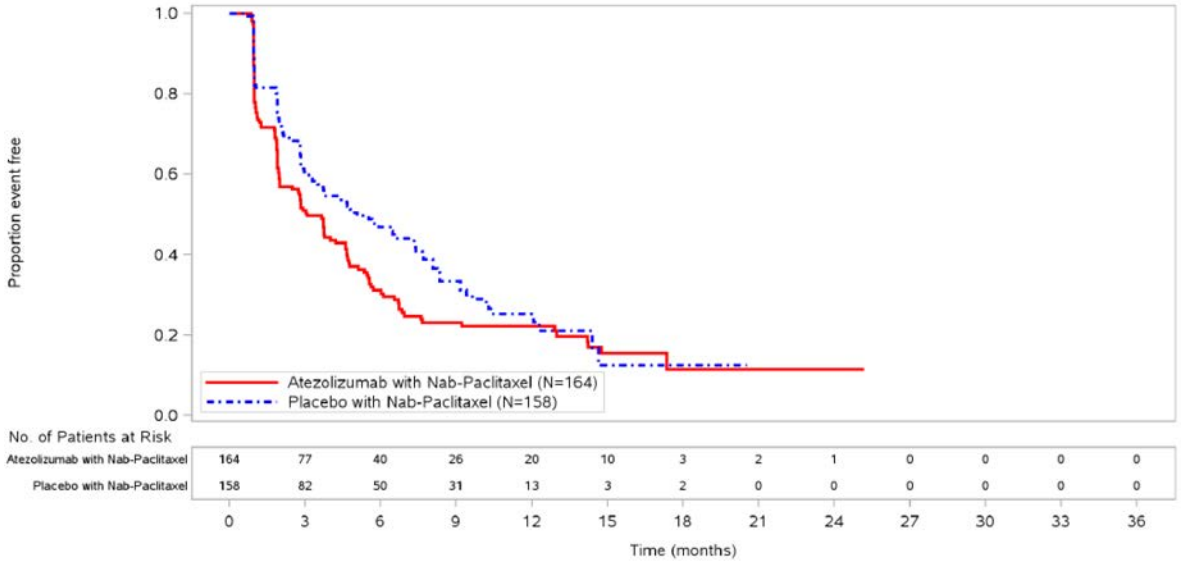

Figure 4: Kaplan-Meier curve for the outcome "time to deterioration: pain" (EORTC QLQ-C30) (data cut-off: 17 April 2018)

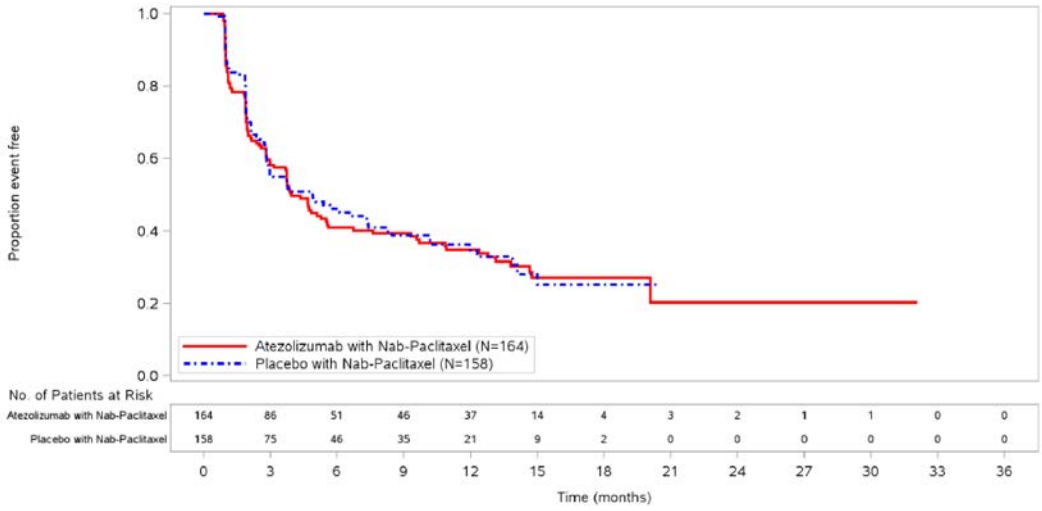

Figure 5: Kaplan-Meier curve for the outcome "time to deterioration: dyspnoea" (EORTC QLQ-C30) (data cut-off: 17 April 2018)

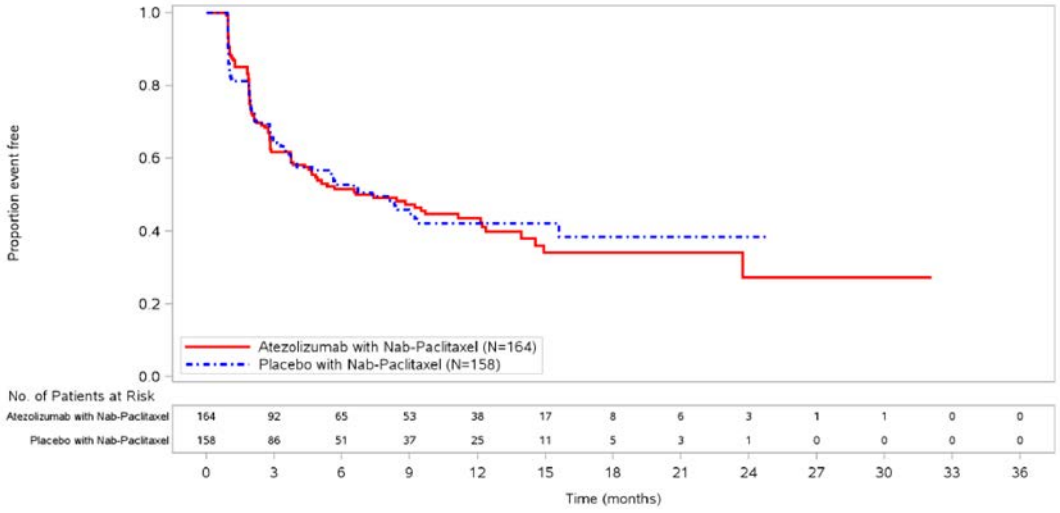

Figure 6: Kaplan-Meier curve for the outcome "time to deterioration: insomnia" (EORTC QLQ-C30) (data cut-off: 17 April 2018)

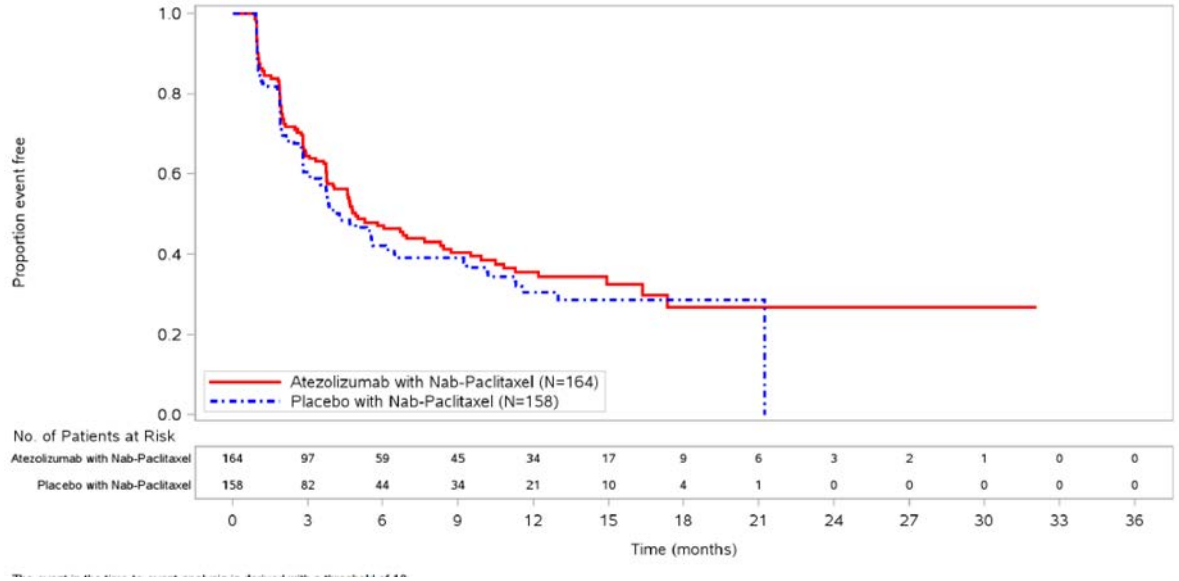

Figure 7: Kaplan-Meier curve for the outcome "time to deterioration: appetite loss" (EORTC QLQ-C30) (data cut-off: 17 April 2018)

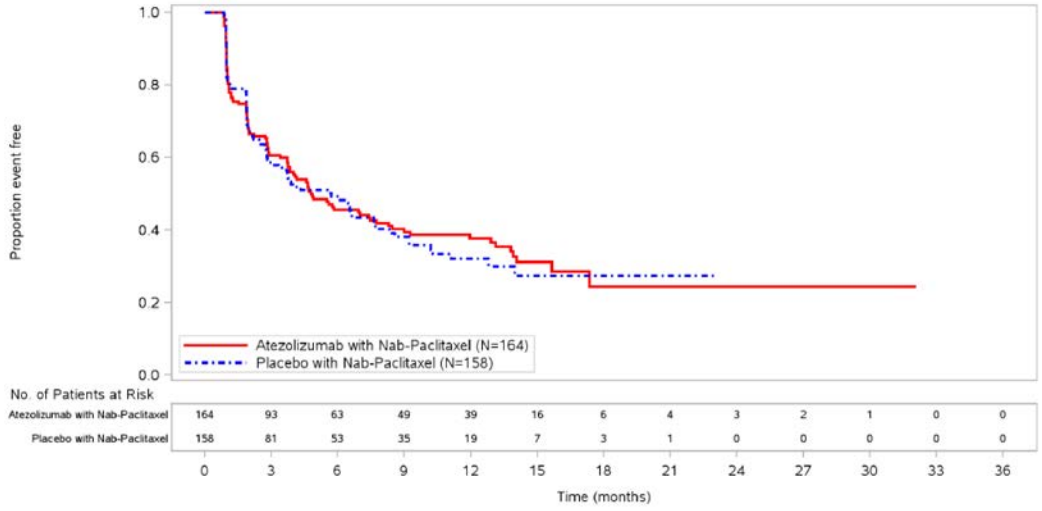

Figure 8: Kaplan-Meier curve for the outcome "time to deterioration: constipation" (EORTC QLQ-C30) (data cut-off: 17 April 2018)

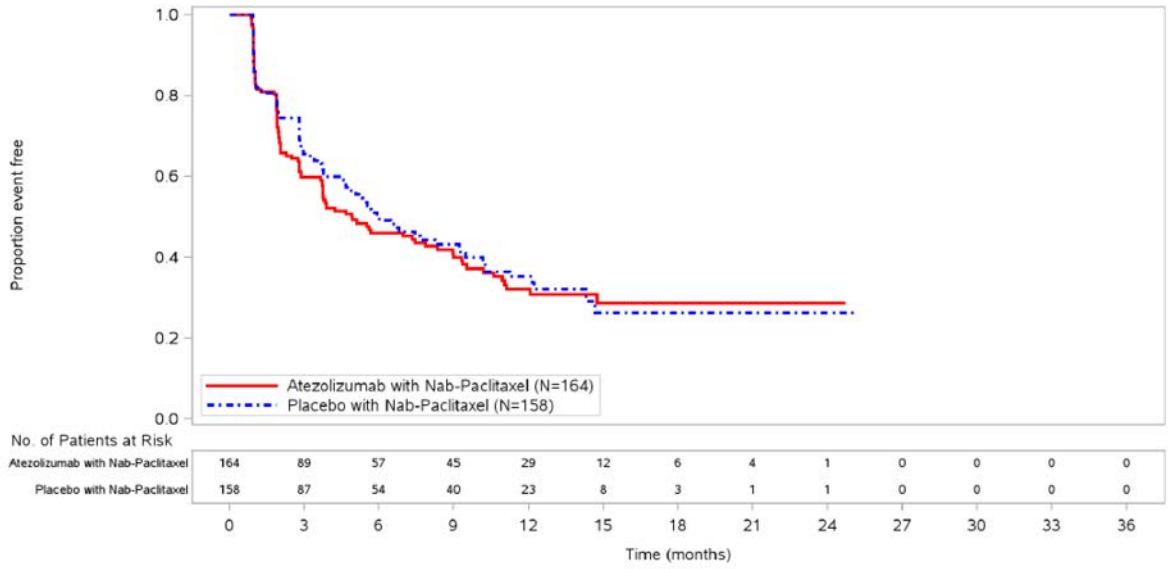

Figure 9: Kaplan-Meier curve for the outcome "time to deterioration: diarrhoea" (EORTC QLQ-C30) (data cut-off: 17 April 2018)

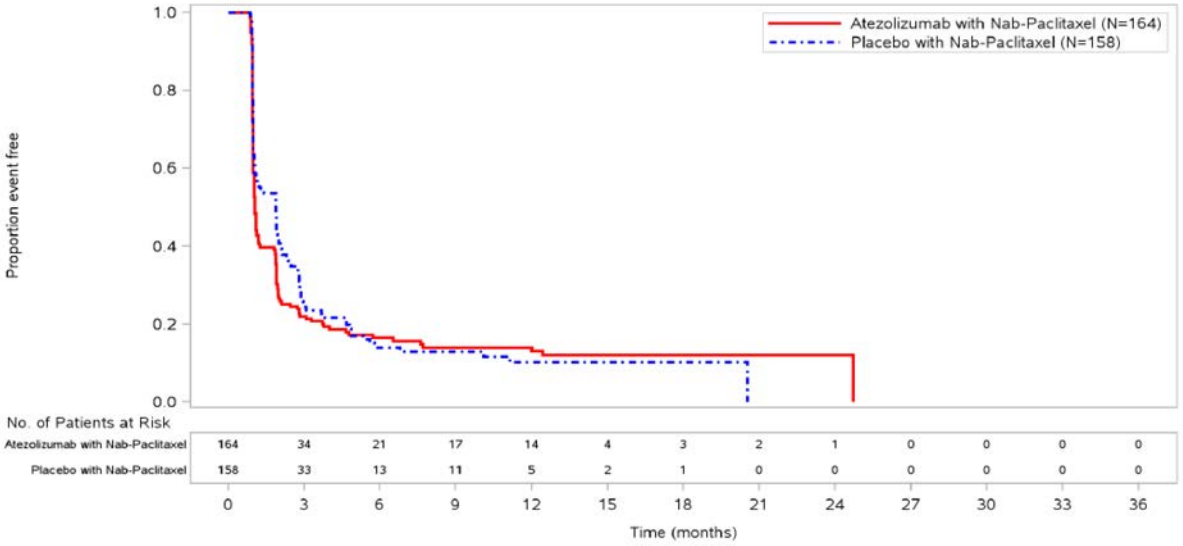

Figure 10: Kaplan-Meier curve for the outcome "time to deterioration: side effects of the systemic therapy" (EORTC QLQ BR23) (data cut-off: 17 April 2018)

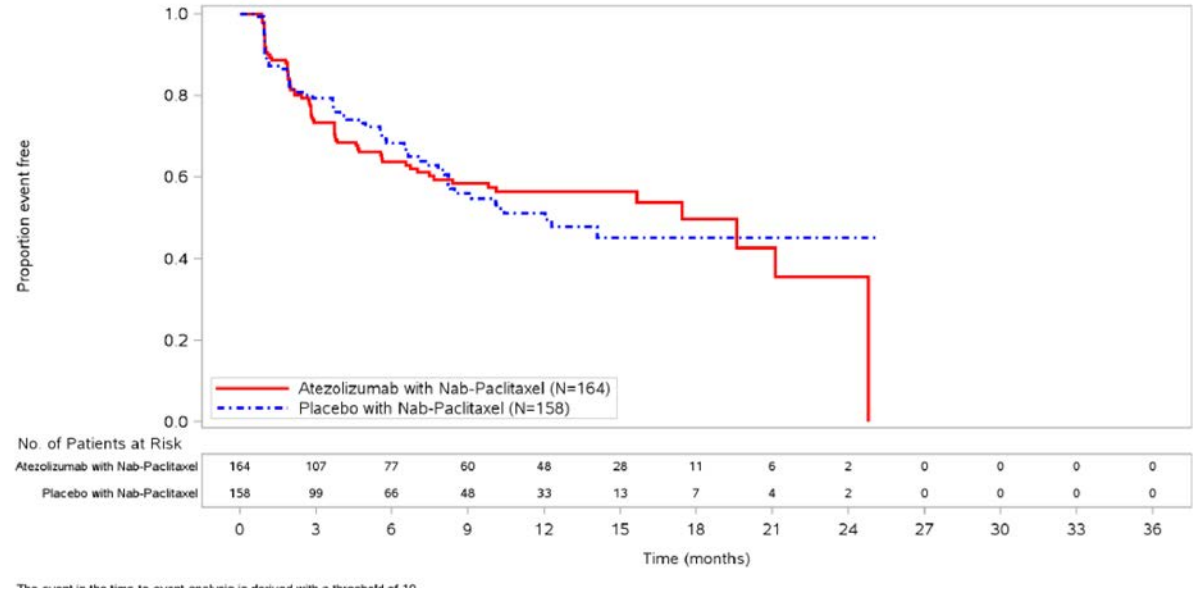

Figure 11: Kaplan-Meier curve for the outcome "time to deterioration: symptoms in chest region" (EORTC QLQ BR23) (data cut-off: 17 April 2018)

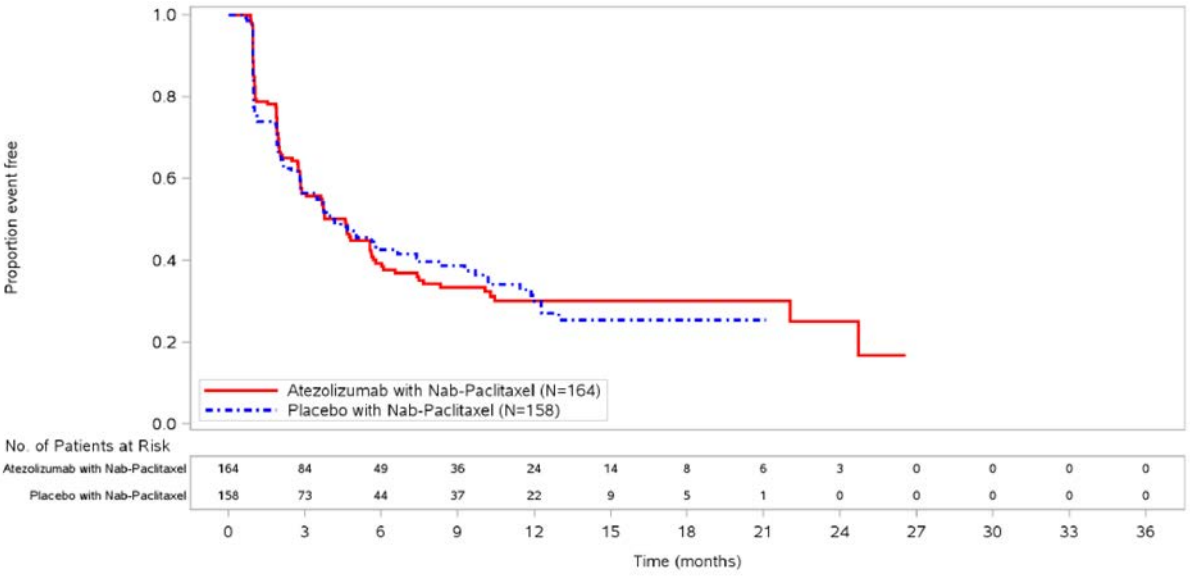

Figure 12: Kaplan-Meier curve for the outcome "time to deterioration: symptoms in arm region" (EORTC QLQ BR23) (data cut-off: 17 April 2018)

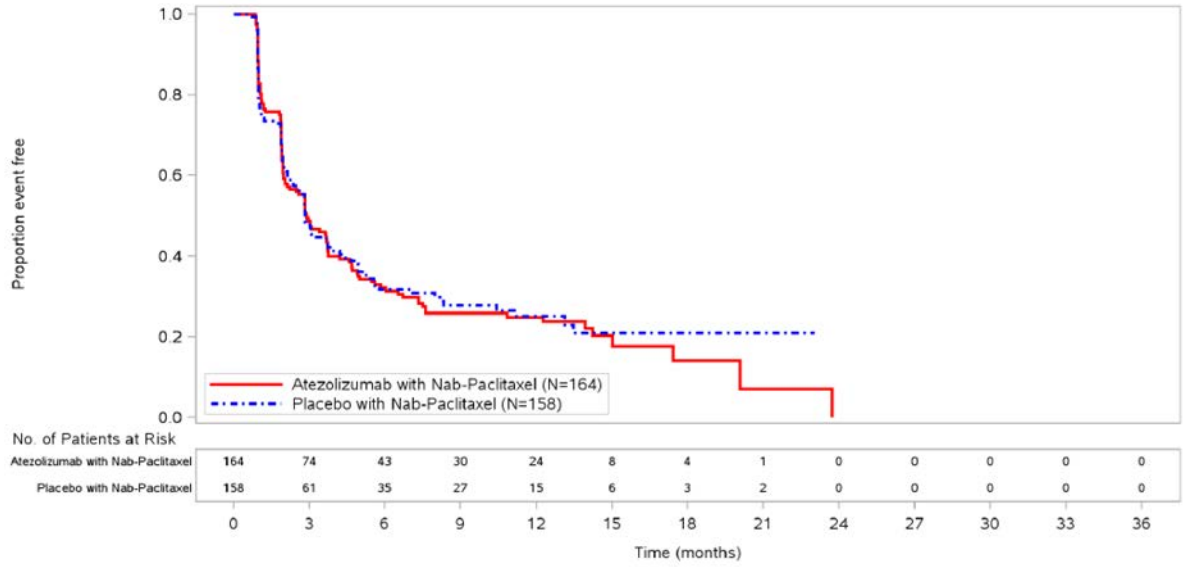

Figure 13: Kaplan-Meier curve for the outcome "time to deterioration: global health status" (EORTC QLQ-C30) (data cut-off: 17 April 2018)

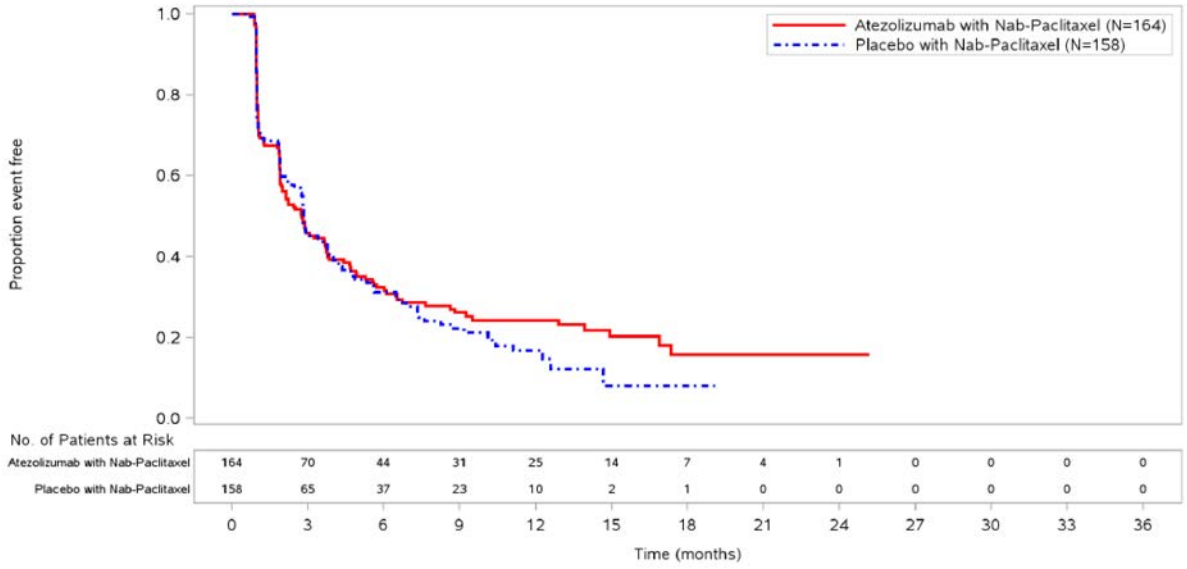

Figure 14: Kaplan-Meier curve for the outcome "time to deterioration: role functioning" (EORTC QLQ-C30) (data cut-off: 17 April 2018)

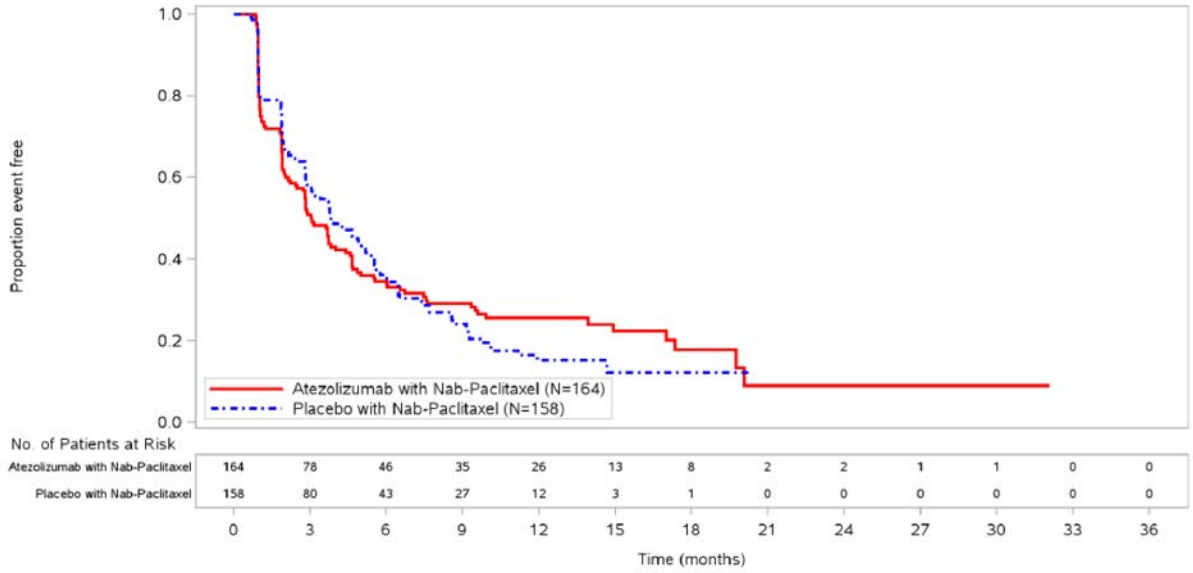

Figure 15: Kaplan-Meier curve for the outcome "time to deterioration: physical functioning" (EORTC QLQ-C30) (data cut-off: 17 April 2018)

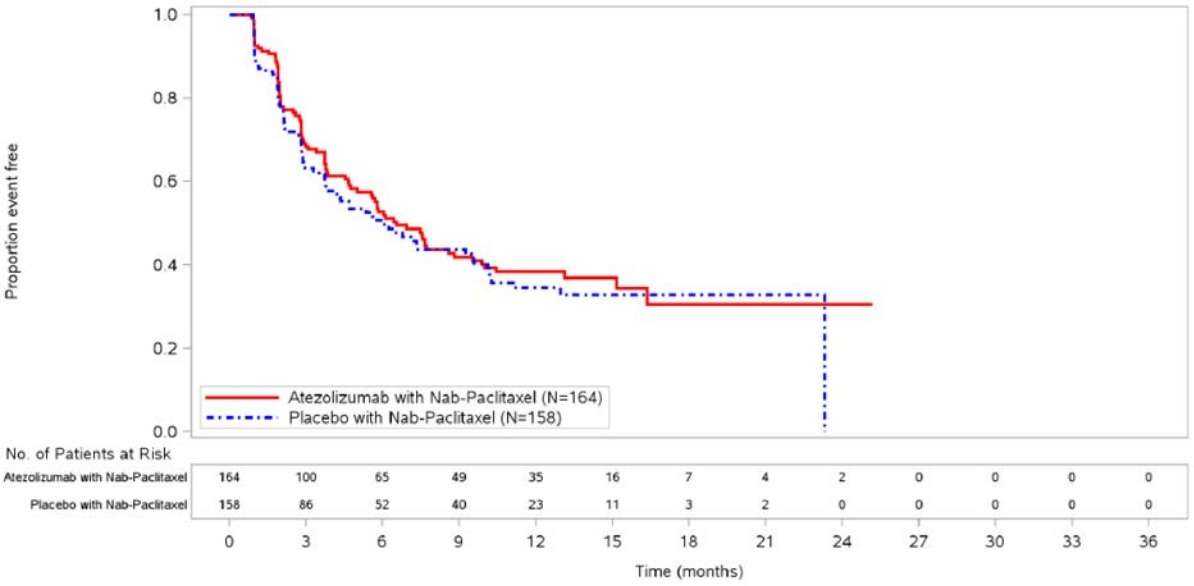

Figure 16: Kaplan-Meier curve for the outcome "time to deterioration: emotional functioning" (EORTC QLQ-C30) (data cut-off: 17 April 2018)

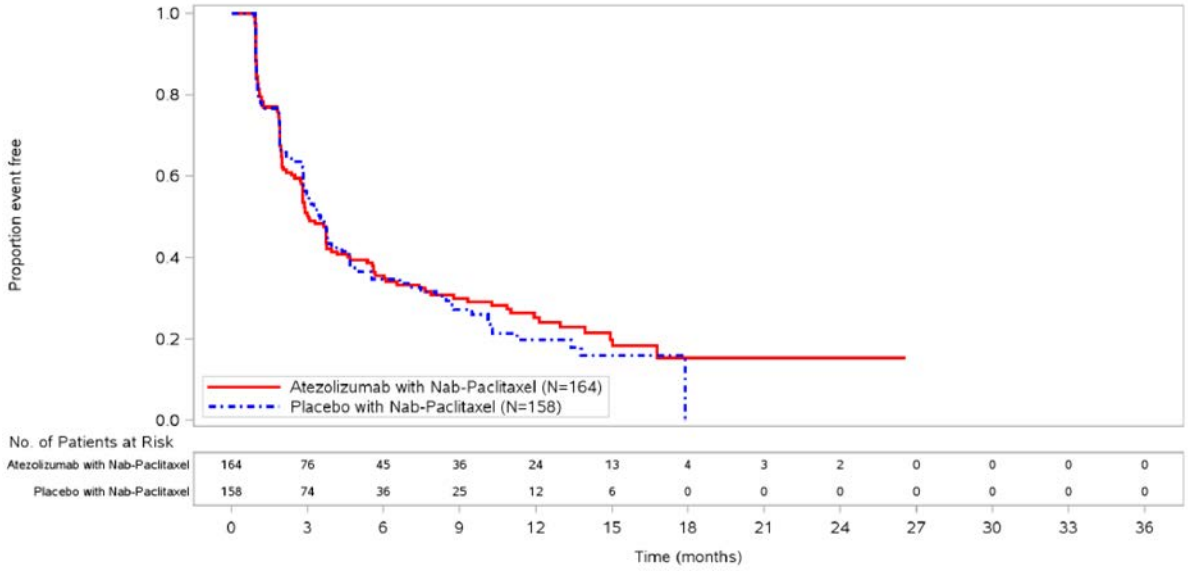

Figure 17: Kaplan-Meier curve for the outcome "time to deterioration: cognitive functioning" (EORTC QLQ-C30) (data cut-off: 17 April 2018)

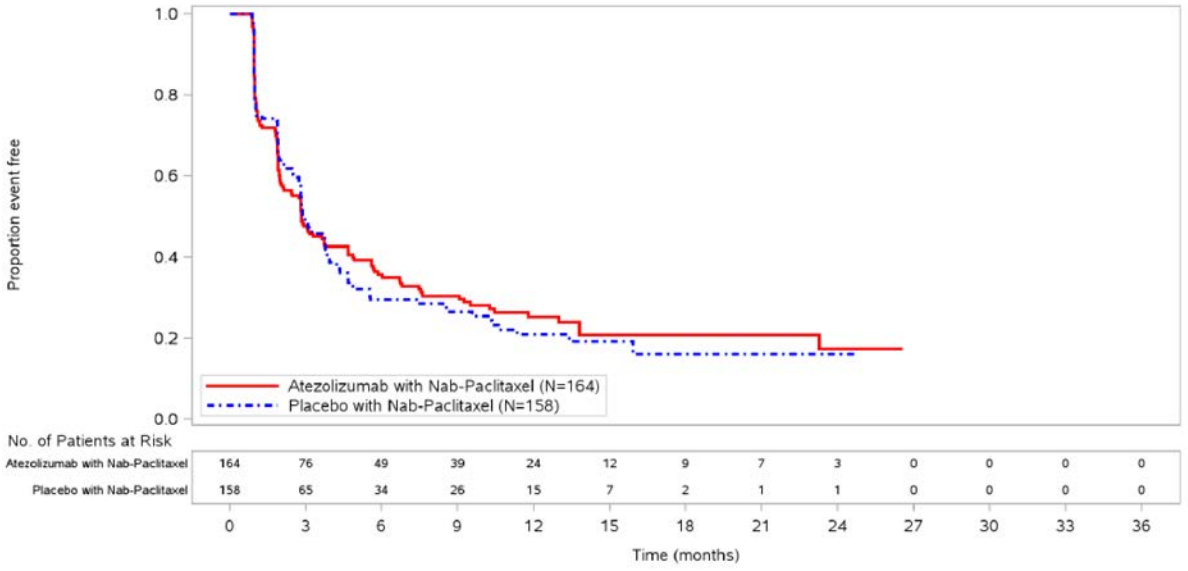

Figure 18: Kaplan-Meier curve for the outcome "time to deterioration: social functioning" (EORTC QLQ-C30) (data cut-off: 17 April 2018)

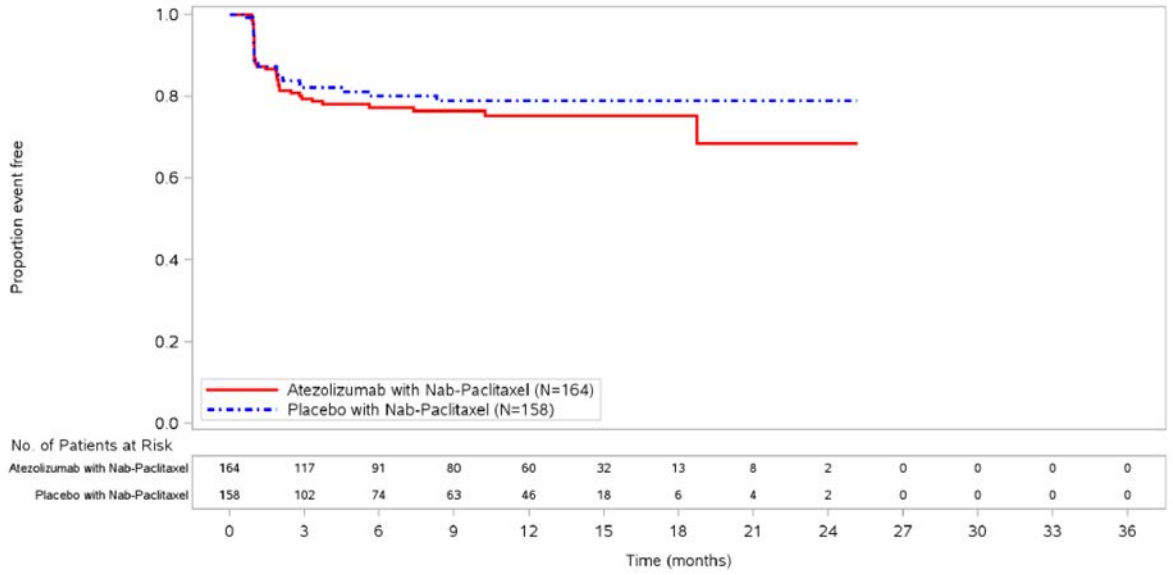

Figure 19: Kaplan-Meier curve for the outcome "time to deterioration: body image" (EORTC QLQ BR23) (data cut-off: 17 April 2018)

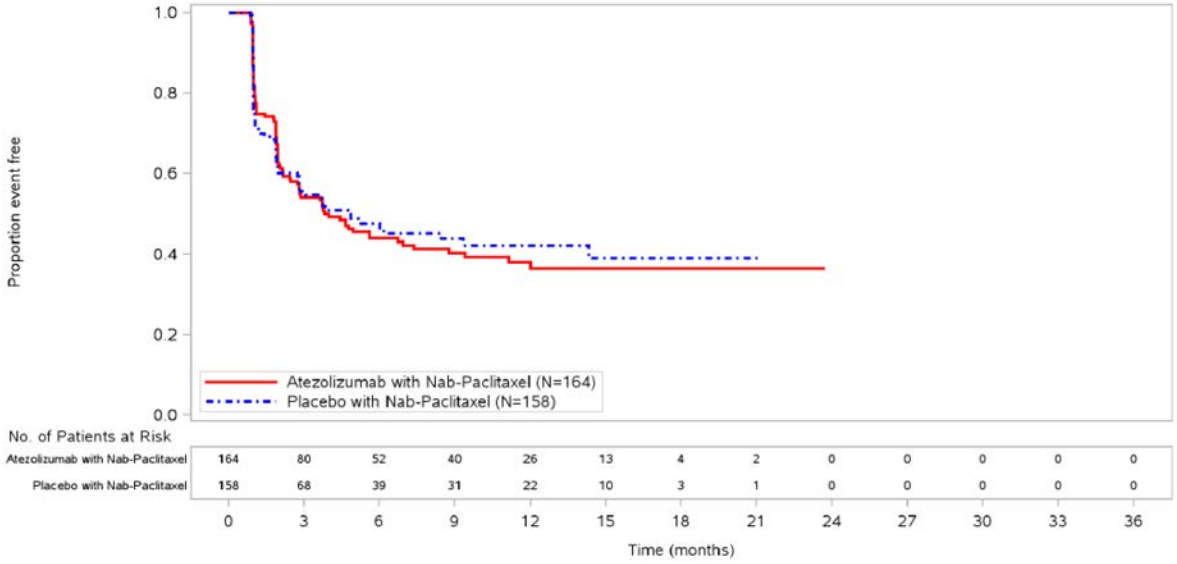

Figure 20: Kaplan-Meier curve for the outcome "time to deterioration: future perspective" (EORTC QLQ BR23) (data cut-off: 17 April 2018)

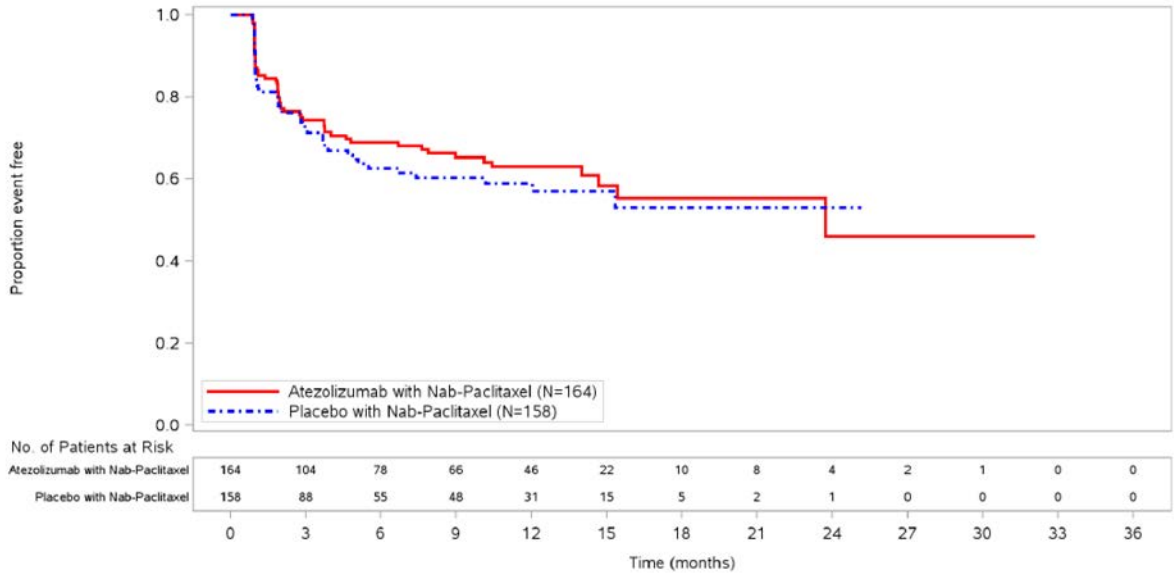

Figure 21: Kaplan-Meier curve for the outcome "time to deterioration: sexual activity" (EORTC QLQ BR23) (data cut-off: 17 April 2018)

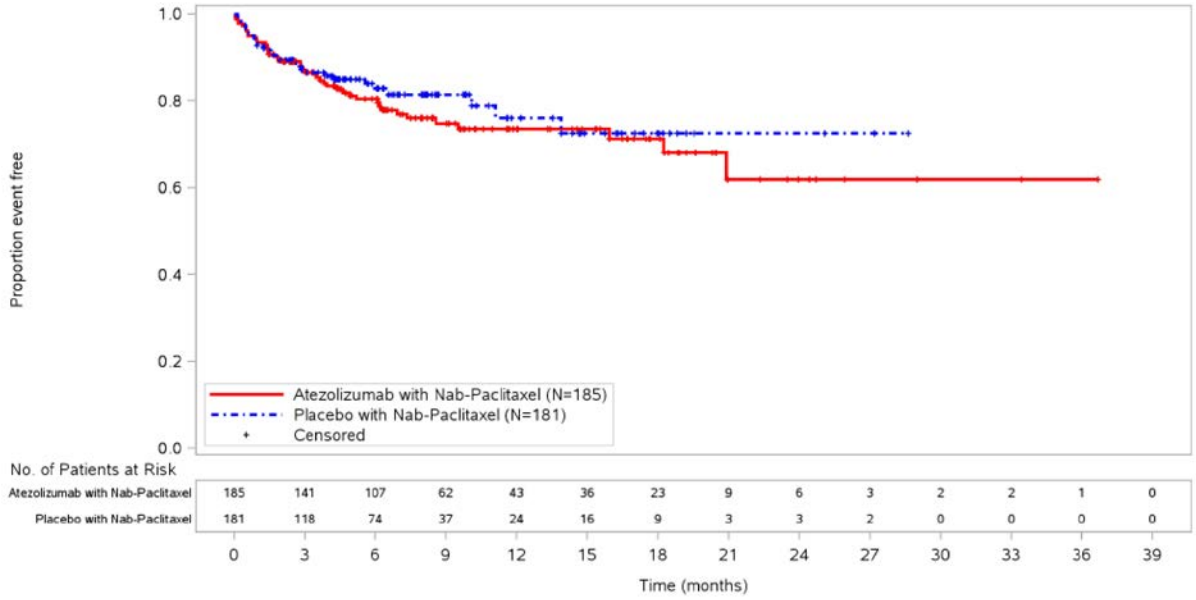

Figure 22: Kaplan-Meier curve for the outcome "SAEs" (data cut-off: 3 September 2018)

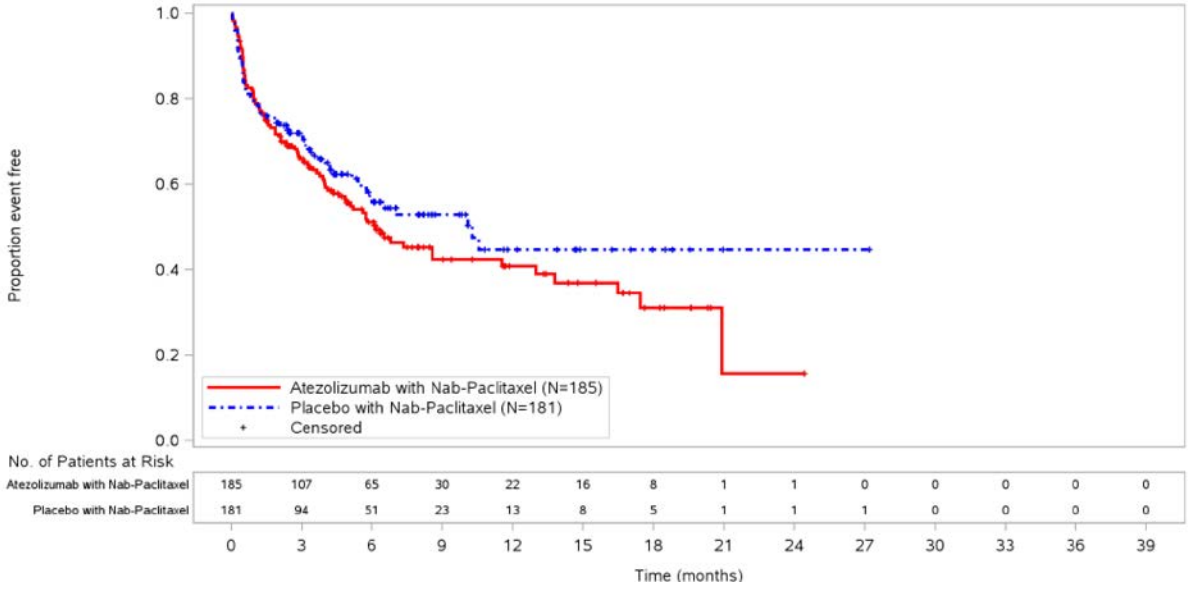

Figure 23: Kaplan-Meier curve on the outcome "severe AEs" (CTCAE grade 3–4) (data cut-off: 3 September 2018)

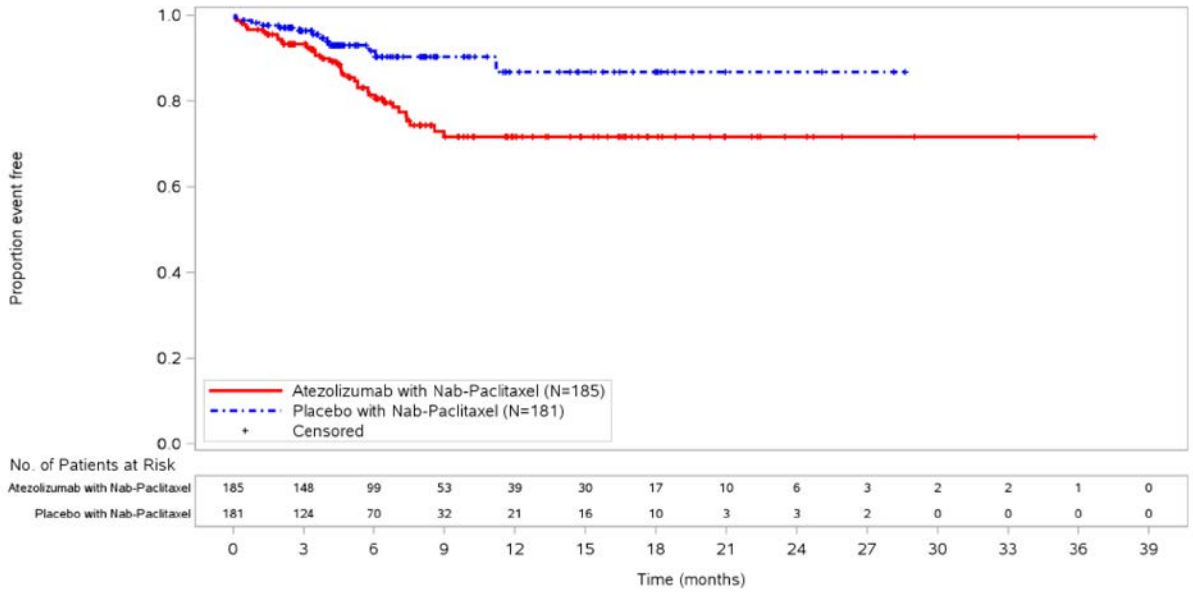

Figure 24: Kaplan-Meier curve for the outcome "discontinuation due to AEs" (data cut-off: 3 September 2018)

Appendix B – Results on side effects

The following tables present events for SOCs and PTs according to MedDRA for the overall rates of "AEs", "SAEs" and "severe AEs (e.g. CTCAE grade 3–4), each on the basis of the following criteria:

- Overall rate AEs (irrespective of the severity grade): events that occurred in at least 10% of the patients in one study arm
- Overall rates SAEs and severe AEs (CTCAE grade 3–4): events that occurred in at least 5% of the patients in one study arm
- in addition for all events irrespective of the severity grade: events that occurred in at least 10 patients and in at least 1% of the patients in one study arm

For the outcome "discontinuation due to adverse events", all events (SOCs/PTs) that resulted in discontinuation were presented".

Table 9: Common AEs[a] – RCT, direct comparison: atezolizumab + nab-paclitaxel versus placebo + nab-paclitaxel (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Atezolizumab + nab-paclitaxel N = 185**	**Placebo + nab-paclitaxel N = 181**
IMpassion130 (data cut-off 3 September 2018)		
Overall rate AEs	185 (100)	177 (97.8)
Skin and subcutaneous tissue disorders	149 (80.5)	125 (69.1)
Alopecia	112 (60.5)	100 (55.2)
Rash	31 (16.8)	29 (16.0)
Pruritus	29 (15.7)	21 (11.6)
Nail discolouration	16 (8.6)	11 (6.1)
Dry skin	15 (8.1)	9 (5.0)
Erythema	12 (6.5)	7 (3.9)
General disorders and administration site conditions	146 (78.9)	120 (66.3)
Fatigue	95 (51.4)	78 (43.1)
Pyrexia	40 (21.6)	13 (7.2)
Oedema peripheral	29 (15.7)	21 (11.6)
Asthenia	24 (13.0)	17 (9.4)
Chest pain	14 (7.6)	9 (5.0)
Chills	14 (7.6)	9 (5.0)
Mucosal inflammation	13 (7.0)	10 (5.5)
Peripheral swelling	10 (5.4)	5 (2.8)
Flu-like illness	10 (5.4)	4 (2.2)
Gastrointestinal disorders	130 (70.3)	126 (69.6)
Nausea	91 (49.2)	73 (40.3)
Diarrhoea	58 (31.4)	55 (30.4)
Constipation	53 (28.6)	41 (22.7)
Vomiting	43 (23.2)	27 (14.9)
Abdominal pain	18 (9.7)	20 (11.0)
Stomatitis	18 (9.7)	11 (6.1)
Abdominal pain upper	10 (5.4)	13 (7.2)
Dyspepsia	14 (7.6)	9 (5.0)
Dry mouth	13 (7.0)	4 (2.2)
Gastrooesophageal reflux disease	12 (6.5)	3 (1.7)
Nervous system disorders	126 (68.1)	108 (59.7)
Headache	45 (24.3)	33 (18.2)
Peripheral neuropathy	40 (21.6)	34 (18.8)
Dizziness	32 (17.3)	20 (11.0)
Dysgeusia	28 (15.1)	22 (12.2)
Peripheral sensory neuropathy	31 (16.8)	15 (8.3)

Table 9: Common AEs[a] – RCT, direct comparison: atezolizumab + nab-paclitaxel versus placebo + nab-paclitaxel (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Atezolizumab + nab-paclitaxel N = 185**	**Placebo + nab-paclitaxel N = 181**
Paraesthesia	16 (8.6)	15 (8.3)
Polyneuropathy	7 (3.8)	10 (5.5)
Infections and infestations	110 (59.5)	79 (43.6)
Urinary tract infection	22 (11.9)	18 (9.9)
Upper respiratory tract infection	25 (13.5)	14 (7.7)
Nasopharyngitis	22 (11.9)	15 (8.3)
Musculoskeletal and connective tissue disorders	102 (55.1)	84 (46.4)
Arthralgia	34 (18.4)	27 (14.9)
Myalgia	29 (15.7)	26 (14.4)
Back pain	31 (16.8)	16 (8.8)
Pain in extremity	22 (11.9)	18 (9.9)
Musculoskeletal chest pain	10 (5.4)	10 (5.5)
Bone pain	12 (6.5)	7 (3.9)
Musculoskeletal pain	9 (4.9)	10 (5.5)
Muscle spasms	14 (7.6)	3 (1.7)
Respiratory, thoracic and mediastinal disorders	94 (50.8)	74 (40.9)
Cough	54 (29.2)	36 (19.9)
Dyspnoea	27 (14.6)	24 (13.3)
Epistaxis	14 (7.6)	21 (11.6)
Oropharyngeal pain	11 (5.9)	7 (3.9)
Blood and lymphatic system disorders	91 (49.2)	62 (34.3)
Anaemia	54 (29.2)	35 (19.3)
Neutropenia	43 (23.2)	28 (15.5)
Investigations	69 (37.3)	55 (30.4)
Neutrophil count decreased	21 (11.4)	21 (11.6)
Alanine aminotransferase increased	10 (5.4)	14 (7.7)
Aspartate aminotransferase increased	12 (6.5)	11 (6.1)
White blood cell count decreased	11 (5.9)	10 (5.5)
Weight decreased	5 (2.7)	12 (6.6)
Metabolism and nutrition disorders	62 (33.5)	49 (27.1)
Decreased appetite	36 (19.5)	23 (12.7)
Hypokalaemia	13 (7.0)	4 (2.2)
Hypocalcaemia	13 (7.0)	2 (1.1)
Eye disorders	49 (26.5)	33 (18.2)
Dry eye	16 (8.6)	7 (3.9)
Lacrimation increased	12 (6.5)	9 (5.0)

Table 9: Common AEs[a] – RCT, direct comparison: atezolizumab + nab-paclitaxel versus placebo + nab-paclitaxel (multipage table)

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**Atezolizumab + nab-paclitaxel N = 185**	**Placebo + nab-paclitaxel N = 181**
Psychiatric disorders	44 (23.8)	38 (21.0)
Insomnia	25 (13.5)	24 (13.3)
Vascular disorders	44 (23.8)	35 (19.3)
Lymphoedema	13 (7.0)	10 (5.5)
Hot flush	10 (5.4)	10 (5.5)
Hypertension	8 (4.3)	11 (6.1)
Injury, poisoning and procedural complications	37 (20.0)	29 (16.0)
Endocrine disorders	41 (22.2)	6 (3.3)
Hypothyroidism	33 (17.8)	4 (2.2)
Reproductive system and breast disorders	21 (11.4)	19 (10.5)
Cardiac disorders	17 (9.2)	17 (9.4)
Renal and urinary disorders	19 (10.3)	9 (5.0)
Immune system disorders	12 (6.5)	3 (1.7)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 21.0.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 10: Common SAEs[a] – RCT, direct comparison: atezolizumab + nab-paclitaxel versus placebo + nab-paclitaxel

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**Atezolizumab + nab-paclitaxel N = 185**	**Placebo + nab-paclitaxel N = 181**
IMpassion130 (data cut-off 3 September 2018)		
Overall rate of SAEs	43 (23.2)	31 (17.1)
Infections and infestations	11 (5.9)	11 (6.1)
Respiratory, thoracic and mediastinal disorders	10 (5.4)	4 (2.2)

a. Events that occurred in ≥ 5% of the patients in at least one study arm.
b. MedDRA version 21.0.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 11: Common severe AEs[a] (CTCAE grade 3–4) – RCT, direct comparison: atezolizumab + nab-paclitaxel versus placebo + nab-paclitaxel

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Atezolizumab + nab-paclitaxel N = 185**	**Placebo + nab-paclitaxel N = 181**
IMpassion130 (data cut-off 3 September 2018)		
Overall rate of severe AEs (CTCAE grade 3–4)	97 (52.4)	73 (40.3)
Blood and lymphatic system disorders	21 (11.4)	21 (11.6)
Neutropenia	14 (7.6)	16 (8.8)
Gastrointestinal disorders	13 (7.0)	4 (2.2)
General disorders and administration site conditions	10 (5.4)	7 (3.9)
Infections and infestations	14 (7.6)	9 (5.0)
Investigations	26 (14.1)	11 (6.1)
Neutrophil count decreased	11 (5.9)	8 (4.4)
Metabolism and nutrition disorders	11 (5.9)	10 (5.5)
Nervous system disorders	25 (13.5)	11 (6.1)
Peripheral neuropathy	11 (5.9)	3 (1.7)
Respiratory, thoracic and mediastinal disorders	11 (5.9)	4 (2.2)

a. Events that occurred in ≥ 5% patients in at least one study arm
b. MedDRA version 21.0.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 12: Discontinuations due to common AEs – RCT, direct comparison: atezolizumab + nab-paclitaxel versus placebo + nab-paclitaxel (approval population) (multipage table)

Study	**Patients with event n (%)**	
PT[a, b]	**Atezolizumab + nab-paclitaxel N = 185**	**Placebo + nab-paclitaxel N = 181**
IMpassion130 (data cut-off 3 September 2018)		
Overall rate of discontinuations due to AEs	37 (20.0)	13 (7.2)
Fatigue	2 (1.1)	4 (2.2)
Peripheral oedema	1 (0.5)	0 (0)
Mucosal inflammation	1 (0.5)	0 (0)
Acute adrenocortical insufficiency	1 (0.5)	0 (0)
Syndrome of inadequate ADH secretion	1 (0.5)	0 (0)
Pharyngitis (inflammation of the throat)	1 (0.5)	0 (0)
Eczema	1 (0.5)	0 (0)
Painfulness nail bed	1 (0.5)	0 (0)
Nail discolouration	1 (0.5)	0 (0)
Acute kidney injury	1 (0.5)	0 (0)
Urinary tract pain	1 (0.5)	0 (0)
Neutropenia	0 (0)	1 (0.6)
Pain in the lower abdomen	1 (0.5)	0 (0)
Stomatitis (oral catarrh)	1 (0.5)	0 (0)
Balance disorders	1 (0.5)	0 (0)
Neurotoxicity	1 (0.5)	0 (0)
Paraesthesia	1 (0.5)	0 (0)
Peripheral neuropathy	12 (6.5)	3 (1.7)
Peripheral sensory neuropathy	6 (3.2)	4 (2.2)
Polyneuropathy	2 (1.1)	1 (0.6)
Skin infection	0 (0)	1 (0.6)
Pneumonia	0 (0)	1 (0.6)
Hepatotoxicity	1 (0.5)	0 (0)
Anxiety	1 (0.5)	0 (0)
Hypokalaemia	1 (0.5)	0 (0)
Increased alanine aminotransferase (ALT)	0 (0)	1 (0.6)
Blood alkaline phosphatase increased	1 (0.5)	0 (0)
Increased aspartate aminotransferase (AST)	1 (0.5)	1 (0.6)
Increased γ-glutamyl transferase	1 (0.5)	0 (0)
Blood creatinine increased	1 (0.5)	0 (0)
Femoral fracture	1 (0.5)	0 (0)

a. MedDRA version 21.0.
b. The company only reported analyses at PT level. The company presented no analyses at SOC level.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RTC: randomized controlled trial; SOC: System Organ Class

Appendix C – Results on EQ-5D VAS (supplementary presentation)

Table 13: Results (supplementary presentation on the health status [EQ-5D VAS]) – RCT, direct comparison: atezolizumab + nab-paclitaxel versus placebo + nab-paclitaxel

Study Outcome category Outcome	Atezolizumab + nab-paclitaxel		Placebo + nab-paclitaxel		Atezolizumab + nab-paclitaxel vs. placebo + nab-paclitaxel
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
IMpassion130					
Morbidity[b] (data cut-off: 17 April 2018)					
Health status (EQ-5D VAS)[c]	161	2.8 [1.9; 3.7] 122 (75.8)	151	3.7 [2.8; 5.2] 102 (67.5)	1.07 [0.82; 1.40]; 0.590

a. Cox regression model and log-rank test, each stratified by presence of liver metastases (yes vs. no) and prior taxane therapy (yes vs. no).
b. Results of all patients for whom an analysis at baseline and at least one analysis after the start of the study was available.
c. Time to first deterioration; defined as decrease of the score by ≥ 10 points compared with baseline.

CI: confidence interval; EQ-5D: European Quality of Life5 Dimensions; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; RCT: randomized controlled trial; VAS: visual analogue scale