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Ibrutinib
(chronic lymphocytic leukaemia, mantle cell lymphoma) –
Addendum to Commission A16-04[1]

Addendum

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Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CLL	chronic lymphocytic leukaemia
CTCAE	Common Terminology Criteria for Adverse Events
EQ-5D	European Quality of Life-5 Dimensions
FACT-G	Functional Assessment of Cancer Therapy-General
FACT-Lym	Functional Assessment of Cancer Therapy-Lymphoma
FACT-LymS	Functional Assessment of Cancer Therapy-Lymphoma Subscale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MCL	mantle cell lymphoma
MID	minimally important difference
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
TOI	Trial Outcome Index
VAS	visual analogue scale

1 Background

On 6 June 2016, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A16-04 (Ibrutinib – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

In its written comments to the dossier assessment [2], the pharmaceutical company (hereinafter referred to as "the company") sent supplementary information, which went beyond the information provided in the dossier on ibrutinib [3-5], to prove the added benefit. To be able to decide on the added benefit, the G-BA therefore requires further analyses. On the one hand the G-BA's commission comprised the assessment of the analyses on adverse events (AEs) in the therapeutic indication of chronic lymphocytic leukaemia (CLL; research question 1b: pretreated CLL patients for whom chemotherapy is unsuitable) submitted by the company, and, on the other, the assessment of the analyses on health-related quality of life and on health status in the therapeutic indication of mantle cell lymphoma (MCL; research question 1a: patients for whom temsirolimus constitutes the individually optimized treatment option) subsequently submitted.

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

2 Assessment of the data subsequently submitted for the therapeutic indication CLL

With its comment, the company presented further analyses on AEs on the PCYC-1112-CA study [2,6]. This study was the only study used for the benefit assessment of ibrutinib in the therapeutic indication CLL, specifically for research question 1b (patients for whom chemotherapy is not indicated) [1]. In its dossier, the company had analysed the subpopulation of at least double-refractory patients in the study for research question 1b [3]. The company subsequently submitted the following data:

- List of AEs that occurred in at least 5% of the patients in the relevant subpopulation. In the original dossier, the company had only presented data for AEs that had occurred in at least 10% of these patients. The comparison with the AE rate in the total population showed that potentially notable differences in individual AEs were not reported because of this [1]. The data subsequently submitted with the company's comment provided no additional information, however, because they did not include all relevant patients (only 52 of the 58 patients analysed in the dossier), which resulted in individual AEs not being included in the subsequent analysis.
- Information on "duration and recovery" of serious AEs (SAEs). Based on these data, the company argued that the AEs under ibrutinib did not outweigh the mortality advantage versus the comparator therapy. Irrespective of the question whether the analyses conducted by the company were conceptually suitable to support this argument, the specific data presented were unsuitable for several reasons. On the one hand, the company did not present these analyses for the relevant subpopulation, but only for the total population. On the other, it conducted these analyses only for the observation period of 9 months, although observations for a period of 18 months were available for ibrutinib. Finally, the company restricted the analyses to events operationalized as SAEs, although severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade 3 or higher) were more common than SAEs.
- Information on the distribution of the severity grades for severe AEs. These data were also not usable because the company presented this analysis also only for the total population and only for the observation period of 9 months. Irrespective of this, the distribution presented by the company corresponded to the one expected and to the distribution observed in many other oncological studies (grade 3 events were more common than grade 4 events, which were more common than grade 5 events).

In summary, the data on AEs subsequently submitted by the company provided no additional information for research question 1b of the therapeutic indication CLL. The conclusion of dossier assessment A16-04 on ibrutinib for the therapeutic indication CLL was therefore not changed by the data subsequently submitted.

3 Assessment of the data subsequently submitted for the therapeutic indication MCL

With its comment, the company presented further analyses on health-related quality of life and on health status for the MCL3001 study [2,7]. This study was the only relevant study for the benefit assessment of ibrutinib in the therapeutic indication MCL, specifically for research question 1a (patients for whom temsirolimus constitutes the individually optimized treatment option) [1]. In the MCL3001 study, health-related quality of life was recorded with the instrument Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym); health status was recorded with the visual analogue scale (VAS) of the instrument European Quality of Life-5 Dimensions (EQ-5D). A detailed description of the instruments including the corresponding subscales can be found in dossier assessment A16-04 [1].

The assessment of the analyses subsequently submitted is presented in the following sections as follows:

- assessment of the analyses on health-related quality of life (Section 3.1)
- assessment of the analyses on health status (Section 3.2)

Section 3.3 contains a derivation of the added benefit of ibrutinib in comparison with the appropriate comparator therapy (ACT) in the therapeutic indication MCL under consideration of the results of the present addendum and of dossier assessment A16-04.

3.1 Health-related quality of life

Data presented

The company had presented no usable analyses on health-related quality of life (recorded with FACT-Lym) in its original dossier [1]. On the one hand, the company had presented no responder analyses for the FACT-General (FACT-G), although a minimally important difference (MID) range of 5 to 7 points is validated for this. On the other, the company had only presented analyses for the upper, but not for the lower threshold value of the validated MID of 3 to 5 points for the FACT-Lym Subscale (FACT-LymS). Finally, the company had conducted responder analyses on the total score and on the Trial Outcome Index (TOI) on the basis of unvalidated MIDs. The analyses on mean differences presented in each case were not usable.

With its comment, the company presented analyses for the FACT-G on the threshold values 5 and 7. It additionally subsequently submitted the missing analyses on the lower threshold value (MID 3 points) for the FACT-LymS. These analyses were suitable for the benefit assessment and will be assessed in the following sections. The company again submitted analyses on the total score and on the TOI on the basis of unvalidated MIDs. These were not relevant for the present benefit assessment and were therefore not considered further.

On the relevant analyses on FACT-G and FACT-LymS, the company presented analyses on the total population and on the primarily relevant subpopulation (≥ 3 prior therapies) of the

MCL3001 study. It conducted no interaction tests for this, however. Due to the similarity of the effects observed in the subpopulation and in the total population, it could be assumed that there was no interaction relevant for the assessment, however. Following the methodology of dossier assessment A16-04, the assessment was therefore conducted on the basis of the total population of the MCL3001 study.

The company also presented subgroup analyses on all analyses mentioned above. However, these were unsuitable for the reasons stated in dossier assessment A16-04, and were therefore not considered further.

Risk of bias

Due to the large proportion of missing values already at the start of the study (see dossier assessment A16-04) and the open-label study design of the MCL3001 study, there was a high risk of bias for the outcomes on health-related quality of life.

It should also be noted as a restriction that health-related quality of life was only recorded until progression or discontinuation of the study medication, which is why the following conclusions are limited to this period of time.

Results

The following Table 1 shows the results on health-related quality of life, recorded with the FACT-Lym instrument.

Table 1: Results on health-related quality of life – RCT, direct comparison: ibrutinib vs. temsirolimus (research question 1a in the therapeutic indication MCL)

Study Outcome Population	Ibrutinib N	Ibrutinib Median time to event [95% CI] Patients with event n (%)	Temsirolimus N	Temsirolimus Median time to event [95% CI] Patients with event n (%)	Ibrutinib vs. temsirolimus HR [95% CI][a]; p-value
MCL3001					
Health-related quality of life: FACT-G					
Time to improvement					
MID 5 points [weeks]					
Total population	139	12 [ND] 74 (53.2)	141	51 [ND] 46 (32.6)	1.57 [1.08; 2.28]; p = 0.017
MID 7 points [weeks]					
Total population	139	18 [ND] 64 (46.0)	141	54 [ND] 40 (28.4)	1.49 [1.00; 2.22]; p = 0.051
Time to deterioration					
MID 5 points [weeks]					
Total population	139	15 [ND] 72 (51.8)	141	6.3 [ND] 87 (61.7)	0.53 [0.39; 0.74]; p < 0.001
MID 7 points [weeks]					
Total population	139	30 [ND] 65 (46.8)	141	9.1 [ND] 80 (56.7)	0.54 [0.38; 0.75]; p < 0.001
Health-related quality of life: FACT-LymS					
Time to improvement					
MID 3 points [weeks]					
Total population	139	3.3 [ND] 95 (68.3)	141	12 [ND] 67 (47.5)	1.65 [1.20; 2.28]; p = 0.002
MID 5 points [weeks]					
Total population	139	6.3 [ND] 86 (61.9)	141	57 [ND] 50 (35.5)	2.19 [1.52; 3.14]; p < 0.001
Time to deterioration					
MID 3 points [weeks]					
Total population	139	81 [ND] 48 (34.5)	141	8.1 [ND] 83 (58.9)	0.30 [0.20; 0.43]; p < 0.001
MID 5 points [weeks]					
Total population	139	NA 37 (26.6)	141	9.7 [ND] 73 (51.8)	0.27 [0.18; 0.41]; p < 0.001

a: Stratified Cox proportional hazards model with the stratification factors used for randomization.
CI: confidence interval; FACT-G: Functional Assessment of Cancer Therapy-General; FACT-LymS: Functional Assessment of Cancer Therapy-Lymphoma Subscale; HR: hazard ratio; MCL: mantle cell lymphoma; MID: minimally important difference; N: number of analysed patients; n: number of patients with event; NA: not achieved; ND: no data; RCT: randomized controlled trial; vs.: versus

FACT-G

A statistically significant result in favour of ibrutinib was shown for time to improvement for the lower threshold value (5 points). The result of the upper threshold value (7 points) was not statistically significant, but, with a p-value of 0.051 and similar effect size, consistent in comparison with the analysis with the lower threshold value. Based on the lower threshold value, improvement under ibrutinib occurred after a median time of about 3 months, and under temsirolimus only after about 1 year.

A statistically significant result in favour of ibrutinib was shown for time to deterioration for the FACT-G for both threshold values. Based on the lower threshold value, deterioration under ibrutinib occurred after a median time of about 4 months, and under temsirolimus already after about 2 months.

Overall, this resulted in a hint of an added benefit of ibrutinib in comparison with temsirolimus for the FACT-G, both for time to improvement and for time to deterioration.

FACT-LymS

A statistically significant result in favour of ibrutinib was shown both for time to improvement and for time to deterioration for both threshold values (3 and 5 points). Based on the lower threshold value, improvement under ibrutinib occurred after a median time of about 1 month, and under temsirolimus after about 3 months; deterioration under ibrutinib after about 19 months versus about 2 months under temsirolimus.

Overall, this resulted in a hint of an added benefit of ibrutinib in comparison with temsirolimus for the FACT-LymS, both for time to improvement and for time to deterioration.

3.2 Health status

With its original dossier, the company had presented responder analyses with the threshold values 7 and 12 points for the EQ-5D VAS. It was explained in dossier assessment A16-04 that the threshold value of 12 points does not correspond to the upper threshold value of a validated MID (10 points). Hence, based on the distribution curves presented in the dossier, the analyses of the time to deterioration were usable, but not the ones of the time to improvement.

With its comment, the company subsequently submitted the missing analyses on the upper threshold value (MID 10 points). Furthermore, it corrected the analysis on the mean differences presented in the dossier because it was incorrect, according to the company [2]. These analyses were suitable for the benefit assessment and will be assessed in the following sections.

The company presented both analyses on the total population and on the primarily relevant subpopulation (≥ 3 prior therapies) of the MCL3001 study. It conducted no interaction tests for this, however. Due to the similarity of the effects observed in the subpopulation and in the total population, it could be assumed that there was no interaction relevant for the assessment, however. Following the methodology of dossier assessment A16-04, the assessment was therefore conducted on the basis of the total population of the MCL3001 study.

The company also presented subgroup analyses on all analyses mentioned above. However, these were unsuitable for the reasons stated in dossier assessment A16-04, and were therefore not considered further.

Risk of bias

Due to the large proportion of missing values already at the start of the study (see dossier assessment A16-04) and the open-label study design of the MCL3001 study, there was a high risk of bias for the outcome “health status”.

Results

The following Table 2 shows the results on health status, recorded with the EQ-5D VAS instrument.

Table 2: Results on health status – RCT, direct comparison: ibrutinib vs. temsirolimus (research question 1a in the therapeutic indication MCL)

Study Outcome Population	Ibrutinib N	Ibrutinib Median time to event [95% CI] Patients with event n (%)	Temsirolimus N	Temsirolimus Median time to event [95% CI] Patients with event n (%)	Ibrutinib vs. temsirolimus HR [95% CI][a]; p-value
MCL3001					
Morbidity (health status): EQ-5D VAS					
Time to improvement					
MID 7 points [weeks]					
Total population	139	9.1 [ND] 79 (56.8)	141	39 [ND] 55 (39.0)	1.52 [1.05; 2.19]; p = 0.025
MID 10 points [weeks]					
Total population	139	12 [ND] 68 (48.9)	141	60 [ND] 50 (35.5)	1.37 [0.93; 2.01]; p = 0.108
Time to deterioration					
MID 7 points [weeks]					
Total population	139	48 [ND] 63 (45.3)	141	9.1 [ND] 78 (55.3)	0.47 [0.33; 0.68]; p < 0.001
MID 10 points [weeks]					
Total population	139	NA 54 (38.8)	141	10 [ND] 75 (53.2)	0.41 [0.28; 0.59]; p < 0.001
		Baseline values mean (SD) / **Change at end of study mean[b] (SD)**		**Baseline values mean (SD)** / **Change at end of study mean[b] (SD)**	**Effect [95% CI]; p-value**
Mean change					
Total population	124	71.5 (17.2) / 6.0 (1.0)	115	64.3 (19.5) / -1.8 (1.2)	7.83 [5.10; 10.55]; p < 0.001

a: Stratified Cox proportional hazards model with the stratification factors used for randomization.
b: MMRM analyses of patients for whom at least one value after the start of the study was available.
CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; MCL: mantle cell lymphoma; MID: minimally important difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients (for mean change: number of patients with at least one value after the start of the study); n: number of patients with event; NA: not achieved; ND: no data; RCT: randomized controlled trial; vs.: versus

A statistically significant result in favour of ibrutinib was shown for time to improvement for the lower threshold value (7 points), but not for the upper threshold value (10 points). In addition, based on the lower limit of the confidence interval (1.05, or, with reversed direction of effect, 0.95), the effect for the lower threshold value was no more than marginal.

A statistically significant result in favour of ibrutinib was shown for time to deterioration for both threshold values. Based on the lower threshold value, deterioration under ibrutinib

occurred after a median time of about 11 months, and under temsirolimus already after about 2 months.

A statistically significant effect in favour of ibrutinib was also shown for the mean change. Due to the available responder analyses, it was not necessary to calculate a standardized mean difference for the assessment of the relevance of the effect.

Overall, there was a hint of an added benefit of ibrutinib in comparison with temsirolimus for the outcome "health status" (time to deterioration).

3.3 Extent and probability of the added benefit

Derivation of extent and probability of added benefit at outcome level

Hereinafter, the derivation of extent and probability of the added benefit is presented at outcome level under consideration of the present addendum and dossier assessment A16-04. The methods used for this purpose are explained in the *General Methods* of IQWiG [8].

Table 3 shows the results of the MCL3001 study relevant for the derivation of the added benefit.

Table 3: Extent of added benefit at outcome level: ibrutinib vs. temsirolimus (research question 1a in the therapeutic indication MCL)

Outcome category **Outcome**	**Ibrutinib vs. temsirolimus** **Median time to event or mean change** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	NA vs. 21.3 months HR: 0.76 [0.53; 1.09]; p = 0.132	Lesser benefit/added benefit not proven
Morbidity		
Health status (EQ-5D VAS)[c]	*Time to improvement* 9.1 vs. 39 weeks HR: 1.52 [1.05; 2.19]; p = 0.025 HR: 0.66 [0.46; 0.95][d] probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.9 \leq CI_u < 1$ lesser benefit/added benefit not proven[e]
	Time to deterioration 48 vs. 9.1 weeks HR: 0.47 [0.33; 0.68]; p < 0.001 probability: "hint"	$CI_u < 0.8$ added benefit, extent: "considerable"
Health-related quality of life		
FACT-G[f]	*Time to improvement* 12 vs. 51 weeks HR: 1.57 [1.08; 2.28]; p = 0.017 HR: 0.64 [0.44; 0.93][d] probability: "hint"	Outcome category: health-related quality of life $0.9 \leq CI_u < 1$ added benefit, extent: "minor"
	Time to deterioration 15 vs. 6.3 weeks HR: 0.53 [0.39; 0.74]; p < 0.001 probability: "hint"	$CI_u < 0.75$, risk ≥ 5% added benefit, extent: "major"
FACT-LymS[g]	*Time to improvement* 3.3 vs. 12 weeks HR: 1.65 [1.20; 2.28]; p = 0.002 HR: 0.61 [0.44; 0.83][d] probability: "hint"	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.9$ added benefit, extent: "considerable"
	Time to deterioration 81 vs. 8.1 weeks HR: 0.30 [0.20; 0.43]; p < 0.001 probability: "hint"	$CI_u < 0.75$, risk ≥ 5% added benefit, extent: "major"

(continued)

Table 3: Extent of added benefit at outcome level: ibrutinib vs. temsirolimus (research question 1a in the therapeutic indication MCL) (continued)

Outcome category **Outcome**	**Ibrutinib vs. temsirolimus** **Median time to event or mean change** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
SAEs	60.7 vs. 17.9 weeks HR: 0.53 [0.38; 0.74]; p < 0.001 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% added benefit, extent: "major"
Discontinuation due to AEs	NA vs. NA HR: 0.40 [0.17; 0.92]; p = 0.031[h]	Outcome category: non-serious/non-severe side effects $0.9 \leq CI_u < 1$ greater harm/added benefit not proven[e]
Severe AEs (CTCAE grade 3/4)	48.0 vs. 2.9 weeks HR: 0.28 [0.20; 0.39]; p < 0.001 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% added benefit, extent: "major"

a: Probability provided if statistically significant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: In each case results provided for the lower threshold value (MID 7 points); direction of effect for upper threshold value (MID 10 points) consistent in each case.
d: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e: Lesser benefit or added benefit is not proven because the effect size was only marginal.
f: In each case results provided for the lower threshold value (MID 5 points); direction of effect for upper threshold value (MID 7 points) consistent in each case.
g: In each case results provided for the lower threshold value (MID 3 points); direction of effect for upper threshold value (MID 5 points) consistent in each case.
h: Based on subpopulation with ≥ 3 prior therapies due to an indication of interaction for < 3 vs. ≥ 3 prior therapies (based on IWRS).
AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-G: Functional Assessment of Cancer Therapy-General; FACT-LymS: Functional Assessment of Cancer Therapy-Lymphoma Subscale; HR: hazard ratio; IWRS: interactive web response system; MCL: mantle cell lymphoma; MID: minimally important difference; NA: not achieved; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Overall conclusion on the added benefit

Table 4 summarizes the results that were considered in the overall conclusion on the extent of added benefit of ibrutinib for research question 1a in the therapeutic indication MCL.

Table 4: Positive and negative effects from the assessment of ibrutinib compared with temsirolimus (research question 1a in the therapeutic indication MCL)

Positive effects	**Negative effects**
Morbidity (non-serious/non-severe symptoms/late complications) ▪ Health status (EQ-5D VAS): hint of an added benefit – extent: "considerable" Health-related quality of life ▪ FACT-G: hint of an added benefit – extent: "major" ▪ FACT-LymS: hint of an added benefit – extent: "major" Serious/severe side effects ▪ SAEs: indication of lesser harm – extent: "major" ▪ Severe AEs (CTCAE grade 3/4): indication of lesser harm – extent: "major"	–
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-G: Functional Assessment of Cancer Therapy-General; FACT-LymS: Functional Assessment of Cancer Therapy-Lymphoma Subscale; MCL: mantle cell lymphoma; SAE: serious adverse event; VAS: visual analogue scale	

For patients for whom temsirolimus constitutes the individually optimized treatment, on the side of positive effects, there is a hint of considerable added benefit for health status, a hint of major added benefit for health-related quality of life, and an indication of lesser harm with the extent "major" for side effects (SAEs and severe AEs [CTCAE grade 3/4]. This is not accompanied by negative effects.

In summary, there is an indication of major added benefit of ibrutinib in comparison with the ACT for patients with relapsed or refractory MCL for whom temsirolimus constitutes the individually optimized treatment (research question 1a).

This concurs with the result of dossier assessment A16-04 [1].

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

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