IQWiG Reports – Commission No. A22-58

Pembrolizumab (endometrial carcinoma) –

Addendum to Commission A21-164[1]

Addendum

Commission: A22-58
Version: 1.0
Status: 15 June 2022

[1] Translation of addendum A22-58 *Pembrolizumab (Endometriumkarzinom) – Addendum zum Auftrag A21-164* (Version 1.0; Status: 15 June 2022). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Pembrolizumab (endometrial carcinoma) – Addendum to Commission A21-164

Commissioning agency
Federal Joint Committee

Commission awarded on
14 May 2022

Internal Commission No.
A22-58

Address of publisher
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Keywords: Pembrolizumab, Lenvatinib, Endometrial Neoplasms, Benefit Assessment, NCT03517449

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
EORTC	European Organisation for Research and Treatment of Cancer
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
QLQ-EN24	Quality of Life Questionnaire – Endometrial Cancer Module 24
SAE	serious adverse event

1 Background

On 24 May 2022, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A21-164 (Pembrolizumab – Benefit assessment according to §35a Social Code Book V) [1].

The commissioned order comprises the assessment of the subgroup analyses presented in the commenting procedure as well as the information provided on the median treatment and observation durations in the overall population of the KEYNOTE 775/309 study at data cut-off 26 October 2020 (1st interim analysis), taking into account the information in the dossier.

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, active control, open-label study KEYNOTE775/309 [2-5] was used to assess the benefit of pembrolizumab in combination with lenvatinib (hereinafter referred to as "pembrolizumab + lenvatinib ") in adult patients with advanced or recurrent endometrial cancer whose disease has progressed during or after prior platinum-based therapy at any stage of disease, when surgery or radiation to cure the cancer is not an option for them. This study compared pembrolizumab + lenvatinib with therapy according to physician's choice, selecting from doxorubicin or paclitaxel. A detailed description of the KEYNOTE 755/309 study can be found in dossier assessment A21-164 [1].

The study's total population is relevant for the benefit assessment. Concerning the total population, however, the dossier presents subgroup analyses for the relevant subgroup characteristics of age and histology only for the outcome of overall survival [6]. After the oral hearing [7], the company subsequently submitted subgroup analyses for the total population of the KEYNOTE 775/309 study at data cut-off 26 October 2020. Furthermore, the company subsequently submitted with its comments missing data on observation durations [8]. The subsequently submitted data are evaluated below.

2.1 Information on the course of the study

For morbidity, health-related quality of life, and side effects outcomes, the company's dossier did not provide any information on outcome-specific observation durations for the total population of the KEYNOTE 775/309 study. Table 1 shows the median/mean treatment duration of patients and the median/mean observation duration for individual outcomes, taking into account the information provided in the dossier and the comments.

Table 1: Information on the course of the study – RCT, direct comparison: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Study **Duration of the study phase** **Outcome category**	**Pembrolizumab + lenvatinib** **N = 411**	**Therapy according to physician's choice (doxorubicin or paclitaxel)** **N = 416**
KEYNOTE 775/309		
Treatment duration[a] [months]		
Pembrolizumab + lenvatinib / therapy according to physician's choice (doxorubicin or paclitaxel)		
Median [min; max]	6.3 [0; 25.8][b,c]	3.4 [0; 25.8][b]
Mean (SD)	7.6 (6.1)[b]	3.6 (3.0)[b]
Lenvatinib		
Median [min; max]	6.9 [0; 26.8][b]	--
Mean (SD)	8.3 (6.3)[b]	--
Pembrolizumab		
Median [min; max]	6.9 [0; 25.8][b]	--
Mean (SD)	8.3 (6.3)[b]	--
Doxorubicin[d]		
Median [min; max]	--	2.8 [ND]
Mean (SD)	--	ND
Paclitaxel[d]		
Median [min; max]	--	ND
Mean (SD)	--	ND
Observation duration [months]		
Overall survival[e]		
Median [min; max]	12.2 [0.3; 26.9][f]	10.7 [0.3; 26.3][f]
Mean (SD)	12.7 (6.3)	11.0 (5.9)
Morbidity and health-related quality of life		
EORTC QLQ-C30, EQ-5D VAS		
Median [min; max]	8.3 [ND; ND]	3.9 [ND; ND]
Mean (SD)	ND	ND
EORTC QLQ-EN24		
Median [min; max]	8.1 [ND; ND]	3.9 [ND; ND]
Mean (SD)	ND	ND
Side effects		
AEs		
Median [min; max]	8.5 [ND; ND]	4.4 [ND; ND]
Mean (SD)	ND	ND
SAEs		
Median [min; max]	10.2 [ND; ND]	6.9 [ND; ND]
Mean (SD)	ND	ND

Table 1: Information on the course of the study – RCT, direct comparison: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Study **Duration of the study phase** **Outcome category**	**Pembrolizumab + lenvatinib** **N = 411**	**Therapy according to physician's choice (doxorubicin or paclitaxel)** **N = 416**
a. Information is based on patients who received at least 1 dose of the study medication: 406 vs. 388 patients. b. Institute's conversion from days to months. c. In its comments, the company reports a median treatment duration of 7.6 months. Based on the comparison with the study report, this data point refers to "duration on therapy". Presumably, this means pembrolizumab and/or lenvatinib treatment. d. In the control arm, 289 patients were treated with doxorubicin and 99 patients with paclitaxel. e. The observation duration is defined as the time from randomization until death or up to the current data cut-off if the patient is still alive. f. Information from dossier assessment A21-164, taken from the study report. The company's comments indicate a median observation duration of 11.9 months in the intervention arm and 9.7 months in the control arm. The source of the deviations is unclear. AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; max: maximum; min: minimum; N: number of analysed patients; ND: no data; QLQ-C30: Quality of Life Questionnaire – Core 30; QLQ-EN24: Quality of Life Questionnaire – Endometrial Cancer Module 24; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; VAS: visual analogue scale		

Compared to the median observation duration for overall survival, the median observation durations for morbidity, health-related quality of life, and side effects outcomes are shortened. Since the observation durations for these outcomes were coupled to the treatment end, both the observation durations and the treatment durations are substantially longer in the intervention arm than in the comparator arm. The subsequently submitted data from the comments thereby confirm the conclusions in dossier assessment A21-164 with regard to observation durations being shortened and differing between study arms. For these outcomes, conclusions can therefore be drawn only for a shortened observation period. The conclusions from dossier assessment A21-164 regarding a high risk of bias for the results on morbidity, health-related quality of life, and side effects are likewise confirmed by the subsequently submitted data.

2.2 Results on added benefit

The results for the total population can be found in dossier assessment A21-164 [1].

2.2.1 Subgroups and other effect modifiers

The following relevant subgroup characteristics were selected:

- age (< 65 years versus ≥ 65 years)
- histology (endometrioid vs. non-endometrioid)

With the addition of the data subsequently submitted after the oral hearing, subgroup analyses are now available regarding both characteristics for all patient-relevant outcomes except

immune-related serious adverse events (SAEs) and severe adverse events (AEs). The company did not justify its failure to submit any subgroup analyses for said outcomes.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least 1 subgroup.

Presented are only the results involving an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05). In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least 1 subgroup. Subgroup results where the extent did not differ between subgroups are not presented.

The results of the subgroup analyses are presented in Table 2 and Table 3. The Kaplan-Meier curves on time-to-event analyses are presented in Appendix A.

Table 2: Subgroups (morbidity) – RCT, direct comparison: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel

Study Outcome Characteristic Subgroup	Pembrolizumab + lenvatinib			Therapy according to physician's choice (doxorubicin or paclitaxel)			Pembrolizumab + lenvatinib vs. therapy according to physician's choice (doxorubicin or paclitaxel)
	N[a]	Values at baseline mean (SD)	Mean change over the course of the study mean (SE)[b]	N[a]	Values at baseline mean (SD)	Mean change over the course of the study mean (SE)[b]	MD [95% CI]; p-value[b]
KEYNOTE 775/309							
EORTC QLQ-EN24 – lymphoedema[c]							
Age							
< 65 years	151	19.8 (28.89)	2.78 (1.40)	144	16.9 (22.47)	6.70 (1.58)	-3,92 [-8,05; 0,22]; ND
≥ 65 years	157	15.2 (23.60)	-0.43 (1.31)	153	16.4 (25.43)	8.94 (1.45)	-9.37 [-13.19; -5.54]; ND SMD: -0.54 [-0.77; -0.32][d]
Total						Interaction:	0.039[e]

a. Number of patients taken into account in the analysis for calculating the effect estimation; baseline values may be based on other patient numbers.
b. From MMRM; effect presents the difference between the treatment groups of the changes averaged over the course of the study between the respective time point of measurement and the start of the study.
c. Higher values on the respective scale indicate worse symptoms; a positive between-group difference indicates an advantage for pembrolizumab + lenvatinib.
d. Institute's calculation.
e. From MMRM, supplemented by the characteristic of subgroup as well as the interaction term of treatment arm x subgroup.

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; MD: mean difference; MMRM: mixed model with repeated measures; N: number of analysed patients; QLQ-EN24: Quality of Life Questionnaire – Endometrial Cancer Module 24; RCT: randomized controlled trial; SD: standard deviation; SMD: standardized mean difference

Table 3: Subgroups (side effects) – RCT, direct comparison: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel

Study Outcome Characteristic Subgroup	Pembrolizumab + lenvatinib		Therapy according to physician's choice (doxorubicin or paclitaxel)		Pembrolizumab + lenvatinib vs. therapy according to physician's choice (doxorubicin or paclitaxel)	
	N	Median time to event in weeks [95% CI] Patients with event n (%)	N	Median time to event in weeks [95% CI] Patients with event n (%)	HR [95% CI][a]	p-value[a]
KEYNOTE 775/309						
Severe AEs[b]						
Histology						
Endometrioid	239	5.4 [3.6; 6.6] 217 (90.8)	240	4.9 [2.4; 6.3] 170 (70.8)	1.22 [1.00; 1.49]	ND
Non-endometrioid	167	5.1 [3.4; 8.1] 144 (86.2)	148	2.3 [2.1; 4.6] 112 (75.7)	0.87 [0.67; 1.11]	ND
Total					Interaction:	0.030[c]
Lipase increased (PT, severe AEs[b])						
Histology						
Endometrioid	239	NR 19 (7.9)	240	NR 1 (0.4)	11.40 [1.49; 87.27]	ND
Non-endometrioid	167	NR 7 (4.2)	148	NR 4 (2.7)	1.04 [0.29; 3.81]	ND
Total					Interaction:	0.036[c]

a. HR, 95% CI and p-value (Wald test) using Cox proportional hazards regression.
b. Operationalized as CTCAE grade ≥ 3.
c. Cox proportional hazards regression supplemented by the characteristic of subgroup as well as the interaction term of treatment arm x subgroup; p-value from likelihood ratio test.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; ND: no data; NR: not reached; PT: Preferred Term; RCT: randomized controlled trial

Morbidity

Lymphoedema (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Endometrial Cancer Module 24 [EORTC QLQ-EN24])

For the outcome of lymphoedema (EORTC QLQ-EN24), there was an effect modification by the characteristic of age. For patients ≥ 65 years, there is a statistically significant difference in favour of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel. The 95% CI of the standardized mean difference (SMD) is fully outside the irrelevance range of -0.2 to 0.2. This was interpreted to

be a relevant effect. For patients ≥ 65 years of age, this results in a hint of added benefit for pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel. However, no statistically significant difference between treatment groups was found for patients < 65 years of age. For patients < 65 years of age, this results in no hint of an added benefit of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel; an added benefit is therefore not proven for these patients.

Side effects

Severe adverse events (severe AEs)

For the outcome of severe AEs, there was an effect modification by the characteristic of histology. For patients with an endometrioid tumour histology, the lower limit of the confidence interval rounded to 2 decimal points was 1.00; a p-value was not available. The statistical significance of the effect can therefore not be assessed based on the present data; a statistically significant difference to the disadvantage of pembrolizumab + lenvatinib cannot be ruled out. Even in case of a statistically significant difference to the disadvantage of pembrolizumab + lenvatinib, however, this would not affect the overall conclusion on added benefit (see Section 2.3.2). For patients with endometrioid tumour histology, the available data do not result in any hint of greater or lesser harm from pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel. There was no statistically significant difference between the treatment groups for patients with non-endometrioid tumour histology. For patients with non-endometrioid tumour histology, this results in no hint of greater or lesser harm from pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel; greater or lesser harm is therefore not proven.

Lipase increased (severe AEs)

For the outcome of lipase increased (severe AEs), there was an effect modification by the characteristic of histology. For patients with endometrioid tumour histology, there is a statistically significant difference to the disadvantage of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel. For patients with endometrioid tumour histology, this results in a hint of greater harm from pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel. However, there was no statistically significant difference between the treatment groups for patients with non-endometrioid tumour histology. For patients with non-endometrioid tumour histology, this results in no hint of greater or lesser harm from pembrolizumab + lenvatinib in comparison with therapy according to physician's choice, selecting from doxorubicin or paclitaxel; greater or lesser harm is therefore not proven.

2.3 Probability and extent of added benefit

2.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.2 and dossier assessment A21-164 [1] (see Table 4).

Table 4: Extent of added benefit at outcome level: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pembrolizumab + lenvatinib vs. therapy according to physician's choice (doxorubicin or paclitaxel)** **Median time to event in weeks or mean** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Total observation period		
Mortality		
Overall survival	18.3 months vs. 11.4 months HR: 0.62 [0.51; 0.75]; p < 0.001 Probability: indication	Outcome category: mortality $CI_u < 0.85$ Added benefit, extent: major
Shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30) – symptom scales		
Fatigue	Mean: 9.01 vs. 12.03 MD: -3.02 [-5.41; -0.63] p = ND SMD: -0.18 [-0.33; -0.04][c],	Lesser/added benefit not proven
Nausea and vomiting	Mean: 5.49 vs. 8.07 MD: -2.58 [-4.66; -0.50] p = ND SMD: -0.18 [-0.33; -0.03][c]	Lesser/added benefit not proven
Pain	Mean: 6.20 vs. 4.35 MD: 1.85 [-0.84; 4.53] p = ND	Lesser/added benefit not proven
Dyspnoea	Mean: 2.05 vs. 7.62 MD: -5.58 [-7.91; -3.24] p = ND SMD: -0.35 [-0.50; -0.202] SMD: 0.35 [0.202; 0.50][c,d] Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $0.20 < CI_u \leq 0.40$ Added benefit, extent: minor
Insomnia	Mean: 1.53 vs. 4.32 MD: -2.79 [-5.60; 0.02] p = ND	Lesser/added benefit not proven

Table 4: Extent of added benefit at outcome level: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pembrolizumab + lenvatinib vs. therapy according to physician's choice (doxorubicin or paclitaxel)** **Median time to event in weeks or mean** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Appetite loss	Mean: 12.95 vs. 8.51 MD: 4.44 [1.37; 7.51] p = ND SMD: 0.21 [0.06; 0.36][c]	Lesser/added benefit not proven
Constipation	Mean: -1.23 vs. 2.67 MD: -3.90 [-6.60; -1.20] p = ND SMD: -0.21 [-0.36; -0.06][c]	Lesser/added benefit not proven
Diarrhoea	Mean: 11.15 vs. 5.38 MD: 5.77 [3.44; 8.10] p = ND SMD: 0.36 [0.21; 0.51][c] Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $0.20 < CI_u \leq 0.40$ Lesser benefit, extent: minor
Symptoms (EORTC QLQ-EN24) – symptom scales		
Lymphoedema Age < 65 years	Mean: 2.78 vs. 6.70 MD: -3.92 [-8.05; 0.22] p = ND	Lesser/added benefit not proven
≥ 65 years	Mean: -0.43 vs. 8.94 MD: -9.37 [-13.19; -5.54] p = ND SMD: -0.54 [-0.77; -0.32] SMD: 0.54 [0.32; 0.77][c,d] Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $0.20 < CI_u \leq 0.40$ Added benefit, extent: minor
Urological symptoms	Mean: -0.93 vs. 2.24 MD: -3.17 [-5.07; -1.27] p = ND SMD: -0.27 [-0.43; -0.11][c]	Lesser/added benefit not proven
Digestive symptoms	Mean: 3.24 vs. 2.81 MD: 0.43 [-1.19; 2.05] p = ND	Lesser/added benefit not proven
Sexual/vaginal problems	No usable data	Lesser/added benefit not proven
Back/pelvis pain	Mean: -0.69 vs. 1.52 MD: -2.21 [-5.09; 0.67]; p = ND	Lesser/added benefit not proven

Table 4: Extent of added benefit at outcome level: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pembrolizumab + lenvatinib vs. therapy according to physician's choice (doxorubicin or paclitaxel)** **Median time to event in weeks or mean** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Tingling/numbness	Mean: -3.33 vs. 3.81 MD: -7.15 [-10.27; -4.03] p = ND SMD: -0.36 [-0.53; -0.204] SMD: 0.36 [0.204; 0.53][c,d] Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $0.20 < CI_u \leq 0.40$ Added benefit, extent: minor
Muscle pain	Mean: 8.69 vs. 2.32 MD: 6.37 [3.22; 9.52] p = ND SMD: 0.32 [0.16; 0.48][c],	Lesser/added benefit not proven
Alopecia	Mean: -4.44 vs. 53.60 MD: -58.03 [-61.54; -54.53] p = ND SMD: -2.64 [-2.85; -2.42] SMD: 2.64 [2.42; 2.85][c,d] Probability: indication	Outcome category: non-serious/non-severe symptoms / late complications $0.40 < CI_u$ Added benefit, extent: considerable
Taste change	Mean: 14.31 vs. 23.90 MD: 9.59 [-13.14; -6.04] p = ND SMD: -0.43 [-0.59; -0.27] SMD: 0.43 [0.27; 0.59][c,d] Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $0.20 < CI_u \leq 0.40$ Added benefit, extent: minor
Health status (EQ-5D VAS)	Mean: -4.99 vs. -7.61 MD: 2.62 [0.67; 4.57] p = ND SMD: 0.19 [0.05; 0.34][c]	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 global health status and functional scales		
Global health status	Mean: -6.58 vs. -8.03 MD: 1.45 [-0.69; 3.60] p = ND	Lesser/added benefit not proven
Physical functioning	Mean: -9.51 vs. -9.24 MD: -0.27 [-2.41; 1.86] p = ND	Lesser/added benefit not proven

Table 4: Extent of added benefit at outcome level: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pembrolizumab + lenvatinib vs. therapy according to physician's choice (doxorubicin or paclitaxel)** **Median time to event in weeks or mean** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Role functioning	Mean: -11.67 vs. -11.92 MD: 0.24 [-2.53; 3.02] p = ND	Lesser/added benefit not proven
Emotional functioning	Mean: 1.34 vs. -2.17 MD: 3.51 [1.38; 5.64] p = ND SMD: 0.24 [0.09; 0.39][c],	Lesser/added benefit not proven
Cognitive functioning	Mean: -3.56 vs. -5.23 MD: 1.68 [-0.44; 3.79] p = ND	Lesser/added benefit not proven
Social functioning	Mean: -6.99 vs. -10.26 MD: 3.27 [0.48; 6.05] p = ND SMD: 0.17 [0.03; 0.32][c],	Lesser/added benefit not proven
EORTC QLQ-EN24		
Sexual interest	Mean: -3.45 vs. -4.24 MD: 0.79 [-0.72; 2.29] p = ND	Lesser/added benefit not proven
Sexual activity	Mean: -3.63 vs. -3.73 MD: 0.11 [-1.16; 1.37] p = ND	Lesser/added benefit not proven
Sexual enjoyment	No usable data	Lesser/added benefit not proven
Body image problems	Mean: 1.51 vs. 13.23 MD: -11.73 [-15.23; -8.22] p = ND SMD: -0.53 [-0.69; -0.37] SMD: 0.53 [0.37; 0.69][c,d] Probability: hint	Outcome category: health-related quality of life $0.30 < CI_u \leq 0.50$ Added benefit, extent: considerable
Side effects		
SAEs	40.9 vs. NR HR: 1.67 [1.33; 2.09] HR: 0.60 [0.48; 0.752][d] p < 0.001 Probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm, extent: considerable

Table 4: Extent of added benefit at outcome level: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pembrolizumab + lenvatinib vs. therapy according to physician's choice (doxorubicin or paclitaxel)** **Median time to event in weeks or mean** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Severe AEs	5.1 vs. 3.6 HR: 1.07 [0.91; 1.25] p = 0.412	Greater/lesser harm not proven[e]
Discontinuation due to AEs	NR vs. NR HR: 2.81 [1.89; 4.20] HR: 0.36 [0.24; 0.53][d] p < 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm, extent: considerable
Immune-related SAEs	NR vs. NR HR: 29.55 [4.05; 215.69] HR: 0.03 [0.01; 0.25][d] p < 0.001 Probability: indication	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% Greater harm, extent: major
Immune-related severe AEs	NR vs. NR HR: 29.93 [4.11; 217.76] HR: 0.03 [0.01; 0.24][d] p < 0.001 Probability: indication	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% Greater harm, extent: major
Hypertension (severe AEs)	NR vs. NR HR: 17.49 [8.92; 34.30] HR: 0.06 [0.03; 0.11][d] p < 0.001 Probability: indication	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% Greater harm, extent: major
Haemorrhages	No usable data	Greater/lesser harm not proven
Cardiotoxicity (operationalized as SOC cardiac disorders, severe AEs)	NR vs. NR HR: 0.42 [0.17; 1.00] p = 0.050	Greater/lesser harm not proven
Headache (AEs)	NR vs. NR HR: 2.59 [1.75; 3.84] HR: 0.39 [0.26; 0.57][d] p < 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm, extent: considerable
Alopecia (AEs)	NR vs. NR HR: 0.12 [0.07; 0.18] p < 0.001 Probability: indication	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Lesser harm, extent: considerable

Table 4: Extent of added benefit at outcome level: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pembrolizumab + lenvatinib vs. therapy according to physician's choice (doxorubicin or paclitaxel)** **Median time to event in weeks or mean** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Urinary tract infection (SAEs)	NR vs. NR HR: 5.04 [1.13; 22.58] HR: 0.20 [0.04; 0.88][d] p = 0.034 Probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm, extent: considerable
Blood and lymphatic system disorders (severe AEs)	NR vs. NR HR: 0.18 [0.13; 0.26] p < 0.001 Probability: indication	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Lesser harm; extent: major
Gastrointestinal disorders (severe AEs)	NR vs. NR HR: 1.63 [1.12; 2.37] HR: 0.61 [0.42; 0.89][d] p = 0.010 Probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm, extent: considerable
Hepatobiliary disorders (severe AEs)	NR vs. NR HR: 13.95 [1.87; 103.91] HR: 0.07 [0.01; 0.53][d] p = 0.010 Probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: major
Lipase increased (severe AEs) Histology		
Endometrioid	NR vs. NR HR: 11.40 [1.49; 87.27] HR: 0.09 [0.01; 0.67][d] p = ND Probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: major
Non-endometrioid	NR vs. NR HR: 1.04 [0.29; 3.81] p = ND	Greater/lesser harm not proven
Weight decreased (severe AEs)	NR vs. NR HR: 16.29 [2.21; 119.86] HR: 0.06 [0.01; 0.45][d] p = 0.006 Probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: major

Table 4: Extent of added benefit at outcome level: pembrolizumab + lenvatinib versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pembrolizumab + lenvatinib vs. therapy according to physician's choice (doxorubicin or paclitaxel)** **Median time to event in weeks or mean** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Metabolism and nutrition disorders (severe AEs)	NR vs. NR HR: 2.44 [1.58; 3.77] HR: 0.41 [0.27; 0.63][d] p < 0.001 Probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: major
Musculoskeletal and connective tissue disorders (severe AEs)	NR vs. NR HR: 3.65 [1.39; 9.57] HR: 0.27 [0.10; 0.72][d] p = 0.008 Probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: major
Proteinuria (severe AEs)	NR vs. NR HR: 16.16 [2.16; 120.89] HR: 0.06 [0.01; 0.46][d] p = 0.007 Probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: major
Respiratory, thoracic, and mediastinal disorders (severe AEs)	NR vs. NR HR: 0.44 [0.23; 0.82] p = 0.009 Probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Lesser harm, extent: considerable
Palmar-plantar erythrodysaesthesia syndrome (severe AEs)	NR vs. NR HR: ND p = 0.006 Probability: hint	Outcome category: serious/severe side effects Greater harm, extent: non-quantifiable

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category and the scale level of the outcome, effect size is estimated with different limits based on the upper or lower limit of the confidence interval (CI_u or CI_l).
c. If the CI for the SMD in the form of Hedges' g is fully outside the irrelevance range [-0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.
d. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e. For patients with an endometrioid tumour histology, a statistically significant difference to the disadvantage of pembrolizumab + lenvatinib cannot be ruled out on the basis of the present data (see Section 2.2.1).

AE: adverse event; CI: confidence interval; CI_l: lower limit of confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire – Core 30; QLQ-EN24: Quality of Life Questionnaire – Endometrial Cancer Module 24; SAE: serious adverse event; SMD: standard mean difference; SOC: System Organ Class

2.3.2 Overall conclusion on added benefit

Table 5 summarizes the results of the benefit assessment on Commission A21-164 and of the present addendum; these results were taken into account in the overall conclusion on the extent of the added benefit.

Table 5: Favourable and unfavourable effects from the assessment of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice selecting from doxorubicin or paclitaxel (multipage table)

Favourable effects	**Unfavourable effects**
Total observation period	
Mortality ▪ Overall survival Indication of added benefit – extent: major	–
Shortened observation period	
Non-serious/non-severe symptoms / late complications ▪ Dyspnoea, tingling/numbness, taste change For each, hint of an added benefit – extent: minor ▪ Alopecia Indication of added benefit – extent: considerable ▪ Lymphoedema ▫ Age (≥ 65 years) Hint of an added benefit – extent: minor	Non-serious/non-severe symptoms / late complications ▪ Diarrhoea Hint of lesser benefit – extent: minor
Health-related quality of life ▪ Body image problems Hint of added benefit – extent: considerable	–

Table 5: Favourable and unfavourable effects from the assessment of pembrolizumab + lenvatinib in comparison with therapy according to physician's choice selecting from doxorubicin or paclitaxel (multipage table)

Favourable effects	**Unfavourable effects**
Severe/serious side effects ▪ Blood and lymphatic system disorders (severe AEs) Indication of lesser harm – extent: major ▪ Respiratory, thoracic, and mediastinal disorders (severe AEs) Hint of lesser harm – extent: considerable	Severe/serious side effects ▪ SAEs Hint of greater harm – extent: considerable ▪ Immune-related SAEs, immune-related severe AEs For each: indication of greater harm – extent: major ▪ Urinary tract infection (SAEs) Hint of greater harm – extent: considerable ▪ Hypertension (severe AEs) Indication of greater harm – extent: major ▪ Gastrointestinal disorders (severe AEs) Hint of greater harm – extent: considerable ▪ Hepatobiliary disorders, weight decreased, metabolic and nutritional disorders, musculoskeletal and connective tissue disorders, proteinuria (each severe AEs) For each, hint of greater harm – extent: considerable ▪ Palmar-plantar erythrodysaesthesia syndrome (severe AEs) Hint of greater harm – extent: non-quantifiable ▪ Lipase increased (severe AEs) ▫ Histology (endometrioid) Hint of greater harm – extent: major
Non-severe/non-serious adverse events ▪ Alopecia (AEs) Indication of lesser harm – extent considerable	Non-severe/non-serious adverse events ▪ Discontinuation due to AEs ▪ Headache (AEs) For each, hint of greater harm – extent: considerable
AEs: adverse events; SAE: serious adverse event	

The subsequently submitted subgroup analyses result in the following change in comparison with dossier assessment A21-164: the favourable effect for the outcome of lymphoedema is found only for patients ≥ 65 years, and the unfavourable effect for the outcome of lipase increased (severe AEs) is determined only for patients with endometrioid tumour histology. In addition, there is a potentially unfavourable effect for the outcome of severe AEs in patients with endometrioid tumour histology, but the statistical significance cannot be assessed due to (a) the rounded lower limit of the confidence interval being 1.00 and (b) the missing p-value.

The subsequently submitted subgroup analyses do not change the overall conclusion on added benefit drawn in dossier assessment A21-164.

2.4 Summary

The data subsequently submitted by the company in the commenting procedure do not change the conclusion drawn in dossier assessment A21-164 on the added benefit of pembrolizumab + lenvatinib.

Table 6 below shows the result of the benefit assessment of pembrolizumab + lenvatinib taking into account dossier assessment A21-164 and the present addendum.

Table 6: Pembrolizumab + lenvatinib – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with advanced or recurrent endometrial cancer whose disease has progressed during or after prior platinum-based therapy at any stage of the disease when surgery or radiation to cure the cancer is not an option for them	Therapy according to physician's choice[b]	Patients for whom doxorubicin or paclitaxel is the suitable therapy according to physician's choice: indication of considerable added benefit[c]
		Patients for whom a treatment option other than doxorubicin or paclitaxel is the suitable therapy according to physician's choice: added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. Overall, the following treatment options are deemed suitable comparators in connection with therapy according to physician's choice: endocrine therapy (medroxyprogesterone acetate, megestrol acetate), systemic chemotherapy, which may include platinum-based retreatment (cisplatin [monotherapy or in combination with doxorubicin], doxorubicin [monotherapy or in combination with cisplatin], carboplatin in combination with paclitaxel, paclitaxel [monotherapy]), and BSC alone. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
c. The KEYNOTE 775/309 study included only patients with an ECOG-PS of 0 or 1 and disease progression after prior platinum-based therapy. It remains unclear whether the observed effects can be extrapolated to patients with an ECOG-PS ≥ 2 or to patients with disease progression during prior platinum-based therapy.

ACT: appropriate comparator therapy; BSC: best supportive care; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee

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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Appendix A – Kaplan-Meier curves on subgroup analyses

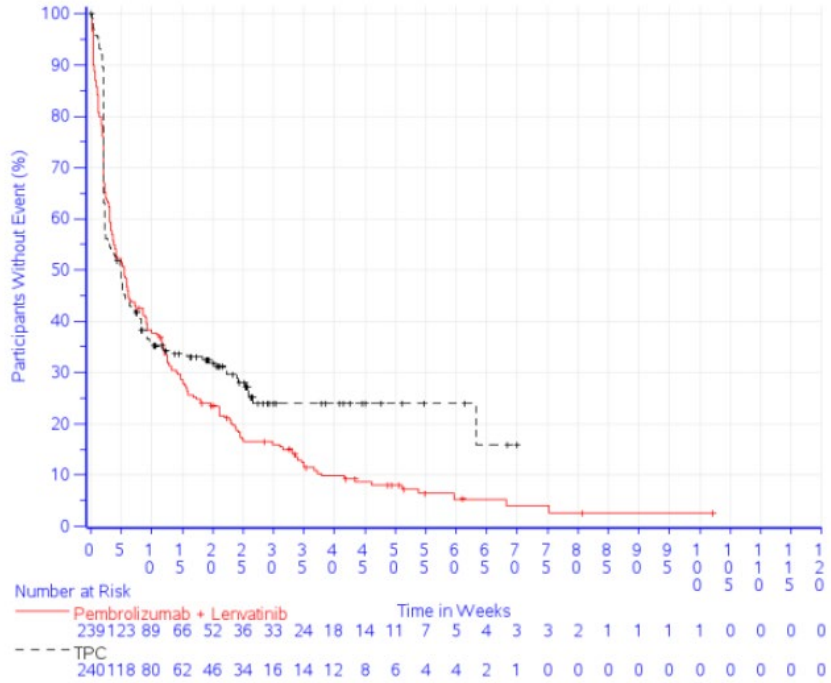

Figure 1: Kaplan-Meier curve for the outcome of severe AEs (subgroup of histology: endometrioid) from the KEYNOTE 775/309 study

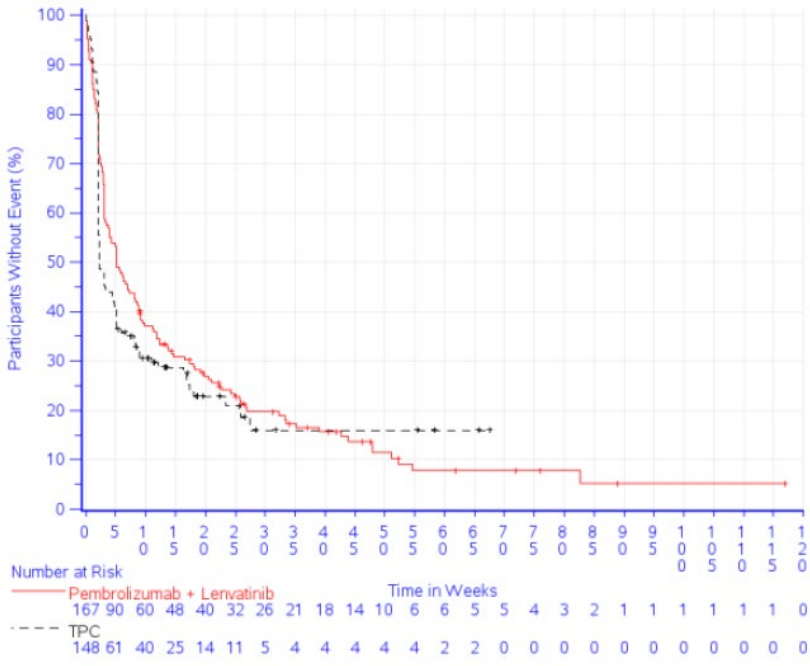

Figure 2: Kaplan-Meier curve for the outcome of severe AEs (subgroup of histology: non-endometrioid) from the KEYNOTE 775/309 study

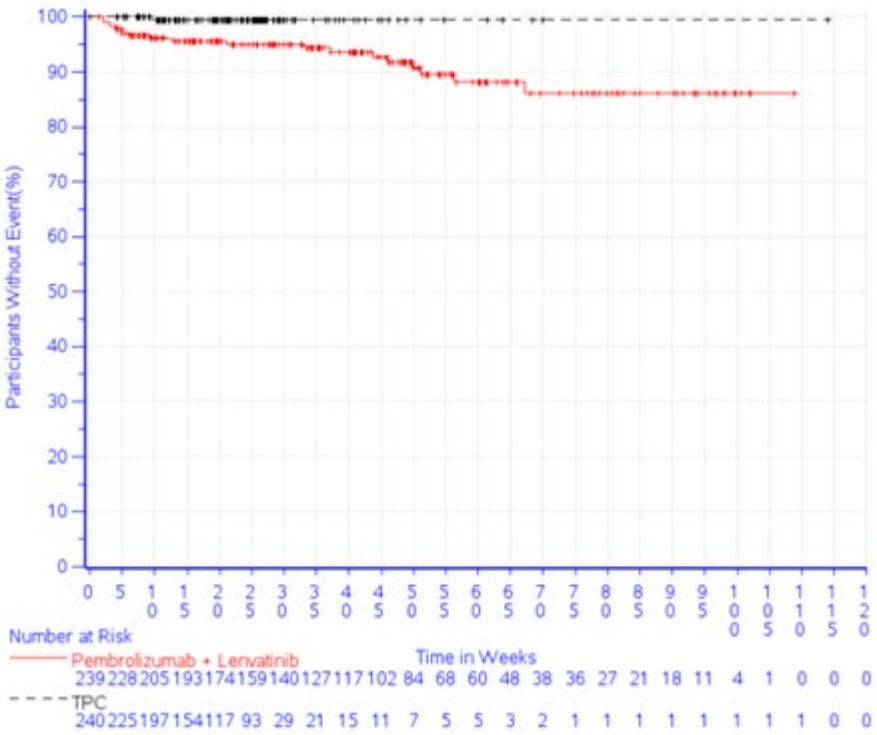

Figure 3: Kaplan-Meier curve for the outcome of lipase increased (preferred term [PT], severe AEs) (subgroup of histology: endometrioid) from the KEYNOTE 775/309 study

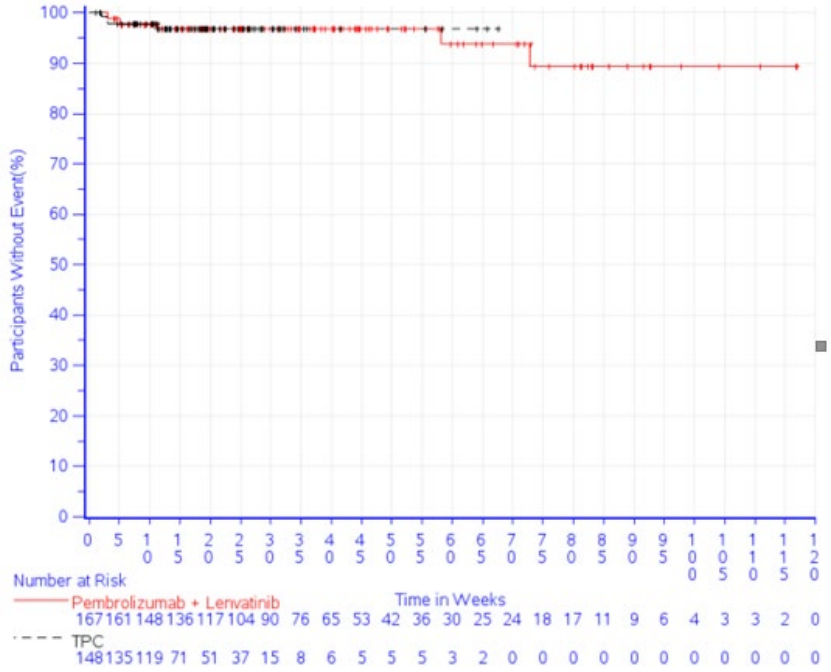

Figure 4: Kaplan-Meier curve for the outcome of lipase increased (PT, severe AEs) (subgroup of histology: endometrioid) from the KEYNOTE 775/309 study