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Pembrolizumab (classical Hodgkin lymphoma; adults, children and adolescents aged 3 years and older) –

Addendum to Commission A21-35[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
AEOSI	adverse events of special interest
auto SCT	autologous stem cell transplant
CTCAE	Common Terminology Criteria for Adverse Events
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PT	preferred term
SAE	serious adverse event
SCT	stem cell transplant
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 10 August 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A21-35 (Pembrolizumab – Benefit assessment according to § 35a Social Code Book V) [1].

The A21-35 benefit assessment used the KEYNOTE 204 study to assess the benefit of pembrolizumab in adults with relapsed or refractory classical Hodgkin lymphoma (cHL) following failure of autologous stem cell transplant (auto SCT) or following at least 2 prior therapies if auto SCT is not an option. In its comment [2], the pharmaceutical company (hereinafter "company") submitted further analyses for the relevant subpopulation of this study (patients with at least 2 prior therapies), going beyond the information provided in the dossier.

The G-BA commissioned IQWiG with assessing the following analyses submitted by the company in the commenting procedure, taking into account the information provided in the dossier [2]:

- Analyses for the outcomes of immune-related serious adverse events (SAEs) and immune-related severe adverse events (AEs) (Common-Terminology-Criteria-for-Adverse-Events [CTCAE] grade ≥ 3) in third-line therapy: outcomes of immune-related SAEs (Adverse Events of Special Interest [AEOSI]) and severe (CTCAE grades 3 to 5) immune-mediated AEs (AEOSI)
- AEs – nervous system disorders: Subgroup analyses for preferred terms (PTs) neuropathies for patients with at least 2 prior therapies

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

2 Assessment

2.1 Subsequently submitted analyses of immune-mediated AEs

In the KEYNOTE 204 study, immune-related SAEs and severe AEs (CTCAE grade ≥ 3) were surveyed using a list predefined by the company. In dossier assessment A21-35, data were available only for the total population. In its comment, the company presented these analyses for the relevant subpopulation. The relevant subpopulation comprised 124 patients (82.1% of the total population) in the pembrolizumab arm and 125 patients (81.7% of the total population) in the brentuximab vedotin arm.

Risk of bias

Like the risk of bias of results for the higher-level category of side effects (SAEs and severe AEs), the risk of bias of results of immune-related SAEs and severe AEs (CTCAE grade ≥ 3) is rated as high, in line with dossier assessment A21-35, because these outcomes were surveyed incompletely for potentially informative reasons; this was in large part due to treatment discontinuation after disease progression or AE.

Results

Table 1 shows the results for the outcomes of immune-related SAEs and severe AEs (CTCAE grade ≥ 3). No Kaplan-Meier curves are available for the subsequently submitted analyses of immune-related AEs.

Table 1: Results (side effects) – RCT, direct comparison: pembrolizumab vs. brentuximab vedotin (relevant subpopulation)

Study Outcome category Outcome	Pembrolizumab		Brentuximab vedotin		Pembrolizumab vs. brentuximab vedotin
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months[a] [95% CI] Patients with event n (%)	HR [95% CI][b]; p-value[b, c]
KEYNOTE 204					
Side effects					
Immune-related SAEs	121	NR 11 (9.1)	125	NR 5 (4.0)	1.80 [0.62; 5.27]; 0.282
Immune-related severe AEs[d]	121	NR 10 (8.3)	125	NR 5 (4.0)	1.45 [0.49; 4.32]; 0.506

a. Product limit (Kaplan-Meier) estimator method.
b. Cox proportional hazards model.
c. Wald test.
d. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NR: not reached; RCT: randomized controlled trial; SAE: serious adverse event

Side effects

Immune-related SAEs and immune-related severe AEs (CTCAE grade ≥ 3)

No statistically significant difference between treatment groups was found for the outcome of immune-related SAEs or for the outcome of immune-related severe AEs. This results in no hint of greater or lesser harm of pembrolizumab in comparison with brentuximab vedotin; greater or lesser harm is therefore not proven.

Subgroups and other effect modifiers

For the analyses of immune-related AEs in the relevant subpopulation, which were subsequently submitted with the comment, the company did not submit any subgroup analyses.

2.2 Subsequently submitted analyses on neuropathies

As discussed in dossier assessment A21-35, it is not possible to select specific AEs because the data on common AEs, severe AEs (CTCAE grade ≥ 3), and SAEs are incomplete for the relevant subpopulation. This is due to the fact that the analyses on the relevant subpopulation were based on the company's subgroup analyses. However, Module 4 provides subgroup analyses only for common AEs / severe AEs / SAEs for which a statistically significant difference between treatment groups was found in the total population.

In the comment, the company subsequently submitted data only on neuropathies (PTs of peripheral neuropathy and peripheral sensory neuropathy). Due to the selectivity of this subsequent data submission, selecting specific AEs is not meaningful. For the relevant subpopulation, data are therefore still lacking on relevant side effects of pembroluzimab, such as pneumonitis. The results on neuropathy are consequently presented as supplementary information only (see Appendix A and Appendix B).

2.3 Assessment of added benefit at outcome level (subsequently submitted analyses)

Table 2 shows the probability and extent of added benefit for the subsequently submitted analyses.

Table 2: Extent of added benefit at outcome level: pembrolizumab vs. brentuximab vedotin

Outcome category **Outcome**	**Pembrolizumab vs. brentuximab vedotin** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
Immune-related SAEs	NR vs. NR HR: 1.80 [0.62; 5.27]; p = 0.282	Greater/lesser harm not proven
Immune-related severe AEs[c]	NR vs. NR HR: 1.45 [0.49; 4.32]; p = 0.506	Greater/lesser harm not proven
a. Probability is stated whenever a statistically significant and relevant effect is present. b. Estimations of effect size are made depending on the outcome category, with different limits according to the upper limit of the confidence interval (CI_u). c. Operationalized as CTCAE grade ≥ 3. AE: adverse event; CI: confidence interval; CI_u: upper confidence limit; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; NR: not reached; SAE: serious adverse event		

2.4 Overall conclusion on added benefit

Table 3 summarizes the results of the benefit assessment for commission A21-35 and the present addendum, both of which were used to inform the overall conclusion on the extent of added benefit.

Table 3: Favourable and unfavourable effects from the assessment of pembrolizumab in comparison with therapy upon the physician's discretion

Favourable effects	**Unfavourable effects**
Non-serious/non-severe symptoms / late complications ▪ Fatigue, pain, appetite loss (EORTC QLQ-C30): Hint of added benefit for each – extent: non-quantifiable	-
Health-related quality of life ▪ Global health status, physical functioning, role functioning, emotional functioning, social functioning (EORTC QLQ-C30): Hint of added benefit for each – extent: non-quantifiable	-
Serious/severe side effects ▪ Severe AEs Hint of lesser harm – extent: minor	-
Specific AEs ▪ Selecting specific AEs is not meaningful because complete data on common AEs, SAEs, and severe AEs are not available for the relevant subpopulation and using the data for the total population is inadequate (see A21-35, Section 2.3.2.1).	
AE: adverse event; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; SAE: serious adverse event	

The data subsequently submitted with the comment do not show an additional favourable or unfavourable effect other than the effects presented in dossier assessment A21-23. In addition, data on specific AEs for the relevant subpopulation are missing.

2.5 Summary

The data subsequently submitted by the company in the commenting procedure do not change the conclusion drawn in dossier assessment A21-35 on the added benefit of pembrolizumab.

Table 4 below shows the result of the benefit assessment of pembrolizumab in consideration of both dossier assessment A21-35 and the present addendum.

Table 4: Pembrolizumab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with relapsed or refractory classical Hodgkin lymphoma following failure of auto SCT or following at least 2 prior therapies if auto SCT is not an option	Therapy upon the physician's discretion	Patients for whom brentuximab vedotin is the suitable therapy upon the physician's discretion: hint of non-quantifiable added benefit[c]
		Patients for whom brentuximab vedotin is not the suitable therapy upon the physician's discretion: added benefit not proven
Children and adolescents 3 years and older with relapsed or refractory classical Hodgkin lymphoma following failure of auto SCT or following at least 2 prior therapies where auto SCT is not an option	Therapy upon the physician's discretion	added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. Adult patients in the previously assessed therapeutic indication (adults with relapsed or refractory classical Hodgkin lymphoma after autologous SCT and treatment with brentuximab vedotin or after failure of a treatment with brentuximab vedotin if autologous SCT is not an option, see dossier assessment A17-23 [3]; the decision [4], and the G-BA's justification paper [5]) are not the subject of the present benefit assessment. For the present benefit assessment, the newly added therapeutic indication as per the expansion of the therapeutic indication is relevant.
c. Only patients with an ECOG-PS of 0 or 1 were included in the KEYNOTE 204 study. It remains unclear whether the observed effects can be assumed to occur also in patients with an ECOG-PS ≥ 2.

auto SCT: autologous stem cell transplantation; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

3 References

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5. Gemeinsamer Bundesausschuss. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewer-tung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Pembrolizumab (neues Anwendungsgebiet: Hodgkin-Lymphom) [online]. 2017 [Accessed: 15.06.2021]. URL: https://www.g-ba.de/downloads/40-268-4659/2017-11-17_AM-RL-XII_Pembrolizumab_D-288_TrG.pdf.

Appendix A – Supplementary presentation on the outcome of neuropathy

Table 5: Results (side effects) – RCT, direct comparison: pembrolizumab vs. brentuximab vedotin (relevant subpopulation)

Study Outcome category	Pembrolizumab		Brentuximab vedotin		Pembrolizumab vs. brentuximab vedotin
Outcome	**N**	**Median time to event in months [95% CI] Patients with event n (%)**	**N**	**Median time to event in months[a] [95% CI] Patients with event n (%)**	**HR [95% CI][b]; p-value[b, c]**
KEYNOTE 204					
Side effects					
Neuropathy[d] (AEs)	121	NR 8 (6.6)	125	10.7 [8.8; NC][e] 39 (31.2)	0.12 [0.05, 0.26]; < 0.001
Neuropathy[d] (SAEs)	121	NR 0 (0)	125	NR 2 (1.6[f])	–[g]
Neuropathy[d] (severe AEs[h])	121	NR 1 (0.8[f])	125	NR 2 (1.6[f])	–[g]

a. Product limit (Kaplan-Meier) estimator method.
b. Cox proportional hazards model.
c. Wald test.
d. Made up of the following events (coded using MedDRA): peripheral neuropathy (PT); peripheral sensory neuropathy (PT).
e. IQWiG calculation (Weeks*7*12/365.25).
f. IQWiG calculations.
g. In the comment, the company states that analyses for the calculation of effect estimators were foregone due to the small numbers of events (n = 0 and n = 1 in the pembrolizumab arm; n = 2 and n = 2 in the brentuximab vedotin arm).
h. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached; RCT: randomized controlled trial; SAE: serious adverse event

Appendix B Kaplan-Meier curves

B.1 Side effects

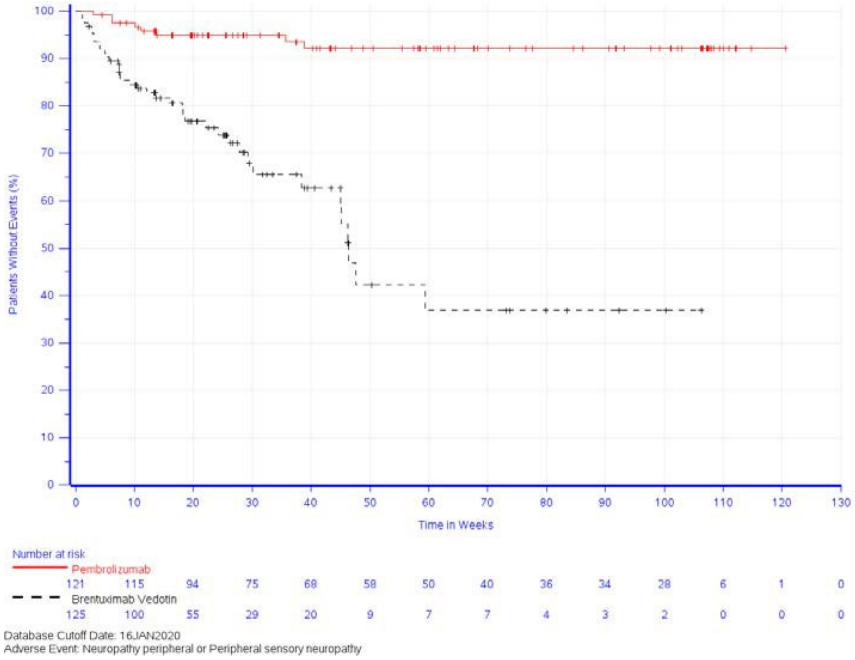

Figure 1: Kaplan-Meier curves, outcome of neuropathy (made up of the events of peripheral neuropathy [PT]; peripheral sensory neuropathy [PT]) (AEs), KEYNOTE 204 study (relevant subpopulation); 2nd data cut-off of (16/01/2020)