Ibrutinib (previously untreated chronic lymphocytic leukaemia)

Addendum to Project A23-04 (dossier assessment)[1]

ADDENDUM

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse events
CLL	chronic lymphocytic leukaemia
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life 5 Dimensions
FCR	fludarabine + cyclophosphamide + rituximab
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire – Core 30
RCT	randomized controlled trial
SAE	serious adverse event
SMQ	Standardized Medical Dictionary for Regulatory Activities Query
SOC	System Organ Class
VAS	visual analogue scale

1 Background

On 6 June 2023, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-04 (Ibrutinib – benefit assessment according to § 35a Social Code Book V) [1].

As ordered, the commission comprises evaluating the analyses from the GLOW study's 3rd data cutoff, which the company submitted in the commenting procedure [2,3], regarding the subpopulation relevant for the benefit assessment, taking into account the information on the subsequent therapies as well as the information in the dossier [4].

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

2 Assessment

2.1 Background of the analyses subsequently submitted

A subpopulation of the GLOW study comparing ibrutinib in combination with venetoclax (designated below as ibrutinib + venetoclax) versus chlorambucil + obinutuzumab is relevant for the benefit assessment. In its dossier, the pharmaceutical company (hereinafter "the company") presents the results for the non-prespecified 4th data cutoff from 25 August 2022. Only for the patient-reported outcomes on morbidity and health-related quality of life does Module 4 A of the company's dossier present analyses for the prespecified 1st data cutoff from 26 February 2021 because these outcomes were not collected further after the 1st data cutoff. Because the 4th data cutoff was neither prespecified nor requested by a regulatory authority, it is impossible to rule out reporting bias. Therefore, the subpopulation results for the 4th data cutoff as presented by the company are unusable for the benefit assessment. Furthermore, the dossier submitted by the company was incomplete in terms of content because according to the module templates, the dossier is to contain the results of the data cutoffs planned a priori or required by the regulatory authorities. Consequently, the subpopulation results from the 3rd data cutoff dated 17 January 2022 are primarily relevant for the benefit assessment because this data cutoff was requested by the European Medicines Agency (EMA) as part of the European approval process. The company subsequently submitted these results with its comments [2,3]. In its comments, the company also states that the 5th data cutoff, which was requested by the EMA and is to be submitted to the EMA in August 2023, was implemented in February 2023. As per the module templates in the dossier, the 5th data cut is therefore also relevant for the benefit assessment. However, the company has not provided the data for the 5th data cut.

The subsequently submitted results of the relevant subpopulation from the 3rd data cutoff are analysed below as commissioned and are used for the present benefit assessment. Since the patient-reported outcomes were surveyed only up to the 1st data cutoff, the results from the 1st data cutoff are used for the benefit assessment for these outcomes.

2.2 Study characteristics

The study characteristics, the interventions used, the data cutoffs implemented, and the relevant subpopulation of the GLOW study are described in dossier assessment A23-04 [1].

Treatment duration and follow-up observation

Table 1 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 1: Planned duration of follow-up observation – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab

Study **Outcome category** **Outcome**	**Planned follow-up observation**
GLOW	
Mortality	
overall survival	Until death, withdrawal of consent, lost to follow-up, or end of study
Morbidity	
symptoms (EORTC QLQ-C30 and FACIT-Fatigue) health status (EQ-5D VAS)	Until disease progression or primary study analysis (whichever was first)[a]
Health-related quality of life (EORTC QLQ-C30)	Until disease progression or primary study analysis (whichever was first)
Side effects	Until 30 days after the last dose of the study medication or until start of a subsequent therapy
a. After disease progression, EQ-5D VAS survey was implemented twice every 24 weeks (+/- 7 days) EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life 5 Dimensions; FACIT: Functional Assessment of Chronic Illness Therapy; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core30; RCT: randomized controlled trial; VAS: visual analogue scale	

The observation periods for the outcomes of morbidity, health-related quality of life, and side effects were systematically shortened because they were surveyed only until disease progression or the 1st data cutoff or for the period of treatment with the study medication plus 30 days. Drawing a reliable conclusion on the total study period or the time to patient death, however, would require surveying these outcomes for the total period, as was done for survival.

Characteristics of the study population

Table 2 shows the characteristics of the patients in the included study.

Table 2: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab (multipage table)

Study Characteristic **Category**	**Ibrutinib + venetoclax** **N[a] = 23**	**Chlorambucil + obinutuzumab** **N[a] = 24**
GLOW		
Age [years], mean (SD)	75 (6)	71 (5)
Age [years], n (%)		
< 65 years	0 (0)	2 (8)
≥ 65 years	23 (100)	22 (92)
Sex [f/m], %	35/65	58/42
Family origin, n (%)		
Caucasian	21 (91)	22 (92)
Asian	0 (0)	1 (4)
No data	2 (9)	1 (4)
Disease duration: time from first diagnosis to randomization [months]		
Mean (SD)	71 (47)	54 (44)
Median (minimum, maximum)	53 (14; 185)	54 (1; 134)
Diagnosis, n (%)		
CLL	22 (96)	24 (100)
SLL	1 (4)	0
Rai stage, n (%)		
0/I/II	5 (22)	10 (42)
III/IV	17 (74)	14 (58)
Unknown	1 (4)	0 (0)
Binet stage, n (%)		
A	2 (9)	5 (21)
B	6 (26)	9 (38)
C	14 (61)	10 (42)
Unknown	1 (4)	0
Bulky disease, n (%)		
< 5 cm	14 (61)	16 (67)
≥ 5 cm	8 (35)	8 (33)
Unknown	1 (4)	0 (0)
ECOG-PS, n (%)		
0	10 (44)	8 (33)
1–2	13 (57)	16 (67)

Table 2: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab (multipage table)

Study Characteristic **Category**	**Ibrutinib + venetoclax** **N[a] = 23**	**Chlorambucil + obinutuzumab** **N[a] = 24**
Beta 2 microglobulin (mg/L), n (%)		
≤ 3.5	5 (22)	7 (29)
> 3.5	18 (78)	17 (71)
11q deletion, n (%)		
Yes	3 (13)	4 (17)
No	20 (87)	20 (83)
TP53 mutation, n (%)		
Unmutated	23 (100)	24 (100)
Mutated	0 (0)	0 (0)
IGHV status, n (%)		
Unmutated	0 (0)	0 (0)
Mutated	23 (100)	24 (100)
CIRS, n (%)		
≤ 6	10 (44)	10 (42)
> 6	13 (57)	14 (58)
Thrombocytopenia[b], n (%)		
Yes	11 (48)	6 (25)
No	12 (52)	18 (75)
Anaemia[c], n (%)		
Yes	11 (48)	13 (54)
No	12 (52)	11 (46)
Neutropenia[d], n (%)		
Yes	1 (4)	4 (17)
No	22 (96)	20 (83)
Cytopenia[e], n (%)		
Yes	16 (70)	16 (67)
No	7 (30)	8 (33)
Treatment discontinuation, n (%)	ND[f]	ND[f]
Study discontinuation, n (%)	ND	ND

Table 2: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab (multipage table)

Study Characteristic Category	Ibrutinib + venetoclax N[a] = 23	Chlorambucil + obinutuzumab N[a] = 24
a. Number of randomized patients. Values which are based on different patient numbers are marked in the corresponding line if the deviation is relevant. b. Platelet count ≤ 100 x 10^9/L c. Haemoglobin ≤ 110 g/L d. Neutrophil count ≤ 1.5 x 10^9/L e. Either haemoglobin ≤ 110 g/L or platelet count ≤ 100 x 10^9/L or neutrophil count ≤ 1.5 x 10^9/L f. Data on treatment discontinuations are available only for the total population of the GLOW study (intervention arm N = 106; comparison arm N = 105): at the time of the first data cutoff on 26/02/2021, 22.6% of the patients in the intervention arm and 4.8% of the patients in the comparison arm had discontinued treatment. Reasons for treatment discontinuation in the intervention versus the control arm were: AEs (10.4% vs. 1.9%), decision of the patient (3.8% vs. 1.0%). Death (3.8% vs. 0%), disease progression (2.8% vs. 1.0%), and investigator decision (1.9% vs. 1.0%). 11q deletion: deletion on chromosome 11; AE: adverse event; CIRS: Cumulative Illness Rating Scale; CLL: chronic lymphocytic leukaemia; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; f: female; IGHV: immunoglobulin heavy-chain variable region; m: male; n: number of patients in the category; N: number of randomized (or included) patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; SLL: small lymphocytic lymphoma; TP53 mutation: mutation of the tumour protein p53		

The patient characteristics of the relevant subpopulation of patients ineligible for treatment with fludarabine in combination with cyclophosphamide and rituximab (FCR) were sufficiently comparable between the intervention arm ibrutinib + venetoclax and the comparator arm chlorambucil + obinutuzumab. Any imbalances in patient characteristics between the study arms are due to the small number of patients in the relevant subpopulation.

Information on the course of the study

Table 3: Information on the course of the study – RCT, direct comparison: ibrutinib + venetoclax versus obinutuzumab + chlorambucil

Study Duration of the study phase Outcome category	Ibrutinib + venetoclax N = 23	Obinutuzumab + chlorambucil N = 24
GLOW		
Treatment duration [months]		
Median [min; max]	13.8 [ND]	5.1 [ND]
Observation period [months]		
Overall survival		
Median [min; max]	ND[a]	ND[a]
Morbidity (EQ-5D VAS)		
Median [min; max]	24.0 [ND]	25.7 [ND]
Morbidity (EORTC QLQ-C30)		
Median [min; max]	27.4 [ND]	24.0 [ND]
Morbidity (FACIT-Fatigue)		
Median [min; max]	27.3 [ND]	22.3 [ND]
Health-related quality of life (EORTC QLQ-C30)		
Median [min; max]	27.4 [ND]	24.0 [ND]
Side effects		
Median [min; max]	14.8 [ND]	6.1 [ND]

a. In its comments, the company reports a median observation period of 39 months for both treatment arms jointly. Separate data for each treatment arm are not available. Presumably, there is no marked difference in observation period between the arms.

EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; FACIT: Functional Assessment of Chronic Illness Therapy; max.: maximum; min: minimum; N: number of analysed patients; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; VAS: visual analogue scale

Within the relevant subpopulation, the patients' median treatment duration was far higher in the intervention arm, at 13.8 months, than in the comparator arm, at 5.1 months. This is due to the fact that, in the intervention arm, ibrutinib in combination with venetoclax was to be administered for 15 cycles, whereas in the comparator arm, treatment was to be administered for a maximum of 6 cycles.

Regarding the 3rd data cutoff, the company's comments did not present the median observation duration for the outcome of overall survival separately for the treatment arms. The observation period presumably does not differ significantly between the intervention and comparator arms. For the outcomes of the categories of morbidity and health-related quality

of life, with the exception of the EQ-5D, the median observation duration is slightly longer in the intervention arm.

For the outcomes in the side effects category, the difference in treatment duration and the linking of the observation period to the treatment duration led to a notably longer observation period in the intervention arm (median 14.8 months) than in the comparator arm (median 6.1 months). This difference is taken into account in the outcome-specific risk of bias of results for the side effects outcomes.

Information on follow-up therapy

By the 4th data cut cutoff, no ibrutinib + venetoclax arm participant from the relevant subpopulation had started follow-up therapy. In the chlorambucil + obinutuzumab arm, two participants from the relevant subpopulation received follow-up therapy. The company does not specify which therapy these patients received. Since in total, only a few patients received subsequent therapy, this missing information is of no consequence for the benefit assessment.

Risk of bias across outcomes (study level)

Table 4 shows the risk of bias across outcomes (risk of bias at study level).

Table 4: Risk of bias across outcomes (study level) – RCT, direct comparison: ibrutinib + venetoclax versus obinutuzumab + chlorambucil

Study	Adequate random sequence generation	Allocation concealment	Blinding		Absence of reporting bias	Absence of additional aspects	Risk of bias at study level
			Patients	Treating staff			
GLOW	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

Transferability of the study results to the German health care context

The company reports that the vast majority of patients is from Europe and that approximately 96% is white. According to the company, there was no evidence of biodynamic or kinetic differences between the individual population groups or regarding health services received in Germany to an extent which would significantly impact study results. Therefore, the company deems it safe to assume that, when taking into account the uncertainty associated with the transferability of clinical data, the results are in principle transferable to the German health

care context. The treatment regimen used in the control arm of the GLOW study is reportedly approved and used in clinical practice in Germany.

The company has not provided any further information on the transferability of the study results to the German health care context.

2.3 Results on added benefit

2.3.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - overall survival
- Morbidity
  - symptoms, surveyed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Core 30 (QLQ-C30) and Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue)
  - health status, recorded using the European Quality of Life 5 Dimensions (EQ-5D) visual analogue scale (VAS)
- Health-related quality of life
  - surveyed with the EORTC QLQ-C30
- Side effects
  - SAEs
  - severe adverse events (AEs) (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - haemorrhages (Standardized Medical Dictionary for Regulatory Activities Query [SMQ], AEs)
  - haemorrhages (SMQ, severe AEs)
  - cardiac disorders (System Organ Class [SOC], severe AEs)
  - infections and infestations (SOC, severe AEs)
  - infusion-related reaction
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4 A).

Table 5 shows the outcomes for which data were available in the included study.

Table 5: Matrix of outcomes – RCT, direct comparison: ibrutinib + venetoclax versus obinutuzumab + chlorambucil

Study	Outcomes												
	Overall survival	Symptoms (EORTC QLQ-C30; FACIT-Fatigue)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Haemorrhages (SMQ[b], AEs)	Haemorrhages (SMQ[b], severe AEs)	Cardiac disorders (SOC, severe AEs)	Infections and infestations (SOC, severe AEs)	Infusion-related reaction	Further specific AEs
GLOW	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes[c]	Yes	Yes	Yes	No[d]	No[d]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. Without events based on laboratory values.
c. Results for the 3rd data cutoff were not submitted in the context of the comments. However, since no patients were at risk any longer even as early as the 1st data cutoff, and it was thus impossible for any relevant changes in this outcome to occur in further data cutoffs, the results from Module 4 A for the 4th data cutoff are presented.
d. The analysis presented by the company is unsuitable for the benefit assessment (see text below).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire – Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class

Note on outcomes of the side effects category

Serious adverse events (SAEs), severe AEs, and discontinuation due to AEs

The analyses of the outcomes of SAEs, severe AEs, and discontinuations due to AEs include events such as the Preferred Terms (PTs) of anaemia, neutropenia, and thrombocytopenia, which may either represent side effects or reflect the progression of the underlying disease. It cannot be conclusively clarified to what extent the events can be assigned to the outcome category of morbidity or side effects [5]. This remains of no consequence for the present benefit assessment because the majority of haematological AEs occur shortly after the start of therapy, while progression events occur with a marked delay after the start of therapy. Therefore, the majority of the haematological events informing the outcomes of SAEs, serious AEs, and discontinuations due to AEs are more likely to belong in the side effects category.

Infusion-related reaction

In the GLOW study, infusion-related reactions were documented as AEs (PT "infusion-related reaction"). In principle, due to the open-label study design (without placebo infusion) and regular intravenous administration only in the comparator arm in contrast to oral administration in the intervention arm, events for the PT of infusion-related reaction could be recorded only in the comparator arm. In addition, it is not clear from the information provided by the company which events were deemed infusion-related and therefore included in the PT of infusion-related reaction. Thus, there are no suitable (comparative) data for the benefit assessment for this outcome, but serious and severe infusion reactions are taken into account in the overall rates of SAEs and severe AEs (see below). In order to obtain the comparative data required for the benefit assessment, it is necessary to take into account all symptomatic AEs (irrespective of whether they are infusion-related, e.g. dyspnoea) in the context of the AE analysis. For this purpose, the respective symptoms must be included in the AE analyses via the corresponding PT (e.g. the PT of dyspnoea) (as was the case in the MAIA study, for example, see [6]). This allows taking these events into account in the benefit assessment even if they occurred in nonblinded studies comparing orally and intravenously administered drugs.

It is not clear from the information provided in the company's dossier whether events underlying the outcome of infusion-related reaction were included in the analyses of AEs at PT or SOC level. It therefore remains unclear whether these events were fully surveyed in the PT/SOC analyses presented by the company in Module 4A. This has no relevant impact on the higher-level AE outcomes (SAEs, severe AEs) because it makes no difference whether a patient is included in the analysis with the event of infusion-related reaction or with an underlying event (e.g. dyspnoea). To obtain a complete picture of infusion-related reactions, it is in principle desirable to conduct an aggregated analysis of these specific AEs (e.g. by means of a predefined PT list) including the corresponding PTs for both treatment groups, regardless of any documented relation to an infusion.

Specific AEs

For AEs, SAEs, and severe AEs, the company presents analyses by SOCs, PTs, and in some cases SMQs. For SOCs, PTs, and SMQs in which no events occurred in 1 of the 2 study arms, the company presents only effect estimates and p-values, provided that this results in a benefit (corresponding to no event in the intervention arm) for ibrutinib + venetoclax. If, on the other hand, disadvantages are found for ibrutinib + venetoclax (corresponding to no event in the comparator arm), the company does not provide an effect estimate or p-values. This suggests reporting bias. Therefore, the evaluations on common specific AEs at SOC and PT level are disregarded in the benefit assessment. The SMQ of haemorrhage, the SOC of heart disease, and the SOCs of infections and infestations are nevertheless used in the benefit assessment because as per the SPC, these may occur frequently with the drugs used in the study.

2.3.2 Risk of bias

Table 6 describes the risk of bias for the results of the relevant outcomes.

Table 6: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: ibrutinib + venetoclax versus obinutuzumab + chlorambucil

Study		Outcomes												
	Study level	Overall survival	Symptoms (EORTC QLQ-C30; FACIT-Fatigue)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Haemorrhages (SMQ[b], AEs)	Haemorrhages (SMQ[b], severe AEs)	Cardiac disorders (SOC, severe AEs)	Infections and infestations (SOC, severe AEs)	Infusion-related reaction	Further specific AEs
GLOW	L	L	H[c, d]	H[c, d]	H[c, d]	H[e]	H[e]	H[c, e]	H[c, e]	H[e]	H[e]	H[e]	-[f]	-[f]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. Without events based on laboratory values.
c. Lack of blinding in subjective recording of outcomes or subjective decision to discontinue treatment.
d. Incomplete observations for potentially informative reasons due to missing (EORTC QLQ-C30 and FACIT-Fatigue) or incomplete (EQ-5D VAS) follow-up observation after disease progression.
e. Large difference in median observation duration across the study population between the intervention arm (14.8 months) and the comparison arm (6.1 months), with incomplete observations for potentially informative reasons.
f. The analysis presented by the company is unsuitable for the benefit assessment (see Section 2.3).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire – Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

For the results on the outcome of overall survival, the risk of bias is low. For the patient-reported outcomes of symptoms (EORTC QLQ-C30), health status (EQ-5D VAS), and health-related quality of life (EORTC QLQ-C30), the high risk of bias of the results is due to the open-label study design. In addition, the tables on the response rates show that from the 22nd cycle onwards (i.e. around Month 22), no questionnaires were available for relevant proportions of patients. As a result, the observations are incomplete for potentially informative reasons.

For the side effects outcomes, the risk of bias of the results is rated as high due to marked differences in observation durations between the intervention arm and the comparator arm

and incomplete observations for potentially informative reasons. For the outcomes of the side effects category which cannot be assigned to SAEs or severe AEs, the open-label study design is another potentially biasing factor.

2.3.3 Results

Table 7 summarizes the results for the comparison of ibrutinib + venetoclax versus chlorambucil + obinutuzumab in patients with previously untreated chronic lymphocytic leukaemia (CLL).

Kaplan-Meier curves on the presented time-to-event analyses can be found in Appendix A. Results on common AEs, SAEs, severe AEs, and discontinuation due to AEs are presented in Appendix B of the full dossier assessment.

Table 7: Results (mortality, morbidity, and side effects) – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab (multipage table)

Study Outcome category Outcome	Ibrutinib + venetoclax		Chlorambucil + obinutuzumab		Ibrutinib + venetoclax vs. chlorambucil + obinutuzumab
	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[a]
GLOW					
Mortality (3rd data cutoff: 17/01/2022)					
Overall survival	23	NR 1 (4.3)	24	NR [38.73; NC] 3 (12.5)	0.34 [0.04; 3.30] p = 0.353
Morbidity (1st data cutoff: 26/02/2021)					
Symptoms (EORTC QLQ-C30 – time to 1st deterioration)[b]					
Fatigue	23	5.82 [1.87; 8.67] 13 (56.5)	24	6.26 [2.37; NC] 11 (45.8)	1.75 [0.78; 3.92]; p = 0.174
Nausea and vomiting	23	13.83 [5.62; NC] 9 (39.1)	24	NR [13.86; NC] 6 (25.0)	2.17 [0.77; 6.12]; p = 0.144
Pain	23	11.30 [3.91; NC] 11 (47.8)	24	16.62 [3.94; 27.86] 13 (54.2)	1.11 [0.50; 2.49]; p = 0.790
Dyspnoea	23	NR [5.82; NC] 8 (34.8)	24	13.93 [3.71; NC] 11 (45.8)	0.79 [0.32; 1.97]; p = 0.619
Insomnia	23	14.09 [3.75; NC] 9 (39.1)	24	31.38 [2.37; NC] 10 (41.7)	1.01 [0.41; 2.48]; p = 0.988
Appetite loss	23	10.97 [2.56; NC] 10 (43.5)	24	NR [6.77; NC] 5 (20.8)	2.87 [0.98; 8.40]; p = 0.055
Constipation	23	NR [5.58; NC] 7 (30.4)	24	NR [8.35; NC] 5 (20.8)	1.83 [0.58; 5.78]; p = 0.301
Diarrhoea	23	8.51 [3.78; NC] 11 (47.8)	24	NR [13.86; NC] 5 (20.8)	3.11 [1.07; 9.00]; p = 0.037
Fatigue (FACIT QLQ-C30 – time to 1st deterioration)[c]	23	NR [8.48; NC] 6 (26.1)	24	NR [20.40; NC] 6 (25.0)	1.24 [0.40; 3.86]; p = 0.707
Health status (EQ-5D VAS –time to 1st deterioration)[d]	23	NR [5.82; NC] 7 (30.4)	24	NR [24.18; NC] 4 (16.7)	2.56 [0.74; 8.76]; p = 0.136
Health-related quality of life (1st data cut-off: 26/02/2021)					
EORTC QLQ-C30, time to 1st deterioration[e]					
Global health status	23	20.50 [8.15; NC] 9 (39.1)	24	24.18 [5.58; NC] 9 (37.5)	1.18 [0.47; 2.96]; p = 0.732
Physical functioning	23	NR [3.75; NC] 7 (30.4)	24	NR [9.72; NC] 6 (25.0)	1.52 [0.51; 4.53]; p = 0.452

Table 7: Results (mortality, morbidity, and side effects) – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab (multipage table)

Study Outcome category Outcome	Ibrutinib + venetoclax		Chlorambucil + obinutuzumab		Ibrutinib + venetoclax vs. chlorambucil + obinutuzumab
	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[a]
Role functioning	23	14.16 [3.75; NC] 11 (47.8)	24	7.24 [2.53; NC] 12 (50.0)	0.96 [0.42; 2.18]; p = 0.923
Emotional functioning	23	NR [11.27; NC] 6 (26.1)	24	18.97 [3.94; NC] 12 (50.0)	0.44 [0.16; 1.18]; p = 0.103
Cognitive functioning	23	NR [3.75; NC] 7 (30.4)	24	11.07 [3.71; NC] 11 (45.8)	0.68 [0.26; 1.78]; p = 0.435
Social functioning	23	10.97 [1.94; NC] 11 (47.8)	24	20.07 [3.78; NC] 12 (50.0)	1.21 [0.53; 2.75]; p = 0.650
Side effects (3rd data cut-off: 17/01/2022)					
AEs (supplementary information)	23	0.49 [0.26; 0.99] 23 (100)	24	0.03 [0.03; 0.07] 24 (100)	-
SAEs	23	NR [2.79; NC] 10 (43.5)	24	NR [1.15; NC] 7 (29.2)	1.40 [0.53; 3.69]; p = 0.500
Severe AEs[f]	23	3.94 [1.91; 6.01] 17 (73.9)	24	1.53 [0.23; 3.38] 19 (79.2)	0.67 [0.35; 1.32]; p = 0.247
Discontinuation due to AEs	23	NR 4 (17.4)	24	NR 2 (8.3)	0.55 [0.05; 6.07]; p = 0.626
Haemorrhages (SMQ[g], AEs)[h]	23	NR 9 (39.1)	24	NR 3 (12.5)	3.42 [0.91; 12.88]; p = 0.070
Haemorrhages (SMQ[g], severe AEs[f])	23	NR 2 (8.7)	24	NR 0 (0)	NC[i]
Cardiac disorders (SOC, severe AEs[f])	23	NR 2 (8.7)	24	NR 2 (8.3)	0.57 [0.05; 6.24]; p = 0.642
Infections and infestations (SOC, severe AEs[f])	23	NR 3 (13.0)	24	16.89 [6.21; NC] 5 (20.8)	0.72 [0.16; 3.27]; p = 0.673
Infusion-related reaction	Analysis unsuitable[j]				

Table 7: Results (mortality, morbidity, and side effects) – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab (multipage table)

Study Outcome category Outcome	Ibrutinib + venetoclax		Chlorambucil + obinutuzumab		Ibrutinib + venetoclax vs. chlorambucil + obinutuzumab
	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[a]

a. Effect, CI, and p-value: Cox proportional hazards model (unstratified).
b. Time to first deterioration. A score increase by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
c. Time to first deterioration. A decrease by ≥ 7.8 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 52).
d. Time to first deterioration. A decrease by ≥ 15 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
e. Time to first deterioration. A decrease by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
f. Operationalized as CTCAE grade ≥ 3.
g. Without events based on laboratory values.
h. Results for the 3rd data cut were not submitted in the context of the comments. However, the results from Module 4A for the 4th data cutoff are presented here because as early as this point, no patients were at risk any longer.
i. The company has not provided an effect estimate or p-value because no events occurred in the comparator arm (see Section 2.3.1).
j. The analysis presented by the company is unsuitable for the benefit assessment; however, serious and severe infusion reactions are taken into account in the overall rates of SAEs and severe AEs (see Section 2.3.1).

CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NC: not calculable; NR: not reached; QLQ-C30: Quality of Life Questionnaire – Core 30; RCT: randomized controlled trial

On the basis of the available information, at most an indication, e.g. of an added benefit, can be derived for the outcome of overall survival, and at most hints can be derived for all other outcomes due to the high risk of bias.

Mortality

Overall survival

No statistically significant difference between treatment groups was found. This results in no evidence of an added benefit of ibrutinib + venetoclax in comparison with chlorambucil + obinutuzumab; an added benefit is therefore not proven.

Morbidity

Symptoms (EORTC QLQ-C30 and FACIT-Fatigue)

Symptom outcomes were surveyed using the EORTC QLQ-C30 and FACIT-Fatigue symptom scales.

Diarrhoea (EORTC QLQ-C30)

There was no statistically significant difference between treatment groups for the outcome of diarrhoea, surveyed using the EORTC QLQ-C30. The effect in this outcome of the category of non-serious/non-severe symptoms / late complications was no more than marginal, however. This results in no evidence of an added benefit of ibrutinib + venetoclax in comparison with chlorambucil + obinutuzumab.

Further symptom outcomes

No statistically significant difference between treatment groups was found for any of the outcomes of fatigue, nausea and vomiting, pain, dyspnoea, insomnia, loss of appetite, and constipation, surveyed using the EORTC QLQ-C30, nor for the outcome of fatigue, surveyed using the FACIT-Fatigue. This results in no hint of an added benefit of ibrutinib + venetoclax in comparison with chlorambucil + obinutuzumab for any of them; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

No statistically significant difference between treatment groups was found for the outcome of health status, surveyed with the EQ-5D VAS. This results in no hint of an added benefit of ibrutinib + venetoclax in comparison with chlorambucil + obinutuzumab; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

There was no statistically significant difference between treatment groups for the outcome of health-related quality of life, surveyed using the EORTC QLQ-C30. This results in no hint of an added benefit of ibrutinib + venetoclax in comparison with chlorambucil + obinutuzumab; an added benefit is therefore not proven.

Side effects

SAEs, severe AEs, and discontinuation due to AEs

No statistically significant difference between the treatment groups was shown for the outcomes of SAEs, severe AEs (CTCAE grade ≥ 3), or discontinuation due to AEs. This results in no hint of an added benefit of ibrutinib + venetoclax in comparison with chlorambucil + obinutuzumab for any of them; an added benefit is therefore not proven.

Specific AEs

Haemorrhages (AEs)

No statistically significant difference between treatment groups was found for the outcome of haemorrhages (AEs). This results in no hint of an added benefit of ibrutinib + venetoclax in comparison with chlorambucil + obinutuzumab; an added benefit is therefore not proven.

Haemorrhages (severe AEs)

No effect estimate and no p-value are available for the outcome of haemorrhages (serious AEs) (see Section 2.3.1). This results in no hint of an added benefit of ibrutinib + venetoclax in comparison with chlorambucil + obinutuzumab; an added benefit is therefore not proven.

Cardiac disorders (severe AEs)

No statistically significant difference between treatment groups was found for the outcome of cardiac disorders (severe AEs). This results in no hint of an added benefit of ibrutinib + venetoclax in comparison with chlorambucil + obinutuzumab; an added benefit is therefore not proven.

Infections and infestations (severe AEs)

No statistically significant difference between the treatment groups was shown for the outcome of infections and infestations (severe AE). This results in no hint of an added benefit of ibrutinib + venetoclax in comparison with chlorambucil + obinutuzumab; an added benefit is therefore not proven.

Infusion-related reaction

No suitable data are available for the outcome of infusion-related reaction (see Section 2.3.1). This results in no hint of greater or lesser harm from ibrutinib + venetoclax in comparison with chlorambucil + obinutuzumab; an added benefit is therefore not proven.

Further specific AEs

Due to potential reporting bias, no suitable data are available on other specific AEs at SOC and PT level (see Section 2.3.1).

2.3.4 Subgroups and other effect modifiers

The following subgroup characteristics are relevant for the present benefit assessment:

- age (< 65 years versus ≥ 65 years)
- sex (men versus women)
- Binet stage (A versus B versus C)

Interaction tests are conducted when at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there had to be at least 10 events in at least 1 subgroup.

Presented are only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05). In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least 1 subgroup.

Using the methods described above, the available subgroup results do not reveal any effect modifications.

2.4 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG *General Methods* [7].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.4.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.3.3 (see Table 8).

Determination of the outcome category for outcomes on symptoms and side effects

For the symptoms outcomes below, it cannot be inferred from the dossier whether they are serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Symptoms

Diarrhoea (EORTC QLQ-C30)

For the outcome of diarrhoea, insufficient severity data are available which would allow classifying them as serious/severe. The outcome of diarrhoea was therefore assigned to the outcome category of non-serious/non-severe symptoms / late complications.

Table 8: Extent of added benefit at outcome level: ibrutinib + venetoclax versus chlorambucil + obinutuzumab (multipage table)

Outcome category **Outcome**	**Ibrutinib + venetoclax vs. chlorambucil + obinutuzumab** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	NR vs. NR HR: 0.34 [0.04; 3.30]; p = 0.353	Lesser/added benefit not proven
Outcomes with shortened observation period		
Morbidity		
Symptoms		
EORTC QLQ-C30 (time to 1st deterioration)		
Fatigue	5.82 vs. 6.26 HR: 1.75 [0.78; 3.92]; p = 0.174	Lesser/Added benefit not proven
Nausea and vomiting	13.83 vs. NR HR: 2.17 [0.77; 6.12]; p = 0.144	Lesser/Added benefit not proven
Pain	11.30 vs. 16.62 HR: 1.11 [0.50; 2.49]; p = 0.790	Lesser/Added benefit not proven
Dyspnoea	NR vs. 13.93 HR: 0.79 [0.32; 1.97]; p = 0.619	Lesser/Added benefit not proven
Insomnia	14.09 vs. 31.38 HR: 1.01 [0.41; 2.48]; p = 0.988	Lesser/Added benefit not proven
Appetite loss	10.97 vs. NR HR: 2.87 [0.98; 8.40]; p = 0.055	Lesser/Added benefit not proven
Constipation	NR vs. NR HR: 1.83 [0.58; 5.78]; p = 0.301	Lesser/Added benefit not proven
Diarrhoea	8.51 vs. NR HR: 3.11 [1.07; 9.00]; HR: 0.32 [0.11; 0.93][c]; p = 0.037	Outcome category: non-serious/non-severe symptoms / late complications $0.90 \leq CI_u < 1.00$ Lesser/Added benefit not proven[d]

Table 8: Extent of added benefit at outcome level: ibrutinib + venetoclax versus chlorambucil + obinutuzumab (multipage table)

Outcome category **Outcome**	**Ibrutinib + venetoclax vs. chlorambucil + obinutuzumab** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Fatigue (FACIT-Fatigue – time to 1st deterioration)	NR vs. NR HR: 1.24 [0.40; 3.86]; p = 0.707	Lesser/Added benefit not proven
Health status		
EQ-5D VAS (time to 1st deterioration)	NR vs. NR HR: 2.56 [0.74; 8.76]; p = 0.136	Lesser/Added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 (time to 1st deterioration)		
Global health status	20.50 vs. 24.18 HR: 1.18 [0.47; 2.96]; p = 0.732	Lesser/Added benefit not proven
Physical functioning	NR vs. NR HR: 1.52 [0.51; 4.53]; p = 0.452	Lesser/Added benefit not proven
Role functioning	14.16 vs. 7.24 HR: 0.96 [0.42; 2.18]; p = 0.923	Lesser/Added benefit not proven
Emotional functioning	NR vs. 18.97 HR: 0.44 [0.16; 1.18]; p = 0.103	Lesser/Added benefit not proven
Cognitive functioning	NR vs. 11.07 HR: 0.68 [0.26; 1.78]; p = 0.435	Lesser/Added benefit not proven
Social functioning	10.97 vs. 20.07 HR: 1.21 [0.53; 2.75]; p = 0.650	Lesser/Added benefit not proven

Table 8: Extent of added benefit at outcome level: ibrutinib + venetoclax versus chlorambucil + obinutuzumab (multipage table)

Outcome category **Outcome**	**Ibrutinib + venetoclax vs. chlorambucil + obinutuzumab** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
SAEs	NR vs. NR HR: 1.40 [0.53; 3.69]; p = 0.500	Greater/Lesser harm not proven
Severe AEs	NR vs. NR HR: 0.67 [0.35; 1.32]; p = 0.247	Greater/Lesser harm not proven
Discontinuation due to AEs	NR vs. NR HR: 0.55 [0.05; 6.07]; p = 0.626	Greater/Lesser harm not proven
Haemorrhages (AEs)	NR vs. NR HR: 3.42 [0.91; 12.88]; p = 0.070	Greater/Lesser harm not proven
Haemorrhages (severe AEs)	NR vs. NR HR + p-value: no data	Greater/Lesser harm not proven
Cardiac disorders (severe AEs)	NR vs. NR HR: 0.57 [0.05; 6.24]; p = 0.642	Greater/Lesser harm not proven
Infections and infestations (severe AEs)	NR vs. 16.89 HR: 0.72 [0.16; 3.27]; p = 0.673	Greater/Lesser harm not proven
Infusion-related reaction	Analysis unsuitable[f]	Greater/Lesser harm not proven

a. Probability provided there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
d. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
e. The company does not provide an effect estimate and p-value as no events occurred in the comparator arm (see Section 2.3.1).
f. The analysis presented by the company is not suitable for the benefit assessment; however, serious and severe infusion reactions are taken into account in the overall rates of SAEs and severe AEs (see Section 2.3.1).

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EQ-5D: European Quality of Life 5 Dimensions; QLQ-C30: Quality of Life Questionnaire – Core 30; SAE: serious adverse event; VAS: visual analogue scale

2.4.2 Overall conclusion on added benefit

Table 9 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 9: Favourable and unfavourable effects from the assessment of ibrutinib + venetoclax in comparison with chlorambucil + obinutuzumab

Favourable effects	Unfavourable effects
-	-

Overall, there were neither favourable nor unfavourable effects of ibrutinib + venetoclax in comparison with chlorambucil + obinutuzumab. In summary, there is therefore no proof of added benefit of ibrutinib + venetoclax in adult patients with previously untreated CLL compared to the appropriate comparator therapy (ACT).

2.5 Summary

The data subsequently submitted by the company in the commenting procedure do not change the conclusion drawn in dossier assessment A23-04 on the added benefit of ibrutinib + venetoclax.

Table 10 below shows the result of the benefit assessment of ibrutinib in combination with venetoclax, taking into account dossier assessment A23-04 and the present addendum.

Table 10: Ibrutinib + venetoclax – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with previously untreated CLL[b,c]	Ibrutinib or Ibrutinib in combination with rituximab or obinutuzumab or Fludarabine in combination with cyclophosphamide and rituximab (FCR)[d, e] or Bendamustine in combination with rituximab[e, f] or **Chlorambucil in combination with** rituximab or **obinutuzumab**[e, f]	Added benefit not proven

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 of the company is printed in bold.
b. In the present therapeutic indication, patients presumably require treatment (e.g. Binet stage C).
c. For the present therapeutic indication, allogeneic stem cell transplantation is presumably not indicated at the time of treatment.
d. Only for patients without any genetic risk factors and < 65 years of age who, based on their general health and comorbidities, are eligible for FCR therapy.
e. According to current medical knowledge, the following factors are deemed genetic risk factors: presence of 17p deletion / TP53 mutation / unmutated IGHV.
f. Only for patients without genetic risk factors who are ineligible for FCR therapy. According to the G-BA, this includes both patients ≥ 65 years of age and patients < 65 years of age who, based on their general health and comorbidities, are ineligible for FCR therapy.

17p: deletion of the short arm of chromosome 17; ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; FCR: fludarabine + cyclophosphamide + rituximab; G-BA: Federal Joint Committee; IGHV: immunoglobulin heavy chain variable region; TP53 mutation: mutation of the tumour protein p53

The G-BA decides on the added benefit.

3 References

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Appendix A Graphic display of the time-to-event analyses presented in the benefit assessment (Kaplan-Meier curves)

A.1 Mortality

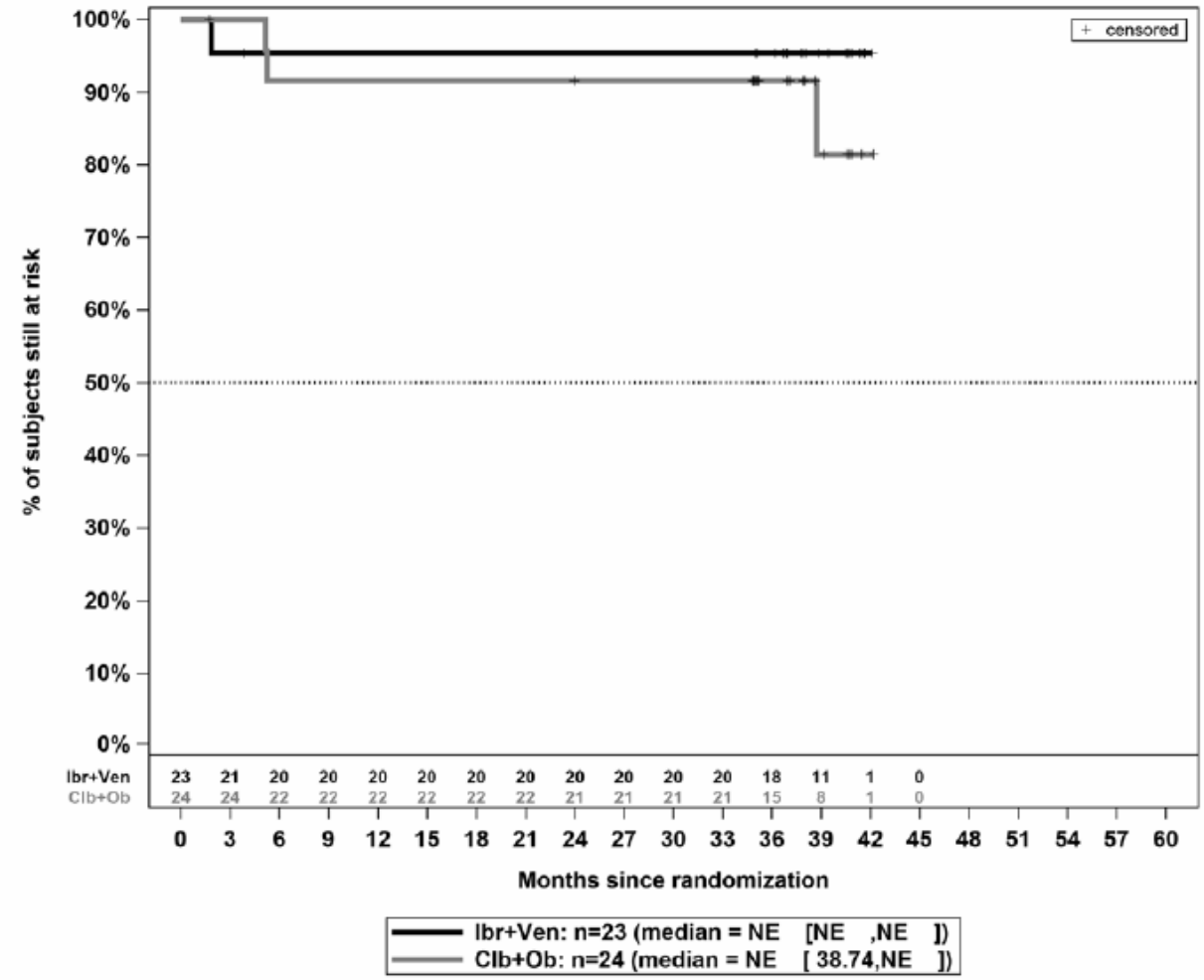

Figure 1: : Kaplan-Meier curve, outcome of overall survival – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab, 3rd data cutoff – GLOW study

A.2 Morbidity

A.2.1 Symptoms

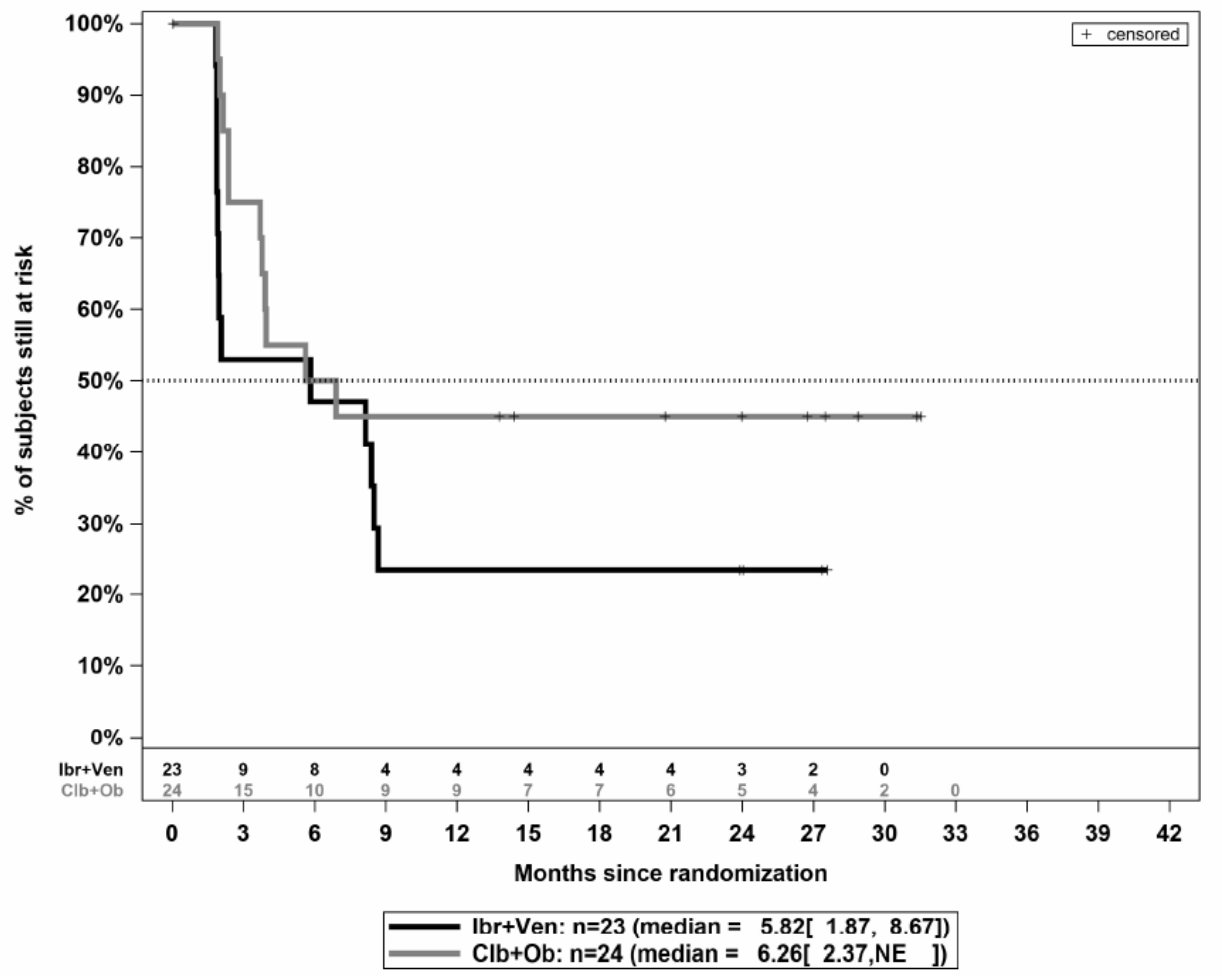

Figure 2: Kaplan-Meier curve on symptoms, outcome of fatigue (EORTC QLQ-C30, first deterioration by ≥ 10 points) – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab, 3rd data cutoff – GLOW study

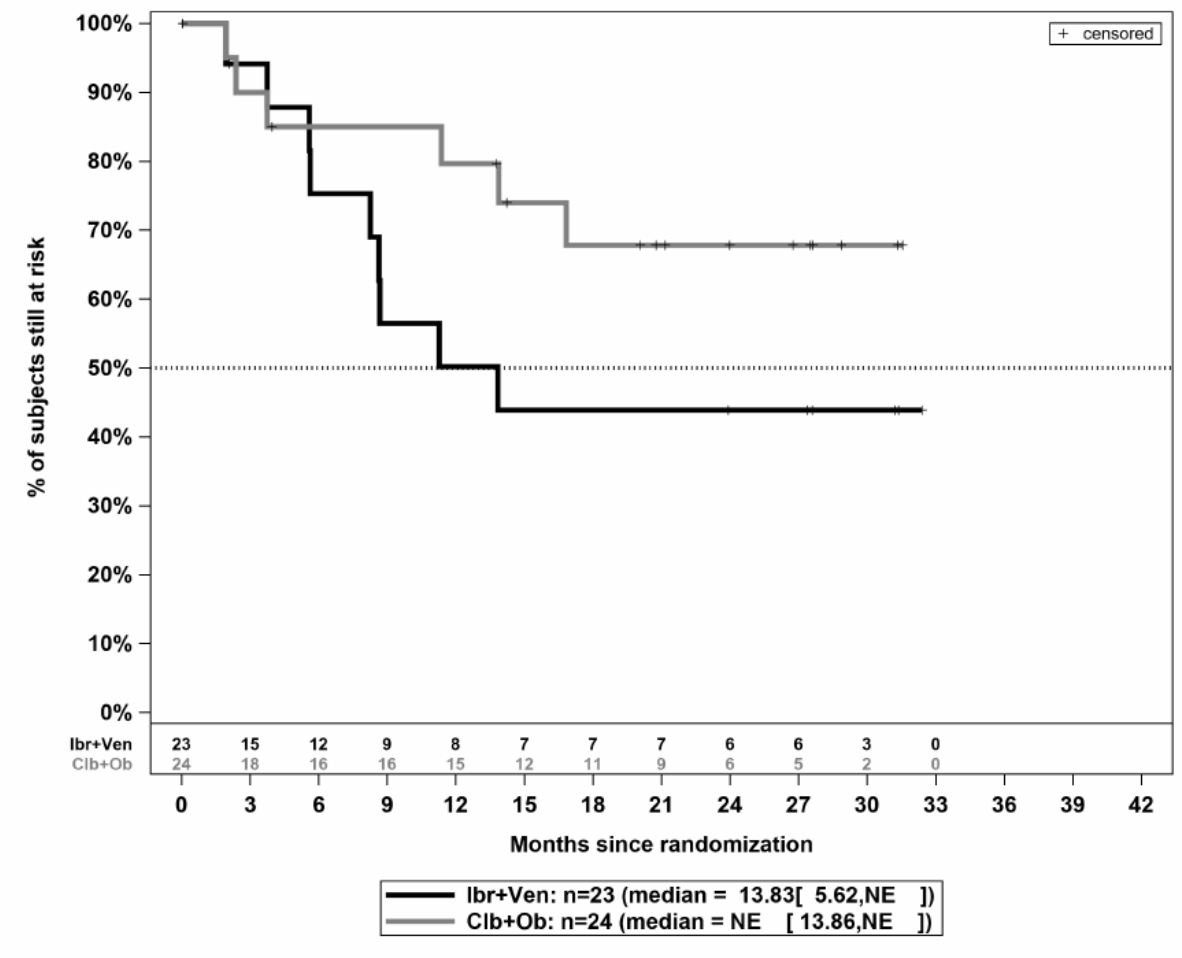

Figure 3: Kaplan-Meier curve on symptoms, outcome of nausea and vomiting (EORTC QLQ-C30, first worsening by ≥ 10 points) – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab, 3rd data cutoff – GLOW study

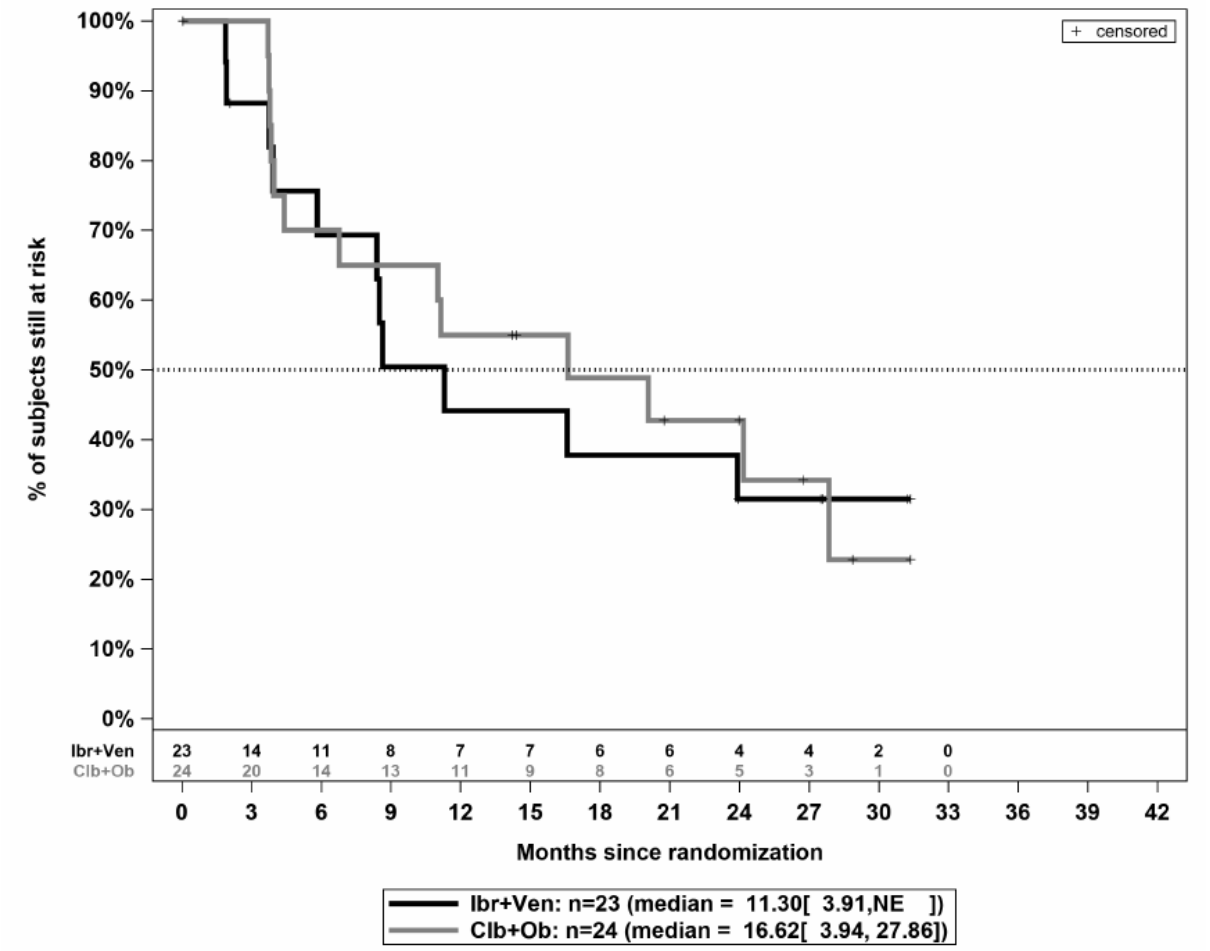

Figure 4: Kaplan-Meier curve on symptoms, pain outcome (EORTC QLQ-C30, first deterioration by ≥ 10 points) – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab, 3rd data cutoff – GLOW study

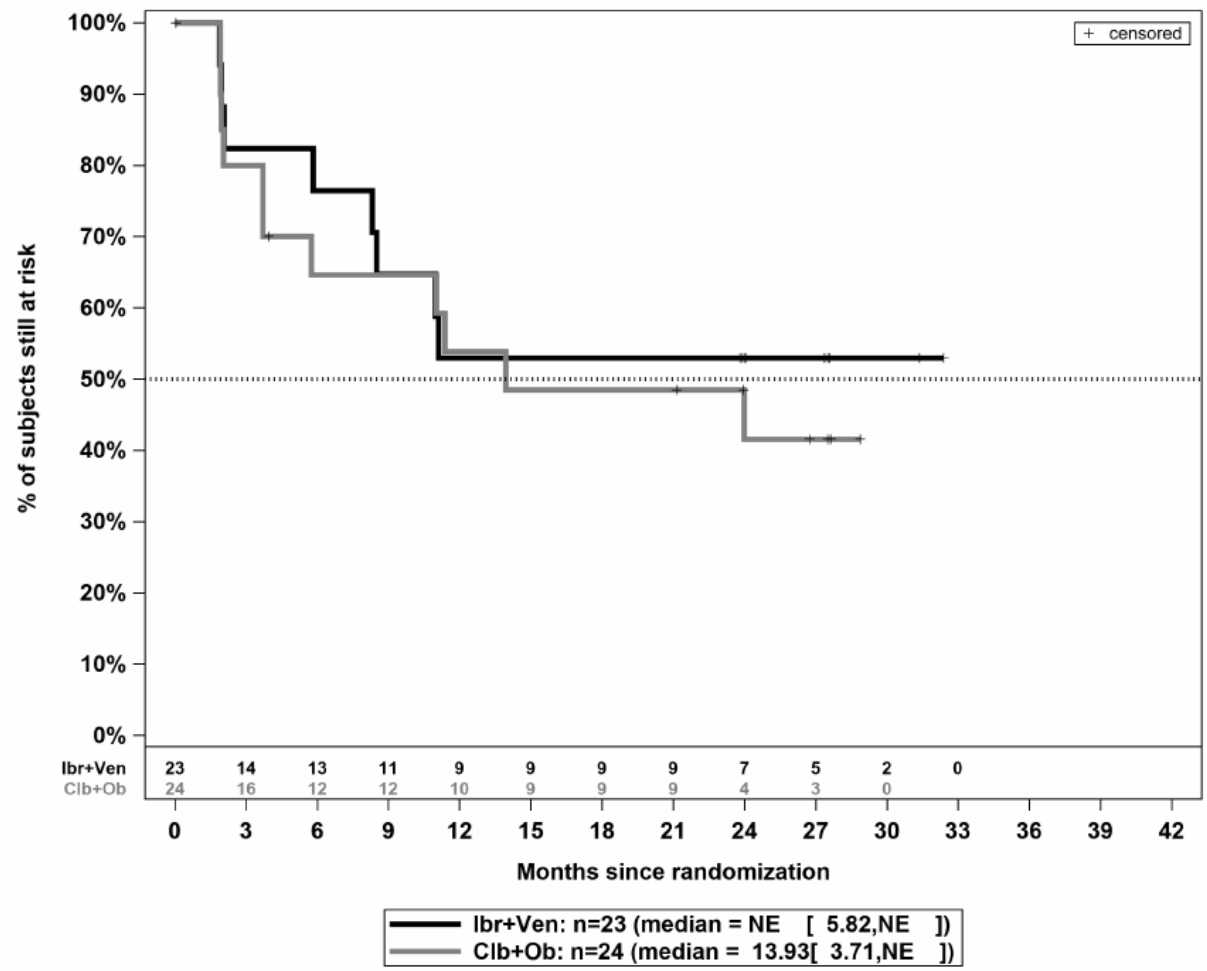

Figure 5: Kaplan-Meier curve on symptoms, outcome of dyspnoea (EORTC QLQ-C30, first deterioration by ≥ 10 points) – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab, 3rd data cutoff – GLOW study

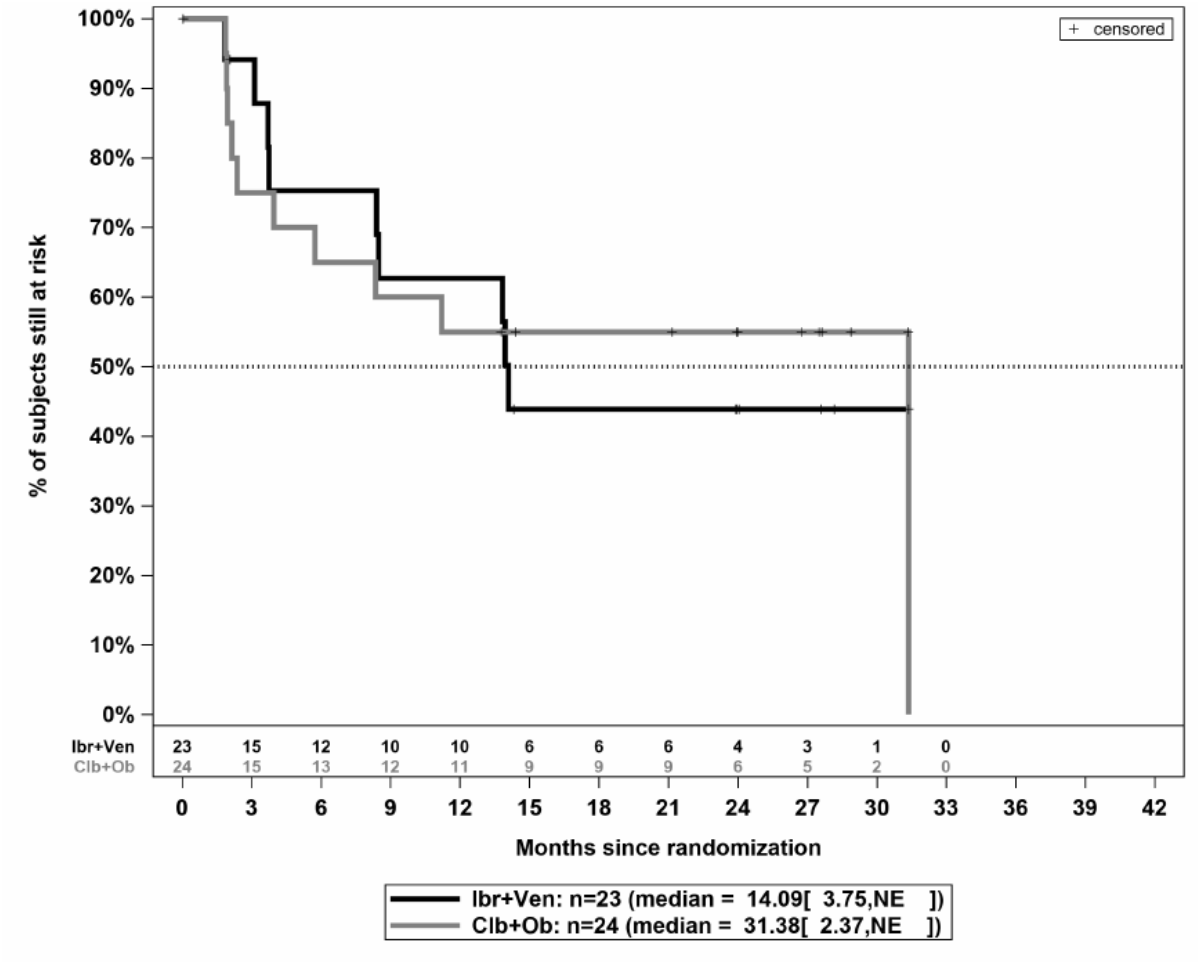

Figure 6: Kaplan-Meier curve on symptoms, outcome of insomnia (EORTC QLQ-C30, first deterioration by ≥ 10 points) – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab, 3rd data cutoff – GLOW study

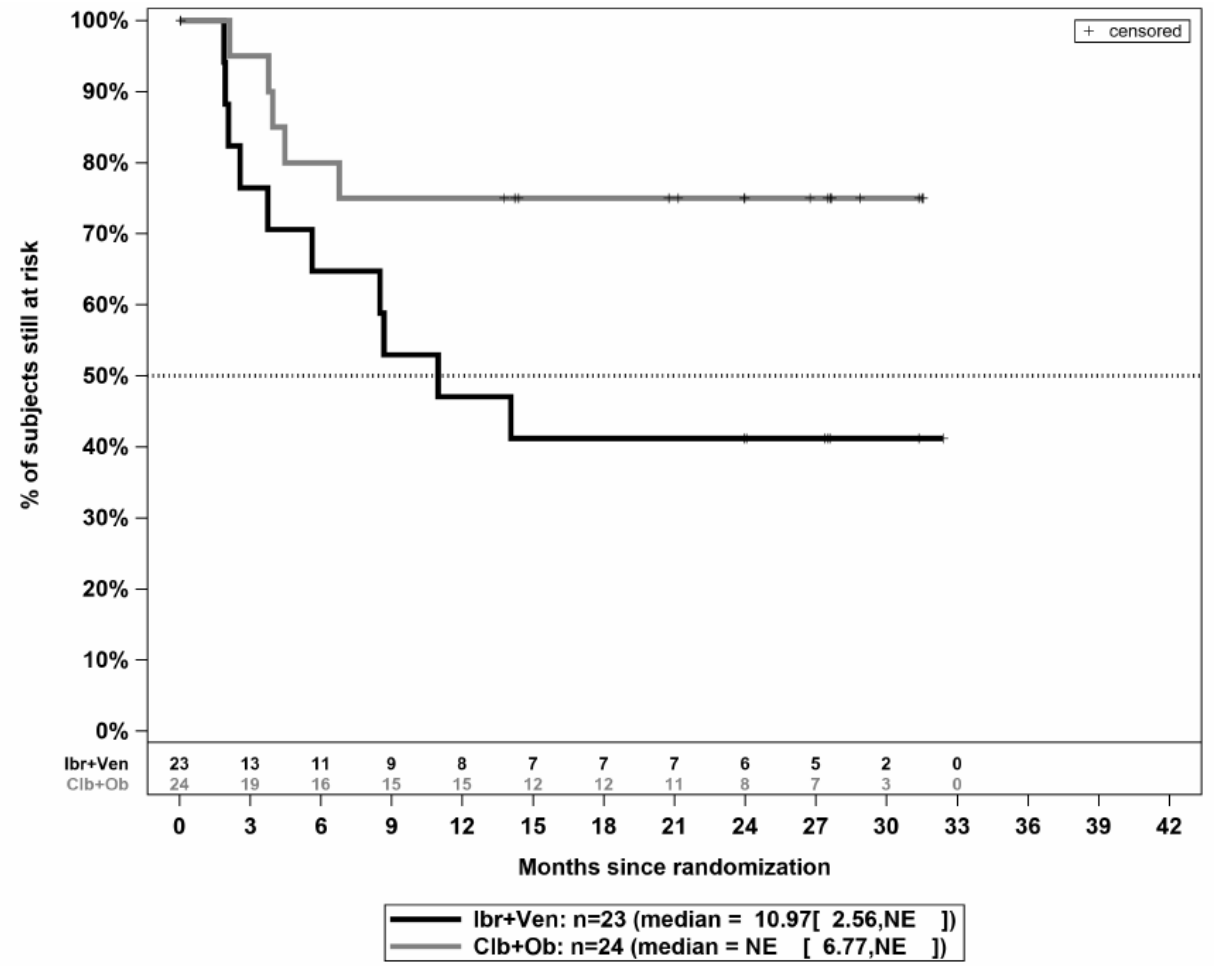

Figure 7: Kaplan-Meier curve on symptoms, outcome of appetite loss (EORTC QLQ-C30, first deterioration by ≥ 10 points) – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab, 3rd data cutoff – GLOW study

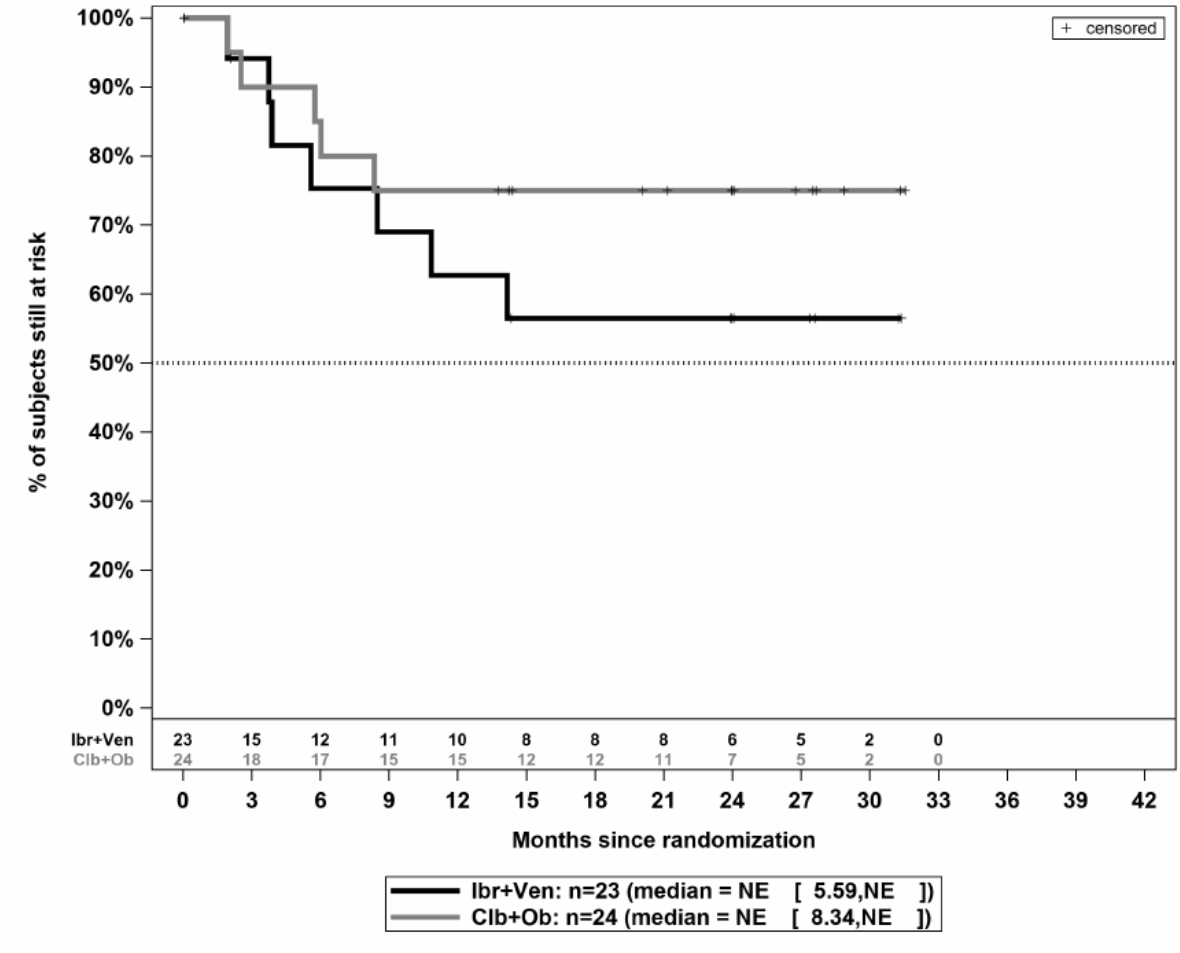

Figure 8: Kaplan-Meier curve on symptoms, outcome of constipation (EORTC QLQ-C30, first deterioration by ≥ 10 points) – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab, 3rd data cutoff – GLOW study

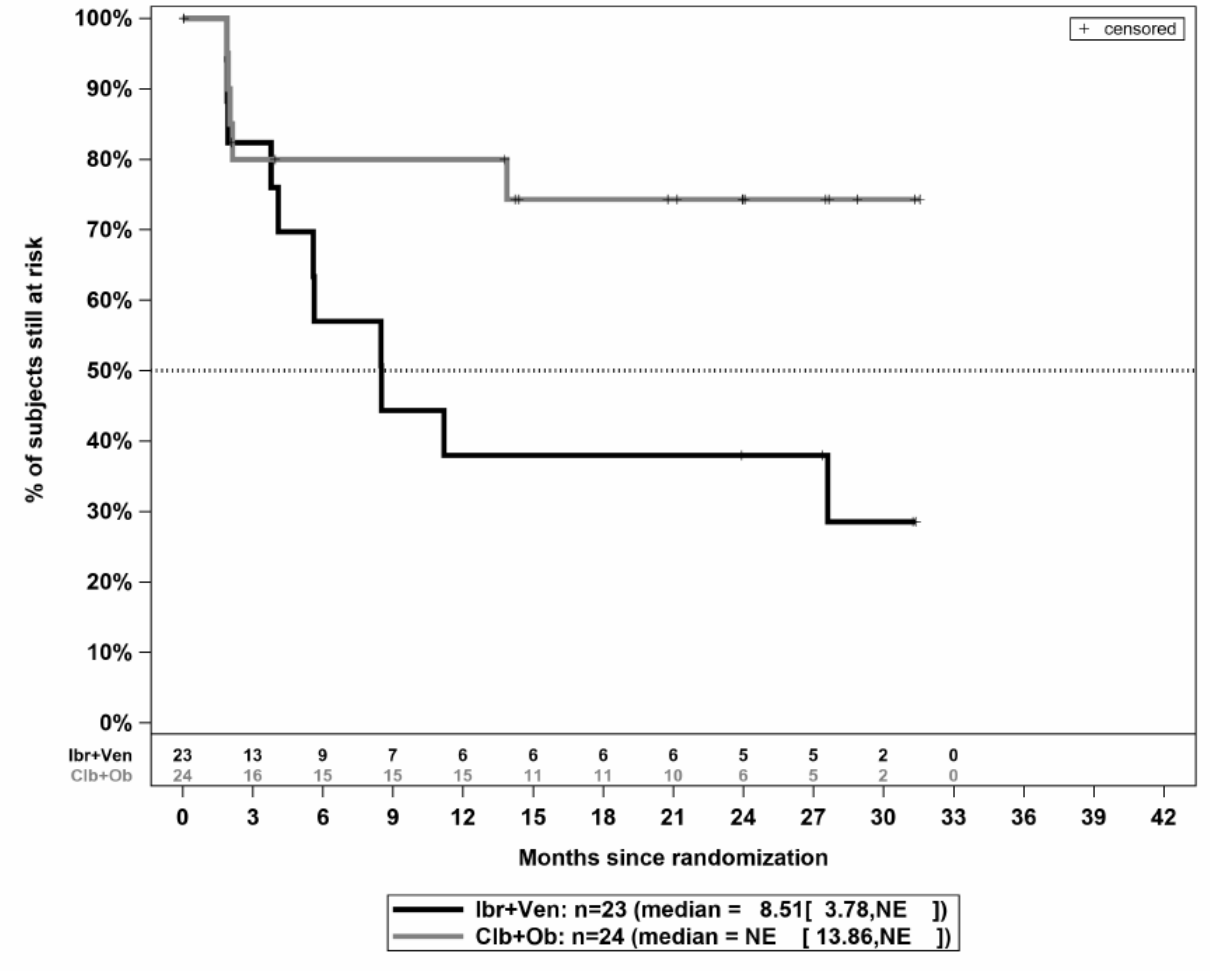

Figure 9: Kaplan-Meier curve on symptoms, outcome of diarrhoea (EORTC QLQ-C30, first deterioration by ≥ 10 points) – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab, 3rd data cutoff – GLOW study

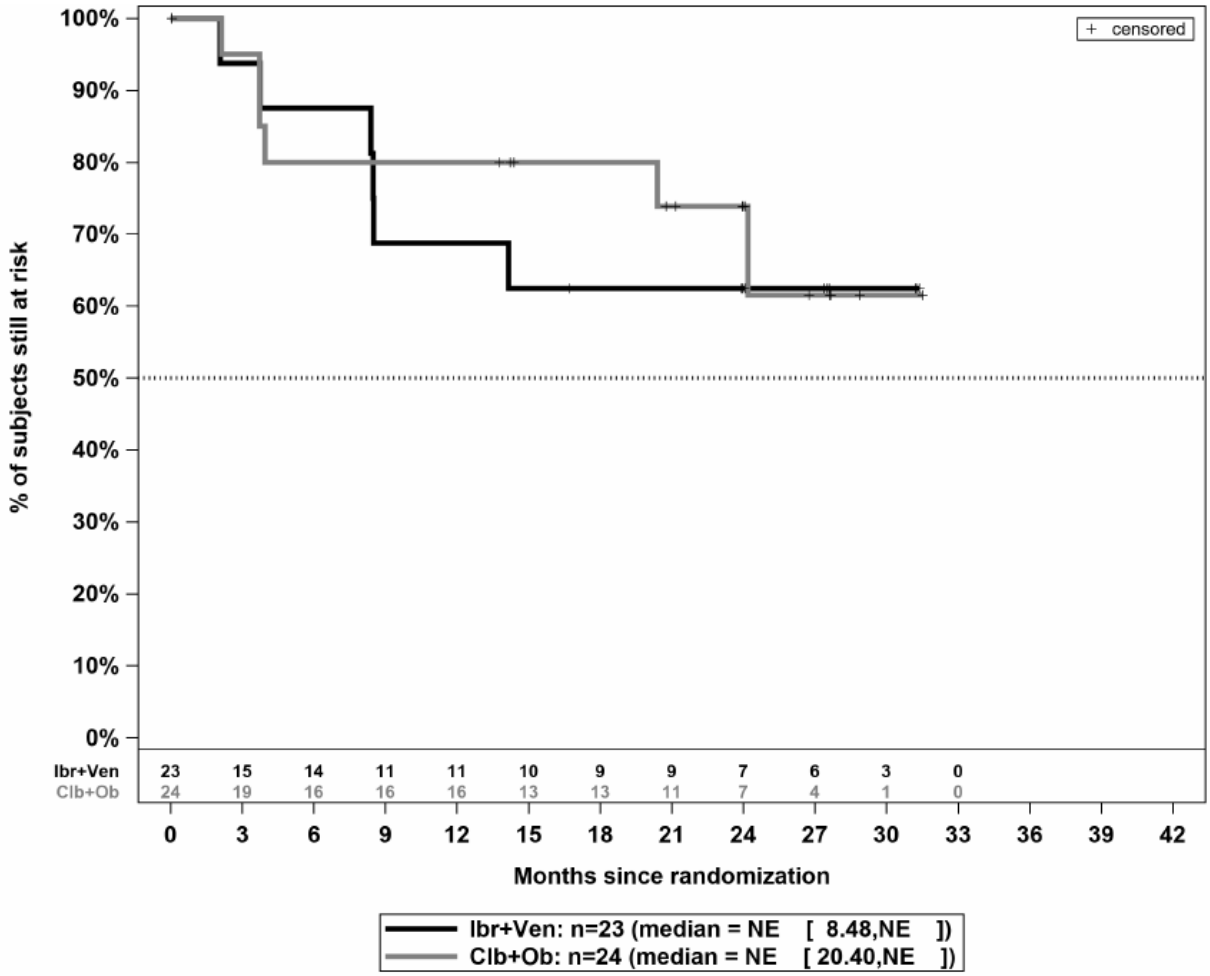

Figure 10: Kaplan-Meier curve on symptoms, outcome of FACIT-Fatigue (EORTC QLQ-C30, first deterioration by ≥ 10 points) – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab, 3rd data cutoff – GLOW study

A.2.2 Health status

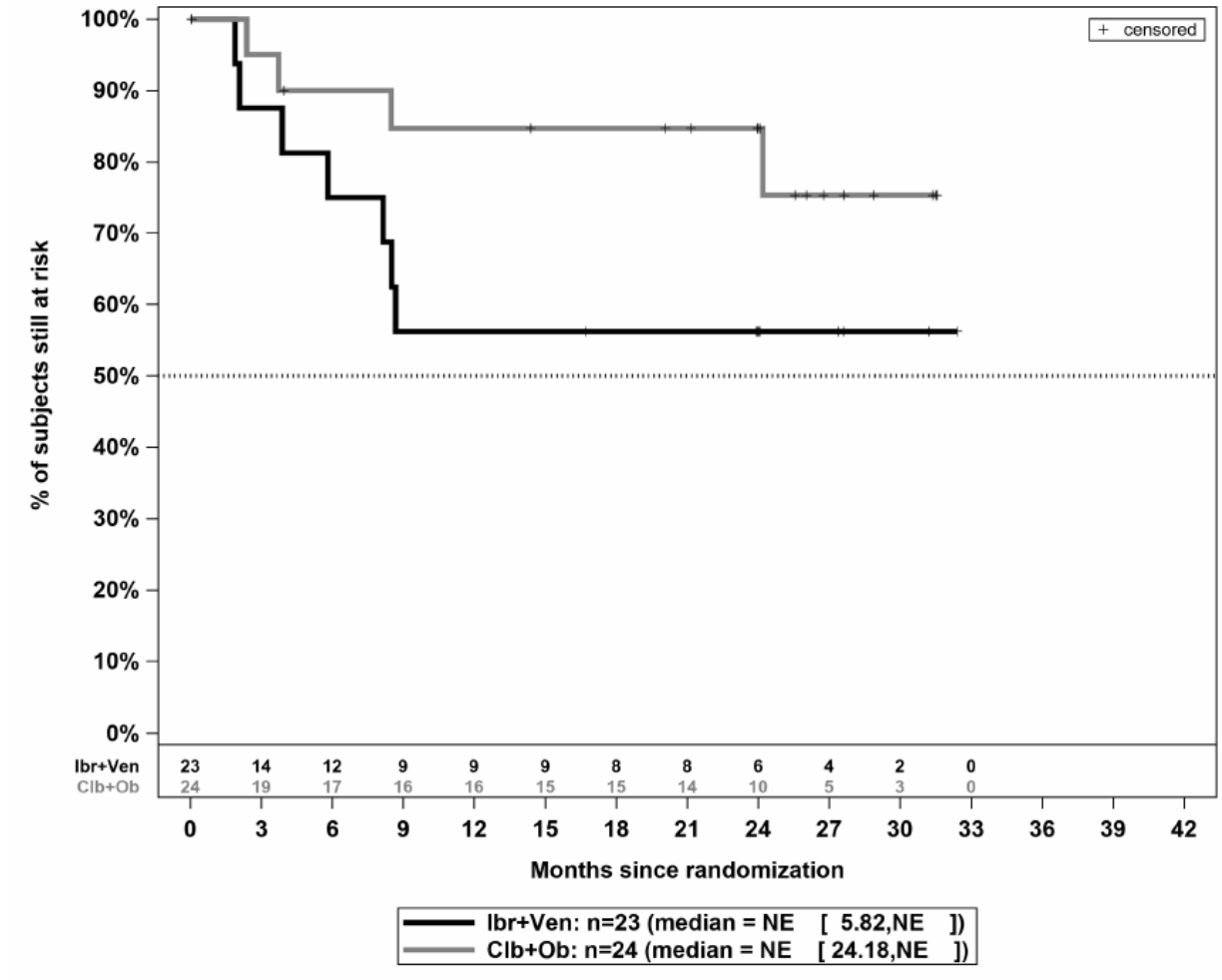

Figure 11: Kaplan-Meier curve, outcome of health status (EQ-5D VAS, first deterioration by ≥ 15 points) – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab, 3rd data cutoff – GLOW study

A.2.3 Health-related quality of life

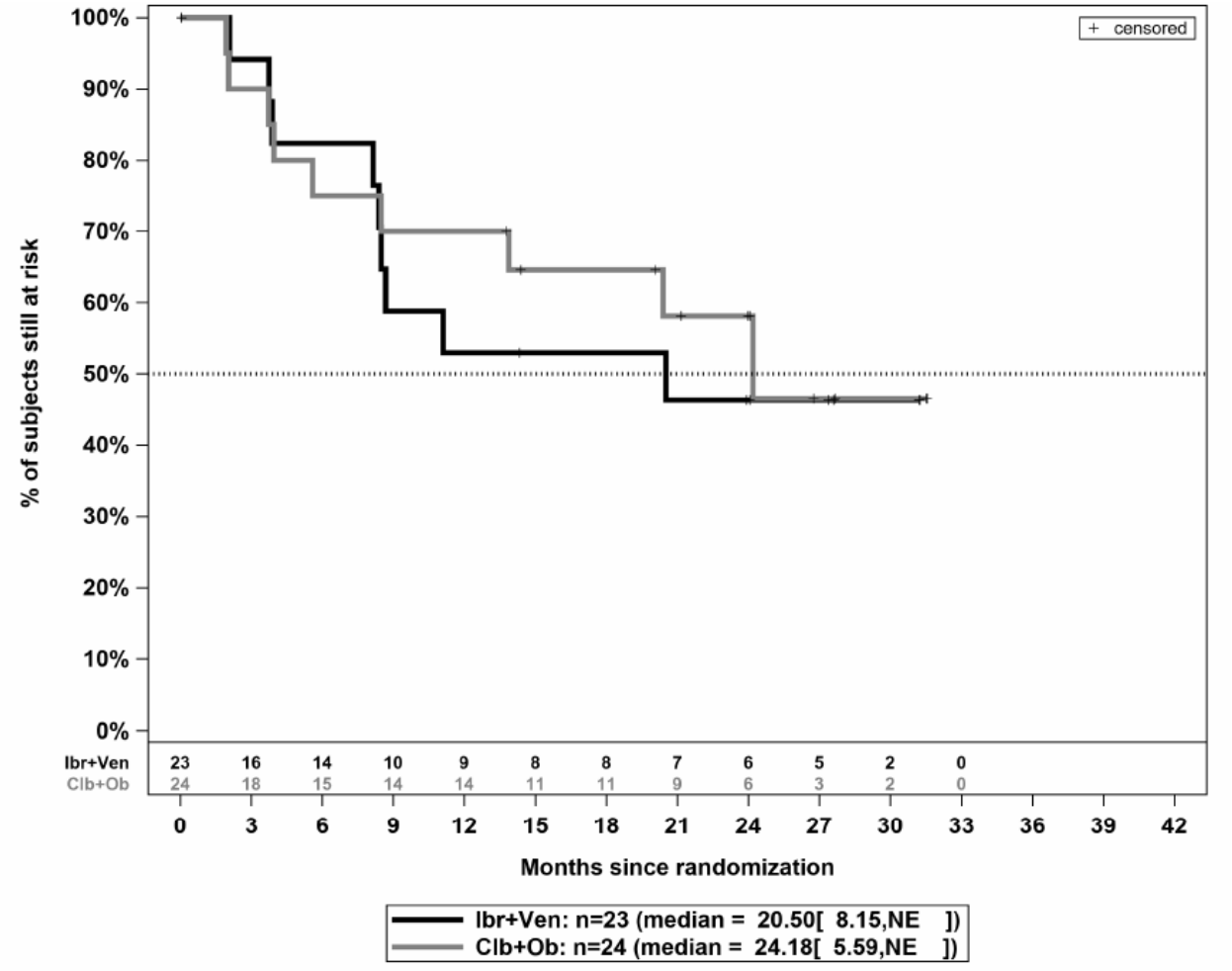

Figure 12: Kaplan-Meier curve on health-related quality of life, outcome of global health status (EORTC QLQ-C30, first deterioration by ≥ 10 points) – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab, 3rd data cutoff – GLOW study

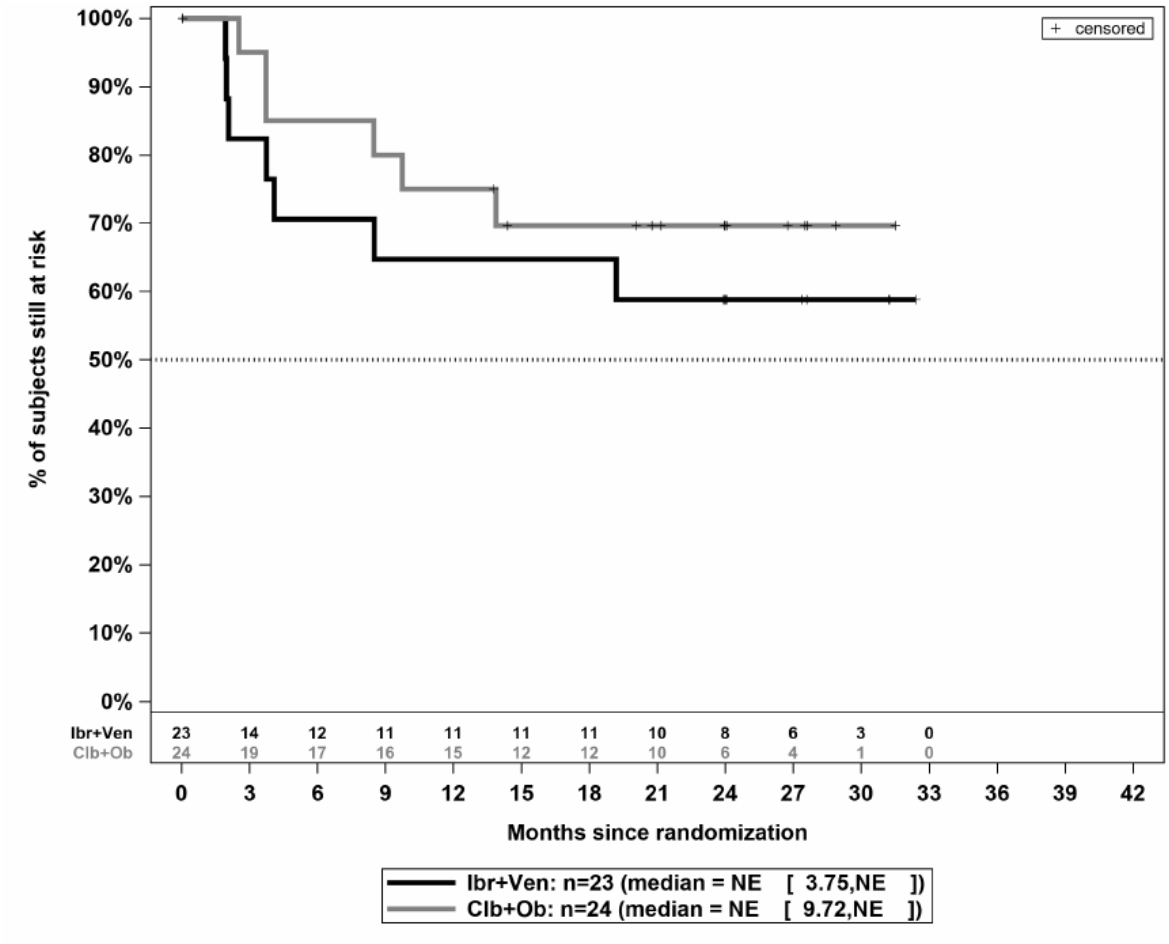

Figure 13: Kaplan-Meier curve on health-related quality of life, outcome of physical functioning (EORTC QLQ-C30, first deterioration by ≥ 10 points) – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab, 3rd data cutoff – GLOW study

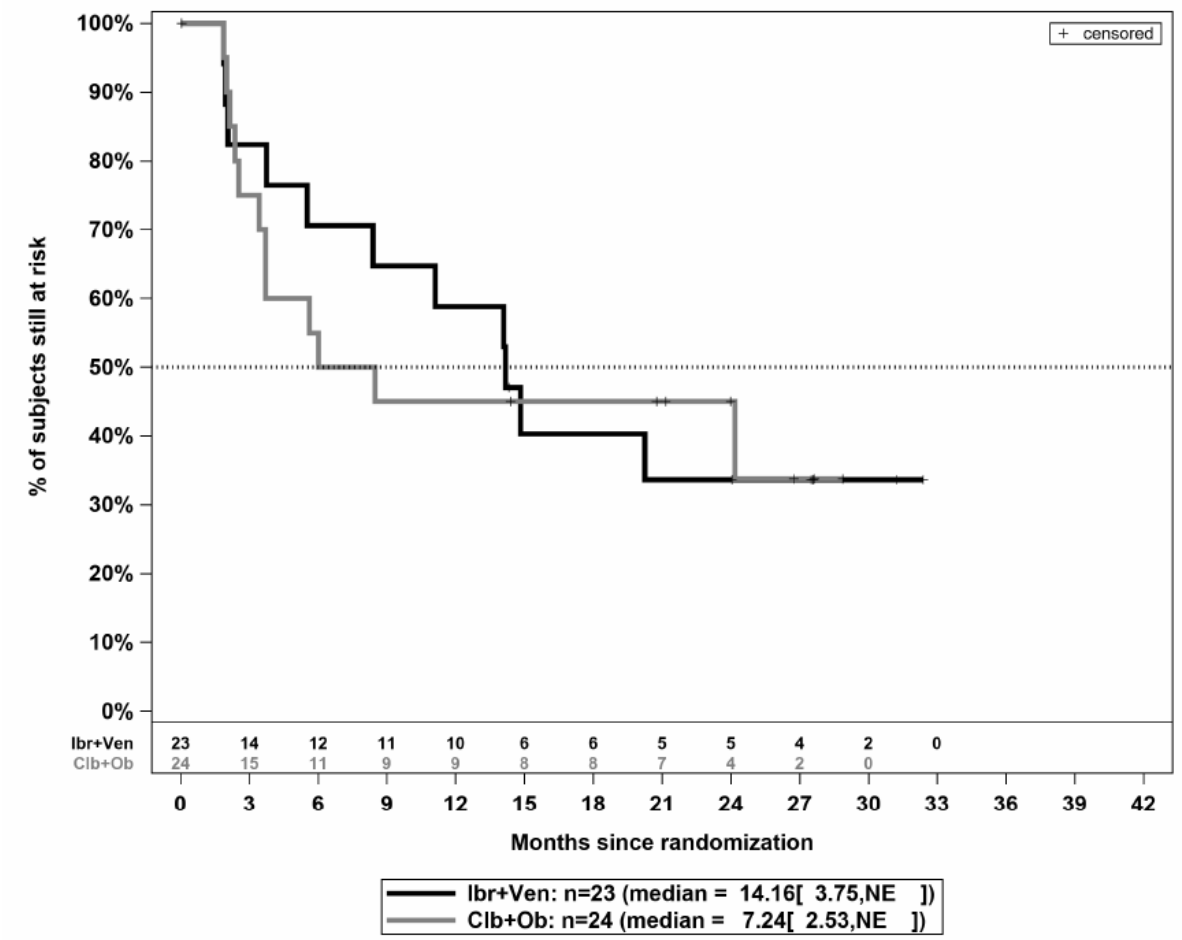

Figure 14: Kaplan-Meier curve on health-related quality of life, outcome of role functioning (EORTC QLQ-C30, first deterioration by ≥ 10 points) – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab, 3rd data cutoff – GLOW study

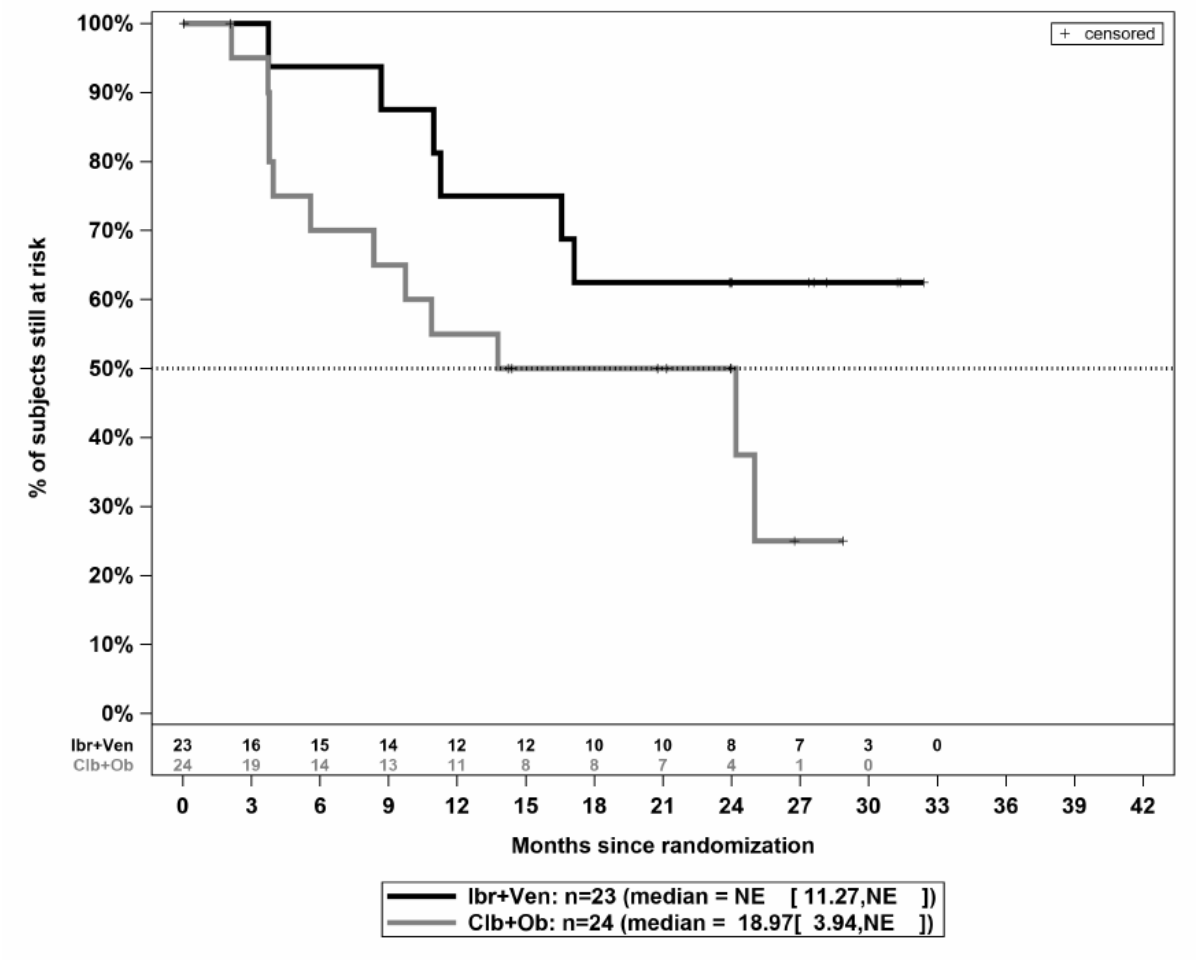

Figure 15: Kaplan-Meier curve on health-related quality of life, outcome of emotional functioning (EORTC QLQ-C30, first deterioration by ≥ 10 points) – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab, 3rd data cutoff – GLOW study

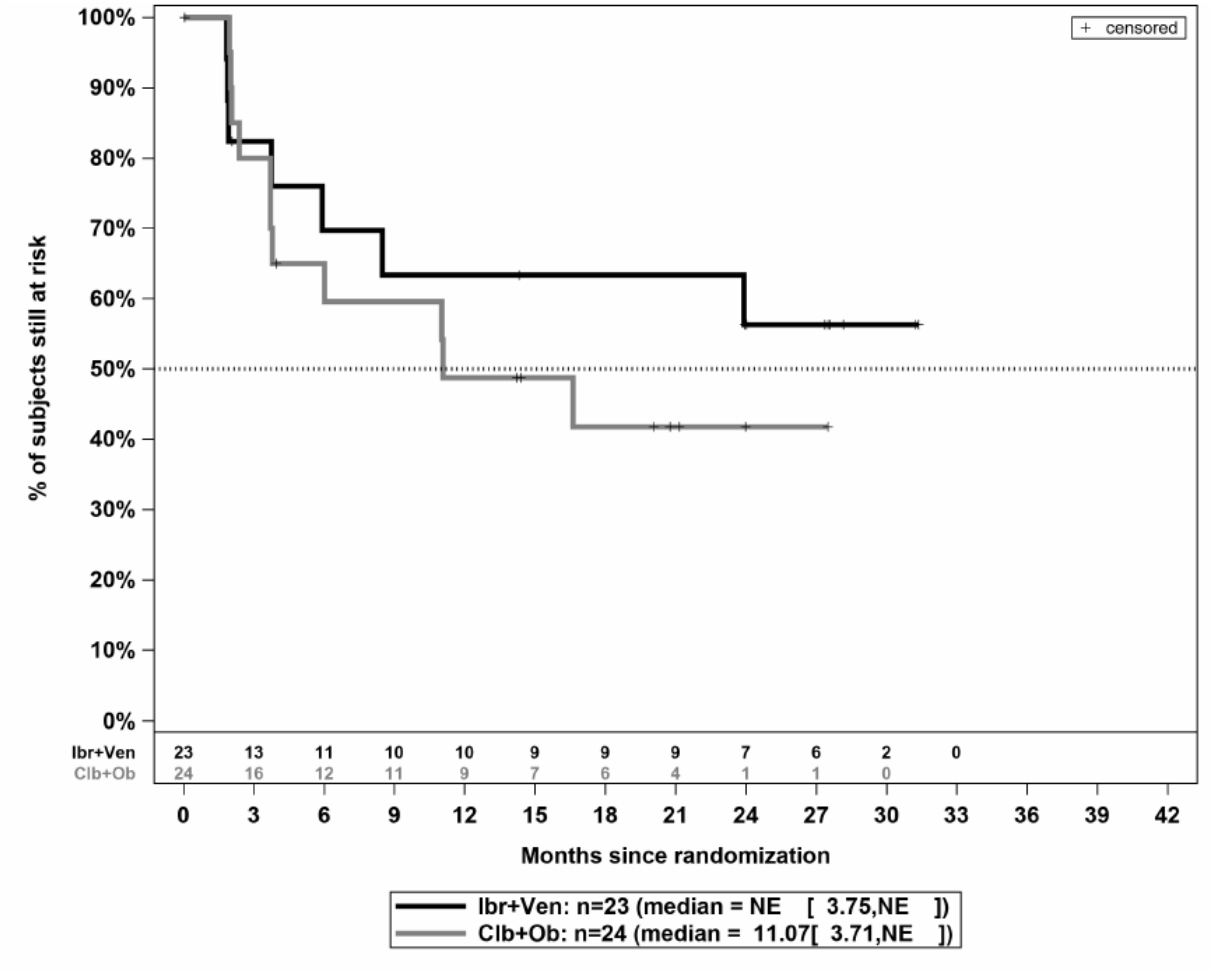

Figure 16: Kaplan-Meier curve on health-related quality of life, outcome of cognitive functioning (EORTC QLQ-C30, first deterioration by ≥ 10 points) – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab, 3rd data cutoff – GLOW study

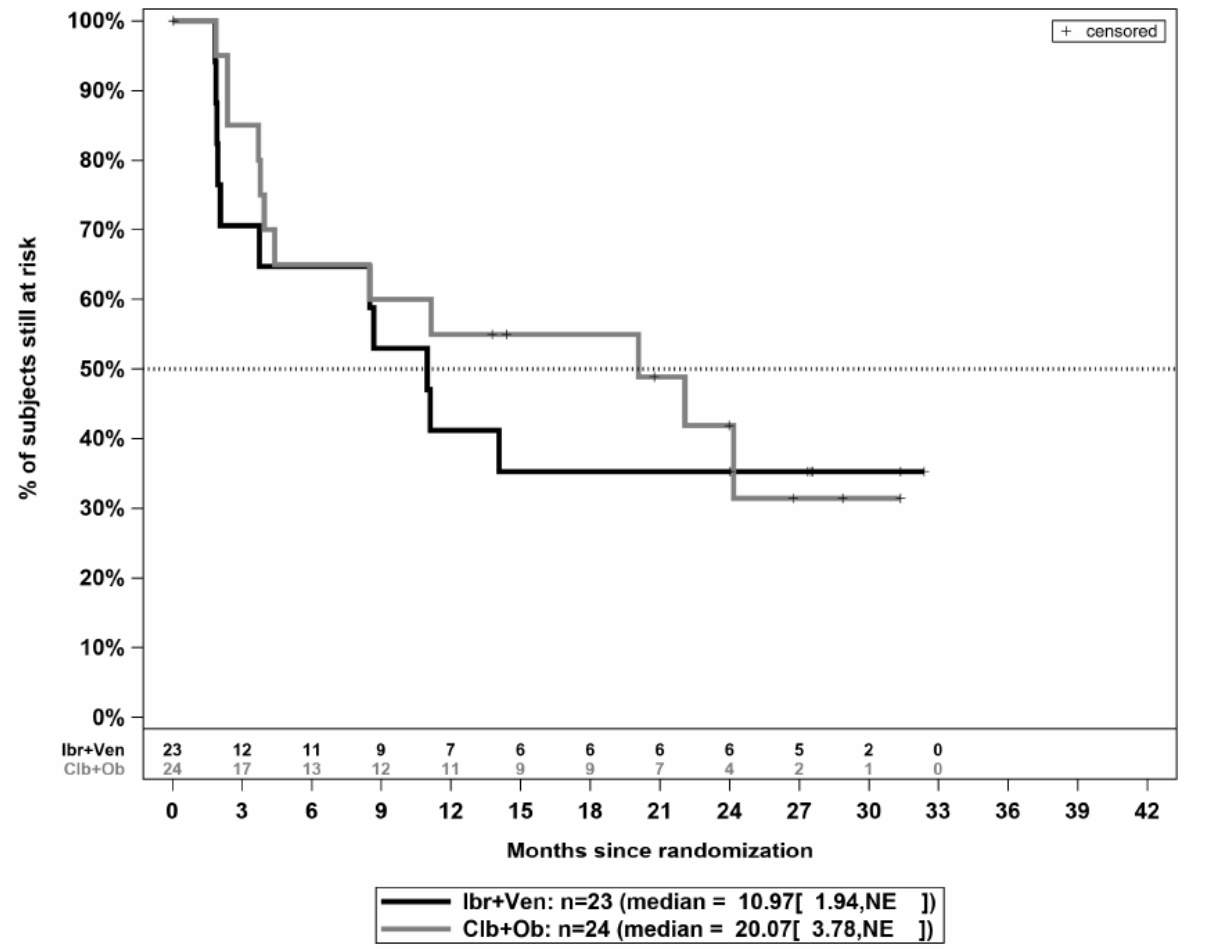

Figure 17: Kaplan-Meier curve on health-related quality of life, outcome of social functioning (EORTC QLQ-C30, first deterioration by ≥ 10 points) – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab, 3rd data cutoff – GLOW study

A.3 Side effects

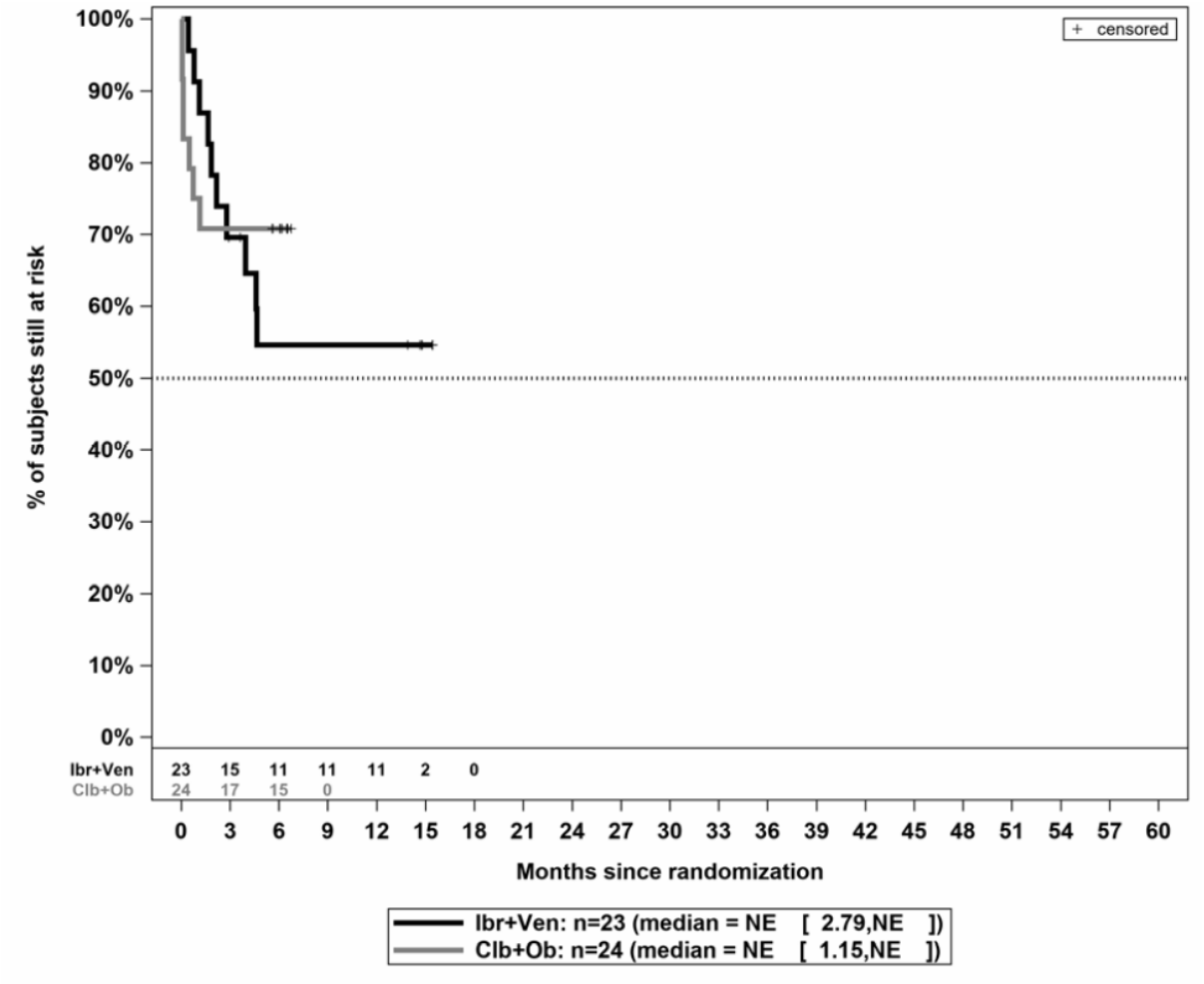

Figure 18: Kaplan-Meier curve, outcome of SAEs – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab, 3rd data cutoff - GLOW study

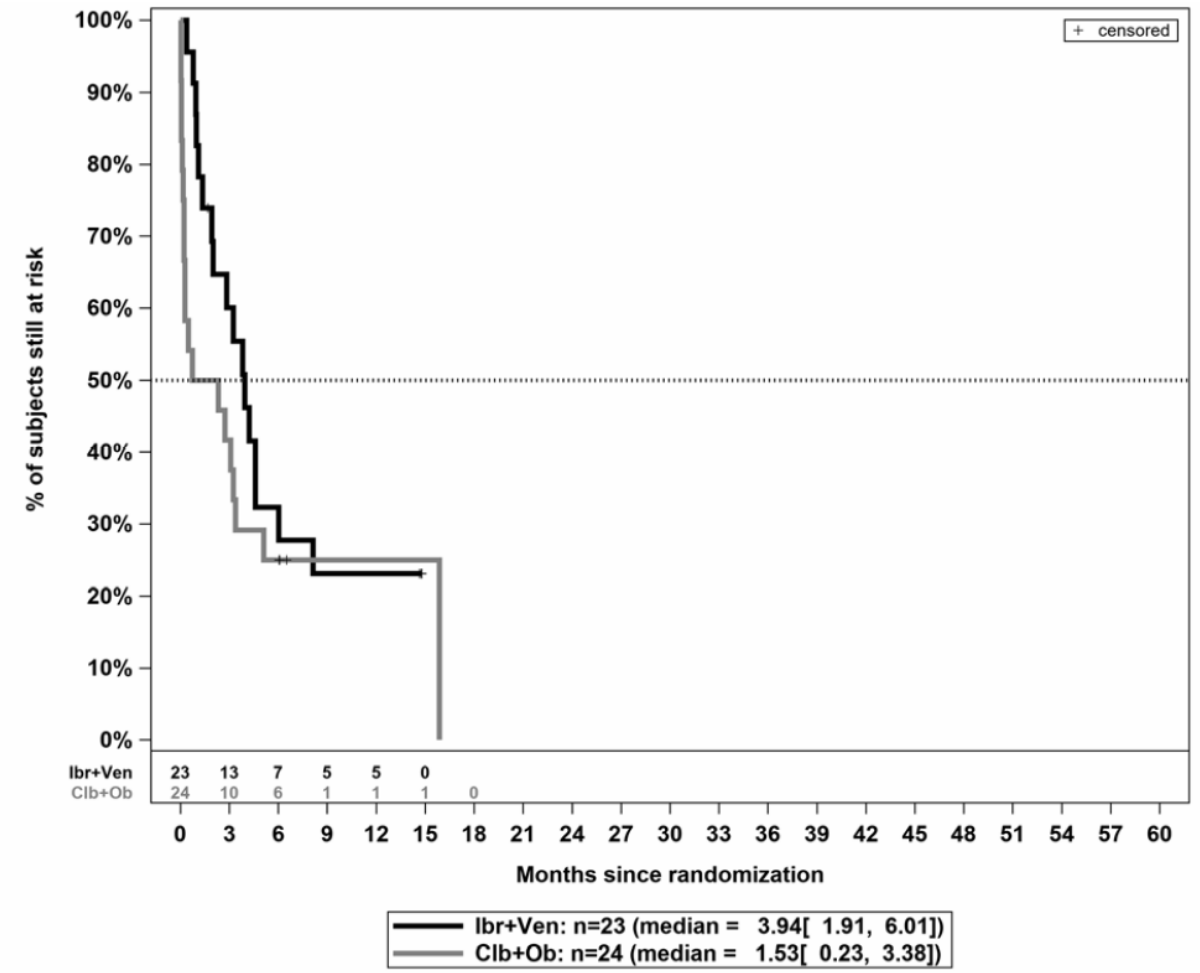

Figure 19: Kaplan-Meier curve, outcome of severe AEs – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab, 3rd data cutoff – GLOW study

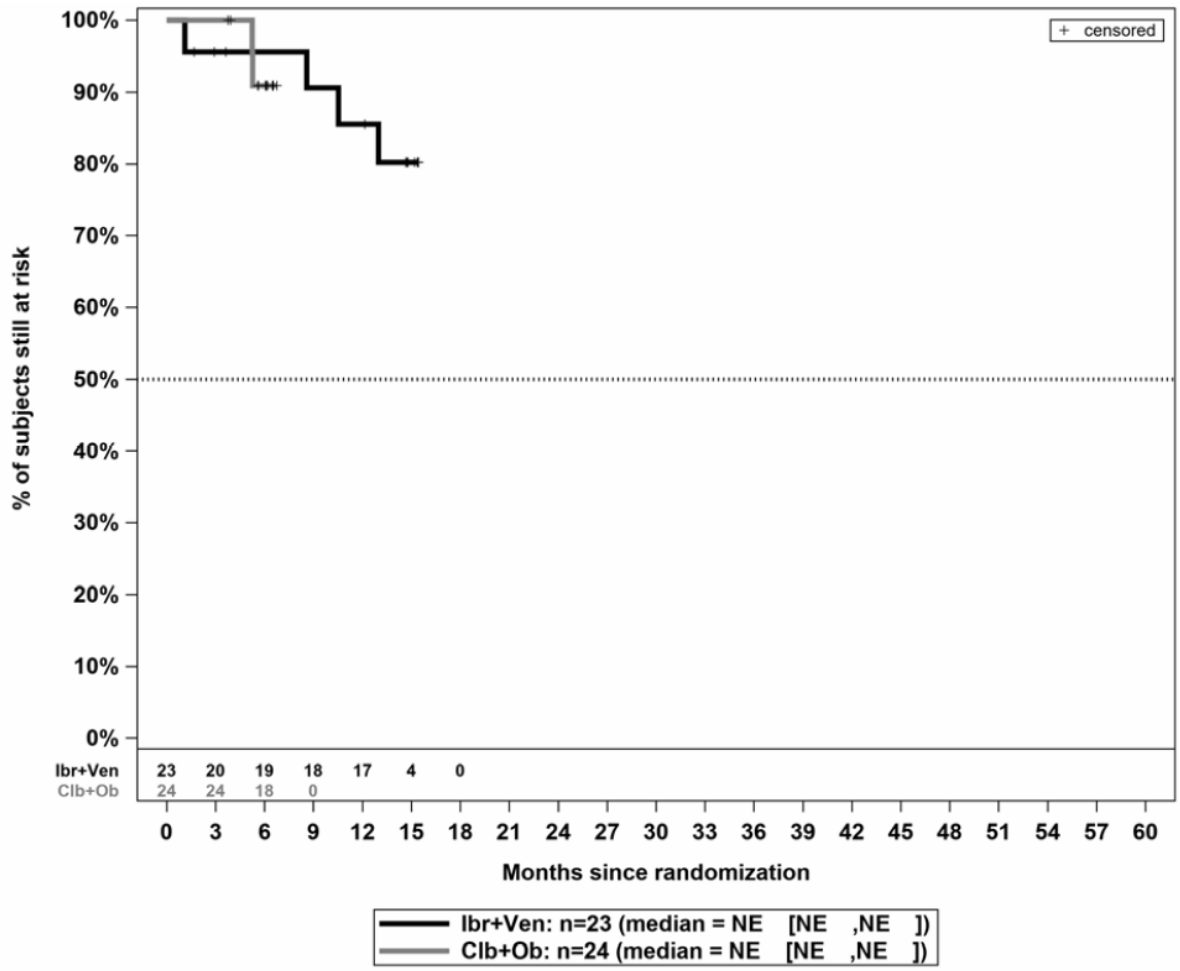

Figure 20: Kaplan-Meier curve, outcome of discontinuation due to AEs – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab, 3rd data cutoff – GLOW study

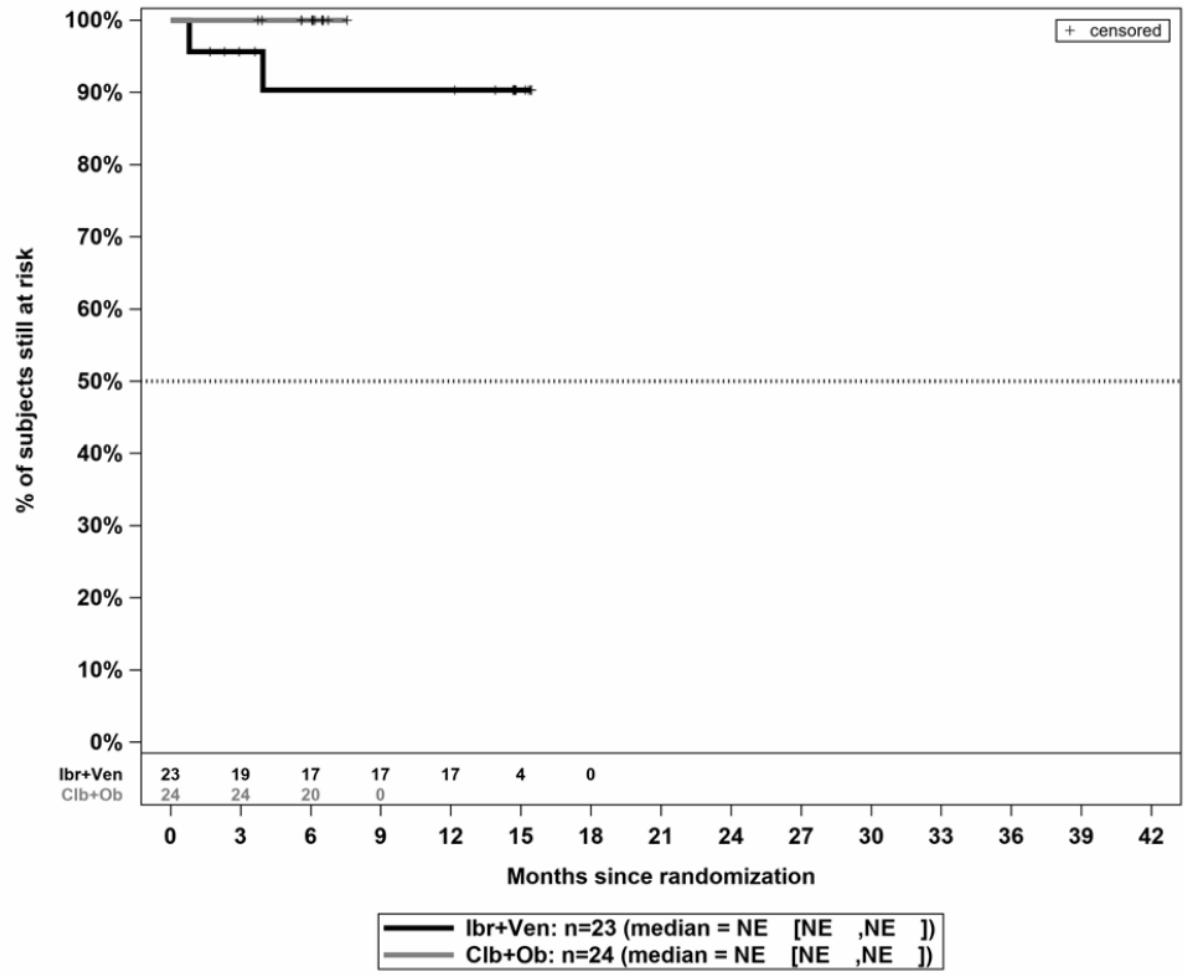

Figure 21: Kaplan-Meier curve, outcome of haemorrhages (severe AEs) – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab, 3rd data cutoff – GLOW study

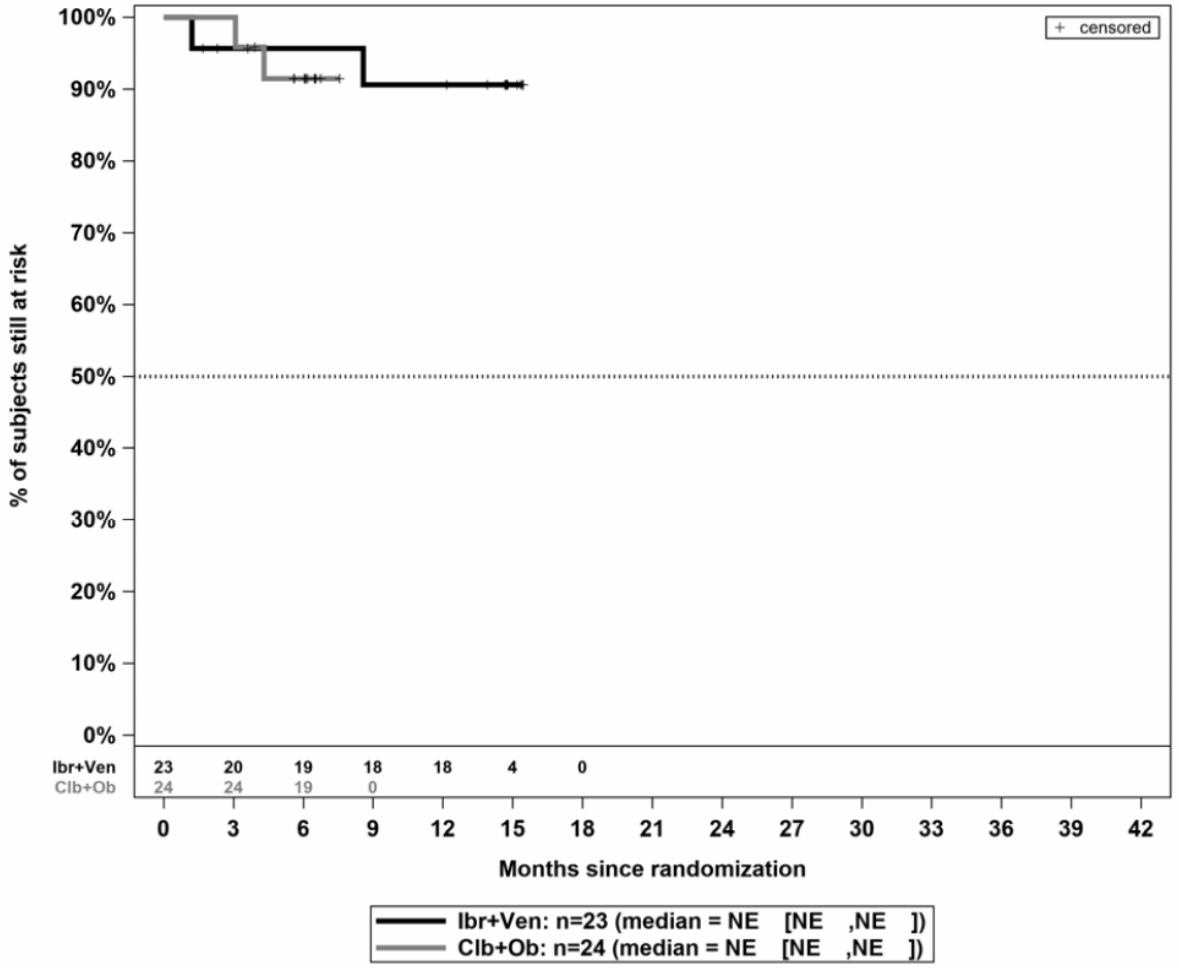

Figure 22: Kaplan-Meier curve, outcome of cardiac disorders (severe AEs) – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab, 3rd data cutoff – GLOW study

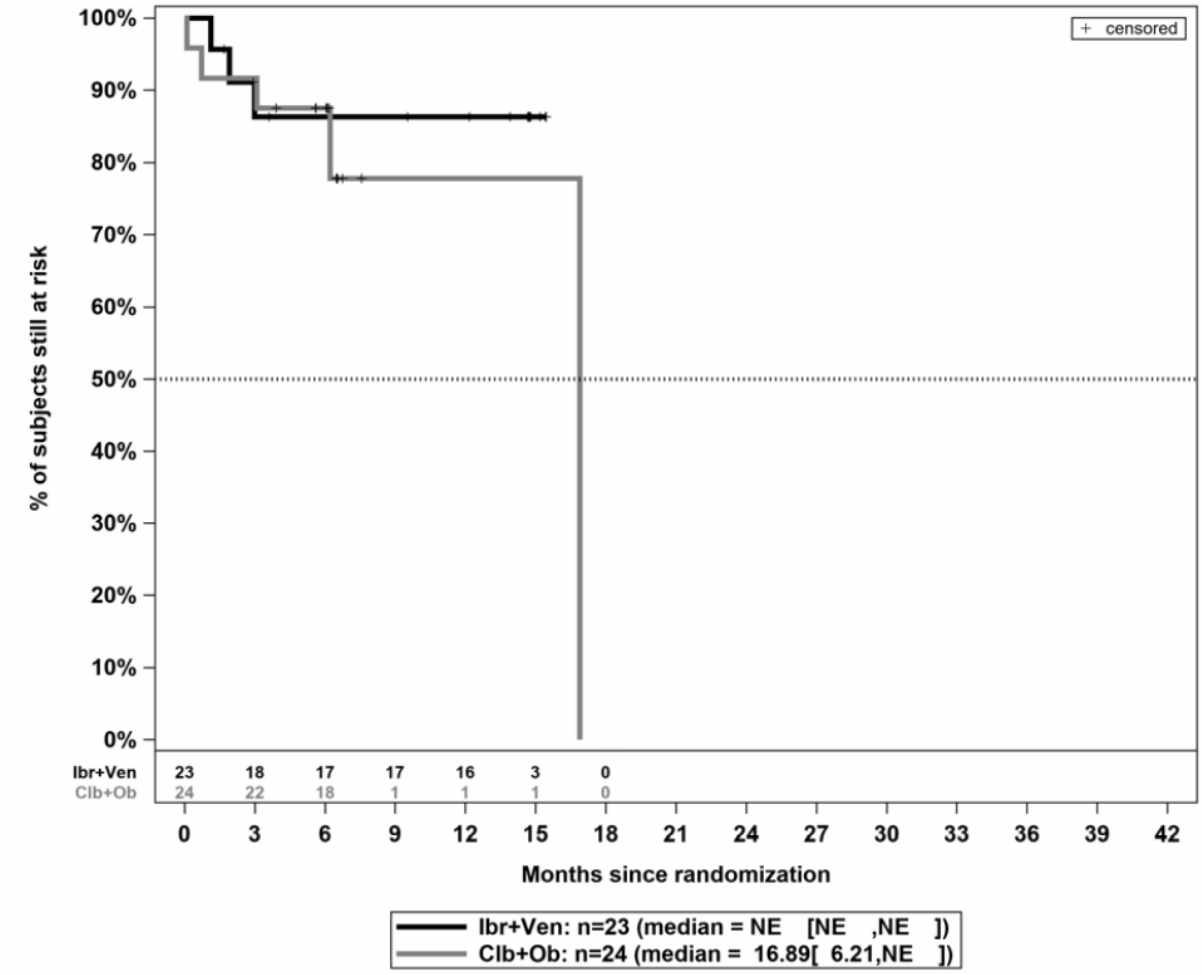

Figure 23: Kaplan-Meier curve, outcome of infections and infestations (severe AEs) – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab, 3rd data cutoff – GLOW study

Appendix B Results on side effects

For the total rates AEs, SAEs and severe AEs (e.g. CTCAE grade ≥ 3), the following tables present events for SOCs and PTs as per Medical Dictionary for Regulatory Activities (MedDRA), each based on the following criteria:

- overall rate of AEs (irrespective of severity): events which occurred in at least 10% of patients in one study arm
- overall rate of severe AEs (e.g. CTCAE grade ≥ 3) and SAEs: events which occurred in at least 5% of patients in 1 study arm
- additionally, for all events irrespective of severity grade: events which occurred in at least 10 patients and in at least 1% of patients in one study arm

For the outcome of discontinuation due to AEs, a complete presentation of all events (SOCs/PTs) that resulted in discontinuation is provided.

Table 11: Common AEs[a] – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab (multipage table)

Study	Patients with event n (%)	
SOC[b] PT[b]	Ibrutinib + venetoclax N = 23	Chlorambucil + obinutuzumab N = 24
GLOW		
Overall AE rate	23 (100)	24 (100)
Gastrointestinal disorders	19 (82.6)	10 (41.7)
Diarrhoea	15 (65.2)	1 (4.2)
Mouth ulceration	6 (26.1)	0 (0)
Nausea	5 (21.7)	9 (37.5)
Dyspepsia	4 (17.4)	0 (0)
Vomiting	4 (17.4)	4 (16.7)
Constipation	2 (8.7)	3 (12.5)
Infections and infestations	17 (73.9)	14 (58.3)
Urinary tract infection	5 (21.7)	2 (8.3)
Conjunctivitis	4 (17.4)	0 (0)
Pharyngitis	3 (13.0)	0 (0)
Upper respiratory tract infection	3 (13.0)	4 (16.7)
Pneumonia	2 (8.7)	3 (12.5)
Nasopharyngitis	1 (4.3)	4 (16.7)
Skin and subcutaneous tissue disorders	16 (69.6)	4 (16.7)
Rash	6 (26.1)	1 (4.2)
Onychoclasis	3 (13.0)	0 (0)
Blood and lymphatic system disorders	15 (65.2)	18 (75.0)
Neutropenia	11 (47.8)	16 (66.7)
Anaemia	4 (17.4)	7 (29.2)
Thrombocytopenia	3 (13.0)	5 (20.8)
General disorders and administration site conditions	13 (56.5)	12 (50.0)
Fatigue	7 (30.4)	1 (4.2)
Oedema peripheral	5 (21.7)	2 (8.3)
Pyrexia	3 (13.0)	7 (29.2)
Metabolism and nutrition disorders	11 (47.8)	8 (33.3)
Decreased appetite	5 (21.7)	3 (12.5)
Hyperphosphataemia	4 (17.4)	0 (0)
Respiratory, thoracic and mediastinal disorders	11 (47.8)	8 (33.3)
Epistaxis	4 (17.4)	1 (4.2)
Cough	3 (13.0)	5 (20.8)
Dyspnoea	3 (13.0)	2 (8.3)

Table 11: Common AEs[a] – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab (multipage table)

Study	Patients with event n (%)	
SOC[b] PT[b]	Ibrutinib + venetoclax N = 23	Chlorambucil + obinutuzumab N = 24
Nervous system disorders	10 (43.5)	5 (20.8)
Headache	3 (13.0)	3 (12.5)
Restless legs syndrome	3 (13.0)	0 (0.0)
Investigations	8 (34.8)	8 (33.3)
Neutrophil count decreased	3 (13.0)	3 (12.5)
Vascular disorders	8 (34.8)	6 (25.0)
Hypertension	3 (13.0)	1 (4.2)
Hypotension	2 (8.7)	4 (16.7)
Cardiac disorders	6 (26.1)	5 (20.8)
Atrial fibrillation	3 (13.0)	0 (0)
Palpitations	3 (13.0)	2 (8.3)
Musculoskeletal and connective tissue disorders	6 (26.1)	7 (29.2)
Arthralgia	4 (17.4)	2 (8.3)
Pain in extremity	2 (8.7)	3 (12.5)
Injury, poisoning and procedural complications	5 (21.7)	8 (33.3)
Infusion-related reaction	0 (0)	8 (33.3)
Ear and labyrinth disorders	4 (17.4)	0 (0)
Eye disorders	3 (13.0)	4 (16.7)
Psychiatric disorders	2 (8.7)	4 (16.7)
Renal and urinary disorders	2 (8.7)	4 (16.7)

a. Events which occurred in ≥ 10% of the patients in at least 1 study arm.
b. MedDRA version 23.0; SOC and PT notation taken without adaptation from the comments provided by the company.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 12: Common SAEs[a] – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Ibrutinib + venetoclax** **N = 23**	**Chlorambucil + obinutuzumab** **N = 24**
GLOW		
Overall SAE rate	10 (43.5)	7 (29.2)
Blood and lymphatic system disorders	3 (13.0)	2 (8.3)
Neutropenia	2 (8.7)	0 (0)
General disorders and administration site conditions	2 (8.7)	1 (4.2)
Infections and infestations	2 (8.7)	5 (20.8)
Pneumonia	1 (4.3)	3 (12.5)
Vascular disorders	2 (8.7)	0 (0)
Cardiac disorders	1 (4.3)	2 (8.3)
Investigations	1 (4.3)	2 (8.3)

a. Events which occurred in ≥ 5% of the patients in at least 1 study arm.
b. MedDRA version 23.0; SOC and PT notation taken without adaptation from the comments provided by the company.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 13: Common severe AEs[a] – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Ibrutinib + venetoclax** **N = 23**	**Chlorambucil + obinutuzumab** **N = 24**
GLOW		
Overall rate of severe AEs (CTCAE grade ≥ 3)	17 (73.9)	19 (79.2)
Blood and lymphatic system disorders	10 (43.5)	17 (70.8)
Neutropenia	9 (39.1)	16 (66.7)
Thrombocytopenia	0 (0)	5 (20.8)
Investigations	4 (17.4)	4 (16.7)
Neutrophil count decreased	3 (13.0)	2 (8.3)
Gastrointestinal disorders	3 (13.0)	0 (0)
Diarrhoea	3 (13.0)	0 (0)
Infections and infestations	3 (13.0)	5 (20.8)
Pneumonia	1 (4.3)	3 (12.5)
Skin and subcutaneous tissue disorders	3 (13.0)	0 (0)
Rash	2 (8.7)	0 (0)
Cardiac disorders	2 (8.7)	2 (8.3)
General disorders and administration site conditions	2 (8.7)	1 (4.2)
Asthenia	2 (8.7)	0 (0)
Vascular disorders	2 (8.7)	1 (4.2)
Hypertension	2 (8.7)	1 (4.2)
Metabolism and nutrition disorders	1 (4.3)	3 (12.5)

a. Events which occurred in ≥ 5% of the patients in at least 1 study arm.
b. MedDRA version 23.0; SOC and PT notation taken without adaptation from the comments provided by the company.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 14: Discontinuation due to AEs – RCT, direct comparison: ibrutinib + venetoclax versus chlorambucil + obinutuzumab

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Ibrutinib + venetoclax** **N = 23**	**Chlorambucil + obinutuzumab** **N = 24**
GLOW		
Total rate of discontinuations due to AEs	4 (17.4)	2 (8.3)
Infections and infestations	2 (8.7)	0 (0)
Pneumonia	1 (4.3)	0 (0)
Pneumonia due to streptococci	1 (4.3)	0 (0)
Cardiac disorders	1 (4.3)	0 (0)
Cardiac failure	1 (4.3)	0 (0)
Nervous system disorders	1 (4.3)	0 (0)
Ischaemic stroke	1 (4.3)	0 (0)
Blood and lymphatic system disorders	0 (0)	1 (4.2)
Neutropenia	0 (0)	1 (4.2)
Injury, poisoning and procedural complications	0 (0)	1 (4.2)
Multiple injuries	0 (0)	1 (4.2)

a. MedDRA version 23.0; SOC and PT notation taken without adaptation from the comments provided by the company.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class