Gemeinsamer Bundesausschuss

Brigatinib (New Therapeutic Indication: NSCLC, ALK+, ALK-inhibitor-naïve patients)

Resolution of: 15 October 2020 valid until: unlimited
Entry into force on: 15 October 2020
Federal Gazette, BAnz AT 07.12.2020 B5

New therapeutic indication (according to the marketing authorisation of 1 April 2020):

Alunbrig is indicated as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor.

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

a) Adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) with brain metastases previously not treated with an ALK inhibitor:

Appropriate comparator therapy:

- Crizotinib

or

- Alectinib

Extent and probability of the additional benefit of brigatinib compared with crizotinib:

Hint for a considerable additional benefit

b) Adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) without brain metastases previously not treated with an ALK inhibitor:

Appropriate comparator therapy:

- Crizotinib

or

- Alectinib

Extent and probability of the additional benefit of brigatinib compared with crizotinib:

Hint for a minor additional benefit

Study results according to endpoints:

a) Adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) with brain metastases previously not treated with an ALK inhibitor

and

b) Adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) without brain metastases previously not treated with an ALK inhibitor:

ALTA-1L study: Brigatinib **vs** crizotinib[1,2]

Mortality

Endpoint	**Brigatinib**		**Crizotinib**		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD) [a]
Overall survival					
	137	n.a. [no data available] 33 (24.1)	138	n.a. [no data available] 37 (26.8)	0.91 [0.57; 1.47] 0.771
Effect modification was by the characteristic “brain metastases at the start of study”					
Presence of brain metastases at the start of study					
	41	n.a. [28.1; n.a.] 10 (24.4)	40	n.a. [18.5; n.a.] 18 (45.0)	0.45 [0.21; 0.99] 0.046
No presence of brain metastases at the start of study					
	96	n.a. 23 (24.0)	98	n.a. 19 (19.4)	1.41 [0.77; 2.60] 0.272
Total				Interaction:	0.024

(Continuation)

[1] Data from the dossier assessment of the IQWiG (A20-42) and the addendum (A20-85-XX) unless otherwise indicated.

[2] Data cut-off of 28 June 2019

Morbidity

Endpoint	Brigatinib		Crizotinib		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD) [a]
Progression-free survival (PFS) [b]					
	137	24.0 [18.5; n.c.][c] 63 (46.0)	138	11.00 [9.2; 12.9][c] 87 (63.0)	0.48 [0.35; 0.68] < 0.0001 13.0 months
Time to CNS progression (presented additionally)					
Without censoring because of progression outside the CNS [d,e]					
	137	32.29 [no data available] 30 (21.9)	138	n.a. 42 (30.4)	0.34 [0.21; 0.56] < 0.001
With censoring because of progression outside the CNS [e]					
	137	no data available 22 (16.1)	138	no data available 36 (26.1)	0.30 [0.17; 0.53] < 0.001
Disease symptomatology – time to first deterioration [f]					
Symptom scales of the EORTC QLQ-C30					
Fatigue	131	15.6 [7.5; n.a.] 66 (50.4)	131	4.8 [3.3; 8.6] 83 (63.4)	0.67 [0.48; 0.93] 0.013 10.8 months
Nausea and vomiting	131	12.0 [4.0; n.a.] 67 (51.1)	131	2.8 [1.9; 5.6] 92 (70.2)	0.55 [0.40; 0.76] < 0.001 9.2 months
Pain	131	12.1 [6.4; 23.2] 69 (52.7)	131	8.1 [5.7; 11.6] 75 (57.3)	0.82 [0.59; 1.15] 0.301
Dyspnoea	131	28.6 [10.2; n.a.] 58 (44.3)	131	16.8 [10.2; n.a.] 53 (40.5)	0.98 [0.67; 1.43] 0.839
Insomnia	131	n.a. [18.6; n.a.] 52 (39.7)	131	22.1 [12.7; n.a.] 48 (36.6)	0.91 [0.61; 1.35] 0.736

(Continuation)

Loss of appetite	131	n.a. [17.5; n.a.]	131	9.2 [6.3; 24.9]	0.62 [0.43; 0.90]

Endpoint	Brigatinib		Crizotinib		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD) [a]
		52 (39.7)		63 (48.1)	0.009
Constipation	131	12.0 [6.5; n.a.] 65 (49.6)	131	2.8 [1.9; 3.9] 84 (64.1)	0.52 [0.38; 0.73] < 0.001 9.2 months
Diarrhoea	131	2.1 [1.9; 3.8] 91 (69.5)	131	2.8 [1.9; 3.8] 90 (68.7)	1.00 [0.75; 1.34] 0.968
Symptom scales of the EORTC QLQ-LC13 [g]					
Dyspnoea	63	24.0 [7.4; n.a.] 27 (42.9)	78	8.3 [4.5; 19.3] 42 (53.8)	0.64 [0.39; 1.05] 0.076
Pain (chest)	63	n.a. [15.8; n.a.] 23 (36.5)	78	13.9 [7.7; n.a.] 31 (39.7)	0.77 [0.44; 1.32] 0.307
Pain (arm/shoulder)	63	n.a. [13.9; n.a.] 21 (33.3)	78	12.1 [6.5; 16.7] 38 (48.7)	0.51 [0.30; 0.88] 0.011
Pain (other)	63	15.9 [2.9; n.a.] 29 (46.0)	78	11.5 [4.7; 27.8] 37 (47.4)	0.88 [0.54; 1.45] 0.620
Coughing	63	n.a. [7.4: n.a.] 25 (39.7)	78	24.2 [11.8; n.a.] 29 (37.2)	0.97 [0.57; 1.67] 0.971
Haemoptysis	63	n.a. 8 (12.7)	78	n.a. 6 (7.7)	1.45 [0.50; 4.20] 0.507
Alopecia	63	n.a. [18.5; n.a.] 19 (30.2)	78	n.a. [9.5; n.a.] 25 (32.1)	0.76 [0.42; 1.39] 0.452
Dysphagia	63	24.9 [12.9; n.a.] 26 (41.3)	78	22.1 [13.9; n.a.] 27 (34.6)	0.98 [0.57; 1.69] 0.873

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Mouth pain	63	8.3 [3.1; n.a.] 32 (50.8)	78	14.8 [5.5; n.a.] 35 (44.9)	1.14 [0.70; 1.84] 0.624

Endpoint	Brigatinib		Crizotinib		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD) [a]
Peripheral neuropathy	63	n.a. [8.3; n.a.] 24 (38.1)	78	7.4 [3.7; 14.8] 43 (55.1)	0.53 [0.32; 0.89] 0.017

Health-related quality of life

Endpoint	Brigatinib		Crizotinib		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Health-related quality of life – time to first deterioration [h]					
Global health status and functional scales of the EORTC QLQ-C30					
Global health status	131	26.7 [8.3; n.a.] 57 (43.5)	131	8.3 [5.7; 13.5] 70 (53.4)	0.70 [0.49; 1.00] 0.049 18.4 months
Physical functioning	131	n.a. [13.9; n.a.] 55 (42.0)	131	10.3 [6.5; 17.5] 67 (51.1)	0.67 [0.47; 0.97] 0.051
Role functioning	131	10.2 [4.3; 21.2] 72 (55.0)	131	6.5 [3.9; 9.5] 77 (58.8)	0.84 [0.61; 1.17] 0.356
Emotional functioning	131	n.a. [22.2; n.a.] 48 (36.6)	131	10.1 [7.6; 14.8] 68 (51.9)	0.56 [0.38; 0.81] 0.002
Cognitive functioning	131	9.3 [4.7; 16.2] 76 (58.0)	131	4.5 [3.4; 8.3] 83 (63.4)	0.75 [0.54; 1.02] 0.066
Social functioning	131	27.7 [14.3; n.a.] 58 (44.3)	131	4.8 [2.9; 12.7] 74 (56.5)	0.59 [0.42; 0.85] 0.004 22.9 months

(Continuation)

Side effects

Endpoint	Brigatinib		Crizotinib		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Side effects [i]					
Adverse events (AE) (presented additionally)					
	136	0.2 [0.1; 0.3] 135 (99.3)	137	0.03 [0.03; 0.07] 137 (100)	-
Serious adverse events (SAE)					
	136	n.a. 45 (33.1)	137	n.a. [27.6.; n.a.] 51 (37.2)	0.68 [0.44; 1.06] 0.079
Severe adverse events (CTCAE grade ≥ 3)					
	136	5.1 [2.8; 8.4] 99 (72.8)	137	6.5 [4.0; 12.1] 84 (61.3)	1.25 [0.94; 1.68] 0.139
Discontinuation because of AE					
	136	n.a. 17 (12.5)	137	n.a. 12 (8.8)	1.42 [0.68; 2.99] 0.297
Specific adverse events					
Eye disorders (SOC, AEs)	136	n.a. 22 (16.2)	137	2.8 [0.4; n.a.] 75 (54.7)	0.19 [0.12; 0.32] < 0.001
Gastrointestinal disorders (SOC, AEs)	136	1.0 [0.7; 2.0] 104 (76.5)	137	0.1 [0.1; 0.2] 121 (88.3)	0.50 [0.38; 0.66] < 0.001 0.9 months
Skin and subcutaneous tissue disorders (SOC, AEs)	136	8.0 [5.5; 15.4] 73 (53.7)	137	n.a. 42 (30.7)	2.07 [1.42; 3.05] < 0.001
Peripheral oedema (PT, AEs)	136	n.a. 9 (6.6)	137	17.9 [9.7; n.a.] 61 (44.5)	0.10 [0.05; 0.22] < 0.001

(Continuation)

Endpoint	Brigatinib		Crizotinib		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR [95% CI] p value Absolute difference (AD)[a]
Creatine phosphokinase increased (PT, severe AE with CTCAE grade ≥ 3)	136	n.a. 33 (24.3)	137	n.a. 2 (1.5)	18.26 [4.38; 76.13] < 0.001
High blood pressure (PT, severe AE (CTCAE grade ≥ 3))	136	n.a. 16 (11.8)	137	n.a. 4 (2.9)	4.19 [1.40; 12.57] 0.007

[a] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[b] Data from: Dossier on brigatinib Module 4B of 24 April 2020
[c] Data from: European Medicines Agency. CHMP extension of indication variation assessment report: Alunbrig. 27 February 2020, page 38
[d] For the following patients, even after progress outside the CNS, data concerning CNS progression were included in the analysis: 1. Patients who, after systemic progression under brigatinib, were able to continue their treatment according to the investigator's instructions, 2. Patients in both treatment arms who continued to be treated until notification of systemic progression (according to the blinded independent committee) when no progression was detected by the investigator, and 3. Patients in the crizotinib arm who received brigatinib as follow-up therapy after disease progression at the investigator's discretion but only up to the first dose of brigatinib
[e] Incomplete follow-up (according to the study protocol, systematic follow-up was carried out only until the last administration of the study medication, until disease progression, or the start of a new systemic cancer therapy)
[f] Defined as an increase of the score by ≥ 10 points compared with the start of study
[g] Data from Addendum A20-85; survey started approx. 4 months after inclusion of the 1st patients (data for 134 patients (48.9%) not recorded)
[g] Defined as a decrease of the score by ≥ 10 points compared with the start of study
[i] Events that are attributable to the progression of the underlying disease are also recorded as AEs

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organisation for Research and Treatment of Cancer; HR = Hazard Ratio; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; PT = preferred term; QLQ-C30 = Quality of Life Questionnaire Core 30; QLQ-LC13 = Quality of Life Questionnaire Lung Cancer 13; RCT = randomised controlled study; SOC = system organ class; SAE = serious adverse event; AE = adverse event; vs = versus; CNS = central nervous system

a) Adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) with brain metastases previously not treated with an ALK inhibitor:

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↑	Advantage in overall survival
Morbidity	↑	Advantages in the endpoints nausea and vomiting, constipation, fatigue, loss of appetite, pain (arm/shoulder) and peripheral neuropathy
Health-related quality of life	↑	Advantages in the endpoints global health status, emotional functioning, and social functioning
Side effects	↔	No difference relevant for the benefit assessment
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

b) Adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) without brain metastases previously not treated with an ALK inhibitor:

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	No difference relevant for the benefit assessment
Morbidity	↑	Advantages in the endpoints nausea and vomiting, constipation, fatigue, loss of appetite, pain (arm/shoulder) and peripheral neuropathy
Health-related quality of life	↑	Advantages in the endpoints global health status, emotional functioning, and social functioning
Side effects	↔	No difference relevant for the benefit assessment
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data		

↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: There are no usable data for the benefit assessment. n.a.: not assessable

2. Number of patients or demarcation of patient groups eligible for treatment

a) Adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) with brain metastases previously not treated with an ALK inhibitor

and

b) Adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) without brain metastases previously not treated with an ALK inhibitor

together approx. 420–910 patients

3. Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Alunbrig® (active ingredient: brigatinib) at the following publicly accessible link (last access: 28 July 2020):

https://www.ema.europa.eu/documents/product-information/alunbrig-epar-product-information_de.pdf

Treatment with brigatinib should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in internal medicine and pneumology, specialists in pulmonary medicine, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with advanced bronchial carcinoma.

ALK verification

The ALK-positive NSCLC status should be known before initiating treatment with Alunbrig.

A validated ALK test is necessary to identify patients with ALK-positive NSCLC (see Section 5.1). The ALK-positive NSCLC status should be determined by laboratories with proven experience in the specific technique required.

4. Treatment costs

Annual treatment costs:

a) Adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer previously not treated with an ALK inhibitor

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Brigatinib	€ 65,322.09
Appropriate comparator therapy:	
Crizotinib	€ 64,329.91
Alectinib	€ 71,515.75

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 September 2020

Costs for additionally required SHI services: not applicable

b) Adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) without brain metastases previously not treated with an ALK inhibitor

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Brigatinib	€ 65,322.09
Appropriate comparator therapy:	
Crizotinib	€ 64,329.91
Alectinib	€ 71,515.75

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 September 2020

Costs for additionally required SHI services: not applicable