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Pembrolizumab (breast cancer) –

Addendum to Commission A21-145[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CPS	combined positive score
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PD-L1	programmed cell death ligand 1
RCT	randomized controlled trial

1 Background

On 30 March 2022, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A21-145 (Pembrolizumab – Benefit assessment according to §35a Social Code Book V) [1].

This commission comprises assessing the outcome of treatment discontinuation due to adverse events (AEs) from the KEYNOTE 355 study based on the data provided in the dossier and taking into account the clarification on the operationalization submitted by the company in the commenting procedure.

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

The randomized controlled trial (RCT) KEYNOTE 355 was used to assess the benefit of pembrolizumab in combination with chemotherapy in comparison with the appropriate comparator therapy (ACT) in adult patients with locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC) whose tumours express programmed cell death ligand 1 (PD-L1) (combined positive score [CPS] ≥ 10) and who have not received prior chemotherapy for metastatic disease. The benefit assessment analysed the subpopulation of patients with CPS > 10 and a pre-randomization allocation to paclitaxel or nab-paclitaxel chemotherapy.

For the outcome of discontinuation due to AEs, the dossier [2] did not show whether it was operationalized as discontinuation of at least 1 drug or discontinuation of all drugs (see dossier assessment A21-145 [1]).

The company's comments [3] clarify that the analysis takes into account patients who discontinued at least 1 drug component.

The analysis conducted in the dossier is therefore deemed usable.

Risk of bias

The risk of bias for the results of the outcome of discontinuation due to AEs is rated as low. Despite this low risk of bias, however, the certainty of results is reduced for the outcome of discontinuation due to AEs. Premature treatment discontinuation for reasons other than AEs represents a competing event for the outcome to be recorded, discontinuation due to AEs. Consequently, after discontinuation for other reasons, AEs which would have led to discontinuation may have occurred, but the criterion of discontinuation can no longer be applied to them. It is impossible to estimate how many AEs are affected by this issue.

Results

Table 1shows the result for the outcome of discontinuation due to AEs. Results on frequent discontinuations due to AEs are presented in Appendix A.

Table 1: Results (side effects) – RCT, direct comparison: pembrolizumab + chemotherapy[a] versus placebo + chemotherapy[a]

Study Outcome category Outcome	Pembrolizumab + chemotherapy[a]		Placebo + chemotherapy[a]		pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a]
	L	Median time to event in months [95% CI] Patients with event n (%)	L	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][b]; p-value[b]
KEYNOTE 355					
Side effects					
Discontinuation due to AEs[c,d]	95	NR [23.5; NC][e] 24 (25.3)	47	NR [19.9; NC][e] 4 (8.5)	2.43 [0.84; 7.02]; 0.101

a. For the analysed subpopulation: paclitaxel or nab-paclitaxel.
b. Cox proportional hazards model with treatment as covariate, stratified by prior treatment with the same chemotherapy substance class in the (neo)adjuvant setting (yes vs. no); 2-sided p-value (Wald test, score test in case of 0 events in 1 of the study arms).
c. Without recording of progression of the underlying disease.
d. Operationalized as discontinuation of at least 1 drug component.
e. IQWiG converted from weeks to months (month = week x 7 x 12 / 365.25).

AE: adverse event; CI: confidence interval; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached; RCT: randomized controlled trial

No statistically significant difference was found between treatment groups for the outcome of discontinuation due to AEs. This results in no hint of greater or lesser harm from pembrolizumab + chemotherapy in comparison with the ACT; greater or lesser harm is therefore not proven.

2.1 Summary

The information subsequently submitted by the company during the commenting procedure does not change the conclusion on the added benefit of pembrolizumab drawn in dossier assessment A21-145 [1].

Table 2 below shows the result of the benefit assessment of pembrolizumab, taking into account dossier assessment A21-145 and the present addendum.

Table 2: Pembrolizumab + chemotherapy – probability and extent of added benefit

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

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

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

The G-BA decides on the added benefit.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Pembrolizumab (Mammakarzinom) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2022 [Accessed: 12.04.2022]. URL: https://www.iqwig.de/download/a21-145_pembrolizumab_nutzenbewertung-35a-sgb-v_v1-0.pdf.

2. MSD Sharp & Dohme. Pembrolizumab (KEYTRUDA); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2022 [Accessed: 31.03.2022]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/757/#dossier.

3. MSD Sharp & Dohme. Stellungnahme zum IQWiG-Bericht Nr. 1289: Pembrolizumab (Mammakarzinom) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung.: [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/757/#beschluesse in the document "Zusammenfassende Dokumentation"].

Appendix A – Results on frequent discontinuations due to AEs

Table 3: Discontinuations due to AEs – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a] (multipage table)

Study	Patients with event n (%)	
SOC[b] PT[b]	**Pembrolizumab + chemotherapy[a] N = 95**	**placebo + chemotherapy[a] N = 47**
KEYNOTE 355		
Overall rate of discontinuations due to AEs[c, d]	24 (25.3)	4 (8.5)
Blood and lymphatic system disorders	1 (1.1)	0 (0)
Leukopenia	1 (1.1)	0 (0)
Eye disorders	1 (1.1)	0 (0)
Cystoid macular oedema	1 (1.1)	0 (0)
Gastrointestinal disorders	1 (1.1)	0 (0)
Pancreatitis	1 (1.1)	0 (0)
General disorders and administration site conditions	2 (2.1)	0 (0)
Mucosal inflammation	1 (1.1)	0 (0)
Oedema peripheral	1 (1.1)	0 (0)
Hepatobiliary disorders	2 (2.1)	0 (0)
Autoimmune hepatitis	1 (1.1)	0 (0)
Liver disease	1 (1.1)	0 (0)
Infections and infestations	4 (4.2)	1 (2.1)
Paronychia	1 (1.1)	0 (0)
Pneumonia	1 (1.1)	1 (2.1)
Sepsis	1 (1.1)	0 (0)
Staphylococcus infection	1 (1.1)	0 (0)
Injury, poisoning, and procedural complications	1 (1.1)	0 (0)
Alcohol poisoning	1 (1.1)	0 (0)
Investigations	4 (4.2)	0 (0)
Alanine aminotransferase increased	3 (3.2)	0 (0)
Aspartate aminotransferase increased	2 (2.1)	0 (0)
Blood creatinine increased	1 (1.1)	0 (0)
Metabolic and nutritional disorders	0 (0)	1 (2.1)
Decreased appetite	0 (0)	1 (2.1)
Musculoskeletal and connective tissue disorders	2 (2.1)	1 (2.1)
Arthralgia	1 (1.1)	0 (0)
Polyarthritis	1 (1.1)	0 (0)
Scleroderma	0 (0)	1 (2.1)

Table 3: Discontinuations due to AEs – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a] (multipage table)

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**Pembrolizumab + chemotherapy[a] N = 95**	**placebo + chemotherapy[a] N = 47**
Nervous system disorders	4 (4.2)	1 (2.1)
Peripheral neuropathy	2 (2.1)	1 (2.1)
Peripheral motor neuropathy	1 (1.1)	0 (0)
Peripheral sensory neuropathy	1 (1.1)	0 (0)
Reproductive system and breast disorders	1 (1.1)	0 (0)
Pelvic pain	1 (1.1)	0 (0)
Respiratory, thoracic, and mediastinal disorders	3 (3.2)	0 (0)
Dyspnoea	1 (1.1)	0 (0)
Pneumonitis	2 (2.1)	0 (0)
Skin and subcutaneous tissue disorders	1 (1.1)	0 (0)
Allergic dermatitis	1 (1.1)	0 (0)

a. For the analysed subpopulation: paclitaxel or nab-paclitaxel.
b. MedDRA version 24.0; SOCs and PTs taken from Module 4 B.
c. Without recording of progression of the underlying disease.
d. Operationalized as discontinuation of at least 1 drug component.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class