Tremelimumab and durvalumab (NSCLC)

Addendum to Project A23-29 | A23-31 (dossier assessment)[1]

ADDENDUM

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ALK	anaplastic lymphoma kinase
EGFR	epidermal growth factor receptor
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NSCLC	non-small cell lung cancer
PD-L1	programmed cell death ligand 1
RCT	randomized controlled trial
SAE	serious adverse events

1 Background

On 9 August 2023, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-31 (Tremelimumab and durvalumab – Benefit assessment according to § 35a Social Code Book V) [1].

As ordered, the commission comprises the assessment and presentation of the following analyses presented by the company for adult patients for the first-line treatment of metastatic non-small cell lung cancer (NSCLC) with programmed cell death ligand 1 (PD-L1) expression ≥ 50% without sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK)-positive mutations (patient population of research question 1 of the benefit assessment; hereinafter referred to as patients with PD-L1 expression ≥ 50%):

- Side effects (if available); in particular the results (effect estimates) on side effects (serious adverse events [SAEs] and discontinuation due to adverse events [AEs]) from the indirect comparison submitted by the company.

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

For assessing the added benefit of tremelimumab + durvalumab + platinum-based chemotherapy compared with the appropriate comparator therapy (ACT) in adult patients with PD-L1 expression ≥ 50% (research question 1 of dossier assessment A23-29 | A23-31), an adjusted indirect comparison was used in which tremelimumab + durvalumab + platinum-containing chemotherapy was investigated in comparison with pembrolizumab via the common comparator of platinum-based chemotherapy.

The indirect comparison includes on the intervention side the randomized controlled trial (RCT) POSEIDON [2-4] and on the comparator side the 2 RCTs KEYNOTE-024 [5-7] and KEYNOTE-042 [8-10]. A detailed description of the 3 RCTs can be found in dossier assessment A23-29 | A23-31 [1].

As described in the dossier assessment, no data on side effects were available for the relevant subpopulation of the KEYNOTE-042 study (for reasoning, see dossier assessment A23-29 | A23-31 [1]). As data on side effects were not available for the relevant subpopulation of the KEYNOTE-042 study, the company's dossier presented indirect comparisons which included the KEYNOTE-024 study on the comparator side and an unsuitable restricted subpopulation of the KEYNOTE-042 study (Treatment of Physician's Choice [TPC] population, see dossier assessments A19-30 and A19-31 [11,12]). Overall, for the present assessment of the outcomes of SAEs and discontinuation due to AEs, both sides of the indirect comparison therefore contain complete data from only 1 study (POSEIDON study and KEYNOTE study-024). In its dossier, however, the company does not present any results on indirect comparisons which include only these 2 studies [13,14].

Irrespective of the absence of these results, the requirements for certainty of results for the outcomes of SAEs and discontinuation due to AEs are not met for conducting an adjusted indirect comparison. This is due to the fact that there is a high outcome-specific risk of bias for the results of these outcomes in both studies [1]. For the results of the outcome of SAEs, the high risk of bias in the studies is due to different observation durations between the treatment arms and the high proportion of incomplete observations for potentially informative reasons. The high risk of bias for the results of the outcome of discontinuation due to AEs in both studies is due to lack of blinding (open-label study design) in the presence of subjective outcome assessment.

As commissioned, the results of the adjusted indirect comparison for the outcomes of SAEs and discontinuation due to AEs are presented below in Table 1 according to our own calculations. The Kaplan-Meier curves are presented in Appendix A.

Table 1: Results (SAEs and discontinuation due to AEs) – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy vs. pembrolizumab: research question 1 (PD-L1 expression ≥ 50%) (multipage table)

Outcome category **Outcome** **Comparison** **Study**	**Tremelimumab + durvalumab + platinum-based chemotherapy or pembrolizumab**		**Platinum-based chemotherapy**		**Between-group difference**
	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**
Side effects					
SAEs					
Tremelimumab + durvalumab + platinum-based chemotherapy versus platinum-based chemotherapy					
POSEIDON[a]	99	15.4 [7.2; NC] 47 (47.5)	93	18.3 [6.8; NC] 37 (39.8)	0.92 [0.59; 1.43]; 0.697[b]
Pembrolizumab vs. platinum-based chemotherapy					
KEYNOTE-024 (9 May 2016 data cutoff)	154	54.1 [27.1; NC] 68 (44.2)	150	65.4 [23.1; NC] 66 (44.0)	1.00 [0.71; 1.41]; 0.994[c]
KEYNOTE-042 (26 February 2018 data cutoff)[d]	299	ND	300	ND	ND
Indirect comparison using common comparators[e]:					
Tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab					0.92 [0.53; 1.61]; 0.770[f]
Discontinuation due to AEs					
Tremelimumab + durvalumab + platinum-based chemotherapy versus platinum-based chemotherapy					
POSEIDON[g, h]	99	NR [16.4; NC] 31 (31.3)	93	NR 16 (17.2)	1.31 [0.72; 2.50]; 0.385[b]
Pembrolizumab vs. platinum-based chemotherapy					
KEYNOTE-024 (9 May 2016 data cutoff)	154	NR 14 (9.1)	150	NR 21 (14.0)	0.60 [0.31; 1.19]; 0.144[c]
KEYNOTE-042 (26 February 2018 data cutoff)	299	ND	300	ND	ND
Indirect comparison using common comparators[e]:					
Tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab					2.18 [0.87; 5.46]; 0.095[f]

Table 1: Results (SAEs and discontinuation due to AEs) – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy vs. pembrolizumab: research question 1 (PD-L1 expression ≥ 50%) (multipage table)

Outcome category **Outcome** **Comparison** **Study**	**Tremelimumab + durvalumab + platinum-based chemotherapy or pembrolizumab**		**Platinum-based chemotherapy**		**Between-group difference**
	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. For the predefined final data cutoff dated 12/03/2021, no data are available from the relevant subpopulation. The data from the dossier are used since the information on the total population is identical between the final predefined data cutoff and the data cutoff presented by the company in the dossier (11/03/2022). b. HR, 95% CI: unstratified Cox proportional hazards model; p-value: unstratified log-rank test. c. HR and 95% CI: Cox proportional hazards model, stratified by geographical region, ECOG-PS, and histology; p-value from Wald test. d. These analyses are available only separately for patients with squamous cell carcinoma (restricted to stage IV and assigned to carboplatin/paclitaxel therapy prior to randomization) and non-squamous cell carcinoma (restricted to stage IV and assigned to carboplatin/pemetrexed therapy prior to randomization) and cover only just under 50% of the relevant subpopulation. e. Indirect comparison according to Bucher [15]. f. Institute's calculation (effect, CI, p-value); due to the high risk of bias, the requirements for deriving conclusions on added benefit with sufficient certainty of results from an adjusted indirect comparison are not met. g. For the predefined final data cutoff dated 12/03/2021, no data are available from the relevant subpopulation. The data from the dossier are used since the information on the total population exhibits no relevant difference between the final predefined data cutoff and the data cutoff presented by the company in the dossier (25/10/2021). h. No information is available on the operationalization in Module 4 A, but according to the study documents, it can be assumed that at least 1 drug component was discontinued. AE: adverse event; CI: confidence interval; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least 1) event; NC: not calculable; ND: no data; NR: not reached; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SAE: serious adverse event					

2.1 Summary

The present addendum does not change the conclusions on the added benefit of tremelimumab + durvalumab + platinum-based chemotherapy from dossier assessment A23-29 | A23-31.

Table 2 below shows the result of the benefit assessment of tremelimumab + durvalumab + platinum-based chemotherapy taking into account dossier assessment A23-29 | A23-31 and the present addendum.

Table 2: Tremelimumab + durvalumab + platinum-based chemotherapy – probability and extent of added benefit (multipage table)

Research question	**Therapeutic indication**	**ACT**[a, b]	**Probability and extent of added benefit**
1	Adult patients with metastatic NSCLC with PD-1 expression ≥ 50% without sensitizing EGFR mutations or ALK-positive mutations[c]; first-line treatment[d]	▪ **Pembrolizumab as monotherapy** or ▪ atezolizumab as monotherapy or ▪ cemiplimab as monotherapy or ▪ nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG-PS 0–1) or ▪ pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel[c] (only for patients with ECOG-PS 0–1 and squamous NSCLC) or ▪ pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy[c] (only for patients with ECOG-PS 0–1 and non-squamous NSCLC) or ▪ atezolizumab in combination with bevacizumab, paclitaxel, and carboplatin (only for patients with ECOG PS 0–1 and non-squamous NSCLC) or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG-PS 0–1 and non-squamous NSCLC)	Added benefit not proven[e]

Table 2: Tremelimumab + durvalumab + platinum-based chemotherapy – probability and extent of added benefit (multipage table)

Research question	**Therapeutic indication**	**ACT**[a, b]	**Probability and extent of added benefit**
2	Adult patients with metastatic NSCLC with PD-1 expression < 50% without sensitizing EGFR mutations or ALK-positive mutations[c]; first-line treatment[d]	▪ Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy[c] (only for patients with ECOG-PS 0–1 and non-squamous NSCLC) or ▪ pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel[c] (only for patients with ECOG-PS 0–1 and squamous NSCLC) or ▪ atezolizumab as monotherapy (only for patients with PD-L1 expression ≥ 10% in tumour-infiltrating immune cells) or ▪ atezolizumab in combination with bevacizumab, paclitaxel and carboplatin (only for patients with ECOG PS 0–1 and non-squamous NSCLC) or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG PS 0–1 and non-squamous NSCLC) or ▪ **nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG PS 0–1)** or ▪ carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[f]; only for patients with ECOG-PS 2) or ▪ carboplatin in combination with nab-paclitaxel (only for patients with ECOG-PS 2)	Added benefit not proven[e]

Table 2: Tremelimumab + durvalumab + platinum-based chemotherapy – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a, b]	Probability and extent of added benefit
a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold. b. The sole comparison with a therapy option which represents a comparator therapy only for part of the patient population is generally insufficient to demonstrate added benefit for the overall population. c. This refers to a patient population without genomic EGFR mutations or ALK-positive mutations, as designated by the G-BA when it determined the ACT. In the present benefit assessment, the wording according to the SPC was used. d. In terms of the applicable therapeutic indication, in accordance with the G-BA, it is assumed that neither definitive radiochemotherapy nor definitive local therapy are indicated. In addition, it is assumed that molecularly stratified therapy (directed against BRAF, KRAS, G12C, METex14, RET, or ROS1) is not an option for the patients at the time of treatment with tremelimumab in combination with durvalumab. e. Only patients with an ECOG-PS of 0 or 1 were included in the studies for the indirect comparison. f. See Annex VI to Section K of the Pharmaceutical Guideline [16]. ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; KRAS: Kirsten rat sarcoma viral oncogene homologue; MET: mesenchymal-epithelial transition factor; METex14: exon 14 of the MET gene; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1; SPC: Summary of Product Characteristics			

The G-BA decides on the added benefit.

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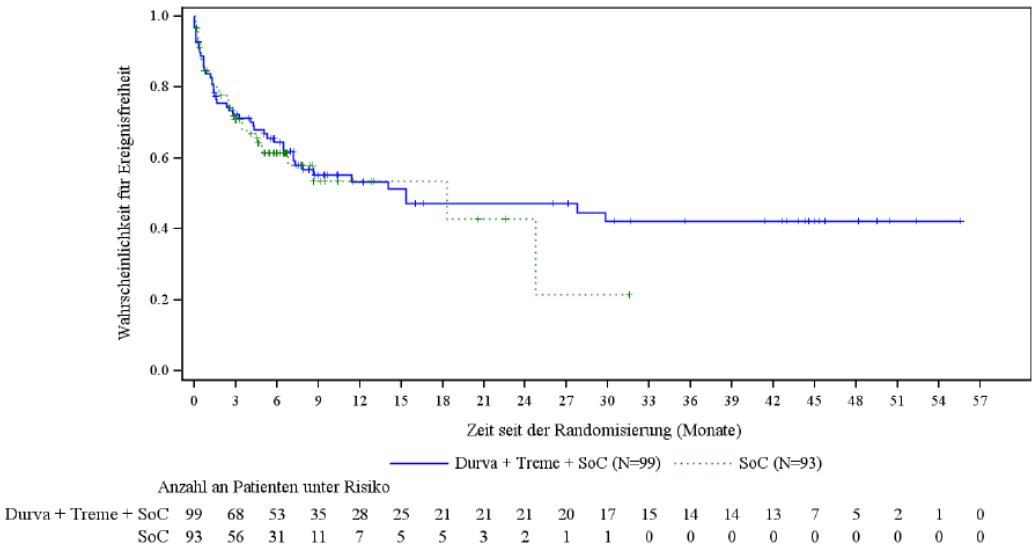
Appendix A Kaplan-Meier curves



For the predefined final data cutoff dated 12 March 2021, no data are available from the relevant subpopulation. The data from the dossier are presented since the information on the total population is identical between the final predefined data cutoff and the data cutoff presented by the company in the dossier (11 March 2022).

Figure 1: Kaplan-Meier curves for the outcome of SAEs (POSEIDON study; research question 1: PD-L1 expression ≥ 50%)

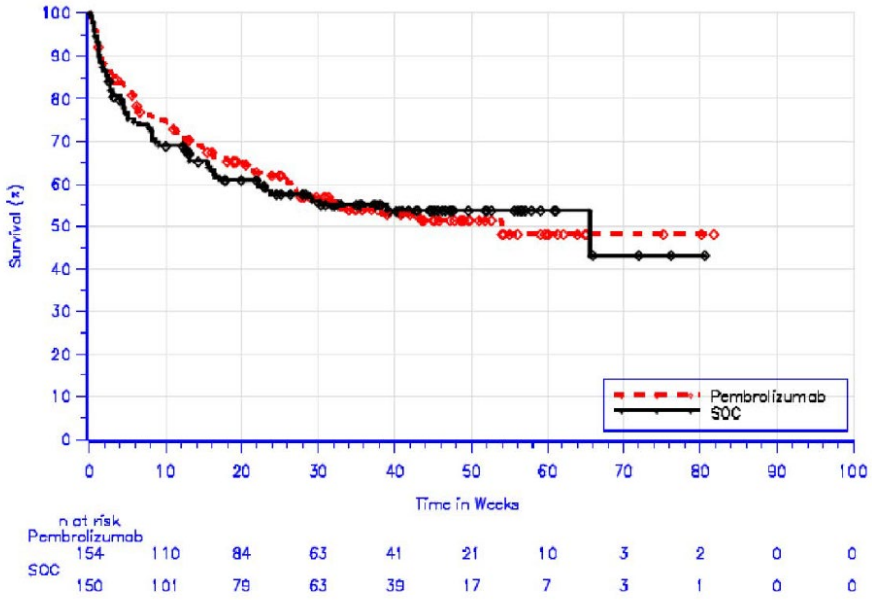
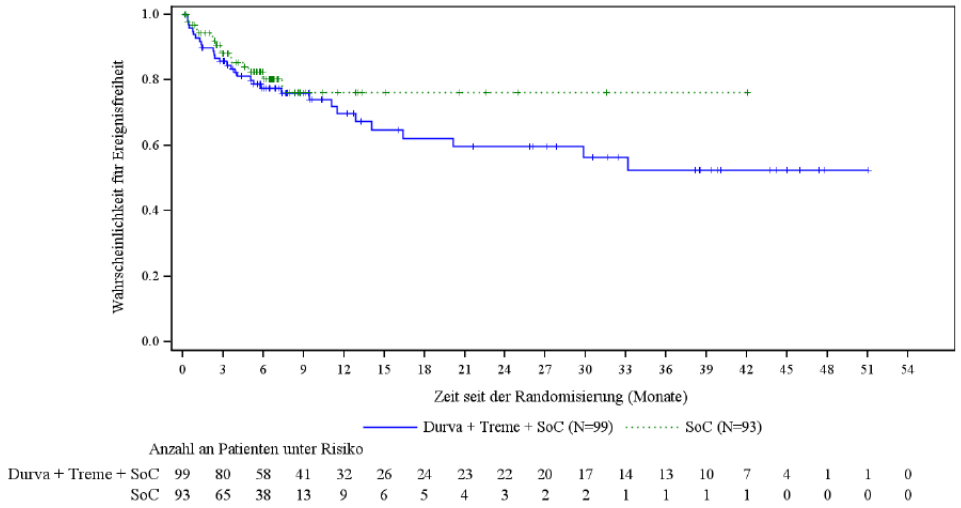


Figure 2: Kaplan-Meier curves for the outcome of SAEs (KEYNOTE-024 study; research question 1: PD-L1 expression ≥ 50%); data cutoff: 9 May 2016



For the predefined final data cutoff dated 12 March 2021, no data are available from the relevant subpopulation. The Kaplan-Meier curves from the dossier are presented since the information on the total population exhibits no relevant difference between the final predefined data cutoff and the data cutoff presented by the company in the dossier (25 October 2021).

Figure 3: Kaplan-Meier curves for the outcome of discontinuation of at least 1 drug component due to AEs (POSEIDON study; research question 1: PD-L1 expression ≥ 50%)

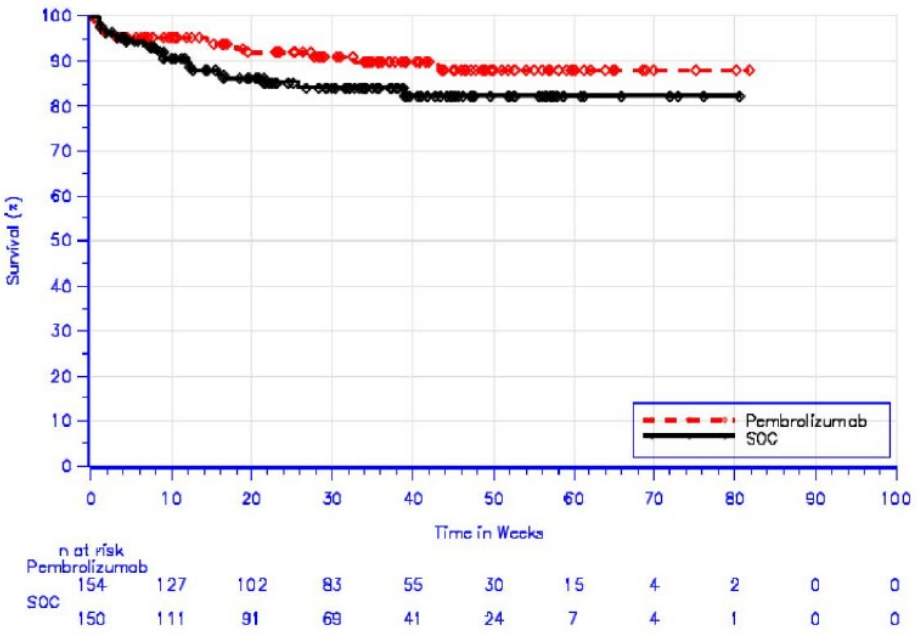


Figure 4: Kaplan-Meier curves for the outcome of discontinuation due to AEs (KEYNOTE-024 study; research question 1: PD-L1 expression ≥ 50%); data cutoff: 9 May 2016