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Ibrutinib (chronic lymphocytic leukaemia) –

Addendum to Commission A16-39[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CIRS	Cumulative Illness Rating Scale
CLL	chronic lymphocytic leukaemia
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organisation for Research and Treatment of Cancer
FACIT	Functional Assessment of Chronic Illness Therapy
FCR	combination therapy consisting of fludarabine, cyclophosphamide and rituximab
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IGHV	immunoglobulin heavy-chain variable
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
SAE	serious adverse event
SLL	small lymphocytic lymphoma

1 Background

On 9 November 2016, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A16-39 (Ibrutinib – Benefit assessment according to §35a Social Code Book V [1]).

In the commenting procedure on the assessment of ibrutinib, the pharmaceutical company (hereinafter referred to as "the company") submitted further data to the G-BA [2-4] that went beyond the information provided in the dossier on ibrutinib [5]. The G-BA commissioned IQWiG to assess the data sent by the company with the written comments and subsequent to the oral hearing. Specifically, IQWiG was to assess whether, under consideration of the data cut-off of the RESONATE-2 study and the newly created patient population subsequently submitted, the analyses on the indirect comparisons in patient population 1b submitted by the company were suitable for the assessment of the added benefit of ibrutinib in this population. Furthermore, the suitability of the analyses on patient population 2 subsequently submitted was to be assessed. Specifically, it was to be checked to what extent the newly created study population represents patient population 2. Irrespective from this, the results of ibrutinib versus chlorambucil from the RESONATE-2 study were to be additionally presented under consideration of the newly created study population for patient population 2.

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

2.1 Research question 1b: patients with previously untreated CLL for whom chemo-immunotherapy (except FCR) is not an option

In its original dossier, the company had presented 3 indirect comparisons on the comparison of ibrutinib with chemo-immunotherapy (obinutuzumab + chlorambucil, rituximab + chlorambucil and ofatumumab + chlorambucil) for research question 1b (patients with previously untreated chronic lymphocytic leukaemia [CLL] for whom chemo-immunotherapy [except the combination therapy consisting of fludarabine, cyclophosphamide and rituximab, FCR]) is an option). These 3 indirect comparisons were conducted using the common comparator chlorambucil and the same study on ibrutinib (RESONATE-2) in each case. The CLL11 study, which compared these 2 chemo-immunotherapies with chlorambucil in a 3-arm design, was used for the indirect comparisons with obinutuzumab + chlorambucil and rituximab + chlorambucil. The COMPLEMENT 1 study, which compared ofatumumab + chlorambucil with chlorambucil, was used for the indirect comparison with ofatumumab + chlorambucil.

All 3 indirect comparisons presented by the company in the dossier on ibrutinib were unsuitable for the assessment of the added benefit of ibrutinib versus the appropriate comparator therapy (ACT) specified by the G-BA for several reasons. On the one hand, the common comparator chlorambucil was not sufficiently similar between the studies. On the other, the included patient populations were not sufficiently similar between the studies. Among other things, the patients in both comparator therapy studies, CLL11 and COMPLEMENT 1, had more and/or more severe comorbidities than the patients in the ibrutinib study RESONATE-2. Furthermore, it can be assumed for all 3 studies that they also included patients who did not concur with the target population relevant for this research question. As measured by guideline-based eligibility criteria, patients of research question 1a (suitable for FCR) and research question 2 (unsuitable for chemo-immunotherapy) were also included in the 3 studies. Details on the reasons mentioned for the missing suitability of the indirect comparisons can be found in dossier assessment A16-39 [1].

With its comment, the company presented new analyses on the 3 indirect comparisons. On the one hand, it used a new data cut-off of the RESONATE-2 study. On the other, it considered only a subpopulation of the RESONATE-2 study excluding specifically those patients whom it deemed ineligible for chemo-immunotherapy (and who therefore were to be allocated to research question 2).

The analyses newly submitted by the company were also unsuitable for the benefit assessment. The new data cut-off of the RESONATE-2 study addressed none of the reasons mentioned for the missing suitability of the indirect comparisons. Creating the new subpopulation of the RESONATE-2 study, the company partly addressed the points of criticism mentioned in the dossier assessment. Its approach was selective, however, and additionally resulted in less similarity of the study populations. Its approach was selective

insofar as it only excluded patients it considered suitable for research question 2, but not patients suitable for research question 1a from the RESONATE-2 study, and it did this only for the RESONATE-2 study, but not for the studies on the comparator therapy. This alone already resulted in less similarity of the populations because only in the studies on the comparator therapy, but not in the used subpopulation of the RESONATE-2 study on ibrutinib, patients were considered who the company considered suitable for research question 2, but not for the research question of interest, research question 1b. Consequently, its approach resulted in even less similarity of the study populations, also based on comorbidities, because the population excluded from the RESONATE-2 study by the company had more comorbidities than the remaining subpopulation (e.g. Cumulative Illness Rating Scale [CIRS] score > 6 in 39% versus 29% of the patients). The RESONATE-2 study already had included patients with fewer and/or less severe comorbidities than the studies on the comparator therapy (e.g. CIRS score > 6 in 76% of the patients in the CLL11 study, and in 79% of the patients in the COMPLEMENT 1 study).

In summary, the new analyses presented by the company with the comments did not change the assessment of dossier assessment A16-39 on research question 1b: The data presented resulted in no hint of an added benefit of ibrutinib in comparison with the ACT (chemo-immunotherapy specified by the physician, under consideration of the approval status).

2.2 Research question 2: patients with previously untreated CLL for whom chemo-immunotherapy is not an option

In its dossier, the company had used a subpopulation of the RESONATE-2 study for research question 2. In this study, ibrutinib was compared with chlorambucil. Besides other aspects, the RESONATE-2 study was unsuitable for research question 2 because the comparator therapy (chlorambucil) did not concur with the ACT specified by the G-BA (best supportive care) [1]. The data on the RESONATE-2 study subsequently submitted by the company did not change this assessment.

The explanations below only refer to the suitability of the subpopulation of the RESONATE-2 study subsequently submitted by the company with the comments for research question 2 and to the results observed in this subpopulation, irrespective of the question whether the comparator therapy of the RESONATE-2 study concurs with the ACT specified by the G-BA.

2.2.1 Assessment of the suitability of the newly created subpopulation for research question 2

The RESONATE-2 study was a randomized, active controlled, multicentre and open-label study on the comparison of ibrutinib with chlorambucil. The study included adult (≥ 65 years) patients with previously untreated CLL or small lymphocytic lymphoma (SLL) requiring therapy. 269 patients were randomized in a ratio of 1:1, stratified by physical status (Eastern Cooperative Oncology Group Performance Status [ECOG PS] 0–2), Rai disease stage 3 or 4, and geographical region. The RESONATE-2 study is described in detail in dossier assessment A16-39 [1].

Definition of the subpopulation for research question 2

The company had already created a subpopulation for research question 2 in its dossier [6]. This subpopulation consisted of patients aged 75 to < 80 years with a creatinine clearance < 70 mL/min and patients aged 80 years and older without further limiting criteria. This subpopulation comprised 81 patients (30% of the total population of the RESONATE-2 study). Aiming to create a patient population of the study more precisely matched to the target population of research question 2, the company further limited this subpopulation and transferred the data of this new subpopulation with its comments. In the following text, this is described as a “new subpopulation”. To create the new subpopulation, the company used additional criteria for the subpopulation already defined in Module 4 A. These are the following:

- For patients aged ≥ 75 and < 80 years:
  - creatinine clearance of < 70 mL/min and additionally one of the following criteria:
    - ECOG PS = 2
    - CIRS score > 6

- mutation status (unmutated immunoglobulin heavy-chain variable [IGHV] status and 11q deletion)

- For patients aged ≥ 80 years:
  - irrespective of renal function, one of the following criteria had to be met:
    - ECOG PS = 2
    - CIRS score > 6
    - mutation status (unmutated IGHV status and 11q deletion)

Since the criteria newly chosen by the company selected a subpopulation of patients with increased (co)morbidity, it can be assumed that the resulting new subpopulation mainly includes patients for whom chemo-immunotherapy is too burdensome and therefore unsuitable. The criteria chosen by the company were not comprehensive, however (see dossier assessment A16-39). On the one hand, it is therefore unclear whether the new subpopulation not also comprises an important proportion of patients for whom chemo-immunotherapy is deemed suitable by the physician. On the other, it can be assumed that the RESONATE-2 study included further patients not comprised by the new subpopulation that would have to be allocated to research question 2 (in particular severely ill patients under 75 years of age).

Table 1 shows the characteristics of the patient population of the RESONATE-2 study newly created by the company. The new subpopulation created by the company includes 29 of 136 patients in the ibrutinib arm and 33 of 133 patients in the chlorambucil arm of the RESONATE-2 study.

Table 1: Characteristics of the study population – RCT, direct comparison: ibrutinib vs. chlorambucil, new subpopulation of the RESONATE-2 study for research question 2

Study **Characteristics** **Category**	**Ibrutinib**	**Chlorambucil**
RESONATE-2	N = 29	N = 33
Age [years], median (min; max)	81 (75; 89)	80 (75; 90)
Sex [F/M], %	34/66	39/61
Ethnicity, n (%)		
White	28 (96.6)	30 (90.9)
Other	1 (3.4)	3 (9.1)
Disease duration: time since diagnosis, [months], median (min; max)	26 (1; 172)	34 (1; 277)
Histology at diagnosis, n (%)		
CLL	23 (79.3)	31 (93.9)
SLL	6 (20.7)	2 (6.1)
Disease stage at screening, n (%)		
Rai 0–II	15 (51.7)	18 (54.5)
Rai III–IV	14 (48.3)	15 (45.5)
ECOG PS, n (%)		
0-1	23 (79.3)	28 (84.8)
2	6 (20.7)	5 (15.2)
Tumour mass, n (%)		
< 5 cm	18 (62.1)	20 (60.6)
≥ 5 cm	11 (37.9)	13 (39.4)
Chromosome anomaly 11q deletion[a], n (%)		
No	15 (51.7)	21 (63.6)
Yes	13 (44.8)	12 (36.4)
Missing	1 (3.5)	–
IGHV status, n (%)		
Unmutated	14 (48.3)	20 (60.6)
Mutant	9 (31.0)	9 (27.3)
Missing	6 (20.7)	4 (12.1)
Creatinine clearance [mL/min], n (%)		
< 70 mL/min	29 (100.0)	32 (97.0)
≥ 70 mL/min	–	1 (3.0)

(continued)

Table 1: Characteristics of the study population – RCT, direct comparison: ibrutinib vs. chlorambucil, new subpopulation of the RESONATE-2 study for research question 2 (continued)

Study Characteristics Category	Ibrutinib	Chlorambucil
RESONATE-2	N = 29	N = 33
β2-microglobulin [mg/mL], n (%)		
≤ 3.5	8 (27.6)	4 (12.1)
> 3.5	20 (69.0)	27 (81.8)
Missing	1 (3.4)	2 (6.1)
Cytopenia at baseline, n (%)		
No	13 (44.8)	11 (33.3)
Yes	16 (55.2)	22 (66.7)
CIRS score at baseline, n (%)		
≤ 6	18 (62.1)	16 (48.5)
> 6	10 (34.5)	14 (42.4)
Missing	1 (3.4)	3 (9.1)
Treatment discontinuation, n (%)	5 (17.2)	10 (30.3)
Study discontinuation, n (%)	ND	ND

a: Presence of 17p deletion was an exclusion criterion of the RESONATE-2 study.
CIRS: Cumulative Illness Rating Scale; CLL: chronic lymphocytic leukaemia; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; IGHV: immunoglobulin heavy-chain variable; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized patients in population 2; ND: no data; RCT: randomized controlled trial; SLL: small lymphocytic lymphoma; vs.: versus

Overall assessment of the suitability of the new subpopulation for research question 2

The criteria chosen by the company for the creation of the new subpopulation constituted meaningful limitations to the criteria chosen in the original dossier. Further important criteria remained unconsidered, however. It therefore remains unclear whether the new subpopulation created by the company represents the patients suitable for research question 2 with sufficient certainty.

2.2.2 Presentation of the results for the newly created subpopulation for research question 2

Risk of bias

The overall risk of bias for the results of the new subpopulation presented by the company is high. The company did not consider important criteria for the creation of the relevant subpopulation; the choice of criteria may influence the results. In addition, the observation period in the total population differed notably between both treatment arms. There was informative censoring for most of the outcomes investigated. There was no information on the observation period for the new subpopulation created by the company. It can be assumed,

however, that there was a relevant difference between the treatment arms also in the new subpopulation.

Time points of documentation

The results on overall survival and the category of side effects presented below are based on the time point of the 30-month follow-up. The company only presented the data at the time point of the 18-month follow-up for the outcomes of the categories of morbidity and health-related quality of life.

Results

Table 2 shows the results on the comparison of ibrutinib versus chlorambucil for the new subpopulation of the RESONATE-2 study created by the company. Appendix A contains tables on the most common adverse events (AEs), serious adverse events (SAEs) and severe AEs (there was no detailed information on the new subpopulation for discontinuations due to AEs).

Where necessary, the data presented by the company were supplemented with the Institute's calculations.

Table 2: Results – RCT, direct comparison: ibrutinib vs. chlorambucil, new subpopulation of the RESONATE-2 study for research question 2

Study Outcome category Outcome Subscale/item	Ibrutinib N	Ibrutinib Median time to event in months [95% CI] Patients with event n (%)	Chlorambucil N	Chlorambucil Median time to event in months [95% CI] Patients with event n (%)	Ibrutinib vs. chlorambucil HR [95% CI][a]; p-value
RESONATE-2					
Mortality					
Overall survival	29	NA ND	33	NA ND	0.48 [0.12; 1.93]; 0.301
Morbidity					
EORTC QLQ-C30 symptom scales – time to improvement of symptoms[b]					
Fatigue	29	1.9 [ND] 22 (75.9)	33	18.2 [ND] 14 (42.4)	2.12 [1.08; 4.17]; 0.028
Nausea and vomiting	29	ND 2 (6.9)	33	ND 5 (15.2)	0.41 [0.08; 2.13]; 0.290
Pain	29	ND 8 (27.6)	33	ND 11 (33.3)	0.74 [0.30; 1.86]; 0.527
Dyspnoea	29	ND 11 (37.9)	33	ND 10 (30.3)	1.10 [0.47; 2.61]; 0.827
Insomnia	29	ND 11 (37.9)	33	ND 12 (36.4)	0.96 [0.42; 2.18]; 0.916
Impaired appetite	29	ND 10 (34.5)	33	ND 9 (27.3)	1.10 [0.44; 2.73]; 0.839
Constipation	29	ND 6 (20.7)	33	ND 8 (24.2)	0.73 [0.25; 2.10]; 0.556
Diarrhoea	29	ND 3 (10.3)	33	ND 4 (12.1)	0.78 [0.18; 3.50]; 0.748
EORTC QLQ-C30 symptom scales – time to deterioration of symptoms[c]					
Fatigue	29	5.5 [ND] 20 (69.0)	33	2.8 [ND] 23 (69.7)	0.75 [0.41; 1.36]; 0.342
Nausea and vomiting	29	5.6 [ND] 17 (58.6)	33	6.2 [ND] 15 (45.5)	0.92 [0.46; 1.84]; 0.803
Pain	29	5.5 [ND] 21 (72.4)	33	2.8 [ND] 23 (69.7)	0.65 [0.36; 1.20]; 0.169
Dyspnoea	29	ND 14 (48.3)	33	14.7 [ND] 15 (45.5)	0.79 [0.38; 1.64]; 0.519
Insomnia	29	6.5 [ND] 19 (65.5)	33	5.5 [ND] 16 (48.5)	1.07 [0.55; 2.09]; 0.846

(continued)

Table 2: Results – RCT, direct comparison: ibrutinib vs. chlorambucil, new subpopulation of the RESONATE-2 study for research question 2 (continued)

Study **Outcome category** **Outcome** **Subscale/item**	**Ibrutinib** **N**	**Ibrutinib** **Median time to event in months [95% CI]** **Patients with event n (%)**	**Chlorambucil** **N**	**Chlorambucil** **Median time to event in months [95% CI]** **Patients with event n (%)**	**Ibrutinib vs. chlorambucil** **HR [95% CI][a]; p-value**
RESONATE-2					
Impaired appetite	29	9.2 [ND] 19 (65.5)	33	3.2 [ND] 22 (66.7)	0.75 [0.41; 1.40]; 0.371
Constipation	29	18.4 [ND] 14 (48.3)	33	ND 12 (36.4)	0.98 [0.45; 2.14]; 0.962
Diarrhoea	29	5.5 [ND] 20 (69.0)	33	7.4 [ND] 17 (51.5)	1.14 [0.59; 2.17]; 0.703
Health status – time to improvement of symptoms					
EQ-5D VAS[b]	29	2.8 [ND] 18 (62.1)	33	3.8 [ND] 18 (54.5)	0.96 [0.50; 1.84]; 0.890
Health status – time to deterioration of symptoms					
EQ-5D VAS[c]	29	5.5 [ND] 18 (62.1)	33	ND 15 (45.5)	1.16 [0.58; 2.30]; 0.679
FACIT-Fatigue – time to improvement					
MID = 3[d]				ND	
Health-related quality of life					
EORTC QLQ-C30 functional scales – time to improvement of symptoms[b]					
Global health status	29	6.7 [ND] 18 (62.1)	33	3.7 [ND] 22 (66.7)	0.69 [0.37; 1.29]; 0.247
Physical functioning	29	6.5 [ND] 19 (65.5)	33	4.1 [ND] 21 (63.6)	0.87 [0.47; 1.62]; 0.657
Role functioning	29	3.7 [ND] 23 (79.3)	33	4.3 [ND] 20 (60.6)	1.27 [0.70; 2.31]; 0.436
Emotional functioning	29	18.4 [ND] 14 (48.3)	33	14.7 [ND] 12 (36.4)	1.02 [0.47; 2.23]; 0.954
Cognitive functioning	29	6.5 [ND] 23 (79.3)	33	5.5 [ND] 20 (60.6)	1.12 [0.61; 2.04]; 0.716
Social functioning	29	5.5 [ND] 22 (75.9)	33	3.7 [ND] 22 (66.7)	0.86 [0.47; 1.56]; 0.614

(continued)

Table 2: Results – RCT, direct comparison: ibrutinib vs. chlorambucil, new subpopulation of the RESONATE-2 study for research question 2 (continued)

Study Outcome category Outcome Subscale/item	Ibrutinib N	Ibrutinib Median time to event in months [95% CI] Patients with event n (%)	Chlorambucil N	Chlorambucil Median time to event in months [95% CI] Patients with event n (%)	Ibrutinib vs. chlorambucil HR [95% CI][a]; p-value
RESONATE-2					
EORTC QLQ-C30 functional scales – time to deterioration of symptoms[c]					
Global health status	29	3.7 [ND] 22 (75.9)	33	ND 13 (39.4)	1.84 [0.92; 3.65]; 0.083
Physical functioning	29	16.5 [ND] 15 (51.7)	33	14.7 [ND] 14 (42.4)	1.06 [0.51; 2.22]; 0.881
Role functioning	29	11.1 [ND] 16 (55.2)	33	22.1 [ND] 13 (39.4)	1.17 [0.56; 2.44]; 0.682
Emotional functioning	29	ND 13 (44.8)	33	ND 9 (27.3)	1.42 [0.60; 3.35]; 0.421
Cognitive functioning	29	ND 13 (44.8)	33	11.3 [ND] 13 (39.4)	0.88 [0.41; 1.93]; 0.757
Social functioning	29	ND 12 (41.4)	33	ND 10 (30.3)	1.33 [0.57; 3.08]; 0.508
Side effects					
AEs (supplementary information)	29	0.2[e] [ND] 29 (100)	33	0.3[e] [ND] 32 (97)	–
SAEs	29	8.3[e] [ND] 22 (75.9)	33	6.1[e] [ND] 13 (39.4)	1.04 [0.50; 2.20]; 0.912
Discontinuation due to AEs	29	NA 5 (17.2)	33	NA 10 (30.3)	0.07 [0.01; 0.59]; 0.014
Severe AEs (CTCAE grade ≥ 3)	29	5.2[e] [ND] 26 (89.7)	33	2.3[e] [ND] 21 (63.6)	0.74 [0.39; 1.40]; 0.350

a: Cox regression model.
b: Time to improvement in score by at least 10 points versus the baseline value.
c: Time to deterioration of the score by at least 10 points versus the baseline value.
d: The company presented no data on the validated MID (3 points) for the new subpopulation. The analyses presented by the company with an MID of 4 points and of 6 points each showed no statistically significant result.
e: Institute's calculation.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D VAS: European Quality of Life-5 Dimensions visual analogue scale; FACIT: Functional Assessment of Chronic Illness Therapy; MID: minimally important difference; n: number of patients with event; N: number of analysed patients of the new subpopulation; NA: not achieved; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Summary of the results

A statistically significant result in favour of ibrutinib versus chlorambucil was shown for the outcome “discontinuation due to AEs”.

There were several operationalizations for the outcome “fatigue”. For the time to improvement, measured with the European Organisation for Research and Treatment of Cancer (EORTC) questionnaire, the result was statistically significant in favour of ibrutinib. For the operationalization “time to deterioration” (measured with the EORTC questionnaire), the result was not statistically significant. The analyses on the symptom-specific instrument Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue were incomplete because the company, in contrast to its original dossier, presented no analyses on the validated MID of 3 points for the new subpopulation.

No statistically significant result was shown for all other outcomes.

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Appendix A – Results on side effects

Table 3: Common AEs (in the PT ≥ 15% in at least one study arm) – RCT, direct comparison: ibrutinib vs. chlorambucil, new subpopulation of the RESONATE-2 study for research question 2

Study	Patients with event n (%)	
PT[a]	Ibrutinib N = 29	Chlorambucil N = 33
RESONATE-2		
Overall rate of AEs	29 (100.0)	32 (97.0)
Diarrhoea	20 (69.0)	10 (30.3)
Fatigue	13 (44.8)	15 (45.5)
Oedema peripheral	13 (44.8)	6 (18.2)
Nausea	10 (34.5)	16 (48.5)
Anaemia	9 (31.0)	12 (36.4)
Dry eye	9 (31.0)	1 (3.0)
Cough	9 (31.0)	5 (15.2)
Constipation	8 (27.6)	7 (21.2)
Weight decreased	8 (27.6)	6 (18.2)
Back pain	8 (27.6)	3 (9.1)
Lacrimation increased	7 (24.1)	3 (9.1)
Vision blurred	7 (24.1)	2 (6.1)
Vomiting	7 (24.1)	5 (15.2)
Fever	7 (24.1)	6 (18.2)
Upper respiratory tract infection	7 (24.1)	5 (15.2)
Decreased appetite	6 (20.7)	10 (30.3)
Basal cell carcinoma	6 (20.7)	1 (3.0)
Dyspnoea	6 (20.7)	6 (18.2)
Hypertension	6 (20.7)	0 (0)
Neutropenia	5 (17.2)	6 (18.2)
Visual acuity reduced	5 (17.2)	1 (3.0)
Vitreous floaters	5 (17.2)	2 (6.1)
Urinary tract infection	5 (17.2)	4 (12.1)
Arthralgia	5 (17.2)	3 (9.1)
Rash maculo-papular	5 (17.2)	2 (6.1)

a: MedDRA version 17.1.
AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients of the new subpopulation; PT: Preferred Term; RCT: randomized controlled trial; vs.: versus

Table 4: Common SAEs (in the PT ≥ 5% in at least one study arm) – RCT, direct comparison: ibrutinib vs. chlorambucil, new subpopulation of the RESONATE-2 study for research question 2

Study	**Patients with event n (%)**	
PT[a]	**Ibrutinib N = 29**	**Chlorambucil N = 33**
RESONATE-2		
Overall rate of SAEs	22 (75.9)	13 (39.4)
Hyponatraemia	4 (13.8)	0 (0)
Atrial flutter	2 (6.9)	0 (0)
Oedema peripheral	2 (6.9)	1 (3.0)
Escherichia sepsis	2 (6.9)	0 (0)
Pneumonia	2 (6.9)	2 (6.1)
Urinary tract infection	2 (6.9)	0 (0)
Basal cell carcinoma	2 (6.9)	0 (0)
Pleural effusion	2 (6.9)	1 (3.0)
Anaemia	1 (3.4)	2 (6.1)
Fever	1 (3.4)	2 (6.1)

a: MedDRA version 17.1.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients in the new subpopulation; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Table 5: Common AEs with CTCAE grade 3 or 4 (in the SOC and in the PT ≥ 5% in at least one study arm) – RCT, direct comparison: ibrutinib vs. chlorambucil, new subpopulation of the RESONATE-2 study for research question 2

Study	**Patients with event n (%)**	
PT[a]	**Ibrutinib N = 29**	**Chlorambucil N = 33**
RESONATE-2		
Overall rate CTCAE grade 3 or 4 AEs	24 (82.8)	19 (57.6)
Neutropenia	5 (17.2)	5 (15.2)
Cellulitis	3 (10.3)	0 (0)
Anaemia	2 (6.9)	7 (21.2)
Fatigue	2 (6.9)	3 (9.1)
Escherichia sepsis	2 (6.9)	0 (0)
Pneumonia	2 (6.9)	2 (6.1)
Upper respiratory tract infection	2 (6.9)	0 (0)
Urinary tract infection	2 (6.9)	0 (0)
Hyponatraemia	2 (6.9)	0 (0)
Pleural effusion	2 (6.9)	0 (0)
Rash maculo-papular	2 (6.9)	1 (3.0)
Syncope	1 (3.4)	2 (6.1)

a: MedDRA version 17.1.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients of the new subpopulation; PT: Preferred Term; RCT: randomized controlled trial; vs.: versus