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Bosutinib (chronic myelogenous leukaemia) –

Addendum to Commission A21-79[1]

Addendum

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

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

IQWiG employees involved in the addendum

- Marc Schulte
- Moritz Felsch
- Katrin Nink

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Abbreviation	Meaning
AE	adverse event
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
mITT	modified intention to treat
Ph+ CML	Philadelphia chromosome-positive chronic myeloid leukaemia
RCT	randomized controlled trial

1 Background

On 12 October 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A21-79 (Bosutinib – Benefit assessment according to § 35a Social Code Book V) [1].

The randomized controlled trial (RCT) BFORE [2] was used for assessing the benefit of bosutinib in comparison with imatinib, nilotinib, or dasatinib as the ACT in adult patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukaemia (Ph+ CML) in chronic phase. The BFORE study compared bosutinib with imatinib. As the relevant subpopulation, the benefit assessment used the modified intention to treat (mITT) population, which comprises patients with Philadelphia chromosome.

The G-BA commissioned IQWiG with assessing the following additional data submitted by the pharmaceutical company (hereinafter "company") together with its written comment [3], taking into account the information provided in the dossier [4].

- Results on time to transition to blast crisis (entire follow-up duration)
- Subsequent therapies in the BFORE study (mITT population)
- Follow-up duration for the outcomes of transformation to blast crisis and adverse events (AEs) as of the final data cut-off (12 June 2020)

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

2 Assessment

2.1 Subsequently submitted information on follow-up duration for the outcomes of transition to blast crisis and side effects as of the final data cut-off (12 June 2020)

For the BFORE study, the dossier [4] contains no information on follow-up duration for the morbidity outcome of transition to blast crisis or for side effects. The company subsequently submitted these data with its written comment. They are presented in Table 1.

Table 1: Information on the course of the study – RCT, direct comparison: bosutinib vs. imatinib

Study Duration of the study phase Outcome category	Bosutinib N = 246	Imatinib N = 241
BFORE		
Follow-up observation duration [weeks]		
Morbidity[a,b] (transition to blast crisis)		
Median [min; max]	239.6 [0.1; 255.0]	239.1 [0.1; 247.6]
Mean (SD)	178.1 (86.0)	167.2 (93.7)
Side effects[c, d]		
Median [min; max]	243.6 [5.1; 260.0]	243.3 [7.0; 249.4]
Mean (SD)	178.7 (91.3)	173.1 (94.5)

a. After treatment end, transformation was surveyed by phone every 3 months.
b. See Section 2.3 for an interpretation of the follow-up duration of the outcome "transition to blast crisis".
c. AEs were surveyed for up to 28 days after the last treatment.
d. When compared with the follow-up duration for overall survival (see Table 10 in dossier assessment A21-79 [1]), the medians and minima/maxima (bosutinib arm) seem implausible. No information was provided on the manner in which the subsequently submitted data were compiled.

max: maximum; min: minimum; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation

The treatment and follow-up durations are balanced between both treatment arms. However, the standard deviation is very high in each case.

2.2 Results subsequently submitted on subsequent therapies in the BFORE study (mITT population)

For the BFORE study, the dossier provided analyses of subsequent therapies for the intention-to-treat (ITT) population. The benefit assessment [1] is based on the mITT population, which comprises patients with Philadelphia chromosome, as the relevant subpopulation. The company's dossier submitted the patients' subsequent therapies only for the ITT population. Together with its written statement, the company later submitted the list of subsequent therapies of the mITT population. It is presented in Table 2.

Table 2: Data on antineoplastic subsequent therapies (≥ 1 patient in ≥ 1 treatment arm) – RCT, direct comparison: bosutinib vs. imatinib (BFORE study)

Study Drug	Patients with subsequent therapy n (%)	
	Bosutinib N = 246	Imatinib N = 241
BFORE		
Total[a]	77 (31.3)	84 (34.9)
Dasatinib	27 (11.0)	43 (17.8)
Imatinib	37 (15.0)	13 (5.4)
Nilotinib	13 (5.3)	24 (10.0)
Bosutinib	4 (1.6)	24 (10.0)
Hydroxycarbamide	7 (2.8)	9 (3.7)
Dasatinib monohydrate	6 (2.4)	9 (3.7)
Ponatinib	4 (1.6)	10 (4.1)
Imatinib mesylate	7 (2.8)	3 (1.2)
Nilotinib hydrochloride	3 (1.2)	2 (0.8)
Asciminib	1 (0.4)	2 (0.8)
Cytarabine	1 (0.4)	1 (0.4)
Paclitaxel	1 (0.4)	0
Ponatinib hydrochloride	0	2 (0.8)
Anagrelide	0	1 (0.4)
Anagrelide hydrochloride	1 (0.4)	0
Busulfan	0	1 (0.4)
Cyclophosphamide	0	1 (0.4)
Daunorubicin	1 (0.4)	0
Doxorubicin; vincristine	0	1 (0.4)
Fluorouracil	0	1 (0.4)
Radotinib hydrochloride	1 (0.4)	0
Trastuzumab	1 (0.4)	0
Other antineoplastic agents	0	1 (0.4)

a. All patients with or without Philadelphia chromosome who took at least 1 dose of the randomized study drug (mITT).

mITT: modified intention to treat; n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

The BFORE study did not restrict potential subsequent therapies. Up to the present data cut-off, about a third of the BFORE study's total population had received an antineoplastic subsequent therapy; in both study arms, most of these involved other tyrosine kinase inhibitors (TKIs) (dasatinib, imatinib, nilotinib). In the comparator arm, 10% of patients received bosutinib as subsequent therapy. This is an approved treatment option, at least for patients for whom imatinib, nilotinib, and dasatinib are deemed unsuitable options. No data are available

on the extent to which these criteria were met for all patients who had received bosutinib as subsequent therapy.

The subsequent therapies used in the mITT population generally correspond to those in the ITT population.

2.3 Subsequently submitted results on time to transition to blast crisis

The dossier's analyses of data from the BFORE study on transition to blast crisis included only events that occurred while patients were on the study drug. The presented analyses do not allow drawing any conclusions on the complete follow-up period. The risk of bias is therefore deemed high due to incomplete follow-up for potentially informative reasons. The company reports to have subsequently submitted, together with its comment, analyses for the outcome of transition to blast crisis for the entire follow-up period. However, the mean follow-up durations for the outcome of transition to blast crisis substantially differ from those for overall survival (see Table 10 of dossier assessment A21-79 [1]). Given the small number of cases with transition to blast crisis, this cannot be due to the occurrence of events alone. The figures provided by the company therefore seem more likely to reflect treatment duration rather than follow-up duration on overall survival. Hence, the information on follow-up duration suggests that, once again, the analysis did not cover the entire follow-up duration.

It remains unclear whether the company's analyses subsequently submitted with its comment on the outcome of transition to blast crisis actually do cover the entire follow-up duration. For said outcome, this results in a continued high risk of bias due to incomplete follow-up for potentially informative reasons.

Table 3 shows the results on time to transition to blast crisis.

Table 3: Results (transition to blast crisis) – RCT, direct comparison: bosutinib vs. imatinib

Study Outcome category Outcome	Bosutinib		Imatinib		Bosutinib vs. imatinib
	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]
BFORE					
Morbidity					
Transition to blast crisis	246	–[b] 3 (1.2)	241	–[b] 1 (0.4)	2.74 [0.28; 26.40]; 0.364

a. Proportional subdistribution hazards model, taking into account the competing risks of treatment discontinuation (except due to progression) and death, stratified by Sokal score and geographic region.
b. Given the small number of events, the median reported by the company does not permit a meaningful interpretation.

CI: confidence interval; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; RCT: randomized controlled trial

For the outcome of transition to blast crisis, there continues to be no statistically significant difference between treatment groups. This results in no hint of added benefit of bosutinib in comparison with imatinib; an added benefit is therefore not proven.

2.4 Summary

The data subsequently submitted by the company in the commenting procedure do not change the conclusion drawn in dossier assessment A21-79 on the added benefit of bosutinib.

Table 4 below shows the result of the benefit assessment of bosutinib in consideration of both dossier assessment A21-79 and the present addendum.

Table 4: Bosutinib – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**[b]
Treatment of adults with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukaemia (Ph^+ CML) in chronic phase	**Imatinib** or nilotinib or dasatinib	Hint of lesser benefit[b]

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is marked in **bold**.
b. Only patients with an ECOG-PS of 0 or 1 were included in the BFORE study. It remains unclear whether the observed effects can be assumed to occur also in patients with an ECOG-PS ≥ 2.

ACT: appropriate comparator therapy; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; Ph^+ CML: Philadelphia chromosome-positive chronic myeloid leukaemia

The G-BA decides on the added benefit.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Bosutinib (chronische myeloische Leukämie) – Nutzenbewertung gemäß § 35a SGB V (Ablauf Befristung); Dossierbewertung [online]. 2021 [Accessed: 02.09.2021]. URL: https://www.iqwig.de/download/a21-79_bosutinib_nutzenbewertung-35a-sgb-v_v1-0.pdf.

2. Pfizer. A Multicenter Phase 3 Randomized, Open-Label Study of Bosutinib versus Imatinib in Adult Patients with Newly Diagnosed Chronic Phase Chronic Myelogenous Leukemia; study AV001 (B1871053); Supplemental Clinical Study Report [unpublished]. 2020.

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4. Pfizer Pharma. Bosutinib (Bosulif); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2021 [Accessed: 06.10.2021]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/703/#dossier.