IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Idelalisib (chronic lymphocytic leukaemia) –

Addendum to Commission A16-18[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
BSC	best supportive care
CI	confidence interval
CLL	chronic lymphocytic leukaemia
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 8 August 2016, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A16-18 (Idelalisib – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

The G-BA's commission comprised the assessment of the study results presented by the company in the dossier that were new compared with the first assessment of idelalisib (A14-35 [2]) and that, in addition, address the justification for the first decision (G-BA decision from 19 March 2015), particularly the new data cut-off of study GS-US-312-0116 and the results of the extension study GS-US-312-0117.

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

For research question 1b (patients with relapsed or refractory chronic lymphocytic leukaemia [CLL] for whom chemotherapy is not indicated), the company presented study GS-US-312-0116 and its extension study GS-US-312-0117 both in the first assessment and in the reassessment after expiry of the decision (A14-35 and A16-18 [1,2]). Information on the respective study design can be found in benefit assessment A14-35 [2].

For the benefit assessments A14-35 and A16-18, the company had presented the results of the second interim analysis of study GS-US-312-0116 (last blinded data cut-off from 9 October 2013) and had used these results both in the first assessment and in the assessment after expiry of the decision for the derivation of the added benefit.

Both studies were not relevant for the benefit assessments conducted because they allowed no comparison of idelalisib with the ACT best supportive care (BSC) specified by the G-BA for this patient population. Furthermore, it was unclear for which proportion of the study population chemotherapy would not have been indicated [1]. Further information on the study design can be found in the first assessment of idelalisib (A14-35 [2]).

For the reassessment after expiry of the decision (A16-18), the company had additionally presented results from 2 new data cut-offs of both studies. These were the final data cut-off of study GS-US-312-0116 from 20 April 2014 and a current interim analysis of the extension study GS-US-312-0117 from 18 September 2015.

The results of both newly submitted analyses were less informative than the second interim analysis already presented in the first assessment. This was due to the fact that the patients in the placebo + rituximab group had the opportunity to cross over to the idelalisib arm in the course of the study. Hence at the time point of the new data cut-offs (20 April 2014 and 18 September 2015), all patients were receiving idelalisib (as monotherapy) or had discontinued the study. The bias of the results of the new data cut-offs was therefore rated as greater than of the results of the data cut-off from 9 October 2013.

Irrespective of this, the results on overall survival of the data cut-off from 9 October 2013 were comparable to both new data cut-offs (data cut-off 9 October 2013: hazard ratio [HR] [95% confidence interval (CI)]; p-value: 0.28 [0.11; 0.69]; 0.003); see Appendix A for the new data cut-offs). The analyses of the adverse events (AEs) were problematic, however. Different treatment periods of the patients in the idelalisib + rituximab group and of the patients in the placebo + rituximab group were included in the AE analyses. No adequate balancing of benefit and risk for both new data cut-offs were possible as a result. The study should therefore be assessed on the basis of the data cut-off from 9 October 2013.

Details on the 3 data cut-offs available are explained below. The results of both newly submitted data cut-offs for the outcomes “overall survival” and “AEs” are presented as additional information in Appendix A.

Underlying data of the newly presented data cut-offs of the studies GS-US-312-0116 and GS-US-312-0117

Figure 1 shows a schematic overview of the study design.

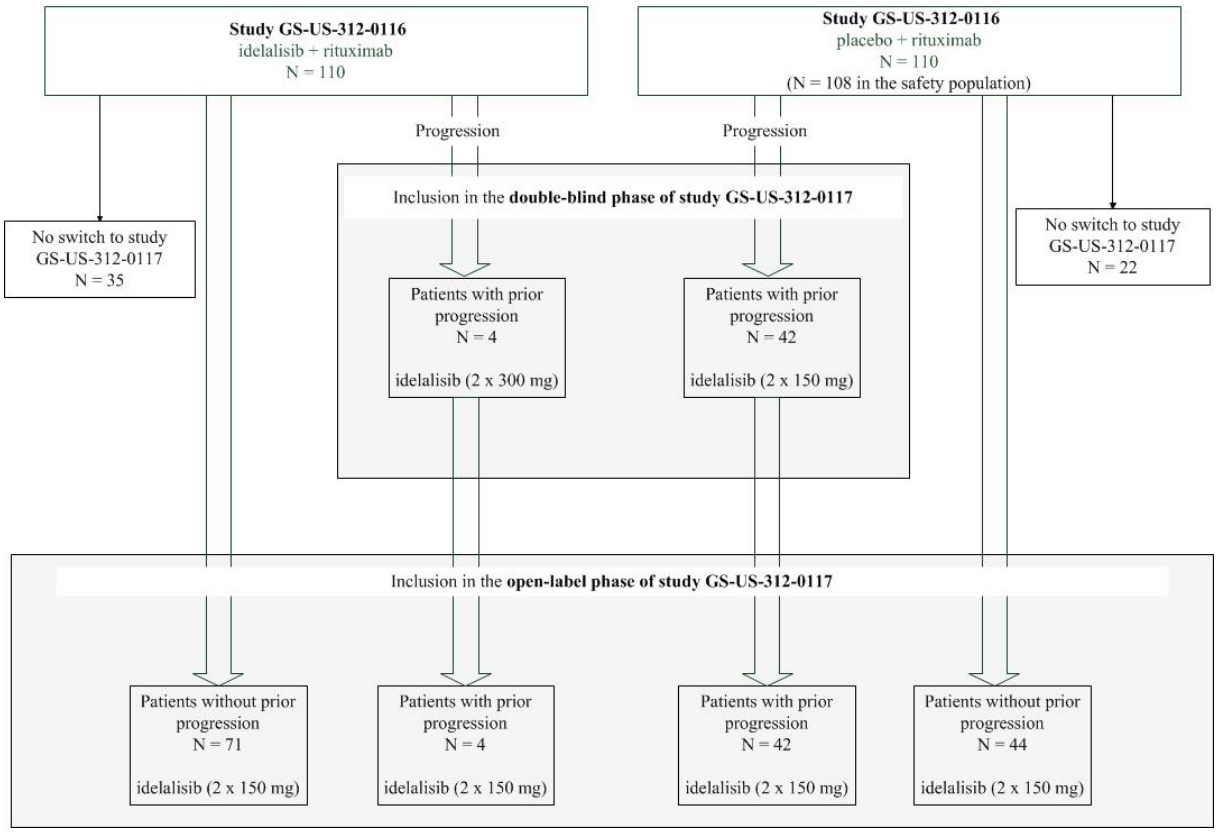

Figure 1: Schematic overview of the study design of the approval study GS-US-312-0116 and its extension study GS-US-312-0117 (adapted from Module 4 A of the dossier for benefit assessment A16-18)

Data cut-off from 9 October 2013 (clinical study report from 23 November 2013) of study GS-US-312-0116

Pretreated patients with CLL who had progressed within 24 months after their last prior therapy were included in the double-blind approval study GS-US-312-0116. Both patients with relapsed and with refractory CLL were included in the study population. A total of 220 patients were randomly assigned in a ratio of 1:1 to the 2 treatment arms idelalisib + rituximab or placebo + rituximab.

Patients who progressed had the opportunity to cross over to the extension study GS-US-312-0117. In the extension study, the patients from the prior verum arm received idelalisib monotherapy (which was initially still blinded) at twice the daily dosage (2 x 300 mg). This treatment (dosage, monotherapy) is not approved. The patients from the prior control arm received 2 x 150 mg idelalisib monotherapy (which was also initially still blinded) daily. This treatment (monotherapy) is also not approved. This concerned 4 patients

in the idelalisib group and 42 patients in the placebo group. Blinding in the study was maintained until the data cut-off on 9 October 2013. The company already used these results of this data cut-off for the first assessment and for the reassessment of idelalisib to derive the added benefit.

After the premature completion of the GS-US-312-0116 study, all patients could be included in the GS-US-312-0117 study, which was then continued unblinded. All patients who changed to the extension study after completion of study GS-US-312-0116 received 2 x 150 mg idelalisib monotherapy. This treatment is not approved.

Data cut-off from 20 April 2014 of study GS-US-312-0116

At the time point of the data cut-off from 20 April 2014 of study GS-US-312-0116, all patients were receiving idelalisib monotherapy or had discontinued the study. Depending on the outcome, different data of the patients were included in the analyses on this data cut-off.

The data of all randomized patients from study GS-US-312-0116 that were recorded until 1 July 2014 (long-term follow-up after data cut-off) in the studies GS-US-312-0116 or GS-US-312-0117 were included in the analysis of the outcome "overall survival". This means that, for patients from the placebo + rituximab group, this analysis also contained treatment phases with idelalisib in study GS-US-312-0117. For patients from the idelalisib + rituximab group of study GS-US-312-0116, the analysis at this cut-off date also contained data recorded under treatment with idelalisib monotherapy. Hence the results were not informative for the present research question.

Different time periods were included in the analysis of AEs for the idelalisib + rituximab group and for the placebo + rituximab group. All events until 20 April 2014 were analysed for the idelalisib + rituximab group. This also included results that occurred in the open-label phase of the extension study GS-US-312-0117 under administration of idelalisib monotherapy. For the placebo + rituximab group, in contrast, only the data until the first administration of idelalisib (2 x 150 mg) in the open-label phase of study GS-US-312-0117 were analysed. Hence for this treatment group, data from the double-blind phase of study GS-US-312-0117 were included (with treatment with idelalisib monotherapy), but not from the open-label phase of the extension study. This additionally resulted in different observation periods between the treatment arms. Overall, these analyses were also not informative.

Data cut-off from 18 September 2015 (unblinded phase of the extension study GS-US-312-0117)

The data of all randomized patients from study GS-US-312-0116 and extension study GS-US-312-0117 that were recorded until the cut-off date 18 September 2015 were included in the analysis of the outcome "overall survival" of the data cut-off of study GS-US-312-0117. This means that treatment phases with idelalisib monotherapy were considered for patients from both treatment arms of study GS-US-312-0116. These analyses

were not informative for a comparison of the randomized treatments of study GS-US-312-0116.

Different patients were included in the analysis of AEs for the idelalisib + rituximab group and for the placebo + rituximab group. Analogous to overall survival, for the idelalisib + rituximab group, the events until 18 September 2015 were analysed for all randomized patients. The analyses for the placebo + rituximab group were not based on the data of all randomized patients from the GS-US-312-0116 study. The data on 22 patients who did not enter the extension study GS-US-312-0117 after completion of study GS-US-312-0116 were missing. Overall, 2 analyses were available for the remaining patients in the placebo + rituximab group: one for the 42 patients from the placebo + rituximab group who had progressed and received idelalisib (2 x 150 mg) in the double-blind phase of study GS-US-312-0117 (see Figure 1), and one for the 44 patients without progression who received idelalisib (2 x 150 mg) in the open-label phase of study GS-US-312-0117. Both analyses only included those AEs that occurred after the first dose of idelalisib. Both analyses were therefore not informative for the comparison of the randomized treatments of study GS-US-312-0116.

3 References

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2. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Idelalisib: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A14-35 [online]. 22.12.2014 [Accessed: 08.01.2015]. (IQWiG-Berichte; Volume 267). URL: https://www.iqwig.de/download/A14-35_Idelalisib_Nutzenbewertung-35a-SGB-V.pdf.

Appendix A – Results of the study GS-US-312-0116 and of the extension study GS-US-312-0117

Table 1: Results (mortality and side effects) – RCT, direct comparison: idelalisib + rituximab vs. placebo + rituximab, data cut-off from 20 April 2014

Study Outcome category Outcome	N	Patients with event n (%)	HR [95% CI][a]; p-value
GS-US-312-0116/GS-US-312-0117 (data cut-off: 20 April 2014)			
Mortality[b]			
Idelalisib + rituximab (in study GS-US-312-0116)[c]	110	17 (15.5) Median survival time: months [95% CI] NA	0.34 [0.19; 0.60]; < 0.001
Placebo + rituximab (in study GS-US-312-0116)[c]	110	40 (36.4) Median survival time: months [95% CI] 20.8 [14.8; NA]	
Serious adverse events			
Idelalisib + rituximab (in study GS-US-312-0116)[c]	110	65 (59.1)	ND[e]
Placebo + rituximab[d] (in study GS-US-312-0116)[c]	108	43 (39.8)	
Severe AEs (CTCAE grade ≥ 3)			
Idelalisib + rituximab (in study GS-US-312-0116)[c]	110	81 (73.6)	ND[e]
Placebo + rituximab[d] (in study GS-US-312-0116)[c]	108	58 (53.7)	
Discontinuation due to adverse events			
Idelalisib + rituximab (in study GS-US-312-0116)[c]	110	19 (17.3)	ND[e]
Placebo + rituximab[d] (in study GS-US-312-0116)[c]	108	13 (12.0)	

a: Without censoring of patients who have switched from the treatment in the control arm to the treatment in the intervention arm.
b: ITT population; information contains data from the study GS-US-312-0116 and from the extension study GS-US-312-0117 (up to the cut-off date 1 July 2014).
c: Part of the patients included in this analysis were treated with idelalisib monotherapy in the extension study GS-US-312-0117 (see Figure 1).
d: For the placebo + rituximab group, data under idelalisib monotherapy of the blinded phase of study GS-US-312-0117 are also included in the analysis.
e: The results based on the relative risk are not meaningfully interpretable because of the differences in the median treatment duration in the study arms.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; ITT: intention to treat; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Table 2: Results (mortality and side effects) – RCT, direct comparison: idelalisib + rituximab vs. placebo + rituximab, data cut-off from 18 September 2015

Study Outcome category Outcome	N	Patients with event n (%)	HR [95% CI][a]; p-value
GS-US-312-0116/GS-US-312-0117 (data cut-off: 18 September 2015)			
Mortality			
Idelalisib + rituximab (with and without progression) (in study GS-US-312-0116)[b]	110	30 (27.3) Median survival time: months [95% CI] NA [28.5; NA]	0.51 [0.32; 0.80]; 0.003
Placebo + rituximab (with and without progression) (in study GS-US-312-0116)[b]	110	48 (43.6) Median survival time: months [95% CI] 24.8 [16.6; NA]	
Serious adverse events			
Idelalisib + rituximab (with and without progression) (in study GS-US-312-0116)[b]	110	86 (78.2)	ND[c]
Placebo + rituximab (with progression)[d] (in study GS-US-312-0116)[e]	42	32 (76.2)	ND[c]
Placebo + rituximab (without progression)[f] (in study GS-US-312-0116)[e]	44	30 (68.2)	ND[c]
Placebo + rituximab (no switching to the extension study)[g]	22	ND	ND
Severe AEs (CTCAE grade ≥ 3)			
Idelalisib + rituximab (with and without progression) (in study GS-US-312-0116)[b]	110	97 (88.2)	ND[c]
Placebo + rituximab (with progression)[d] (in study GS-US-312-0116)[e]	42	35 (83.3)	ND[c]
Placebo + rituximab (without progression)[f] (in study GS-US-312-0116)[e]	44	36 (81.8)	ND[c]
Placebo + rituximab (no switching to the extension study)[g]	22	ND	ND
Discontinuation due to adverse events			
Idelalisib + rituximab (with and without progression) (in study GS-US-312-0116)[b]	110	45 (40.9)	ND[c]
Placebo + rituximab (with progression)[d] (in study GS-US-312-0116)[e]	42	24 (57.1)	ND[c]
Placebo + rituximab (without progression)[f] (in study GS-US-312-0116)[e]	44	22 (50.0)	ND[c]
Placebo + rituximab (no switching to the extension study)[g]	22	ND	ND

(continued)

Table 2: Results (mortality and side effects) – RCT, direct comparison: idelalisib + rituximab vs. placebo + rituximab, data cut-off from 18 September 2015 (continued)

a: Without censoring of patients who have switched from the treatment in the control arm to the treatment in the intervention arm.
b: Part of the patients included in this analysis were treated with idelalisib monotherapy in the extension study GS-US-312-0117 (see Figure 1).
c: The results based on the relative risk are not meaningfully interpretable because of the differences in the median treatment duration in the study arms.
d: Patients from the placebo + rituximab group with progression who received idelalisib monotherapy (2 x 150 mg) starting with the double-blind phase of study GS-US-312-0117.
e: Only those AEs were included that occurred from the first dose of idelalisib monotherapy in the extension study GS-US-312-0117.
f: Patients from the placebo + rituximab group without progression who received idelalisib monotherapy (2 x 150 mg) in the open-label phase of study GS-US-312-0117.
g: No analyses are available for patients in the placebo + rituximab group who did not enter the extension study GS-US-312-0117 after completion of study GS-US-312-0116.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus