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Lenvatinib (endometrial carcinoma) –

Addendum to Commission A21-162[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
SGB	Sozialgesetzbuch (Social Code Book)

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 on Commission A21-162 (Lenvatinib – benefit assessment according to §35a Social Code Book V) [1].

This commission involves assessing the analyses of the KEYNOTE 775/309 study's total population, including the data on subgroup analyses at the 26 October 2020 data cut-off (1st interim analysis) as submitted in the commenting procedure, taking into account the information provided in the dossier.

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

2 Assessment

For assessing the benefit of lenvatinib in combination with pembrolizumab (hereinafter referred to as "lenvatinib + pembrolizumab") 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, the randomized, active control, open-label study KEYNOTE775/309 [2-5] was analysed. This study compared lenvatinib + pembrolizumab with treatment of investigator's choice, consisting of either doxorubicin or paclitaxel. A detailed description of the KEYNOTE 755/309 study can be found in dossier assessment A21-162 [1].

The study's total population is relevant for the benefit assessment. Based on the originally specified appropriate comparator therapy (ACT) (which excluded the treatment option of paclitaxel monotherapy), the company's dossier assessed added benefit using the subpopulation of patients for whom the investigator made the pre-randomization choice of doxorubicin treatment [6]. Together with its comments, the company subsequently submitted the results for the total population of the KEYNOTE775/309 study, including subgroup analyses for the 26 October 2020 data cut-off [7]. The subsequently submitted data are evaluated below.

2.1 Results on added benefit

2.1.1 Results

The results on the total population, which were subsequently submitted by the company in its comments, are identical to the results presented in dossier assessment A21-164 Pembrolizumab [8]. Unlike in dossier assessment A21-164, however, the company did not provide any p-values for the side effects outcomes.

Table 1 summarizes the mortality and side effects results for the comparison of lenvatinib + pembrolizumab with treatment according to physician's choice of selecting from doxorubicin or paclitaxel in 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. For the results on morbidity and health-related quality of life, please refer to dossier assessment A21-164 Pembrolizumab [8].

Table 1: Results (mortality, side effects) – RCT, direct comparison: lenvatinib + pembrolizumab versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Study Outcome category Outcome	Lenvatinib + pembrolizumab		Therapy according to physician's choice (doxorubicin or paclitaxel)		Lenvatinib + pembrolizumab 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]; p-value[a]
KEYNOTE 775 / 309					
Mortality					
Overall survival	411	18.3[15.2; 20.5] months 188 (45.7)	416	11.4 [10.5; 12.9] months 245 (58.9)	0.62 [0.51; 0.75]; < 0.001[b]
Side effects					
AEs (supplementary information)[c]	406	0.6 [0.4; 0.7] 405 (99.8)	388	0.6 [0.4; 0.7] 386 (99.5)	-
SAEs[c]	406	40.9 [30.0; 53.6] 214 (52.7)	388	NR [55.7; NR] 118 (30.4)	1.67 [1.33; 2.09]; ND
Severe AEs[c, d]	406	5.1 [3.9; 6.3] 361 (88.9)	388	3.6 [2.3; 5.1] 282 (72.7)	1.07 [0.91; 1.25]; ND
Discontinuation due to AEs[c,e]	406	NR [77.4; -] 134 (33.0)	388	NR [59.1; NR] 31 (8.0)	2.81 [1.89; 4.20]; ND
Immune-related SAEs[f]	406	NA 41 (10.1)	388	NR 1 (0.3)	29.55 [4.05; 215.69]; ND
Immune-related severe AEs[d,f]	406	NR 53 (13.1)	388	NR 1 (0.3)	29.93 [4.11; 217.76]; ND
Hypertension (PT, severe AEs[d])	406	NR 154 (37.9)	388	NR 9 (2.3)	17.49 [8.92; 34.30]; ND
Haemorrhages	No usable data[g]				
Cardiotoxicity (operationalized as SOC cardiac disorders, severe AEs[d])	406	NR 11 (2.7)	388	NR 12 (3.1)	0.42 [0.17; 1.00]; ND
Headache (PT, AEs)	406	NR 101 (24.9)	388	NR 34 (8.8)	2.59 [1.75; 3.84]; ND
Alopecia (PT, AEs)	406	NR 22 (5.4)	388	NR 120 (30.9)	0.12 [0.07; 0.18]; ND
Urinary tract infection (PT, SAEs)	406	NR 13 (3.2)	388	NR 2 (0.5)	5.04 [1.13; 22.58]; ND
Blood and lymphatic system disorders (SOC, severe AEs[d])	406	NR 45 (11.1)	388	NR [25.9; NR] 159 (41.0)	0.18 [0.13; 0.26]; ND

Table 1: Results (mortality, side effects) – RCT, direct comparison: lenvatinib + pembrolizumab versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Study Outcome category Outcome	Lenvatinib + pembrolizumab		Therapy according to physician's choice (doxorubicin or paclitaxel)		Lenvatinib + pembrolizumab 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]; p-value[a]
Gastrointestinal disorders (SOC, severe AEs[d])	406	NR [85.4; NR] 106 (26.1)	388	NR 41 (10.6)	1.63 [1.12; 2.37]; ND
Hepatobiliary disorders (SOC, severe AEs[d])	406	NR 27 (6.7)	388	NR 1 (0.3)	13.95 [1.87; 103.91]; ND
Lipase increased (PT, severe AEs[d])	406	NR 26 (6.4)	388	NR 5 (1.3)	3.08 [1.15; 8.29]; ND
Weight decreased (PT, severe AEs[d])	406	NR 42 (10.3)	388	NR 1 (0.3)	16.29 [2.21; 119.86]; ND
Metabolism and nutrition disorders (SOC, severe AEs[d])	406	NR 97 (23.9)	388	NR 27 (7.0)	2.44 [1.58; 3.77]; ND
Musculoskeletal and connective tissue disorders (SOC, severe AEs[d])	406	NR 30 (7.4)	388	NR 5 (1.3)	3.65 [1.39; 9.57]; ND
Proteinuria (PT, severe AEs[d])	406	NR 22 (5.4)	388	NR 1 (0.3)	16.16 [2.16; 120.89]; ND
Respiratory, thoracic, and mediastinal disorders (SOC, severe AEs[d])	406	NR 20 (4.9)	388	NR 26 (6.7)	0.44 [0.23; 0.82]; ND
Palmar-plantar erythrodysaesthesia syndrome (PT, severe AEs[d])	406	NR 11 (2.7)	388	NR 0 (0.0)	ND; ND

a. HR, 95% CI using Cox proportional hazards regression.
b. HR, 95% CI and p-value (Wald test) by means of Cox proportional hazards regression, stratified by MMR status, ECOG-PS, region, and prior pelvic radiotherapy.
c. In accordance with information in the study report without recording progression of the underlying illness.
d. Operationalized as CTCAE grade ≥ 3.
e. Discontinuation of 1 or more drug components in the intervention arm.
f. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome of adverse events of special interest ("AEOSI") was used.
g. No suitable operationalization is available.

Table 1: Results (mortality, side effects) – RCT, direct comparison: lenvatinib + pembrolizumab versus therapy according to physician's choice, selecting from doxorubicin or paclitaxel (multipage table)

Study Outcome category Outcome	Lenvatinib + pembrolizumab		Therapy according to physician's choice (doxorubicin or paclitaxel)		Lenvatinib + pembrolizumab 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]; p-value[a]
AE: adverse event; AEOSI: adverse event of special interest; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG-PS: Eastern Cooperative Oncology Group – Performance Status; HR: hazard ratio; MedDRA: Medical Dictionary for Regulatory Activities; MMR: mismatch repair; n: number of patients with event; N: number of analysed patients; ND: no data; NR: not reached; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class					

Since with the exception of the missing p-values for the side effects outcomes, the subsequently submitted results are identical to the results presented in dossier assessment A21-164, please refer to dossier assessment A21-164 Pembrolizumab for the description of results [8].

2.1.2 Subgroups and other effect modifiers

The subgroup analysis data subsequently submitted by the company in the commenting procedure [7] are identical to the subgroup analyses subsequently submitted after the oral hearing in the benefit assessment procedure for pembrolizumab [9]. Therefore, please see Addendum A22-58 Pembrolizumab [10] for results of subgroup analyses.

2.2 Probability and extent of added benefit

Regarding the probability and extent of added benefit, please see Addendum A22-58 Pembrolizumab [10].

2.3 Summary

The data subsequently submitted by the company in the commenting procedure do not change the conclusion drawn in dossier assessment A21-162 regarding the added benefit of lenvatinib + pembrolizumab.

Table 2 below shows the result of the benefit assessment of lenvatinib + pembrolizumab, taking into account both dossier assessment A21-162 and the present addendum.

Table 2: Lenvatinib + pembrolizumab – probability and extent of added benefit

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 therapy 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.

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