Belzutifan
(renal cell carcinoma)

Addendum to Project A25-45 (dossier assessment)[1]

ADDENDUM (DOSSIER ASSESSMENT)

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50679 Köln
Germany

Phone:+49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

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IQWiG employees involved in the addendum

- Alina Reese
- Ulrich Grouven
- Katrin Nink
- Regine Potthast

Table of contents

Page

List of tables v

List of abbreviations vi

1 Background 1

2 Assessment 2

2.1 Summary 4

3 References 5

Appendix A Information on prior therapies of the relevant subpopulation of patients who have received 2 or more prior lines of treatment according to the marketing authorization, including 1 PD-(L)1 inhibitor and at least 2 VEGF-targeted therapies 6

List of tables

Page

Table 1: Information on prior therapies (treatment options comprised by the ACT) in the subpopulation - RCT, direct comparison: belzutifan vs everolimus 3
Table 2: Belzutifan – probability and extent of added benefit 4
Table 3: Prior therapies of the relevant subpopulation of the LITESPARK 005 study 6

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)
mTOR	mechanistic target of rapamycin
PD(L) 1	programmed cell death ligand 1
RCT	randomized controlled trial
VEGF	vascular endothelial growth factor

1 Background

On 12 August 2025, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A25-45 (Belzutifan – benefit assessment according to § 35a Social Code Book V) [1].

The commission comprises the assessment of the analyses presented by the pharmaceutical company (hereinafter referred to as “the company”) after the oral hearing, taking into account the information provided in the dossier [2,3]:

- Data on the pre-treatments of the relevant subpopulation in the LITESPARK 005 study

The responsibility for this 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) LITESPARK 005 was used for the benefit assessment of belzutifan. A detailed description of the study and the relevant subpopulation of patients with 2 or more prior therapies who were treated with 1 programmed cell death protein (ligand)1 (PD-[L]1) inhibitor and at least 2 vascular endothelial growth factor (VEGF)-targeted therapies can be found in dossier assessment A25-45 [1].

The G-BA defined an individualized treatment choosing from axitinib, cabozantinib, everolimus, lenvatinib in combination with everolimus and sunitinib as the ACT. For the LITESPARK 005 study included in the benefit assessment [1], it was assumed that treatment with everolimus in the comparator group of LITESPARK 005 represents a sufficient implementation of an individualized treatment taking into account the prior therapy, as the already extensively pretreated patients included in the study had not yet received the drug in their pretreatment and, moreover, further criteria for the treatment decision are missing. However, the certainty of conclusions regarding the results of the study was reduced because it was unclear whether other treatment options besides everolimus included in the G-BA's appropriate comparator therapy (ACT) would also have been suitable for some of the patients. Based on the LITESPARK 005 study, statements were also only made about those patients for whom everolimus was a suitable individualized therapy. Data for patients for whom everolimus was not a suitable individualized treatment are lacking.

In this therapeutic indication, the treatment decision is made taking into account the previous treatment, and patients should receive substances that were not part of their previous treatment [4-6]. Despite the relevance of prior therapies for the treatment decision, the dossier provided no data for the subpopulation considered for the benefit assessment, but only for the total population.

Following the oral hearing, the company subsequently submitted information on the prior therapies used for the subpopulation under consideration, broken down by line of treatment (first to fourth line) (see Appendix A). The use of the treatment options comprised by the ACT is relevant for the assessment of whether other drugs besides everolimus would also have been suitable. In addition, cumulative information on all lines of therapy is required. Assuming that none of the patients used the same drug in more than 1 line of treatment, the data per line of treatment were therefore added up for the present assessment. The figures shown in Table 1 are therefore to be understood as a best-case scenario. If a drug has been used in more than 1 line of treatment in patients, the proportion would be correspondingly lower.

Table 1: Information on prior therapies (treatment options comprised by the ACT) in the subpopulation - RCT, direct comparison: belzutifan vs everolimus

Study drug	Patients with prior therapy, n (%)	
	belzutifan N = 188	everolimus N = 182
LITESPARK 005 study		
Axitinib	62 (33.0)	67 (36.8)
Cabozantinib[a]	139 (73.9)	127 (67.6)
Everolimus	0 (0)	0 (0)
Lenvatinib	3 (1.6)	3 (1.6)
Sunitinib[b]	110 (58.5)	109 (58.0)

a. Including cabozantinib S-malate (number of patients: 9 vs. 19).
b. Including sunitinib S-malate (number of patients: 31 vs. 29).
n: number of patients with prior therapy; N: number of analysed patients; RCT: randomized controlled trial

In the comparator arm, the drugs cabozantinib and sunitinib were used as pretreatment in 67.6% and 58.0% of patients. Axitinib was administered to 36.8% of patients in the comparator arm and lenvatinib to only 1.6%. It should also be noted that the patients received further multikinase inhibitors in addition to the options listed in the ACT. According to the data in Appendix A, for example, 30.8% of patients in the comparator arm received pazopanib in the prior therapy. However, in accordance with the inclusion criteria of the study, the patients had not previously received treatment with the mechanistic target of rapamycin (mTOR) inhibitor everolimus.

The proportions of patients who received pretreatment with a drug covered by the ACT are comparatively higher in the subpopulation than in the total population [1]. However, based on the information for the subpopulation, it can be assumed that other therapies, in particular a combination therapy of lenvatinib and everolimus, would have been an option for the majority of patients besides everolimus.

Overall, there is therefore still uncertainty as to whether other treatment options included in the G-BA's ACT besides everolimus would have been equally or even more suitable for some of the patients. The limitation of the certainty of conclusions of the results described in the benefit assessment and the restriction of the conclusions on the added benefit of belzutifan based on the LITESPARK 005 study to patients for whom treatment with everolimus is the appropriate individualized treatment therefore remain.

2.1 Summary

The data subsequently submitted by the company in the commenting procedure do not change the conclusion on the added benefit of belzutifan drawn in dossier assessment A25-45.

Table 2 below shows the result of the benefit assessment of belzutifan, taking into account dossier assessment A25-45 and the present addendum.

Table 2: Belzutifan – probability and extent of added benefit

Therapeutic indication	**ACT[a, b]**	**Probability and extent of added benefit**
Adult patients with advanced clear cell renal cell carcinoma that has progressed following 2 or more lines of therapy that included a PD-(L)1 inhibitor and at least 2 VEGF-targeted therapies	Individualized treatment[c, d, e] choosing from ▪ axitinib, ▪ cabozantinib, ▪ everolimus, ▪ lenvatinib in combination with everolimus and ▪ sunitinib	▪ Patients for whom everolimus is a suitable individualized treatment[f]: ▫ < 65 years: hint of minor added benefit ▫ ≥ 65 years: hint of considerable added benefit ▪ patients for whom everolimus is not a suitable individualized treatment: added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, it is assumed for the patients in the present therapeutic indication that surgery and/or radiotherapy with curative intent are not (or no longer) an option at the time point of the treatment decision and that treatment is palliative.
c. The treatment decision is made under particular consideration of the prior therapy. When choosing the treatment option, a change of the transaminase inhibitor (TKI) must be made with regard to the previously administered TKI.
d. For the implementation of individualized treatment in a study of direct comparison, the investigators are assumed to have a choice between several treatment options enabling an individualized treatment decision (multicomparator study). The selection and possibly a limitation of the treatment options must be justified under consideration of the named criteria.
e. The term "individualized treatment" is used instead of previously used terms such as "patient-specific therapy" or "treatment of physician's choice". This ensures consistency with the terms used in European health technology assessments (EU HTAs).
f. The LITESPARK 005 study included only patients with a Karnofsky performance status ≥ 70%. It remains unclear whether the observed effects can be transferred to patients with a Karnofsky performance status < 70 %.

ACT: appropriate comparator therapy G-BA: Federal Joint Committee; PD-(L)1: Programmed Cell Death Protein-(Ligand) 1; TKI: tyrosine kinase inhibitor; VEGF: vascular endothelial growth factor

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 Information on prior therapies of the relevant subpopulation of patients who have received 2 or more prior lines of treatment according to the marketing authorization, including 1 PD-(L)1 inhibitor and at least 2 VEGF-targeted therapies

The following Table 3 of the company was adopted without adjustments.

Table 3: Prior therapies of the relevant subpopulation of the LITESPARK 005 study (multipage table)

	Belzutifan		Everolimus		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	188		182		370	
With one or more prior systemic oncologic therapies	188	(100.0)	182	(100.0)	370	(100.0)
With no prior systemic oncologic therapies	0	(0.0)	0	(0.0)	0	(0.0)
First Line	**188**	**(100.0)**	**182**	**(100.0)**	**370**	**(100.0)**
ATEZOLIZUMAB	10	(5.3)	5	(2.7)	15	(4.1)
AVELUMAB	6	(3.2)	5	(2.7)	11	(3.0)
AXITINIB	20	(10.6)	21	(11.5)	41	(11.1)
BEVACIZUMAB	9	(4.8)	5	(2.7)	14	(3.8)
CABOZANTINIB	5	(2.7)	8	(4.4)	13	(3.5)
CABOZANTINIB S-MALATE	1	(0.5)	0	(0.0)	1	(0.3)
ENTINOSTAT	1	(0.5)	0	(0.0)	1	(0.3)
INTERFERON	0	(0.0)	1	(0.5)	1	(0.3)
INVESTIGATIONAL ANTINEOPLASTIC DRUGS	1	(0.5)	2	(1.1)	3	(0.8)
IPILIMUMAB	13	(6.9)	10	(5.5)	23	(6.2)
LENVATINIB	2	(1.1)	2	(1.1)	4	(1.1)
NIVOLUMAB	15	(8.0)	19	(10.4)	34	(9.2)
OTHER MONOCLONAL ANTIBODIES AND ANTIBODY DRUG CONJUGATES	1	(0.5)	0	(0.0)	1	(0.3)
PAZOPANIB	41	(21.8)	33	(18.1)	74	(20.0)
PAZOPANIB HYDROCHLORIDE	11	(5.9)	10	(5.5)	21	(5.7)
PEMBROLIZUMAB	15	(8.0)	17	(9.3)	32	(8.6)
ROCAPULDENCEL-T	0	(0.0)	1	(0.5)	1	(0.3)
SIMLUKAFUSP ALFA	1	(0.5)	1	(0.5)	2	(0.5)
SORAFENIB	1	(0.5)	1	(0.5)	2	(0.5)
SORAFENIB TOSILATE	0	(0.0)	1	(0.5)	1	(0.3)
SUNITINIB	63	(33.5)	68	(37.4)	131	(35.4)
SUNITINIB MALATE	23	(12.2)	19	(10.4)	42	(11.4)
TIVOZANIB	0	(0.0)	2	(1.1)	2	(0.5)

Table 3: Prior therapies of the relevant subpopulation of the LITESPARK 005 study (multipage table)

	Belzutifan		Everolimus		Total	
	n	(%)	n	(%)	n	(%)
Second Line	**188**	**(100.0)**	**182**	**(100.0)**	**370**	**(100.0)**
ATEZOLIZUMAB	2	(1.1)	1	(0.5)	3	(0.8)
AUTOGENE CEVUMERAN	2	(1.1)	0	(0.0)	2	(0.5)
AXITINIB	25	(13.3)	27	(14.8)	52	(14.1)
BEVACIZUMAB	1	(0.5)	2	(1.1)	3	(0.8)
CABOZANTINIB	37	(19.7)	48	(26.4)	85	(23.0)
CABOZANTINIB S-MALATE	4	(2.1)	11	(6.0)	15	(4.1)
DALANTERCEPT	0	(0.0)	1	(0.5)	1	(0.3)
DURVALUMAB	2	(1.1)	3	(1.6)	5	(1.4)
INVESTIGATIONAL ANTINEOPLASTIC DRUGS	1	(0.5)	3	(1.6)	4	(1.1)
IPILIMUMAB	9	(4.8)	3	(1.6)	12	(3.2)
NIVOLUMAB	98	(52.1)	64	(35.2)	162	(43.8)
PAZOPANIB	7	(3.7)	11	(6.0)	18	(4.9)
PAZOPANIB HYDROCHLORIDE	0	(0.0)	1	(0.5)	1	(0.3)
PEMBROLIZUMAB	4	(2.1)	4	(2.2)	8	(2.2)
SAVOLITINIB	1	(0.5)	0	(0.0)	1	(0.3)
SORAFENIB	1	(0.5)	1	(0.5)	2	(0.5)
SUNITINIB	13	(6.9)	11	(6.0)	24	(6.5)
SUNITINIB MALATE	7	(3.7)	9	(4.9)	16	(4.3)
TELAGLENASTAT	1	(0.5)	0	(0.0)	1	(0.3)
TIVOZANIB	2	(1.1)	1	(0.5)	3	(0.8)
TREMELIMUMAB	1	(0.5)	0	(0.0)	1	(0.3)
Third Line	**160**	**(85.1)**	**146**	**(80.2)**	**306**	**(82.7)**
ATEZOLIZUMAB	0	(0.0)	1	(0.5)	1	(0.3)
AXITINIB	17	(9.0)	18	(9.9)	35	(9.5)
BEVACIZUMAB	2	(1.1)	0	(0.0)	2	(0.5)
CABOZANTINIB	86	(45.7)	50	(27.5)	136	(36.8)
CABOZANTINIB S-MALATE	4	(2.1)	8	(4.4)	12	(3.2)
DURVALUMAB	0	(0.0)	1	(0.5)	1	(0.3)
EPACADOSTAT	0	(0.0)	1	(0.5)	1	(0.3)
INVESTIGATIONAL ANTINEOPLASTIC DRUGS	7	(3.7)	1	(0.5)	8	(2.2)
IPILIMUMAB	5	(2.7)	2	(1.1)	7	(1.9)
LENVATINIB	1	(0.5)	1	(0.5)	2	(0.5)
NIVOLUMAB	42	(22.3)	61	(33.5)	103	(27.8)
PAZOPANIB	3	(1.6)	1	(0.5)	4	(1.1)
PEMBROLIZUMAB	4	(2.1)	4	(2.2)	8	(2.2)
PLACEBO	0	(0.0)	1	(0.5)	1	(0.3)

Table 3: Prior therapies of the relevant subpopulation of the LITESPARK 005 study (multipage table)

	Belzutifan		Everolimus		Total	
	n	(%)	n	(%)	n	(%)
SORAFENIB	0	(0.0)	1	(0.5)	1	(0.3)
SPARTALIZUMAB	0	(0.0)	1	(0.5)	1	(0.3)
SUNITINIB	3	(1.6)	1	(0.5)	4	(1.1)
SUNITINIB MALATE	1	(0.5)	1	(0.5)	2	(0.5)
TAMINADENANT	0	(0.0)	1	(0.5)	1	(0.3)
TELAGLENASTAT	0	(0.0)	3	(1.6)	3	(0.8)
TIVOZANIB	1	(0.5)	1	(0.5)	2	(0.5)
TREMELIMUMAB	0	(0.0)	1	(0.5)	1	(0.3)
Not Applicable	**2**	**(1.1)**	**4**	**(2.2)**	**6**	**(1.6)**
AXITINIB	0	(0.0)	1	(0.5)	1	(0.3)
CABOZANTINIB	2	(1.1)	2	(1.1)	4	(1.1)
NIVOLUMAB	0	(0.0)	1	(0.5)	1	(0.3)

Each participant is counted a single time for each applicable row and column.
'Not applicable' is referring to participants with fourth line therapy.
Number of participants: intention-to-treat population with two or more lines of therapy that included a PD-(L)1 inhibitor and at least two VEGF-targeted therapies
Database cut-off Date: 15APR2024

PD-1: Programmed Cell Death 1; PD-L1: Programmed Cell Death 1 Ligand 1; VEGF: Vascular Endothelial Growth Factor