IQWiG Reports – Commission No. A20-76

Venetoclax (chronic lymphocytic leukaemia) –

Addendum to Commission A20-39[1]

Addendum

Commission: A20-76
Version: 1.0
Status: 25 September 2020

[1] Translation of addendum A20-76 *Venetoclax (chronische lymphatische Leukämie) – Addendum zum Auftrag A20-39* (Version 1.0; Status: 25 September 2020). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Venetoclax (chronic lymphocytic leukaemia) – Addendum to Commission A20-39

Commissioning agency
Federal Joint Committee

Commission awarded on
24 August 2020

Internal Commission No.
A20-76

Address of publisher
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Keywords: Venetoclax, Obinutuzumab, Leukemia – Lymphocytic – Chronic – B-Cell, Benefit Assessment, NCT02242942

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List of abbreviations

Abbreviation	Meaning
17p	short arm of chromosome 17
ACT	appropriate comparator therapy
AE	adverse event
CLL	chronic lymphocytic leukaemia
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EQ-5D	European Quality of Life-5 Dimensions
FCR	fludarabine in combination with 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)
MDASI	MD Anderson Symptom Inventory
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model repeated measures
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SOC	System Organ Class
TP53	gene of the tumour suppressor protein p53
VAS	visual analogue scale

1 Background

On 24 August 2020, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A20-39 (Venetoclax – Benefit assessment according to §35a Social Code Book V) [1].

In its dossier [2], the pharmaceutical company (hereinafter referred to as "the company") presented a subpopulation of the CLL14 study for the benefit assessment of venetoclax in combination with obinutuzumab in comparison with the appropriate comparator therapy (ACT) in patients with previously untreated chronic lymphocytic leukaemia (CLL) for whom fludarabine in combination with cyclophosphamide and rituximab (FCR) is not an option (research question 2 of the benefit assessment).

Dossier assessment A20-39 on venetoclax [1] concluded that the data presented for the assessment of the added benefit of venetoclax in combination with obinutuzumab in comparison with the ACT were unsuitable for research question 2. This is due to the fact that it is unclear whether the subpopulation from the CLL14 study analysed by the company was formed correctly. In addition, the administration of the ACT in the CLL14 study deviated from the recommendations of the S3 guideline [3].

The G-BA commissioned IQWiG with the assessment of the data of the CLL14 study presented in the dossier for research question 2 under consideration of the information provided in the commenting procedure [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 Subpopulation analysed by the company

The company used a subpopulation of the randomized controlled trial (RCT) CLL14 on the comparison of venetoclax + obinutuzumab versus chlorambucil + obinutuzumab for answering research question 2. For this purpose, it assigned all included patients (> 65 years) with mutated immunoglobulin heavy-chain variable (IGHV) gene, but without deletion on the short arm of chromosome 17 (17p deletion) or mutation of the gene of the tumour suppressor protein p53 (TP53) to research question 2. It assigned patients with unmutated IGHV gene or 17p deletion or TP53 mutation, regardless of age, to research question 3 (patients for whom chemo-immunotherapy is not an option). A detailed description of the subpopulations can be found in dossier assessment A20-39 [1].

The company's assignment of the patients to research questions 2 and 3, for which it used the IGHV mutation status as a decisive criterion, is not adequate. The subpopulation for research question 2 is therefore unsuitable for deriving a conclusion on the added benefit of venetoclax + obinutuzumab. Even taking into account the information from the comments [4,5] and the oral hearing [6], it remains unclear to what extent a classification of the patients with regard to their suitability for chemo-immunotherapy, largely based on their IGHV mutation status, sufficiently reflects the actual health care setting in Germany. It is clear from the information provided in the comments and at the oral hearing that an unmutated IGHV gene is not the only criterion for the decision against chemo-immunotherapy. Pre-existing conditions, concomitant medication and patient preferences also play an important role in the therapeutic decision. It is possible that chemo-immunotherapy is still a treatment option for some of the patients with unmutated IGHV gene, so that they ought to be assigned to subpopulation 2 (patients unsuitable for FCR).

2.2 Duration of treatment with chlorambucil

As described in dossier assessment A20-39, the chlorambucil treatment administered over a total of 12 cycles in the CLL14 study does not comply with the recommendations of the S3 guideline [3]. However, the information provided in the oral hearing [6] suggests that treatment with chlorambucil over 12 instead of 6 cycles is not unusual in the actual health care setting and can lead to longer response. At the same time, there is an increased risk of myelosuppression. In its comments, the company presented Kaplan-Meier curves on some selected specific adverse events (AEs) for the population of research question 2. At least for severe neutropenia (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3), these show that events continue to occur after the first 6 months (see Figure 19). Information on the incidence of severe neutropenia (CTCAE grade 3 to 4) in the individual treatment phases is only available for the total population of the CLL14 study. In the total population, 34.6% of the patients had severe neutropenia in the first 6 cycles of therapy (chlorambucil + obinutuzumab) and 30.0% of the patients in cycles 7 to 12 (chlorambucil monotherapy). These data confirm that the administration of chlorambucil for more than 6 cycles has effects on the occurrence of AEs.

2.3 Study CLL14

In accordance with the commission, the subpopulation of the CLL14 study [7-12] presented by the company for research question 2 is assessed below. Detailed characteristics of the CLL14 study, including information on the study design and the interventions used, can be found in benefit assessment A20-39 [1].

The subpopulation formed by the company for research question 2 comprises 148 patients (n = 71 in the venetoclax + obinutuzumab arm and n = 77 in the chlorambucil + obinutuzumab arm).

Data cut-offs

A total of 3 data cut-offs were conducted for the CLL14 study (see dossier assessment A20-39). In accordance with the company, the third data cut-off was used for the present assessment.

Planned duration of follow-up observation

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

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

Study **Outcome category** **Outcome**	**Planned follow-up observation**
CLL14	
Mortality	
Overall survival	Until death, at most until 5 years after inclusion of the last patient
Morbidity	
Symptoms (EORTC QLQ-C30, MDASI-CLL, B symptoms[a]) Health status (EQ-5D VAS)	Until disease progression or initiation of another antineoplastic therapy, at most until 5 years after inclusion of the last patient
Health-related quality of life (EORTC QLQ-C30)	Until disease progression or initiation of another antineoplastic therapy, at most until 5 years after inclusion of the last patient
Side effects	
AEs	Until 28 days after the last dose of the study medication
SAEs	Related to the study medication[b]: unlimited Unrelated to the study medication[b]: until disease progression or initiation of another antineoplastic therapy, at most until 5 years after inclusion of the last patient
Severe AEs (CTCAE grade 3–4)	Until 6 months after the last dose of the study medication or until initiation of another antineoplastic therapy
Severe infections (CTCAE grade 3–4)	Until 2 years after the last dose of the study medication or until initiation of another antineoplastic therapy
Secondary tumour	Unlimited

a. Presence of one of the following symptoms: unexplainable weight loss > 10% in ≤ 6 months, night sweat, unexplainable pyrexia > 38°C.
b. At the investigator's discretion.

AE: adverse event; 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: European Quality of Life-5 Dimensions; MDASI-CLL: MD Anderson Symptom Inventory-Chronic Lymphocytic Leukaemia; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Characteristics of the study population

Table 2 shows the characteristics of the patients of the subpopulation formed for research question 2.

Table 2: Characteristics of the study population – RCT, direct comparison: venetoclax + obinutuzumab vs. chlorambucil + obinutuzumab (multipage table)

Study Characteristic Category	**Venetoclax + obinutuzumab N[a] = 71**	**Chlorambucil + obinutuzumab N[a] = 77**
CLL14		
Age [years], mean (SD)	72 (7.17)	71 (7.68)
Sex [F/M], %	39/61	38/62
Family origin, n (%)		
White	61 (85.9)	71 (92.2)
Missing	10 (14.1)	6 (7.8)
Region, n (%)		
USA/Canada/Central America	5 (7.0)	9 (11.7)
Australia/New Zealand/Asia	6 (8.5)	9 (11.7)
Western Europe	36 (50.7)	29 (37.7)
Central/Eastern Europe	20 (28.2)	27 (35.1)
Latin America	4 (5.6)	3 (3.9)
ECOG PS, n (%)		
0	26 (36.6)	40 (51.9)
1	37 (52.1)	24 (31.2)
≥ 2	8 (11.3)	13 (16.9)
Disease duration: time between first diagnosis and randomization [months], mean (SD)		
< 3 years	30 (42.3)	36 (46.8)
≥ 3 years and < 6 years	17 (23.9)	20 (26.0)
≥ 6 years	24 (33.8)	20 (26.0)
Missing	0	1 (1.3)
Binet stage, n (%)		
Stage A	14 (19.7)	20 (26.0)
Stage B	23 (32.4)	21 (27.3)
Stage C	34 (47.9)	36 (46.8)
B symptoms, n (%)[b]		
Overall rate of B symptoms	30 (42.3)	33 (42.9)
Weight loss	9 (12.7)	14 (18.2)
Night sweat	28 (39.4)	31 (40.3)
Pyrexia	4 (5.6)	4 (5.2)
CIRS score, n (%)		
≤ 6	11 (15.5)	16 (20.8)
> 6	60 (84.5)	61 (79.2)
Renal function disorder (creatinine clearance according to Cockroft-Gault), n (%)		
< 70 mL/min	43 (60.6)	43 (55.8)
≥ 70 mL/min	27 (38.0)	34 (44.2)
Missing	1 (1.4)	0

Table 2: Characteristics of the study population – RCT, direct comparison: venetoclax + obinutuzumab vs. chlorambucil + obinutuzumab (multipage table)

Study Characteristic Category	Venetoclax + obinutuzumab N[a] = 71	Chlorambucil + obinutuzumab N[a] = 77
Cytogenetic anomalies, n (%)		
11q deletion	4 (5.6)	7 (9.1)
13q deletion	39 (53.9)	32 (41.6)
17p deletion	0	0
No 17p/11q deletion	12 (16.9)	18 (23.4)
Trisomy 12/13q deletion		
Trisomy 12	8 (11.3)	12 (15.6)
Missing	8 (11.3)	8 (10.4)
IGHV mutated, n (%)	71 (100.0)	77 (100.0)
TP53 unmutated, n (%)	71 (100.0)	77 (100.0)
Treatment discontinuation[c], n (%)	9 (13.9)	7 (10.5)
Study discontinuation, n (%)	9 (12.7)	9 (11.7)

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Patients can have several symptoms at the same time.
c. Discontinuation of both treatments.

11q: long arm of chromosome 11; 13q: long arm of chromosome 13; 17p: short arm of chromosome 17; CIRS: Cumulative Illness Rating Scale; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; IGHV: immunoglobulin heavy-chain variable; M: male; min: minutes; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; TP53: gene of the tumour suppressor protein 53; vs.: versus

The patient characteristics between both treatment arms of the subpopulation study are largely comparable. The mean age of the patients was between 71 and 72 years. The proportion of men was just above 60%. The majority of the patients were from Europe (> 75%). About 80% had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of ≤ 1, showing an imbalance between the treatment arms: 36.6% of the patients in the intervention arm and 51.9% of the patients in the control arm had an ECOG PS of 0. 52.1% of the patients in the intervention arm had an ECOG PS of 1, whereas in the control arm this was the case in 31.2%. At the start of the study, 47% of the patients were in Binet stage C. All patients in this subpopulation had a mutated IGHV gene. Furthermore, the patients had no 17p deletion or TP53 mutation.

Treatment duration and observation period

Table 3 shows the mean and median treatment duration of the patients as well as the mean and median observation period for individual outcomes.

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

Study **Duration of the study phase** **Outcome category**	**Venetoclax + obinutuzumab** **N = 71**	**Chlorambucil + obinutuzumab** **N = 77**
CLL14		
Treatment duration [months]		
Median [min; max]	11.2 [0.03; 14.0]	10.7 [0.03; 12.98]
Mean (SD)	10.1 (3.3)	9.9 (3.0)
Observation period [months]		
Overall survival		
Median [min; max]	40.3 [0.03; 47.1]	40.6 [4.5; 47.2]
Mean (SD)	38.4 (9.4)	39.1 (8.8)
Morbidity		
Symptoms (EORTC QLQ-C30)		
Median [min; max]	35.7 [1.15; 45.8]	35.6 [0.99; 47.2]
Mean (SD)	33.6 (11.5)	33.1 (10.6)
Symptom severity (MDASI total symptom severity)		
Median [min; max]	35.7 [1.15; 45.8]	35.7 [0.99; 47.2]
Mean (SD)	33.5 (11.7)	33.4 (10.4)
Impact of symptoms on daily functioning (MDASI symptom interference)		
Median [min; max]	35.7 [1.15; 45.8]	35.7 [0.99; 47.2]
Mean (SD)	33.5 (11.7)	33.4 (10.4)
B symptoms[a]		
Median [min; max]	36.2 [0.00; 46.9]	36.4 [0.0; 47.2]
Mean (SD)	33.9 (11.9)	32.6 (12.3)
Health status (EQ-5D VAS)		
Median [min; max]	35.7 [1.15; 45.8]	35.6 [0.99; 47.2]
Mean (SD)	33.7 (11.7)	32.9 (10.7)
Health-related quality of life (EORTC QLQ-C3)		
Median [min; max]	35.7 [1.15; 45.8]	35.6 [0.99; 47.2]
Mean (SD)	33.6 (11.5)	33.1 (10.6)
Side effects		
Median [min; max]	12.1 [0.95; 14.9]	11.6 [0.95; 13.9]
Mean (SD)	11.0 (3.3)	10.8 (3.0)

a. Presence of one of the following symptoms: unexplainable weight loss > 10% in ≤ 6 months, night sweat, unexplainable pyrexia > 38°C.

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; max: maximum; MDASI: MD Anderson Symptom Inventory; min: minimum; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

In the subpopulation for research question 2 of the CLL14 study, there are no relevant differences between the treatment arms in the median and mean treatment duration and the median observation period at outcome level.

Subsequent therapies

The study protocol did not specify the subsequent therapies after completion of the study medication. Switching from the control arm to treatment with venetoclax was not planned in the study. Appendix A presents a list of the subsequent therapies received. Overall, 5 patients in the intervention arm and 7 patients in the control arm had received a first subsequent therapy until the data cut-off from 23 August 2019. The most common subsequent therapy administered was ibrutinib.

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: venetoclax + obinutuzumab vs. chlorambucil + obinutuzumab

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
CLL14	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias across outcomes was rated as low for the CLL14 study. This concurs with the company's assessment. Restrictions resulting from the open-label study design and the observation periods deviating from the study protocol are described in Section 2.3.1.

2.3.1 Results

Outcomes included

In accordance with the G-BA's commission, the results of the subpopulation for research question 2 of the CLL14 study are presented. The following patient-relevant outcomes were to be considered in the assessment:

- Mortality
  - overall survival
- Morbidity
  - symptoms measured with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) symptom scales
  - symptoms measured with the MD Anderson Symptom Inventory (MDASI)
    - symptom severity (MDASI total symptom severity)
    - impact of symptoms on daily functioning (MDASI symptom interference)
  - B symptoms
  - health status measured with the European Quality of Life-5 Dimensions (EQ-5D) visual analogue scale (VAS)
- Health-related quality of life
  - health-related quality of life measured with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) functional scales
- Side effects
  - serious adverse events (SAEs)
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs (at least one drug component)
  - if applicable, further specific AEs

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 for which outcomes data were available in the study included.

Table 5: Matrix of outcomes – RCT, direct comparison: venetoclax + obinutuzumab vs. chlorambucil + obinutuzumab

Study	Outcomes										
	Overall survival	Symptom severity (MDASI total symptom severity)	Impact of symptoms on daily functioning (MDASI symptom interference)	Symptoms (EORTC QLQ-C30)	B symptoms[a]	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs (CTCAE grade ≥ 3)	Discontinuation due to AEs	Further specific AEs[c]
CLL14	Yes	Yes	Yes	Yes	No[b]	Yes	Yes	Yes	Yes	Yes	Yes

a. Presence of one of the following symptoms: unexplainable weight loss > 10% in ≤ 6 months, night sweat, unexplainable pyrexia > 38°C.
b. The data presented do not allow any conclusion on the total subpopulation.
c. The following events are considered (MedDRA coding): respiratory, thoracic and mediastinal disorders (SOC, SAE).

AE: adverse event; 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: European Quality of Life-5 Dimensions; MDASI: MD Anderson Symptom Inventory; MedDRA: Medical Dictionary for Regulatory Activities; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

The company presented responder analyses for the time to deterioration and the time to improvement by 0.98 points for the outcomes "symptom severity" and "impact of symptoms on daily functioning" using the MDASI. It additionally calculated the time to improvement or deterioration by 1.21 points as sensitivity analyses. The response criteria used are not sufficiently validated and were therefore not used for the assessment. The continuous analyses on the basis of a mixed-effects model repeated measures (MMRM) were used instead. Furthermore, the company presented results from the additional module MDASI-CLL. This instrument is not sufficiently validated. The company also did not present any studies for the validation of this instrument. The additional module MDASI-CLL was therefore not used for the assessment.

The company presented analyses on B symptoms as supplementary information in its dossier, but did not use them for the derivation of an added benefit. B symptoms (unexplainable weight loss > 10% in ≤ 6 months, night sweat, unexplainable pyrexia > 38°C) are CLL symptoms directly perceived by the patients. They are therefore patient-relevant by definition. For the presented analyses, the company divided the subpopulation into patients with B symptoms at baseline and without B symptoms at baseline. Patients without B symptoms were operationalized using the time to first occurrence of B symptoms. Patients with B symptoms at baseline were operationalized using the time to absence of B symptoms, and subsequently using the time to recurrence of B symptoms. Due to the different operationalizations, these analyses

do not allow any conclusion on the total subpopulation. The results are therefore presented only as supplementary information in Appendix E.

It is not clear from the data presented why a large proportion of patients were censored for the outcomes "SAEs" and "severe AEs (CTCAE grade ≥ 3)" 28 days after the end of treatment and thus after month 13 (see Kaplan-Meier curves in Appendix B), although longer observation periods were predefined in the study protocol (see Table 1). The censorings can be explained neither by disease progression nor by initiation of subsequent therapy. The company did not present any justification for these censorings. Regardless of this, the available data, which essentially reflect the period of treatment, were used for the assessment, but the uncertainty was taken into account in the assessment of the risk of bias.

Despite comparable median treatment durations and observation periods in the intervention and comparator arm, it cannot be ruled out with certainty that the individual treatment durations and observation periods differed between the patients. Deviating from the company, instead of the relative risk, the hazard ratio was therefore used for the effect estimation for all AE outcomes.

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: venetoclax + obinutuzumab vs. chlorambucil + obinutuzumab

Study	Study level	Outcomes										
		Overall survival	Symptoms (EORTC QLQ-C30)	Symptom severity (MDASI total symptom severity)	Impact of symptoms on daily functioning (MDASI symptom interference)	B symptoms[a]	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs (CTCAE grade ≥ 3)	Discontinuation due to AEs	Further specific AEs[b]
CLL14	L	L	H[c]	H[c]	H[c]	–[d]	H[c]	H[c]	H[c]	H[c]	H[c]	H[c]

a. Presence of one of the following symptoms: unexplainable weight loss > 10% in ≤ 6 months, night sweat, unexplainable pyrexia > 38°C.
b. The following events are considered (MedDRA coding): respiratory, thoracic and mediastinal disorders (SOC, SAE).
c. Lack of blinding in subjective recording of outcomes.
d. No usable data.
e. Incomplete observations for potentially informative reasons with unclear follow-up observations.

AE: adverse event; 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: European Quality of Life-5 Dimensions; H: high; L: low; MDASI: MD Anderson Symptom Inventory; MedDRA: Medical Dictionary for Regulatory Activities; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

There was a low risk of bias for the results on the outcome "mortality". Due to the open-label study design, there was a high risk of bias for all outcomes of the categories of symptoms, health-related quality of life and discontinuation due to AEs.

Due to the incomplete observations for potentially informative reasons with unclear follow-up observation periods and missing information on the censorings described above, the risk of bias of SAEs and severe AEs was rated as high.

The assessment of the risk of bias concurs with that of the company.

Results

Table 7 and Table 8 summarize the results of the comparison of venetoclax + obinutuzumab with the ACT chlorambucil + obinutuzumab in patients with previously untreated CLL and comorbidities for whom treatment with FCR is not an option.

Kaplan-Meier curves on the event time analyses of the outcomes included are presented in Appendix B. Results on common AEs, SAEs and severe AEs (CTCAE grade ≥ 3) are presented in Appendix B. For discontinuations due to AEs, no data separated by System Organ Classes (SOCs) and Preferred Terms (PTs) are available. The responder analyses of the EQ-5D VAS and the B symptoms are presented as supplementary information in Appendix D and Appendix E.

Table 7: Results (mortality, morbidity, health-related quality of life, time to event) – RCT, direct comparison: venetoclax + obinutuzumab vs. chlorambucil + obinutuzumab (multipage table)

Study **Outcome category** **Outcome**	**Venetoclax + obinutuzumab**		**Chlorambucil + obinutuzumab**		**Venetoclax + obinutuzumab 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][a]; p-value[b]**
CLL14					
Mortality					
Overall survival	71	NA 7 (9.9)[c]	77	NA 4 (5.2)	2.20 [0.63; 7.67]; 0.207
Morbidity					
EORTC QLQ-C30 – symptom scales[d]					
Fatigue	67	7.4 [3.8; 20.4] 41 (61.2)	73	7.5 [3.0; 26.3] 44 (60.3)	0.90 [0.57; 1.43]; 0.655
Nausea and vomiting	67	NA [9.0; NC] 30 (44.8)	73	NA [34.9; NC] 27 (37.0)	1.16 [0.67; 2.00]; 0.599
Pain	67	10.3 [4.8; 17.2] 43 (64.2)	73	9.3 [4.7; 23.2] 46 (63.0)	1.09 [0.69; 1.71]; 0.717
Dyspnoea	67	NA [25.6; NC] 28 (41.8)	73	25.2 [13.1; NC] 36 (49.3)	0.71 [0.42; 1.20]; 0.190
Insomnia	67	12.6 [4.7; NC] 37 (55.2)	73	NA [9.5; NC] 34 (46.6)	1.38 [0.84; 2.26]; 0.203
Appetite loss	67	24.3 [10.6; NC] 32 (47.8)	73	NA [40.5; NC] 25 (34.2)	1.53 [0.86; 2.70]; 0.145
Constipation	67	22.6 [5.7; NC] 36 (53.7)	73	NA [19.8; NC] 30 (41.1)	1.21 [0.73; 2.02]; 0.453
Diarrhoea	67	21.2 [7.5; NC] 35 (52.2)	73	NA [31.3; NC] 26 (35.6)	1.65 [0.95; 2.86]; 0.071

Table 7: Results (mortality, morbidity, health-related quality of life, time to event) – RCT, direct comparison: venetoclax + obinutuzumab vs. chlorambucil + obinutuzumab (multipage table)

Study Outcome category Outcome	Venetoclax + obinutuzumab		Chlorambucil + obinutuzumab		Venetoclax + obinutuzumab 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][a]; p-value[b]
Health-related quality of life					
EORTC QLQ-C30 – functional scales[d]					
Global health status	67	7.1 [4.9; 35.0] 42 (62.7)	73	7.8 [4.4; NC] 42 (57.5)	0.99 [0.63; 1.57]; 0.987
Physical functioning	67	18.2 [5.6; NC] 36 (53.7)	73	NA [23.0; NC] 32 (43.8)	1.24 [0.74; 2.05]; 0.410
Role functioning	67	11.6 [3.6; 35.2] 40 (59.7)	73	18.5 [7.5; NC] 41 (56.2)	1.08 [0.68; 1.71]; 0.742
Cognitive functioning	67	9.7 [5.7; 29.2] 40 (59.7)	73	12.2 [3.9; NC] 41 (56.2)	1.07 [0.66; 1.72]; 0.786
Emotional functioning	67	NA [9.0; NC] 31 (46.3)	73	NA [23.8; NC] 27 (37.0)	1.47 [0.84; 2.58]; 0.174
Social functioning	67	4.9 [3.7; 26.0] 41 (61.2)	73	9.4 [4.8; 36.4] 42 (57.5)	1.09 [0.69; 1.73]; 0.698
Side effects					
AEs (supplementary information)	70	0.0 [NC; NC] 68 (97.1)	77	0.0 [NC; NC] 77 (100)	–
SAEs	70	15.9 [13.4; 19.3] 34 (48.6)	77	23.4 [14.8; 32.1] 31 (40.3)	1.10 [0.67; 1.83]; 0.673
Severe AEs (CTCAE grade ≥ 3)	70	1.0 [0.3; 2.6] 57 (81.4)	77	1.3 [0.2; 5.6] 59 (76.6)	1.15 [0.79; 1.66]; 0.428
Discontinuation due to AEs[e]	70	NA [NC; NC] 10 (14.3)	77	NA [NC; NC] 12 (15.6)	0.943 [0.41; 2.18]; 0.891
Specific AEs					
Respiratory, thoracic and mediastinal disorders (SOC, SAEs)		17.9 (17.9; 19.3) 7 (10.0)		37.7 [NC; NC] 1 (1.3)	–[f]; 0.008

Table 7: Results (mortality, morbidity, health-related quality of life, time to event) – RCT, direct comparison: venetoclax + obinutuzumab vs. chlorambucil + obinutuzumab (multipage table)

Study **Outcome category** **Outcome**	**Venetoclax + obinutuzumab**		**Chlorambucil + obinutuzumab**		**Venetoclax + obinutuzumab 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][a]; p-value[b]**
a. HR and CI: Cox proportional hazards model with treatment as covariable, stratified by Binet stage and geographical region. b. p-value: log-rank test stratified by Binet stage and geographical region. c. According to the company, there were contradictory data for one patient: According to overall survival and death data, the patient had not died; the reason for study discontinuation provided in the data on disposition was "death". d. Time to deterioration, defined as an increase in score by ≥ 10 points (for the symptom scales) or a decrease in score by ≥ 10 points (for the functional scales) in comparison with baseline. e. Discontinuation of at least one drug component. f. No presentation of effect estimation and CI, as these are not informative. 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; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus					

Table 8: Results (morbidity, continuous) – RCT, direct comparison: venetoclax + obinutuzumab vs. chlorambucil + obinutuzumab

Study Outcome category Outcome	Venetoclax + obinutuzumab			Chlorambucil + obinutuzumab			Venetoclax + obinutuzumab vs. chlorambucil + obinutuzumab
	N[a]	Values at baseline mean (SD)	Change[b] mean[c] (SE)	N[a]	Values at baseline mean (SD)	Change[b] mean[c] (SE)	MD [95% CI]; p-value[c]
CLL14							
Morbidity							
Symptom severity							
MDASI total symptom severity[d]	68	1.92 (1.79)	−0.51 (0.14)	72	1.31 (1.16)	−0.59 (0.13)	0.08 [−0.24; 0.40]; 0.622
Impact of symptoms on daily functioning							
MDASI symptom interference[d]	67	2.28 (2.39)	−0.71 (0.21)	72	1.84 (2.44)	−1.08 (0.19)	0.37 [−0.11; 0.86]; 0.133
Health status							
EQ-5D VAS[e]	64	64.80 (24.69)	6.14 (1.84)	70	69.68 (20.71)	9.92 (1.69)	−3.78 [−8.06; 0.51]; 0.084

a. Number of patients considered in the analysis for the calculation of the effect estimation; the values at the start of the study (possibly at other time points) may be based on other patient numbers.
b. Averaged over the total study period including follow-up.
c. MD, CI and p-value: mixed-effects model repeated measures (MMRM) with terms for Binet stage, region, treatment group, visit and interaction between treatment and visit.
d. Higher values on the scale correspond to greater symptom severity or impairment; a negative group difference means an advantage of venetoclax + obinutuzumab.
e. Higher values on the scale correspond to a better health status; a positive group difference means an advantage of venetoclax + obinutuzumab.

CI: confidence interval; EQ-5D VAS: European Quality of Life-5 Dimensions visual analogue scale; MD: mean difference; MDASI: MD Anderson Symptom Inventory; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; vs.: versus

Mortality

Overall survival

No statistically significant difference between the treatment groups was shown for the outcome "overall survival".

Morbidity

Symptoms (EORTC QLQ-C30 symptom scales, time to deterioration by at least 10 points on the respective scale)

No statistically significant differences between the treatment groups were shown for the EORTC QLQ-C30 symptom scales.

Symptom severity (total symptom severity) and impact of symptoms on daily functioning (symptom interference) using the MDASI (mean change from baseline)

No significant difference between the treatment groups was shown for symptom severity or for impact of symptoms on daily functioning recorded using the MDASI.

Health status using the EQ-5D VAS (mean change from baseline)

There was no statistically significant difference between the treatment groups for the outcome "health status" recorded with the EQ-5D VAS.

Health-related quality of life

EORTC QLQ-C30 (functional scales, time to deterioration by at least 10 points on the respective scale)

No statistically significant differences between the treatment groups were shown for the EORTC QLQ-C30 functional scales.

Side effects

No statistically significant differences between the treatment groups were shown for the outcomes "SAEs", "severe AEs (CTCAE grade ≥ 3)" and "discontinuation due to AEs" (at least one drug component). A statistically significant difference to the disadvantage of venetoclax + obinutuzumab was shown in the serious respiratory, thoracic and mediastinal disorders (SOC, SAE), however.

Overall conclusion on advantages and disadvantages

In the overall consideration, there is no advantage of venetoclax + obinutuzumab in comparison with the ACT chlorambucil + obinutuzumab; a disadvantage of venetoclax + obinutuzumab was shown in serious respiratory, thoracic and mediastinal disorders (SOC, SAE).

2.4 Summary

Based on the data presented by the company in the dossier and in its comments, there is no advantage of venetoclax + obinutuzumab in comparison with the ACT for any of the research questions. The conclusion on the added benefit of venetoclax + obinutuzumab from dossier assessment A20-39 is not changed by the present addendum.

It is still unclear to what extent the formation of the subpopulations mainly by IGHV mutation status represents the actual health care setting in Germany. It is also questionable how the prolonged administration of chlorambucil affects benefit and harm outcomes. The presented data of the CLL14 study are therefore unsuitable to derive an added benefit of venetoclax + obinutuzumab in comparison with the ACT.

The following Table 9 shows the result of the benefit assessment of venetoclax in combination with obinutuzumab under consideration of dossier assessment A20-39 and the present addendum.

Table 9: Venetoclax + obinutuzumab – probability and extent of added benefit

Research question	**Subindication**[a]	**ACT**[b]	**Probability and extent of added benefit**
1	Adult patients with previously untreated CLL for whom treatment with FCR is an option	FCR	Added benefit not proven
2	Adult patients with previously untreated CLL for whom treatment with FCR is not an option	Bendamustine in combination with rituximab or **chlorambucil in combination** with rituximab or **obinutuzumab**	Added benefit not proven
3	Adult patients with previously untreated CLL with 17p deletion and/or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons	Ibrutinib	Added benefit not proven

a. It is assumed for the present therapeutic indication that the patients require treatment. Moreover, it is assumed that allogeneic stem cell transplantation is not indicated at the time point of treatment.
b. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.

17p: short arm of chromosome 17; ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; FCR: fludarabine in combination with cyclophosphamide and rituximab; G-BA: Federal Joint Committee; TP53: gene of the tumour suppressor protein p53

The G-BA decides on the added benefit.

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Appendix A – Supplementary presentation of the subsequent systemic therapies in the CLL14 study, FCR therapy unsuitable

Table 10: Information on subsequent antineoplastic therapies[a] – RCT, direct comparison: venetoclax + obinutuzumab vs. chlorambucil + obinutuzumab

Study Drug	Patients with subsequent therapy n (%)	
	Venetoclax + obinutuzumab N = 71	Chlorambucil + obinutuzumab N = 77
CLL14		
Total	5 (7.0)	7 (9.1)
R-CHOP	1 (1.4)	1 (1.3)
Rituximab, cyclophosphamide, dexamethasone	1 (1.4)	0
Bendamustine, rituximab	2 (2.8)	1 (1.3)
Ibrutinib	1 (1.4)	4 (5.2)
Venetoclax	0	1 (1.3)

a. The first subsequent therapy is presented.

n: number of patients with subsequent therapy; N: number of analysed patients; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RCT: randomized controlled trial; vs.: versus

Appendix B – Kaplan-Meier curves on results of the CLL14 study, FCR therapy unsuitable

Mortality

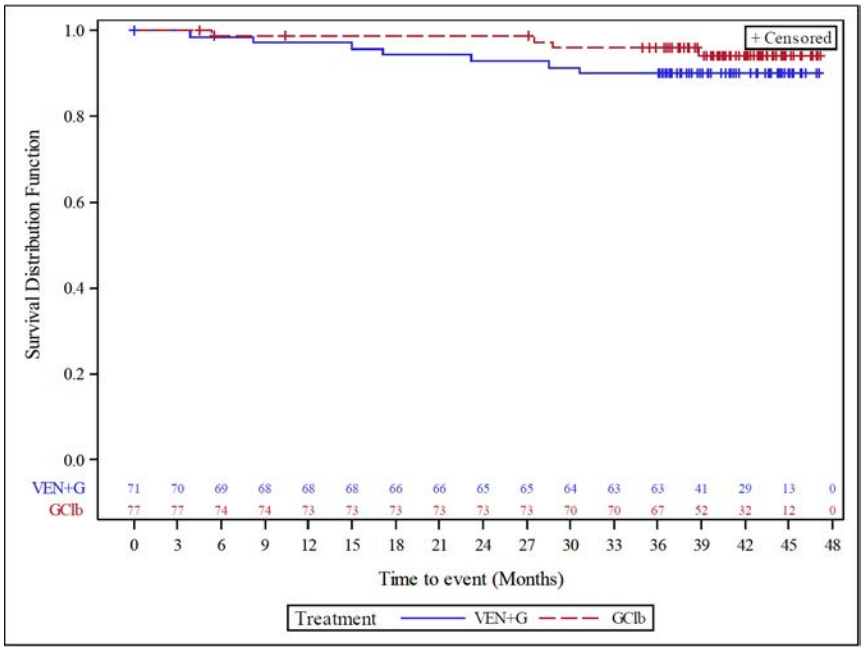

Figure 1: Kaplan-Meier curve on overall survival

Morbidity

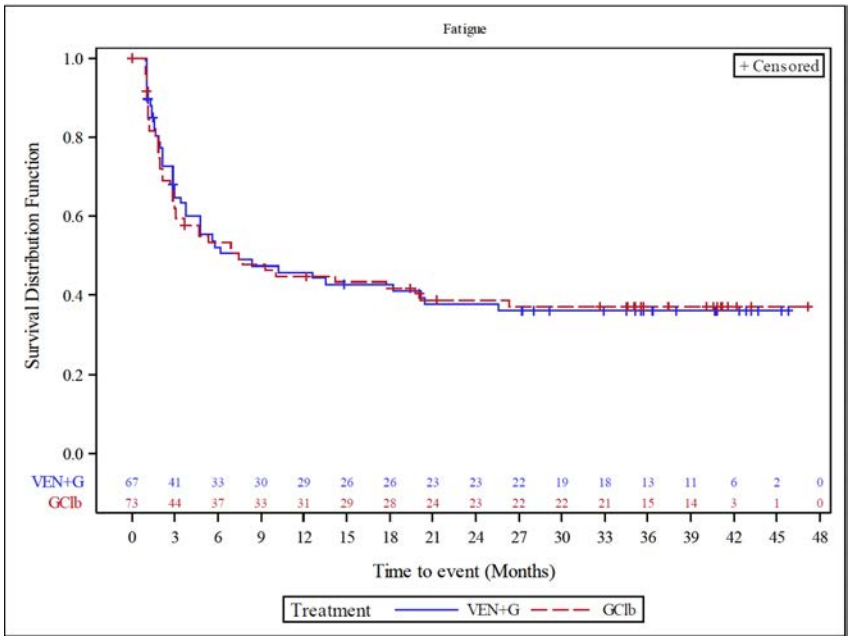

Figure 2: Kaplan-Meier curve on symptoms, outcome “fatigue” (EORTC QLQ-C30, deterioration by ≥ 10 points)

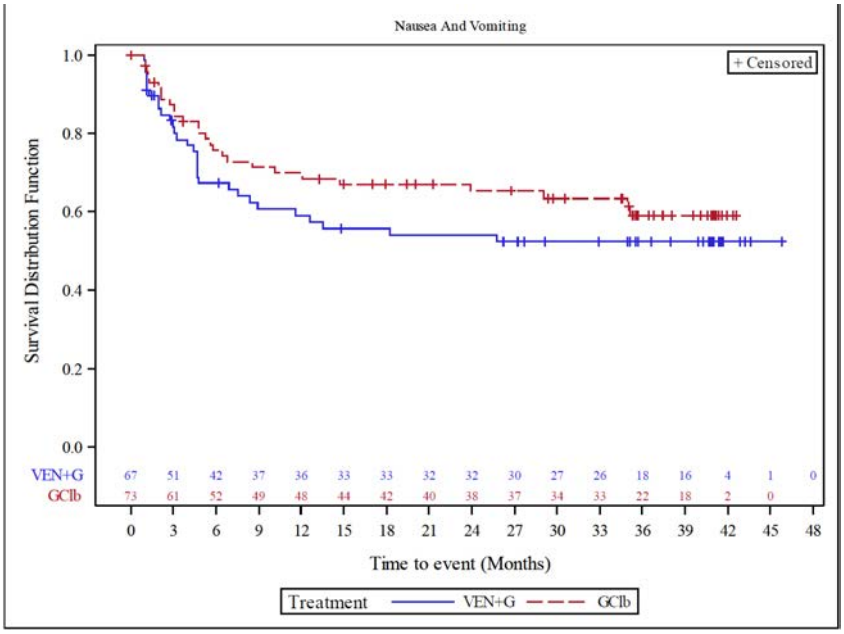

Figure 3: Kaplan-Meier curve on symptoms, outcome "nausea and vomiting" (EORTC QLQ-C30, deterioration by ≥ 10 points)

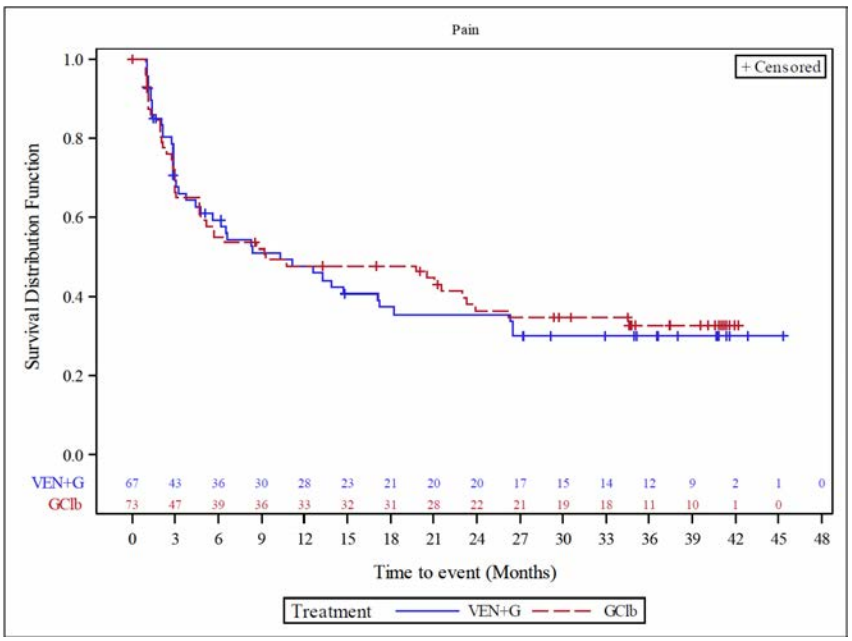

Figure 4: Kaplan-Meier curve on symptoms, outcome "pain" (EORTC QLQ-C30, deterioration by ≥ 10 points)

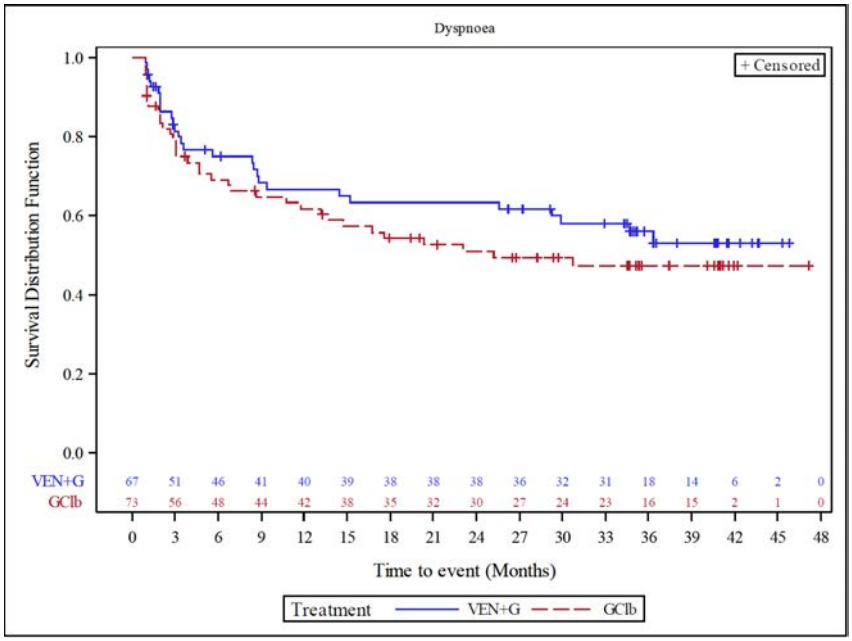

Figure 5: Kaplan-Meier curve on symptoms, outcome "dyspnoea" (EORTC QLQ-C30, deterioration by ≥ 10 points)

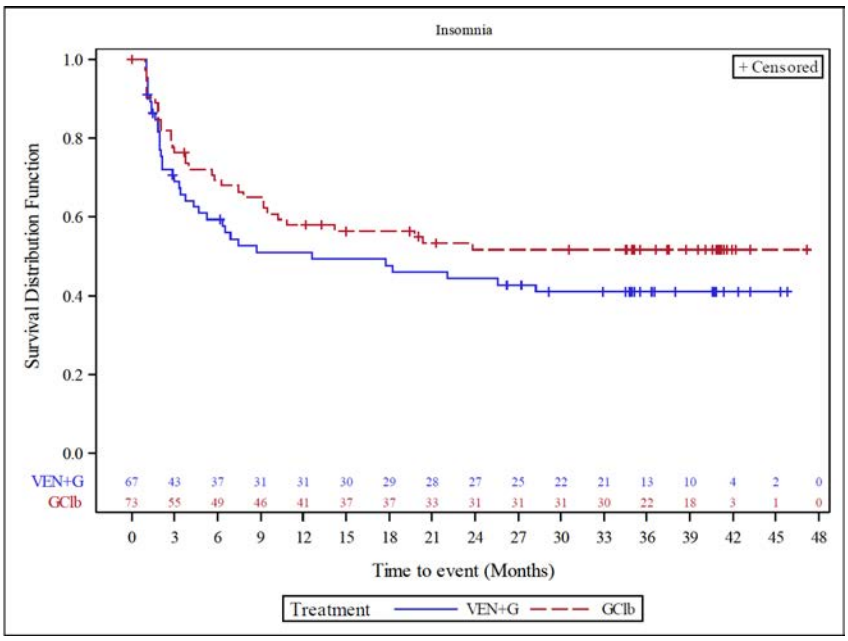

Figure 6: Kaplan-Meier curve on symptoms, outcome "insomnia" (EORTC QLQ-C30, deterioration by ≥ 10 points)

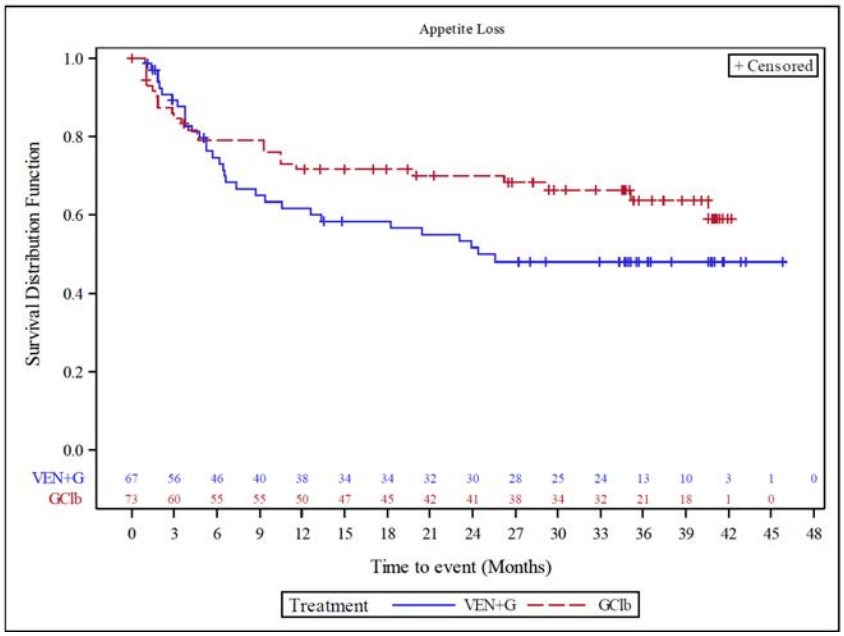

Figure 7: Kaplan-Meier curve on symptoms, outcome "appetite loss" (EORTC QLQ-C30, deterioration by ≥ 10 points)

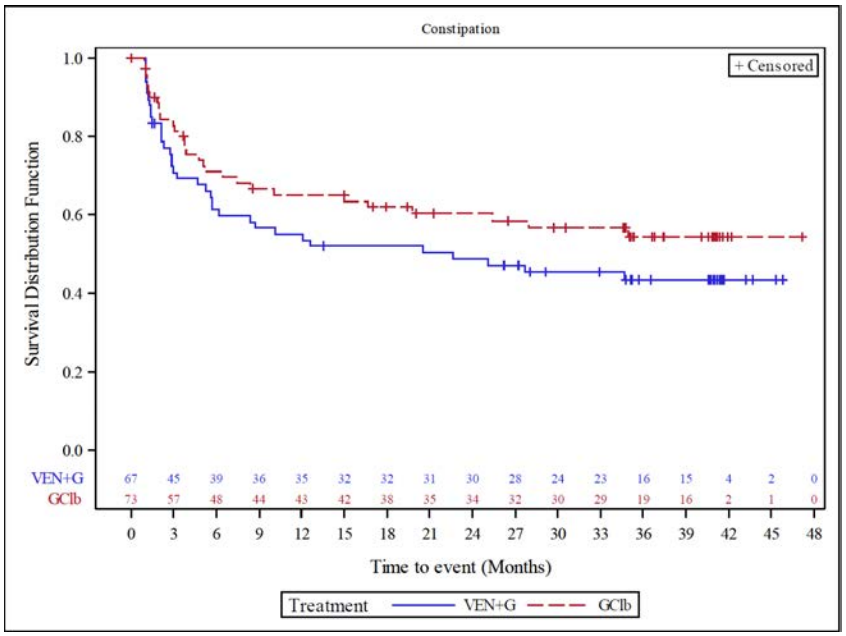

Figure 8: Kaplan-Meier curve on symptoms, outcome "constipation" (EORTC QLQ-C30, deterioration by ≥ 10 points)

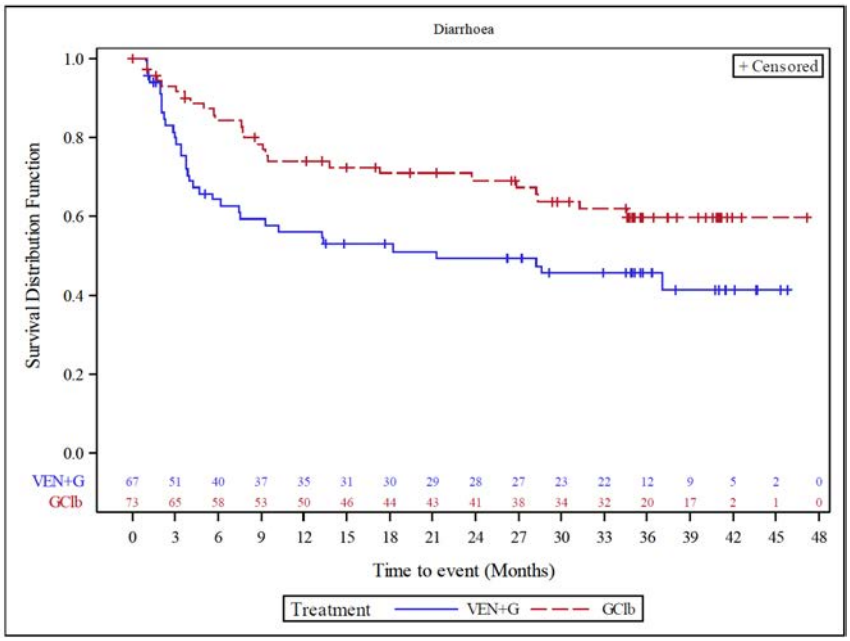

Figure 9: Kaplan-Meier curve on symptoms, outcome “diarrhoea” (EORTC QLQ-C30, deterioration by ≥ 10 points)

Health-related quality of life

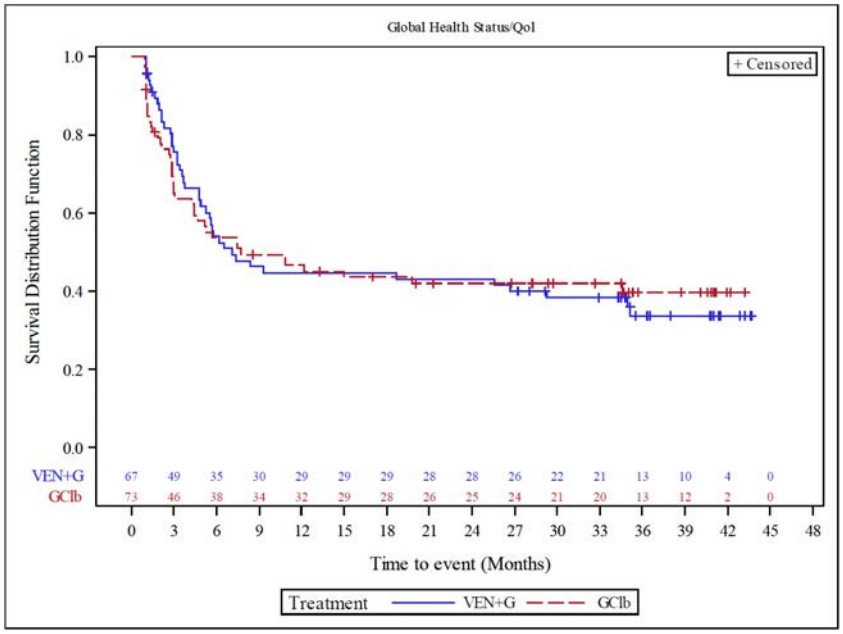

Figure 10: Kaplan-Meier curve on health-related quality of life, outcome "global health status" (EORTC QLQ-C30, deterioration by ≥ 10 points)

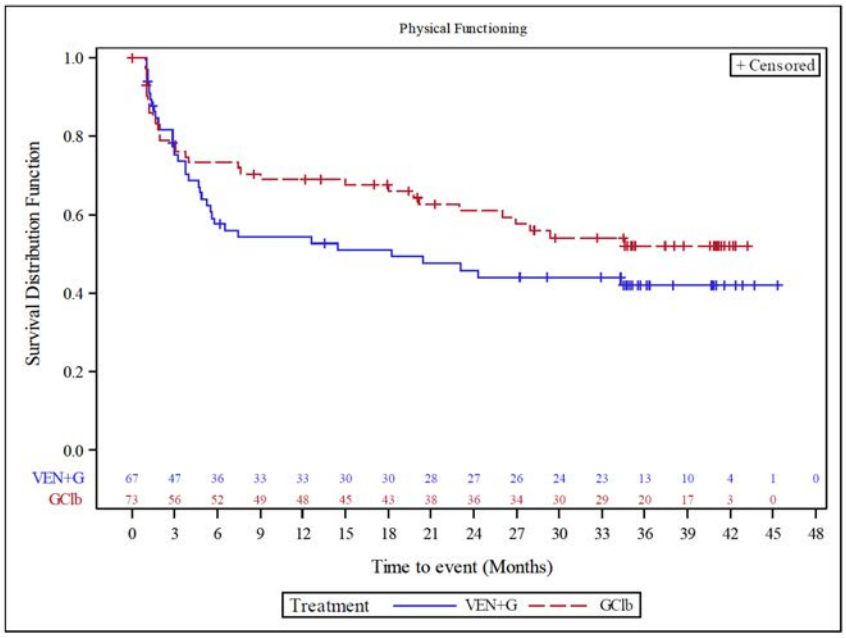

Figure 11: Kaplan-Meier curve on health-related quality of life, outcome "physical functioning" (EORTC QLQ-C30, deterioration by ≥ 10 points)

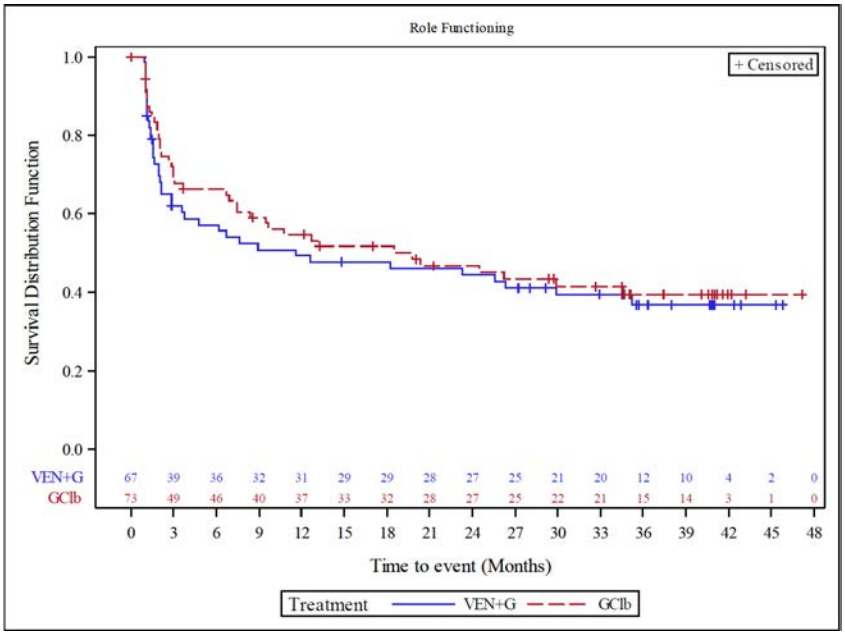

Figure 12: Kaplan-Meier curve on health-related quality of life, outcome "role functioning" (EORTC QLQ-C30, deterioration by ≥ 10 points)

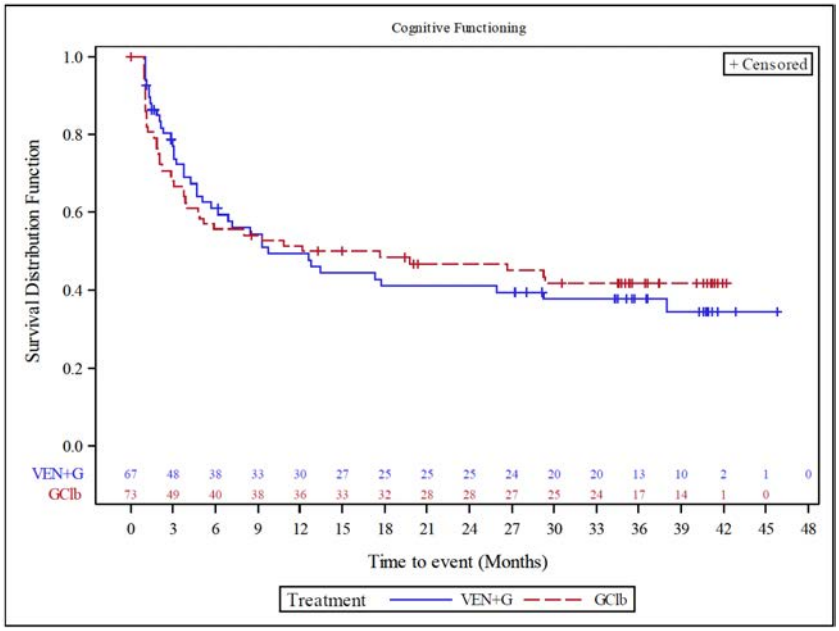

Figure 13: Kaplan-Meier curve on health-related quality of life, outcome "cognitive functioning" (EORTC QLQ-C30, deterioration by ≥ 10 points)

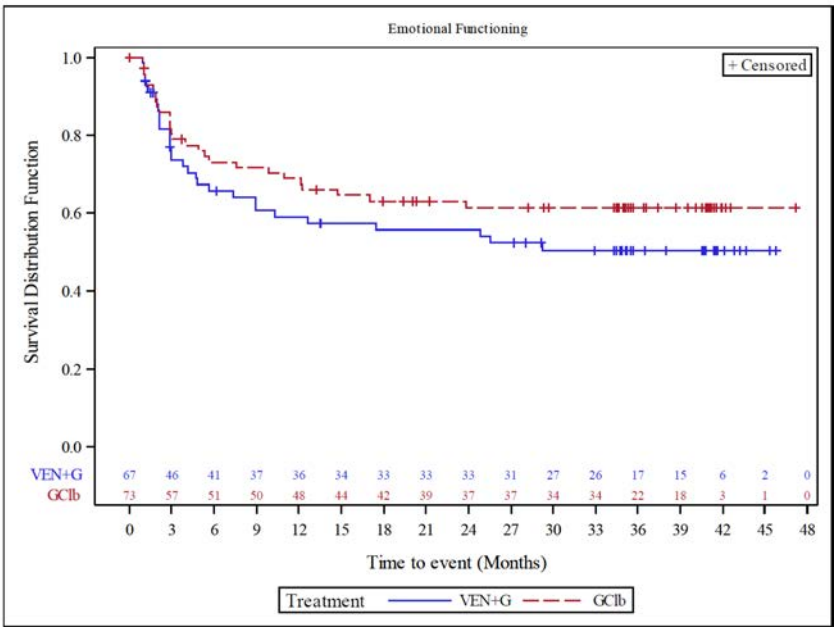

Figure 14: Kaplan-Meier curve on health-related quality of life, outcome "emotional functioning" (EORTC QLQ-C30, deterioration by ≥ 10 points)

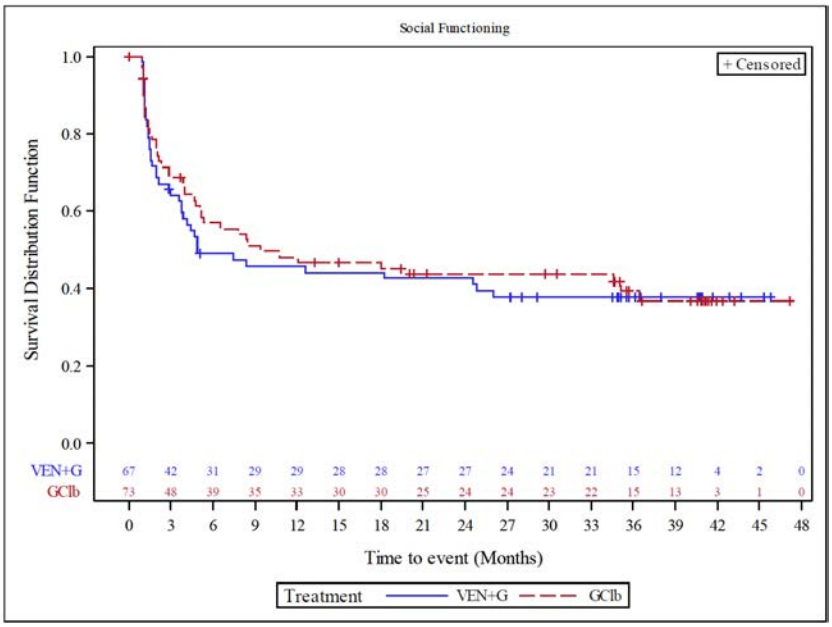

Figure 15: Kaplan-Meier curve on health-related quality of life, outcome "social functioning" (EORTC QLQ-C30, deterioration by ≥ 10 points)

Adverse events

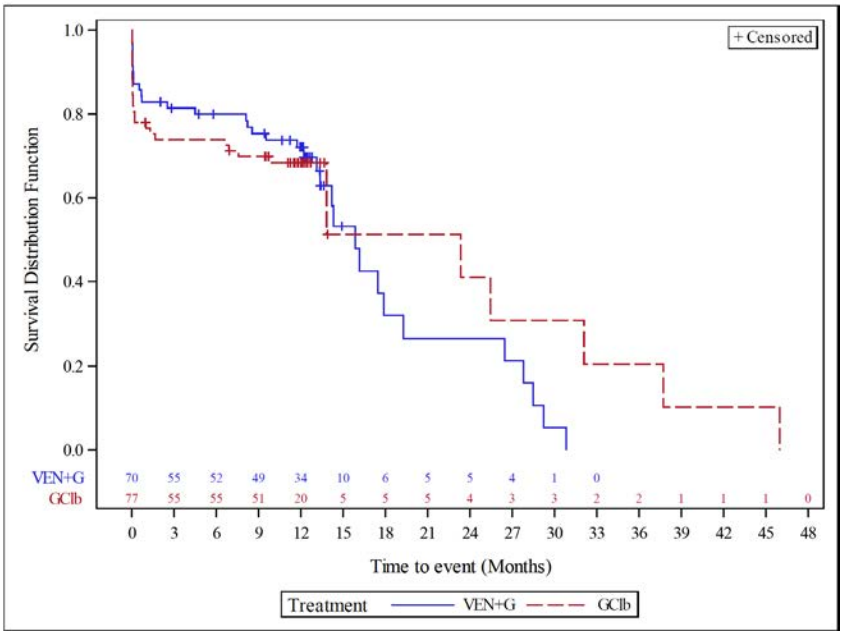

Figure 16: Kaplan-Meier curve on SAEs

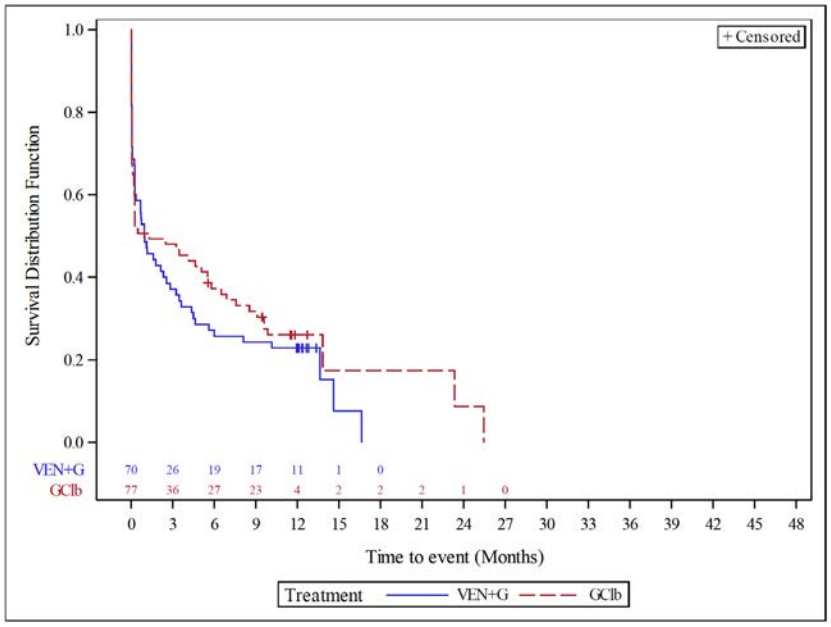

Figure 17: Kaplan-Meier curve on severe AEs (CTCAE ≥ 3)

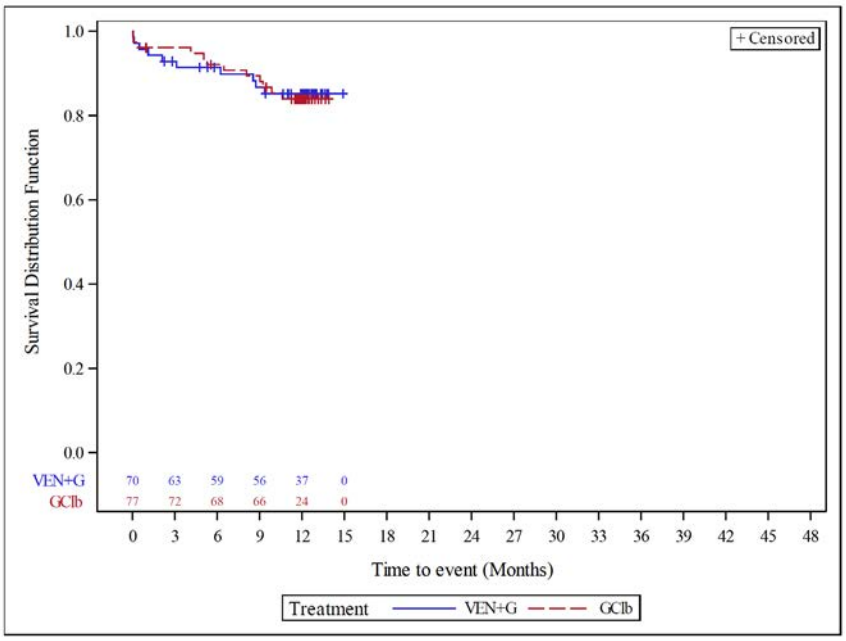

Figure 18: Kaplan-Meier curve on discontinuation due to AEs (discontinuation of at least one drug component)

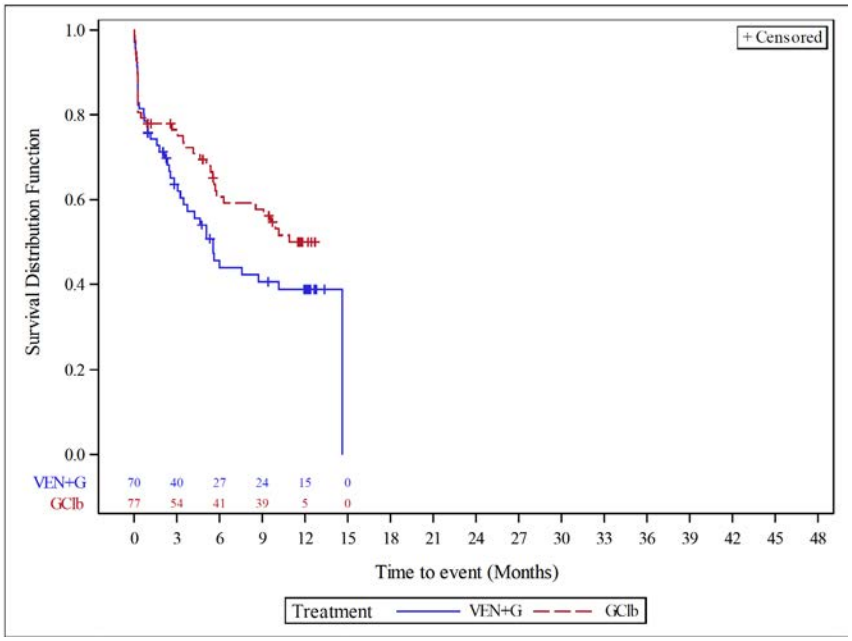

Figure 19: Kaplan-Meier curve on neutropenia (severe AEs, CTCAE ≥ 3)

Appendix C – Results on side effects in the CLL14 study, FCR therapy unsuitable

The following tables present events for Medical Dictionary for Regulatory Activities (MedDRA) SOCs and PTs for the overall rates of AEs, SAEs and severe AEs (CTCAE grade ≥ 3), each on the basis of the following criteria:

- overall rate of AEs (irrespective of the severity grade): events that occurred in at least 10% of the patients in one study arm
- overall rates of SAEs and severe AEs (CTCAE grade ≥ 3): events that occurred in at least 5% of the patients in one study arm
- in addition for all events irrespective of the severity grade: events that occurred in at least 10 patients and in at least 1% of the patients in one study arm

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

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**Venetoclax + obinutuzumab N = 70**	**Chlorambucil + obinutuzumab N = 77**
CLL14		
Overall AE rate	68 (97.1)	77 (100)
Blood and lymphatic system disorders	49 (70.0)	53 (68.8)
Anaemia	11 (15.7)	12 (15.6)
Neutropenia	40 (57.1)	45 (58.4)
Thrombocytopenia	20 (28.6)	14 (18.2)
Gastrointestinal disorders	41 (58.6)	35 (45.5)
Constipation	10 (14.3)	6 (7.8)
Diarrhoea	19 (27.1)	10 (13.0)
Nausea	12 (17.1)	17 (22.1)
Vomiting	10 (14.3)	5 (6.5)
General disorders and administration site conditions	34 (48.6)	35 (45.5)
Fatigue	8 (11.4)	11 (14.3)
Pyrexia	15 (21.4)	7 (9.1)
Infections and infestations	41 (58.6)	35 (45.5)
Nasopharyngitis	7 (10.0)	0 (0.0)
Upper respiratory tract infection	4 (5.7)	8 (10.4)
Injury, poisoning and procedural complications	33 (47.1)	46 (59.7)
Infusion-related reaction	31 (44.3)	43 (55.8)
Investigations	21 (30.0)	29 (37.7)
Aspartate aminotransferase increased	3 (4.3)	10 (13.0)
Metabolism and nutrition disorders	11 (15.7)	18 (23.4)

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

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**Venetoclax + obinutuzumab N = 70**	**Chlorambucil + obinutuzumab N = 77**
Musculoskeletal and connective tissue disorders	23 (32.9)	28 (36.4)
Arthralgia	4 (5.7)	8 (10.4)
Back pain	8 (11.4)	7 (9.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	14 (20.0)	12 (15.6)
Nervous system disorders	24 (34.3)	27 (35.1)
Headache	6 (8.6)	9 (11.7)
Psychiatric disorders	9 (12.9)	4 (5.2)
Renal and urinary disorders	2 (2.9)	8 (10.4)
Respiratory, thoracic and mediastinal disorders	26 (37.1)	18 (23.4)
Cough	15 (21.4)	9 (11.7)
Skin and subcutaneous tissue disorders	27 (38.6)	17 (22.1)
Pruritus	7 (10.0)	3 (3.9)
Vascular disorders	13 (18.6)	14 (18.2)

a. Events that occurred in ≥ 10% of the patients in at least one study arm.
b. MedDRA version 21.0; SOC and PT notation taken from MedDRA without adaptation.

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

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

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**Venetoclax + obinutuzumab N = 70**	**Chlorambucil + obinutuzumab N = 77**
CLL14		
Overall rate of SAEs	34 (48.6)	31 (40.3)
Blood and lymphatic system disorders	6 (8.6)	2 (2.6)
Infections and infestations	11 (15.7)	8 (10.4)
Injury, poisoning and procedural complications	4 (5.7)	10 (13.0)
Infusion-related reaction	4 (5.7)	4 (5.2)
Metabolism and nutrition disorders	2 (2.9)	5 (6.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (11.4)	5 (6.5)
Nervous system disorders	4 (5.7)	4 (5.2)
Respiratory, thoracic and mediastinal disorders	7 (10.0)	1 (1.3)

a. Events that occurred in ≥ 5% of the patients in at least one study arm.
b. MedDRA version 21.0; SOC and PT notation taken from MedDRA without adaptation.

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

Table 13: Common severe AEs (CTCAE grade ≥ 3)[a] – RCT, direct comparison: venetoclax + obinutuzumab vs. chlorambucil + obinutuzumab

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**Venetoclax + obinutuzumab N = 70**	**Chlorambucil + obinutuzumab N = 70**
CLL14		
Overall rate of severe AEs (CTCAE grade ≥ 3)	57 (81.4)	59 (76.6)
Blood and lymphatic system disorders	41 (58.6)	41 (53.2)
Anaemia	4 (5.7)	5 (6.5)
Leukopenia	2 (2.9)	5 (6.5)
Neutropenia	37 (52.9)	33 (42.9)
Thrombocytopenia	13 (18.6)	11 (14.3)
Cardiac disorders	4 (5.7)	3 (3.9)
Gastrointestinal disorders	4 (5.7)	1 (1.3)
General disorders and administration site conditions	4 (5.7)	2 (2.6)
Infections and infestations	12 (17.1)	9 (11.7)
Injury, poisoning and procedural complications	6 (8.6)	11 (14.3)
Infusion-related reaction	6 (8.6)	6 (7.8)
Investigations	12 (17.1)	11 (14.3)
Neutrophil count decreased	5 (7.1)	3 (3.9)
Metabolism and nutrition disorders	5 (7.1)	7 (9.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (11.4)	4 (5.2)
Nervous system disorders	2 (2.9)	4 (5.2)
Respiratory, thoracic and mediastinal disorders	5 (7.1)	0 (0.0)
Vascular disorders	6 (8.6)	1 (1.3)

a. Events that occurred in ≥ 5% of the patients in at least one study arm.
b. MedDRA version 21.0; SOC and PT notation taken from MedDRA without adaptation.

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; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Appendix D – Supplementary presentation of responder analyses for the outcome "health status" (EQ-5D VAS) in the CLL14 study, FCR therapy unsuitable

Table 14: Results (morbidity – results on the outcome "EQ-5D", supplementary presentation) – RCT, direct comparison: venetoclax + obinutuzumab vs. chlorambucil + obinutuzumab

Study Outcome category Outcome	Venetoclax + obinutuzumab		Chlorambucil + obinutuzumab		Venetoclax + obinutuzumab 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][a]; p-value[b]
CLL14					
Morbidity					
Health status (EQ-5D VAS) – supplementary presentation					
Time to deterioration[c]					
7 points	*66*	*18.2 [5.4; NC]* *33 (50.0)*	*73*	*34.6 [4.9; NC]* *34 (46.6)*	*1.01 [0.61; 1.67]; 0.960*
10 points	*66*	*22.9 [5.6; NC]* *32 (48.5)*	*73*	*NA [5.2; NC]* *33 (45.2)*	*1.00 [0.60; 1.66]; > 0.999*

a. HR and CI: Cox proportional hazards model with treatment as covariable, stratified by Binet stage and geographical region.
b. p-value: log-rank test stratified by Binet stage and geographical region.
c. Time to deterioration (decrease) of the score by at least 7 or 10 points versus the baseline value.

CI: confidence interval; EQ-5D VAS: European Quality of Life-5 Dimensions visual analogue scale; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; vs.: versus

Appendix E – Supplementary presentation of responder analyses for the outcome "B symptoms" in the CLL14 study, FCR therapy unsuitable

Table 15: Results (morbidity – results on B symptoms, supplementary presentation) – RCT, direct comparison: venetoclax + obinutuzumab vs. chlorambucil + obinutuzumab

Study Outcome category Outcome	Venetoclax + obinutuzumab		Chlorambucil + obinutuzumab		Venetoclax + obinutuzumab 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][a]; p-value[b]
CLL14					
Morbidity					
Patients without B symptoms[c] at baseline – supplementary presentation					
Time to first occurrence of B symptoms	*41*	*NA [NC; NC]* *2 (4.9)*	*44*	*NA [NC; NC]* *6 (13.6)*	*0.37 [0.07; 2.08]; 0.246*
Patients with at least one B symptom[c] at baseline – supplementary presentation					
Time to absence of symptoms	*30*	*1.1 [1.0; 1.9]* *29 (96.7)*	*33*	*1.0 [1.0; 1.4]* *30 (90.9)*	*1.01 [0.52; 1.97]; 0.957*
Time to recurrence of B symptoms[d]	*30*	*NA (40.9; NC)* *6 (20.0)*	*33*	*NA [NC; NC]* *7 (21.2)*	*0.861 [0.239; 3.107]; 0.819*

a. HR and CI: Cox proportional hazards model with treatment as covariable, stratified by Binet stage and geographical region.
b. p-value: log-rank test stratified by Binet stage and geographical region.
c. Presence of one of the following symptoms: unexplainable weight loss > 10% in ≤ 6 months, night sweat, unexplainable pyrexia > 38°C.
d. Time to recurrence comprises the period between the first day with documented absence of B symptoms and the first day on which at least one B symptom occurred (recurred).

CI: confidence interval; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; vs.: versus