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Venetoclax (chronic lymphocytic leukaemia; combination with rituximab) –

Addendum to Commission A18-81[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CI	confidence interval
CLL	chronic lymphocytic leukaemia
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
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model repeated measures
MRD	minimal residual disease
PCR	polymerase chain reaction
PFS	progression-free survival
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
VAS	visual analogue scale

1 Background

On 8 April 2019, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A18-81 (Venetoclax [combination with rituximab] – Benefit assessment according to §35a Social Code Book V) [1].

The dossier assessment on venetoclax in combination with rituximab concluded that the study MURANO (study GO28667) presented by the pharmaceutical company (hereinafter referred to as "the company") in the dossier was unsuitable for the assessment of the added benefit of venetoclax and rituximab, because the appropriate comparator therapy (ACT) specified by the G-BA had not been implemented in the control arm [1].

The G-BA commissioned IQWiG with the assessment of the analyses on the MURANO study presented by the company with regard to research question 1 of the dossier assessment A18-81 (adult patients with chronic lymphocytic leukaemia [CLL] without 17p deletion and/or TP53 mutation for whom chemoimmunotherapy is indicated and who have received at least one prior therapy) under consideration of the data subsequently submitted in the commenting procedure. The study results on the outcomes "progression-free survival (PFS)" and "minimal residual disease (MRD) negativity" are to be presented as additional information in the appendix. The assessment was conducted based on the data cut-off of 8 May 2018. According to the company's comment on dossier assessment A18-81, this was a data cut-off initiated in consultation with the regulatory authorities in the course of the European approval procedure [2].

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 of the MURANO study

2.1 Study MURANO

The MURANO study is a 2-arm, randomized, active controlled, open-label and multicentre phase 3 study on the comparison of venetoclax + rituximab with bendamustine + rituximab. A total of 389 patients were randomly assigned to the two treatment arms venetoclax + rituximab and bendamustine + rituximab in a ratio of 1:1. Further information on the design of the MURANO study and the interventions is presented in Appendix A of dossier assessment A18-81 (Venetoclax [combination with rituximab]) [1].

The total population of the study comprised adult patients with relapsed or refractory CLL independent of their 17p deletion or TP53 mutation status who had received at least one and at most 3 prior therapies. The patients relevant for research question 1 of dossier assessment A18-81 considered in the present addendum are patients without 17p deletion and/or TP53 mutation for whom chemoimmunotherapy is indicated and who have received at least one prior therapy (research question 1 of dossier assessment A18-81 [1]).

The company used the data of a subpopulation of the MURANO study for research question 1. The company defined this subpopulation as patients without 17p deletion and without TP53 mutation and who have a low risk status according to the stratification factor of the study (recurrence more than 12 months after a chemotherapy or 24 months after a chemoimmunotherapy). These were 74 patients in the venetoclax + rituximab arm and 66 patients in the bendamustine + rituximab arm. Information on the patient characteristics of this subpopulation can be found in Appendix A of dossier assessment A18-81 [1]. It is unclear to which extent the subpopulation formed by the company (simultaneous absence of 17p deletion and TP53 mutation; consideration of patients with recurrence more than 12 months after chemotherapy) enables adequate representation of research question 1.

Suitability of the MURANO study

As described in dossier assessment A18-81 [1], the MURANO study is unsuitable for the assessment of the added benefit of venetoclax + rituximab in comparison with the ACT specified by the G-BA, because the decision on the treatment option in the comparator arm was not made on an individual basis; all patients of this study arm received bendamustine + rituximab as uniform medication instead. The company provided no substantive arguments on why the combination bendamustine + rituximab should be preferred over the other available treatment options.

Planned duration of follow-up observation

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

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

Study **Outcome category** **Outcome**	**Planned follow-up observation**
MURANO	
Mortality	
Overall survival	after progression every 6 months until the end of the study
Morbidity	
B symptoms	every 3 months for 3 years, then every 6 months until progression
Health status (EQ-5D VAS)	every 3 months for 3 years, then every 6 months until progression
Symptoms (EORTC QLQ-C30)	every 3 months for 3 years, then every 6 months until progression
Health-related quality of life (EORTC QLQ-C30)	every 3 months for 3 years, then every 6 months until progression
Side effects	
All outcomes in the category "side effects"	every 3 months for 3 years, then every 6 months until progression[a]

a: The analyses on the side effects only included events that had occurred from the start of the study until 28 days after the last treatment with venetoclax or bendamustine, or 90 days after the last rituximab dose, depending on which period was longer.

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; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

The observation periods for the outcomes of the outcome categories "morbidity", "health-related quality of life" and "side effects" were systematically shortened because they were only recorded until progression. To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for "survival".

Course of the study

At the time point of the data cut-off of 8 May 2018, median treatment duration of the sub-population formed by the company was more than 5 times as long in the intervention arm as in the comparator arm (25.2 months versus 4.7 months). This difference is due to the fact that, in the intervention arm, monotherapy with venetoclax was planned to be administered following to the combination therapy phase (maximally six 28-day cycles) up to a maximum treatment duration of 2 years from the initiation of the combination therapy However, therapy in the control arm was restricted to treatment with bendamustine + rituximab (maximally six 28-day cycles).

Apart from "overall survival", there are no data on the observation periods of outcomes from the categories "morbidity", "health-related quality of life" and "side effects". Outcomes from these categories were observed until progression (see Table 1). The observation period of these

outcomes was therefore determined by progression. Median time to progression was 44.3 months in the intervention arm and 24.2 months in the control group. Based on these differences, it can be assumed that the observation periods for the outcomes on morbidity, health-related quality of life and side effects differed by a factor of about 2 between the study arms.

2.2 Results of the MURANO study

In compliance with the commission, the following sections present the results of the MURANO study. These results are based on the subpopulation of patients presented by the company for research question 1 of dossier assessment A18-81 and the data cut-off of 8 May 2018.

2.2.1 Considered outcomes

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

- Mortality
  - overall survival
- Morbidity
  - B symptoms
  - health status measured with the European Quality of Life-5 Dimensions (EQ-5D) visual analogue scale (VAS)
  - symptoms measured with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) symptom scales
- Health-related quality of life
  - health-related quality of life measured with the EORTC QLQ-C30 functional scales
- Side effects
  - serious adverse events (SAEs)
  - discontinuation due to adverse events (AEs)
  - severe AEs Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3
  - further specific AEs, if applicable

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier on the benefit assessment of venetoclax (Module 4 A) [3].

Table 2 shows for which outcomes data were available for research question 1 in the MURANO study.

Table 2: Matrix of outcomes – RCT, direct comparison: venetoclax + rituximab vs. bendamustine + rituximab

Study	Outcomes								
	Overall survival	B symptoms	Health status (EQ-5D VAS)	Symptoms (EORTC QLQ-C30 symptom scales)	Health-related quality of life (EORTC QLQ-C30 functional scales)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Further specific AEs
MURANO	Yes	No[a]	Yes	Yes	Yes	Yes	Yes	Yes	Yes[b]

a: No informative data, see Section 2.2.1
b: The following events are considered (MedDRA coding): "nausea (PT, AE)", "vomiting (PT, AE)", "infusion-related reaction (PT, AE)", "decreased appetite (PT, AE)" and "dyspnoea (PT, AE)", "rash (PT, AE)", "infections and infestations (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; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

Comment on outcome "B symptoms" and on the respective operationalizations presented by the company

Consideration of the outcome "B symptoms" includes the following symptoms: unexplained weight loss (> 10% in ≤ 6 months), night sweats, unexplained fever (> 38°C). The outcome was rated as patient-relevant. However, the data presented by the company were not considered to be informative.

The company submitted analyses on 2 operationalizations for this outcome [3]:

- Patients with at least one B symptom at the start of the study: time to recurrence of B symptoms after prior absence of symptoms
- Patients without B symptoms at the start of the study: time to first occurrence of B symptoms

The operationalization "time to recurrence of B symptoms" was only used for patients with B symptoms at the start of the study. The 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). Accordingly, patients first had to be free of symptoms to be at risk for the event of interest. Times for patients who had not become free of symptoms in the

course of the study were censored at the start of the analysis and were factually not included in the analysis. However, in the present case, the number of censorings at the start of the analysis appears to be small in both treatment arms (one person in each arm). It must, however, be noted that the period from randomization to first documented freedom of symptoms is ignored in the present analysis. There is no information on how long the period to first documented freedom of B symptoms was and whether it differed between the two treatment arms. A randomized comparison might no longer be feasible.

Analyses for the time to first occurrence of B symptoms were only performed for patients without B symptoms at the start of the study. These were 50 patients (68%) in the intervention arm and 42 patients (64%) in the control arm of the subpopulation presented by the company. Considering only patients without B symptoms at the start of the study does thus not enable a conclusion for all patients of the subpopulation presented by the company. Therefore, results for patients with or without B symptoms at the start of the study are presented as additional information in Appendix B.

2.2.2 Risk of bias

Mortality

The risk of bias for results on the outcome "overall survival" was rated as low.

Morbidity, health-related quality of life

There were no informative data for the outcome "B symptoms" (see Section 2.2.1). The risk of bias for this outcome was therefore not assessed.

The risk of bias was rated as high for the results on the outcomes "health status (EQ-5D VAS)", "symptoms (EORTC QLQ-C30 symptom scales)" and "health-related quality of life (EORTC QLQ-C30 functional scales)" due to the lack of blinding at subjective recording of outcomes and a high proportion of patients who were not included in the analysis or a large difference of these proportions between the treatment arms as well as differences in the baseline values between the treatment arms. This is described in detail below:

The company explained that due to an error in an early version of the study protocol, these outcomes had not been recorded at the start of the study in the venetoclax + rituximab arm during the first study months; therefore, these recordings are only available for 40.5% of the patients in this arm; in the bendamustine + rituximab arm, however, the baseline data are available for 93.9% of the patients. However, it appears plausible that there was a structural equality between the control group and the subset of subsequently recruited patients for whom recordings at baseline were available, so that the results were used deviating from the company's approach. At most patients with baseline value could be included in the mixed-effects model repeated measures (MMRM) analyses. Moreover, to be considered in the analyses, presumably at least one value after baseline had to be available for the respective patient. Even if the number of patients considered in the analysis was not provided, the data per

documentation time permit the conclusion that only few patients among those with baseline value, if any, had not been considered.

As already described, there were partially clear differences in the baseline values between the treatment groups; presumably because the recordings of these values had taken place after randomization with the knowledge of the allocation. Despite an adjustment regarding the baseline value, there was a potential aspect of bias.

Side effects

According to the company, the analyses of the outcomes on AEs included all events that had occurred from the start of the study until 28 days after the last treatment with venetoclax or bendamustine or 90 days after the last rituximab dose, depending on which period was longer. In the control arm, the planned treatment duration comprises six 28-day cycles, while it can be up to two years in the intervention arm; early treatment discontinuation takes place at disease progression or occurrence of toxicities. This means that events in the control arm occurring up to about 8.5 months after the start of the study were considered when treatment was implemented as planned. Comparison of the two treatment arms is thus only possible during these first 8.5 months, because all times of the patients in the control arm still at risk were censored after this period. This means that after this time point, events in the intervention arm had practically no influence on the hazard ratio (HR). Moreover, the described censorings in the control arm are not considered to be informative. Only censorings made before this time point are presumably based on an early treatment discontinuation and can thus be informative. Looking at the Kaplan-Meier curves for the UE endpoints (Figure 2 to Figure 5), it becomes apparent that there were only few censorings in both treatment arms during the first 8.5 months. Therefore, bias due to potentially informative censorings was considered to be unlikely.

The risk of bias for the results of the SAEs and severe AEs (CTCAE grade ≥ 3) is therefore rated as low.

The risk of bias for the results on the outcome “discontinuation due to adverse events”, in contrast, is rated as high due to the lack of blinding.

The risk of bias for the results on the outcome “further specific adverse events” is rated as high for non-serious/non-severe AEs due to subjective recording of outcomes; it is rated as low for serious/severe AEs.

2.2.3 Results

Table 3 and Table 4 summarize the results of the comparison of venetoclax + rituximab with bendamustine + rituximab. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company’s dossier. The common AEs and all AEs resulting in treatment discontinuation are presented in Appendix A; the available Kaplan-Meier curves on the considered outcomes are shown in Appendix C. Results on the outcomes “PFS”

and "MRD negativity" are provided as additional information in accordance with the commission (see Appendix D).

Table 3: Results (mortality, side effects) – RCT, direct comparison: venetoclax + rituximab vs. bendamustine + rituximab

Study Outcome category	Venetoclax + rituximab		Bendamustine + rituximab		Venetoclax + rituximab vs. bendamustine + rituximab
Outcome	**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]**
MURANO					
Mortality					
Overall survival	74	NA 4 (5.4)	66	NA 10 (15.2)	0.32 [0.10; 1.02]; 0.043[b]
Side effects					
AEs (additional information)	74	0.3 [0.1; 0.5] 74 (100)	66	0.1 [0.0; 0.3] 64 (97.0)	–
SAEs	74	NA [25.0; NC] 28 (37.8)	66	8.8 [8.8; 21.8] 25 (37.9)	0.39 [0.20; 0.76]; 0.005
Discontinuation due to AEs[c]	74	NA 12 (16.2)[d]	66	NA 7 (10.6)	0.36 [0.09; 1.40]; 0.125
Severe AEs (CTCAE grade ≥ 3)[c]	74	3.1 [1.4; 6.7] 59 (79.7)	66	3.7 [2.1; 10.3] 43 (65.2)	1.04 [0.69; 1.57]; 0.847
Nausea (PT, AE)	74	NA 13 (17.6)	66	NA [2.3; NC] 27 (40.9)	0.29 [0.14; 0.59]; < 0.001
Vomiting (PT, AE)	74	NA 7 (9.5)	66	NA 11 (16.7)	0.30 [0.10; 0.95]; 0.041
Infusion-related reaction (PT, AE)	74	NA 6 (8.1)	66	NA 17 (25.8)	0.29 [0.12; 0.74]; 0.009
Decreased appetite (PT, AE)	74	NA 2 (2.7)	66	NA 7 (10.6)	0.12 [0.01; 0.96]; 0.046
Dyspnoea (PT, AE)	74	NA 2 (2.7)	66	NA 8 (12.1)	0.10 [0.01; 0.83]; 0.033
Rash (PT, AE)	74	NA 7 (9.5)	66	NA [8.8; NC] 9 (13.6)	0.17 [0.04; 0.70]; 0.014
Infections and infestations (SOC, SAE)	74	NA 13 (17.6)	66	NA [8.8; NC] 12 (18.2)	0.33 [0.12; 0.94]; 0.038

(continued)

Table 3: Results (mortality, side effects) – RCT, direct comparison: venetoclax + rituximab vs. bendamustine + rituximab (continued)

a: HR and CI: Cox proportional hazards model, p-value: log-rank test; for the outcome "overall survival", model and test stratified by geographical region; for the outcomes of the category "side effects", model and test unstratified.
b: Discrepancy between the results of the stratified log-rank test and those of the Cox proportional hazards model (p = 0.054).
c: Also includes events rated as progression of the underlying disease.
D: In 9 patients, events occurred during the up-titration phase, in 3 patients during the combination therapy phase.
AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 4: Results (morbidity, health-related quality of life) – RCT, direct comparison: venetoclax + rituximab vs. bendamustine + rituximab

Study **Outcome category** **Outcome**	**Venetoclax + rituximab**			**Bendamustine + rituximab**			**Venetoclax + rituximab vs. bendamustine + rituximab**
	N[a]	**Values at start of study mean (SD)**	**Change EOCTR visit mean[b] (SE)**	**N[a]**	**Values at start of study mean (SD)**	**Change EOCTR visit mean[b] (SE)**	**MD [95% CI]; p-value[b]**
MURANO							
Morbidity							
Health status (EQ-5D VAS)[c]	ND	75.17 (17.57)	9.21 (2.53)	ND	70.29 (19.51)	3.67 (1.78)	5.54 [−0.54; 11.63]; 0.074
Symptoms (EORTC QLQ-C30)[d]							
Fatigue	ND	26.67 (23.63)	−8.16 (3.55)	ND	34.05 (24.63)	−8.21 (2.51)	0.04 [−8.50; 8.59]; 0.992
Nausea/vomiting	ND	1.11 (4.23)	−0.52 (1.85)	ND	6.18 (14.23)	−1.56 (1.31)	1.05 [−3.42; 5.52]; 0.646
Pain	ND	7.78 (14.34)	−0.46 (2.60)	ND	13.17 (21.58)	−1.10 (1.84)	0.64 [−5.61; 6.89]; 0.841
Dyspnoea	ND	16.67 (24.37)	−10.80 (4.11)	ND	22.04 (26.95)	−6.68 (2.90)	−4.12 [−14.00; 5.76]; 0.413
Insomnia	ND	18.89 (20.87)	−4.58 (5.02)	ND	28.96 (29.49)	3.91 (3.58)	−8.49 [−20.60; 3.62]; 0.169
Appetite loss	ND	3.33 (10.17)	−7.56 (3.76)	ND	20.97 (27.15)	−1.65 (2.67)	−5.92 [−15.00; 3.17]; 0.202
Constipation	ND	3.33 (10.17)	0.38 (3.45)	ND	11.48 (21.85)	−0.81 (2.45)	1.19 [−7.13; 9.51]; 0.779

(continued)

Table 4: Results (morbidity, health-related quality of life) – RCT, direct comparison: venetoclax + rituximab vs. bendamustine + rituximab (continued)

Study Outcome category Outcome	Venetoclax + rituximab			Bendamustine + rituximab			Venetoclax + rituximab vs. bendamustine + rituximab
	N[a]	Values at start of study mean (SD)	Change EOCTR visit mean[b] (SE)	N[a]	Values at start of study mean (SD)	Change EOCTR visit mean[b] (SE)	MD [95% CI]; p-value[b]
MURANO							
Diarrhoea	ND	4.44 (11.52)	12.64 (3.87)	ND	13.89 (23.20)	1.91 (2.77)	10.74 [1.37; 20.10]; 0.025 Hedges' g [95% CI][e]: 0.50 [0.05; 0.94]
Health-related quality of life							
EORTC QLQ-C30 functional scales[d]							
Global health status	ND	71.11 (19.42)	9.48 (3.56)	ND	64.62 (20.62)	2.85 (2.52)	6.63 [−1.94; 15.19]; 0.129
Physical functioning	ND	87.78 (15.17)	2.07 (2.24)	ND	84.81 (17.15)	0.92 (1.58)	1.15 [−4.23; 6.53]; 0.674
Role functioning	ND	87.78 (19.04)	4.75 (3.52)	ND	79.03 (25.24)	2.62 (2.49)	2.13 [−6.34; 10.61]; 0.622
Cognitive functioning	ND	90.00 (16.14)	1.48 (3.55)	ND	87.43 (16.00)	−3.31 (2.51)	4.79 [−3.75; 13.34]; 0.271
Emotional functioning	ND	81.11 (18.82)	7.49 (2.83)	ND	80.87 (21.37)	2.19 (2.00)	5.30 [−1.50; 12.11]; 0.126
Social functioning	ND	90.56 (16.77)	2.53 (3.31)	ND	85.52 (21.83)	−0.80 (2.34)	3.34 [−4.62; 11.30]; 0.411

a: Number of patients considered in the analysis for the calculation of the effect estimation; the values at the start of the study may be based on other patient numbers.
b: Mean and SE (change EOCTR visit per treatment group) and MD, 95% CI and p-value (group comparison): MMRM; adjusted for baseline value.
c: Positive results indicate improvement.
d: For the symptom scales, low values indicate improvement of the symptoms (negative change: improvement), for health-related quality of life, high values indicate higher quality of life (positive change: improvement).
e: Institute's calculation based on MD and CI estimation of the MMRM under the assumption that all patients with baseline values (30 [venetoclax + rituximab] vs. 60 [bendamustine + rituximab]) were considered in the analyses.

CI: confidence interval; EOCTR: end of combination treatment response; 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; MD: mean difference; MMRM: mixed effects model repeated measures; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus

Mortality

Overall survival

For overall survival, the results of the stratified log-rank test (p = 0.043) differ from those of the Cox proportional hazards model (p = 0.054) regarding statistical significance. According to the statistical analysis plan, the stratified log-rank test had been pre-specified and was thus presented with priority. A statistically significant difference in favour of venetoclax + rituximab in comparison with bendamustine + rituximab was therefore shown for the outcome "overall survival".

Morbidity

B symptoms

There were no informative data for the outcome "B symptoms". Neither an advantage nor a disadvantage of venetoclax + rituximab in comparison with bendamustine + rituximab resulted from this.

Health status (EQ-5D VAS)

There was no statistically significant difference between the treatment arms for the outcome "health status (EQ-5D VAS)".

Symptoms (EORTC QLQ-C30 symptom scales)

Symptom outcomes were recorded using the symptom scales of the EORTC QLQ-C30 instrument. No statistically significant difference between the treatment arms was shown for the outcomes "fatigue", "nausea/vomiting", "pain", "dyspnoea", "insomnia", "loss of appetite" and "constipation". However, a statistically significant difference to the disadvantage of venetoclax + rituximab in comparison with bendamustine + rituximab was shown for the outcome "diarrhoea". However, the 95% CI of the standardized mean difference (Hedges' g) was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect is relevant.

Health-related quality of life

Health-related quality of life (EORTC QLQ-C30 functional scales)

Health-related quality of life was recorded using the EORTC QLQ-C30 functional scales. No statistically significant difference between the treatment arms was shown for the outcomes "global health status", "physical functioning", "role functioning", "emotional functioning" and "social functioning".

Side effects

The results maximally refer to the first 8.5 months following the start of treatment (see Section 2.2.2).

SAEs

A statistically significant difference in favour of venetoclax + rituximab in comparison with bendamustine + rituximab was shown for the outcome "SAEs".

Discontinuation due to AEs

There was no statistically significant difference between the treatment arms for the outcome "discontinuation due to AEs".

Severe AEs (CTCAE grade ≥ 3)

No statistically significant difference between the treatment arms was shown for the outcome "severe AEs" (CTCAE grade ≥ 3).

Specific adverse events

Infections and infestations, nausea, infusion-related reaction, rash and dyspnoea

One statistically significant difference in favour of venetoclax + rituximab in comparison with bendamustine + rituximab was shown for each of the outcomes "infections and infestations" (System Organ Class [SOC], SAE), "nausea", "infusion-related reaction" "rash" and "dyspnoea" (Preferred Term [PT], AEs).

Decreased appetite, vomiting

A statistically significant difference in favour of venetoclax + rituximab in comparison with bendamustine + rituximab was shown for the outcomes "decreased appetite" and "vomiting" (PT, AEs in both cases). However, the advantage is no more than marginal.

Summary

Overall, effects were exclusively shown in favour of venetoclax + rituximab in comparison with bendamustine + rituximab.

References

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Appendix A – Results on side effects

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

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

For the outcome "discontinuation due to adverse events", all events (System Organ Class [SOCs]/PTs) that resulted in discontinuation were presented".

Table 5: Common AEs – RCT, direct comparison: venetoclax + rituximab vs. bendamustine + rituximab

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**venetoclax + rituximab N = 74**	**bendamustine + rituximab N = 66**
MURANO		
Overall rate of AEs	74 (100.0)	64 (97.0)
Blood and lymphatic system disorders	51 (68.9)	40 (60.6)
Anaemia	12 (16.2)	13 (19.7)
Febrile neutropenia	2 (2.7)	7 (10.6)
Neutropenia	42 (56.8)	26 (39.4)
Thrombocytopenia	10 (13.5)	11 (16.7)
Gastrointestinal disorders	46 (62.2)	44 (66.7)
Constipation	10 (13.5)	14 (21.2)
Diarrhoea	33 (44.6)	13 (19.7)
Nausea	13 (17.6)	27 (40.9)
Vomiting	7 (9.5)	11 (16.7)
General disorders and administration site conditions	37 (50.0)	36 (54.5)
Fatigue	14 (18.9)	16 (24.2)
Pyrexia	8 (10.8)	13 (19.7)
Immune system disorders	11 (14.9)	7 (10.6)

(continued)

Table 5: Common AEs – RCT, direct comparison: venetoclax + rituximab vs. bendamustine + rituximab (continued)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**venetoclax + rituximab N = 74**	**bendamustine + rituximab N = 66**
MURANO		
Infections and infestations	59 (79.7)	40 (60.6)
Bronchitis	9 (12.2)	5 (7.6)
Nasopharyngitis	13 (17.6)	4 (6.1)
Upper respiratory tract infection	14 (18.9)	13 (19.7)
Injury, poisoning and procedural complications	15 (20.3)	20 (30.3)
Infusion-related reaction	6 (8.1)	17 (25.8)
Investigations	23 (31.1)	18 (27.3)
Metabolism and nutrition disorders	26 (35.1)	17 (25.8)
Decreased appetite	2 (2.7)	7 (10.6)
Musculoskeletal and connective tissue disorders	20 (27.0)	18 (27.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10 (13.5)	8 (12.1)
Nervous system disorders	22 (29.7)	20 (30.3)
Headache	10 (13.5)	7 (10.6)
Psychiatric disorders	9 (12.2)	8 (12.1)
Respiratory, thoracic and mediastinal disorders	29 (39.2)	25 (37.9)
Cough	15 (20.3)	12 (18.2)
Dyspnoea	2 (2.7)	8 (12.1)
Skin and subcutaneous tissue disorders	24 (32.4)	19 (28.8)
Rash	7 (9.5)	9 (13.6)
Vascular disorders	11 (14.9)	10 (15.2)
Hypertension	8 (10.8)	1 (1.5)

a: MedDRA version 20.1.

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 6: Common SAEs – RCT, direct comparison: venetoclax + rituximab vs. bendamustine + rituximab

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**venetoclax + rituximab** **N = 74**	**bendamustine + rituximab** **N = 66**
MURANO		
Overall rate of SAEs	28 (37.8)	25 (37.9)
Blood and lymphatic system disorders	4 (5.4)	9 (13.6)
Febrile neutropenia	2 (2.7)	6 (9.1)
General disorders and administration site conditions	3 (4.1)	5 (7.6)
Pyrexia	1 (1.4)	5 (7.6)
Infections and infestations	13 (17.6)	12 (18.2)
Pneumonia	5 (6.8)	4 (6.1)
Neoplasms benign, malignant and unspecified neoplasms (incl cysts and polyps)	4 (5.4)	4 (6.1)

a: MedDRA version 20.1.

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 7: Common severe AEs, CTCAE grade ≥ 3 – RCT, direct comparison: venetoclax + rituximab vs. bendamustine + rituximab

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**venetoclax + rituximab** **N = 74**	**bendamustine + rituximab** **N = 66**
MURANO		
Overall rate of severe AEs, CTCAE grade ≥ 3	59 (79.7)	43 (65.2)
Blood and lymphatic system disorders	45 (60.8)	32 (48.5)
Anaemia	8 (10.8)	10 (15.2)
Febrile neutropenia	2 (2.7)	6 (9.1)
Neutropenia	39 (52.7)	25 (37.9)
Thrombocytopenia	4 (5.4)	6 (9.1)
Infections and infestations	11 (14.9)	11 (16.7)
Pneumonia	4 (5.4)	4 (6.1)
Investigations	8 (10.8)	10 (15.2)
Neutrophil count decreased	2 (2.7)	4 (6.1)
Metabolism and nutrition disorders	7 (9.5)	1 (1.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (6.8)	7 (10.6)

a: MedDRA version 20.1.

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; vs.: versus

Table 8: All AEs resulting in treatment discontinuation – RCT, direct comparison: venetoclax + rituximab vs. bendamustine + rituximab

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**venetoclax + rituximab** **N = 74**	**bendamustine + rituximab** **N = 66**
MURANO		
Overall rate of AEs resulting in treatment discontinuation	12 (16.2)	7 (10.6)
Blood and lymphatic system disorders	5 (6.8)	1 (1.5)
Neutropenia	3 (4.1)	0 (0)
Thrombocytopenia	2 (2.7)	1 (1.5)
Gastrointestinal disorders	1 (1.4)	0 (0)
Small intestinal obstruction	1 (1.4)	0 (0)
General disorders and administration site conditions	1 (1.4)	0 (0)
Sudden death	1 (1.4)	0 (0)
Infections and infestations	1 (1.4)	3 (4.5)
Lung infection	1 (1.4)	0 (0)
Pneumonia	0 (0)	2 (3.0)
Sepsis	0 (0)	1 (1.5)
Injury, poisoning and procedural complications	0 (0)	1 (1.5)
Infusion-related reaction	0 (0)	1 (1.5)
Investigations	1 (1.4)	1 (1.5)
Alanine aminotransferase increased	1 (1.4)	0 (0)
Platelet count decreased	0 (0)	1 (1.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (2.7)	0 (0)
Colorectal cancer	1 (1.4)	0 (0)
Pancreatic cancer	1 (1.4)	0 (0)
Nervous system disorders	1 (1.4)	0 (0)
Memory impairment	1 (1.4)	0 (0)
Skin and subcutaneous tissue disorders	0 (0)	1 (1.5)
Rash	0 (0)	1 (1.5)

a: MedDRA version 20.1.

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

Appendix B – Results on B symptoms

Table 9: Results (morbidity – supplementary presentation on the outcome "B symptoms") – RCT, direct comparison: venetoclax + rituximab vs. bendamustine + rituximab

Study Outcome category Outcome	Venetoclax + rituximab N	Venetoclax + rituximab Median time to event in months [95% CI] Patients with event n (%)	Bendamustine + rituximab N	Bendamustine + rituximab Median time to event in months [95% CI] Patients with event n (%)	Venetoclax + rituximab vs. bendamustine + rituximab HR [95% CI]; p-value[a]
MURANO					
Morbidity					
Patients without B symptoms[b] at the start of the study					
Time to first occurrence of B symptoms	50	NA 10 (20.0)	42	NA [34.4; NC] 8 (19.0)	1.06 [0.41; 2.75]; 0.901
Patients with at least one B symptom[b] at the start of the study					
Time to recurrence of B symptoms[c]	24	NA [23.5; NC] 9 (37.5)	22	13.0 [0.5; NC] 12 (54.5)	0.42 [0.16; 1.11]; 0.065

a: HR and CI: Cox proportional hazards model, p-value: log-rank test, model and test stratified by geographical region.
b: Presence of one of the following symptoms: unexplained weight loss > 10% in ≤ 6 months, night sweats, unexplained fever > 38°C.
c: 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 event; N: number of analysed patients; NA: not achieved; NC: not calculable; vs.: versus

Appendix C – Kaplan-Meier curves

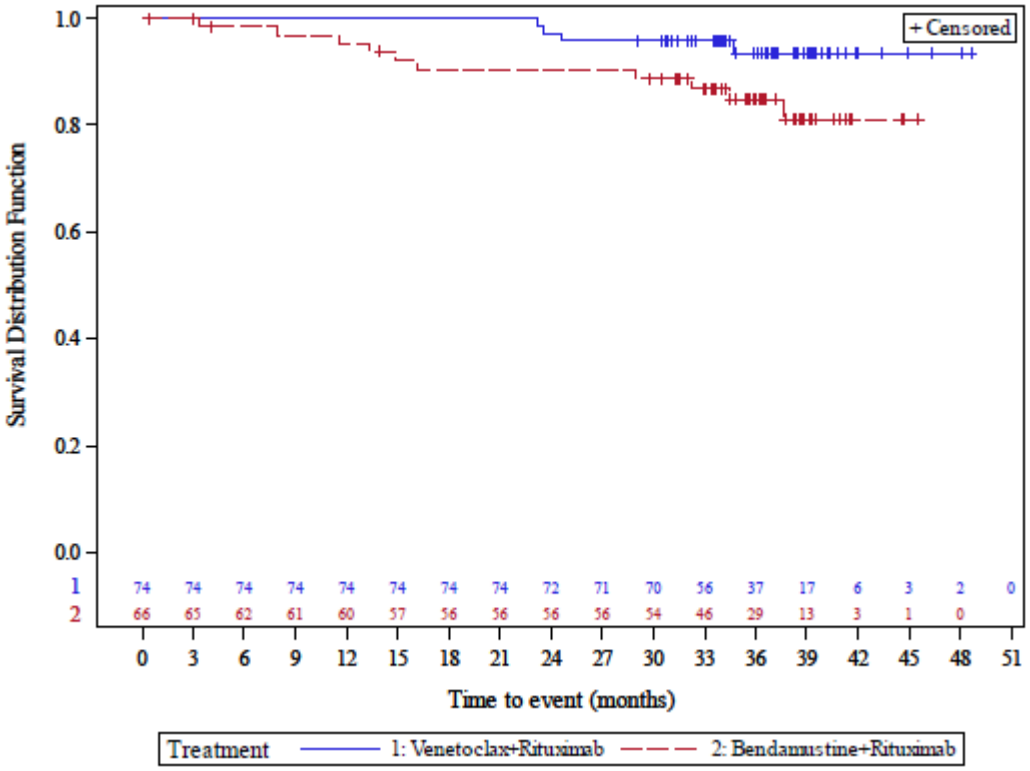

Figure 1: Kaplan-Meier curves on overall survival from the MURANO study

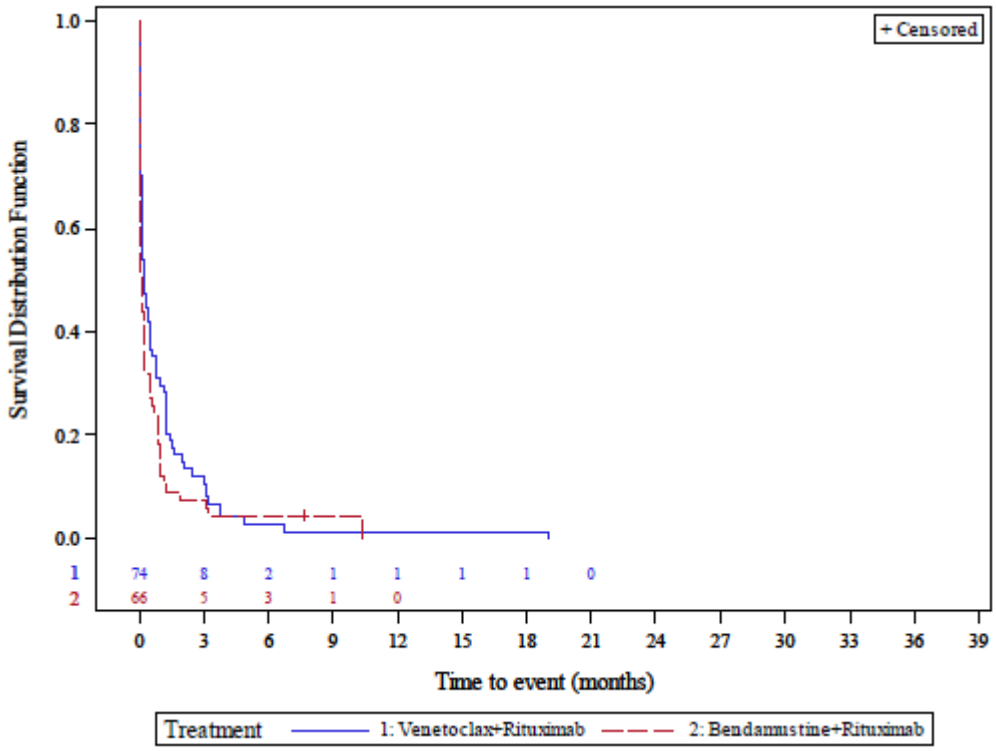

Figure 2: Kaplan-Meier curves for the time to first occurrence of an AE from the MURANO study

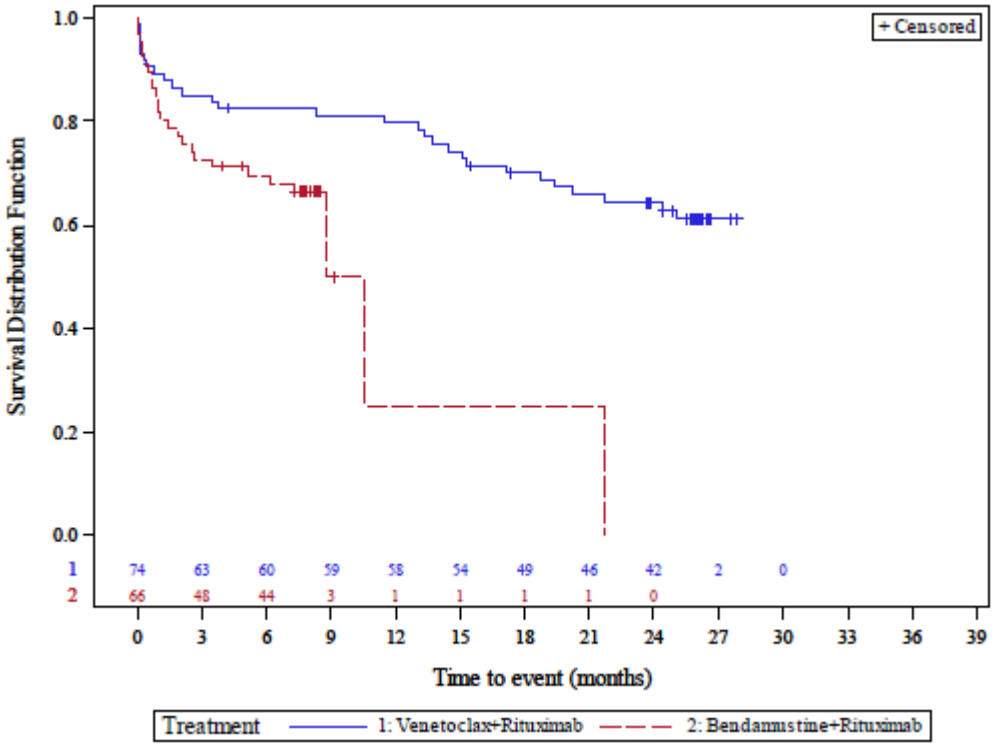

Figure 3: Kaplan-Meier curves for the time to first occurrence of an SAE from the MURANO study

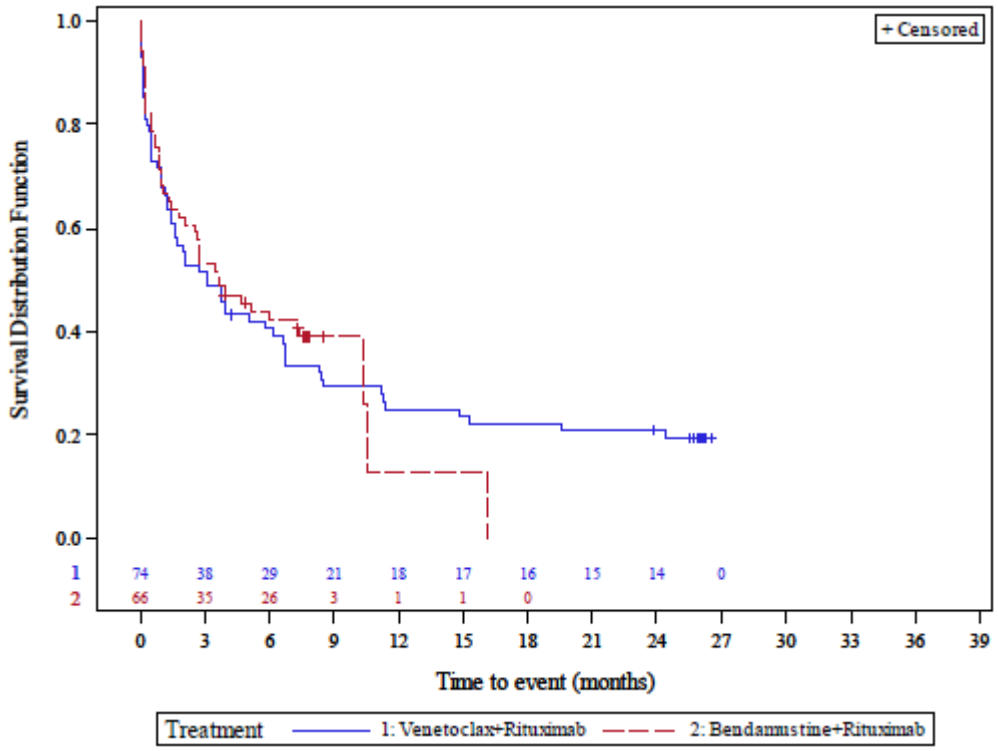

Figure 4: Kaplan-Meier curves for the time to first occurrence of a severe AE (CTCAE grade ≥ 3) from the MURANO study

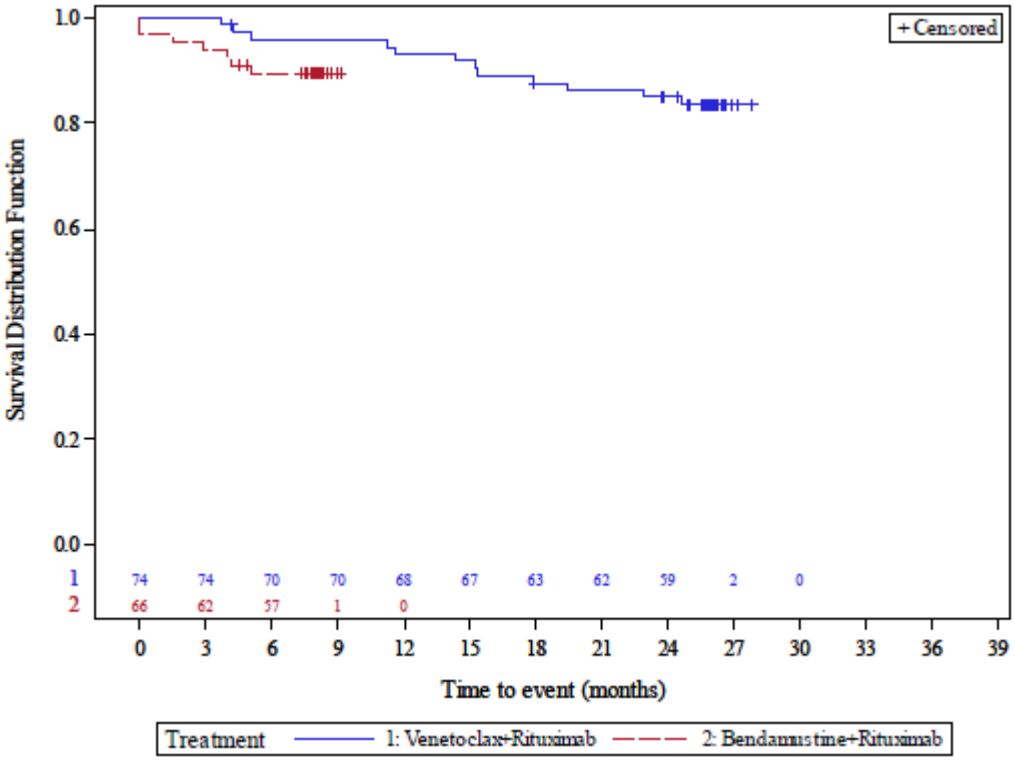

Figure 5: Kaplan-Meier curves for the time to discontinuation due to AEs from the MURANO study

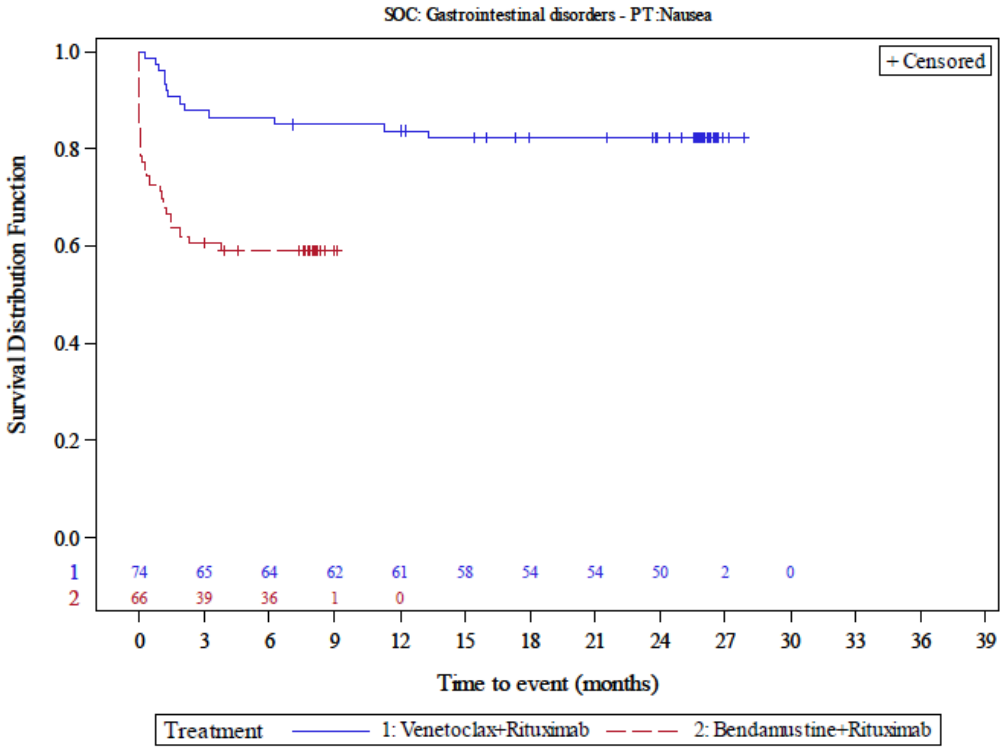

Figure 6: Kaplan-Meier curves for the time to first occurrence of nausea (PT, AE) from the MURANO study

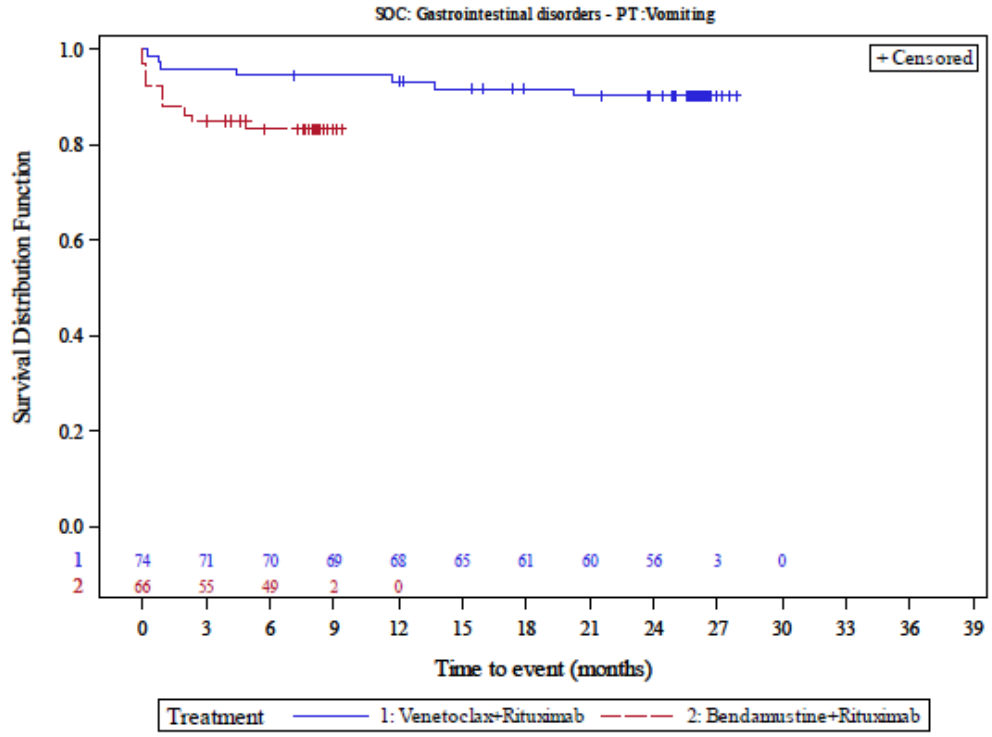

Figure 7: Kaplan-Meier curves for the time to first occurrence of vomiting (PT, AE) from the MURANO study

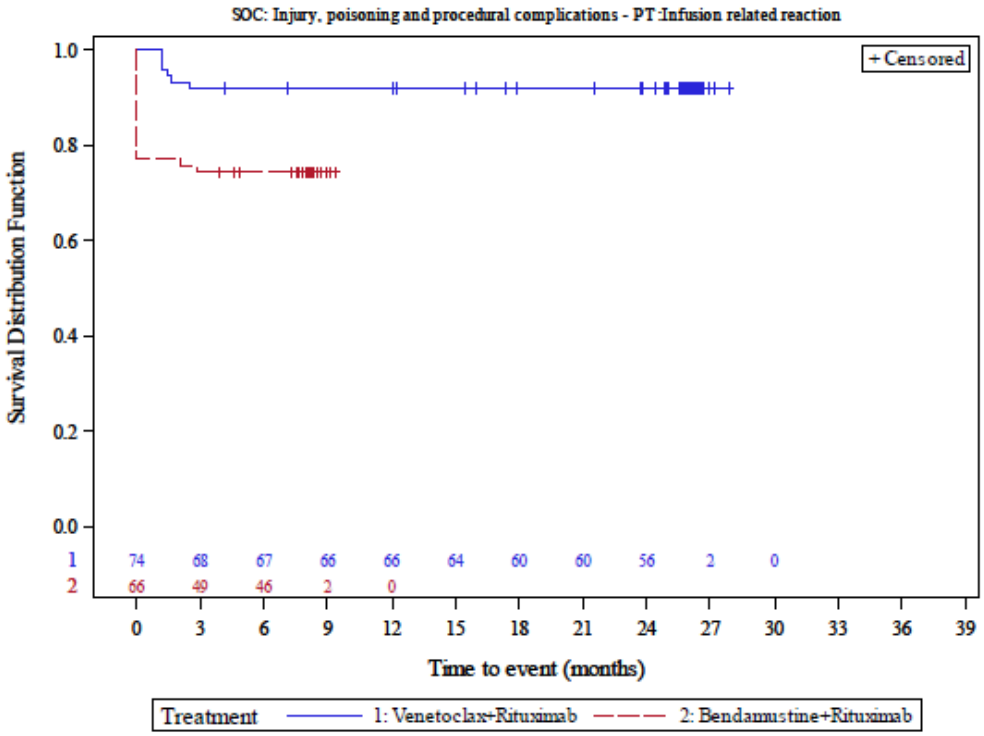

Figure 8: Kaplan-Meier curves for the time to first occurrence of infusion-related reaction (PT, AE) from the MURANO study

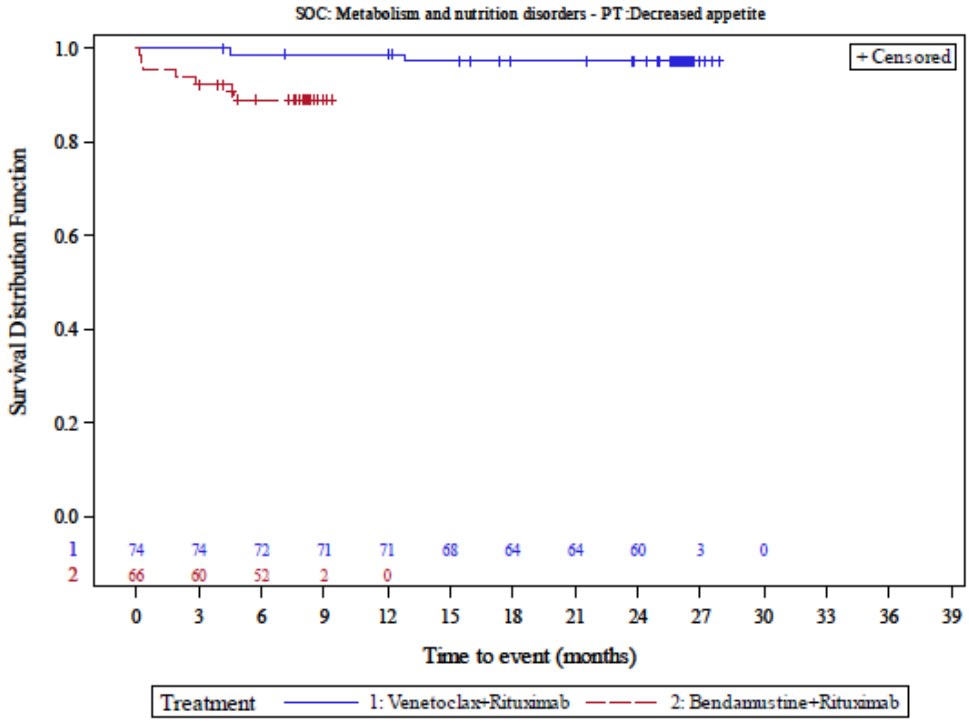

Figure 9: Kaplan-Meier curves for the time to first occurrence of decreased appetite (PT, AE) from the MURANO study

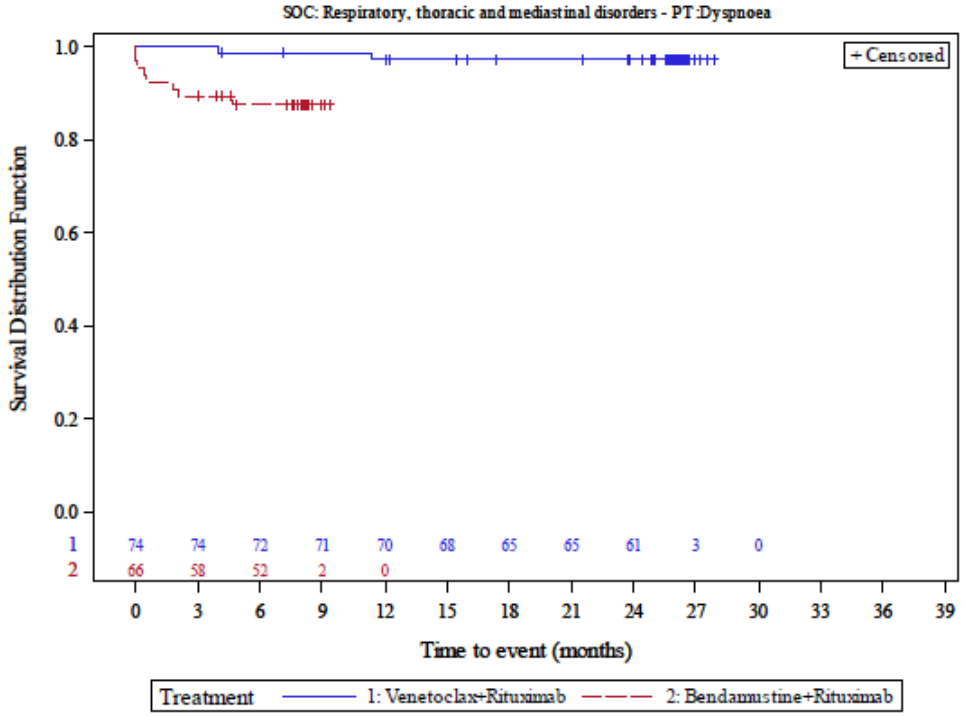

Figure 10: Kaplan-Meier curves for the time to first occurrence of dyspnoea (PT, AE) from the MURANO study

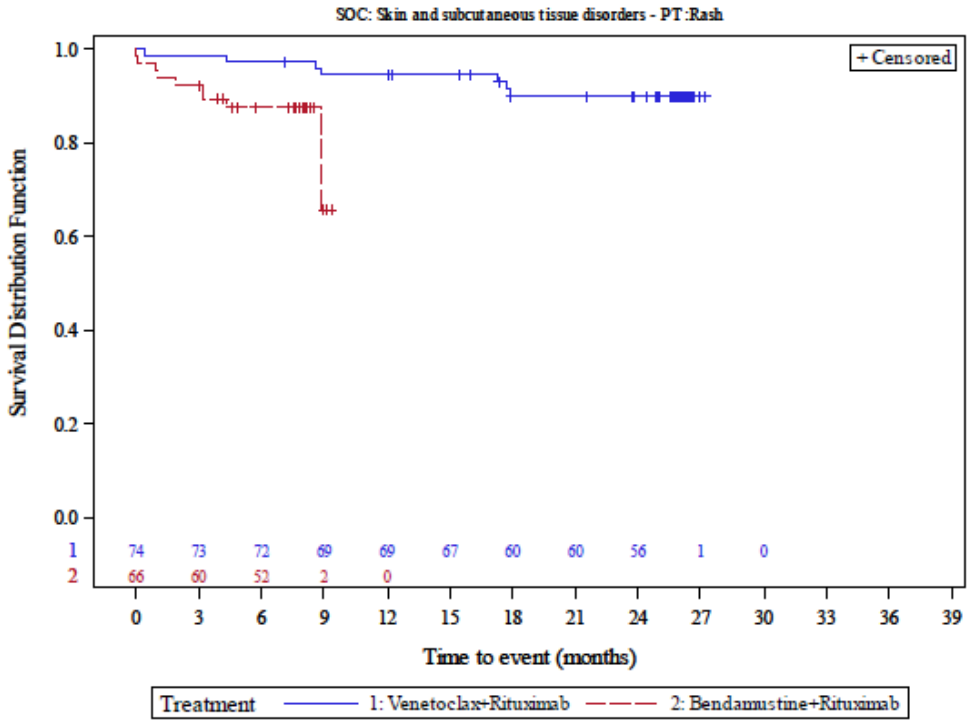

Figure 11: Kaplan-Meier curves for the time to first occurrence of rash (PT, AE) from the MURANO study

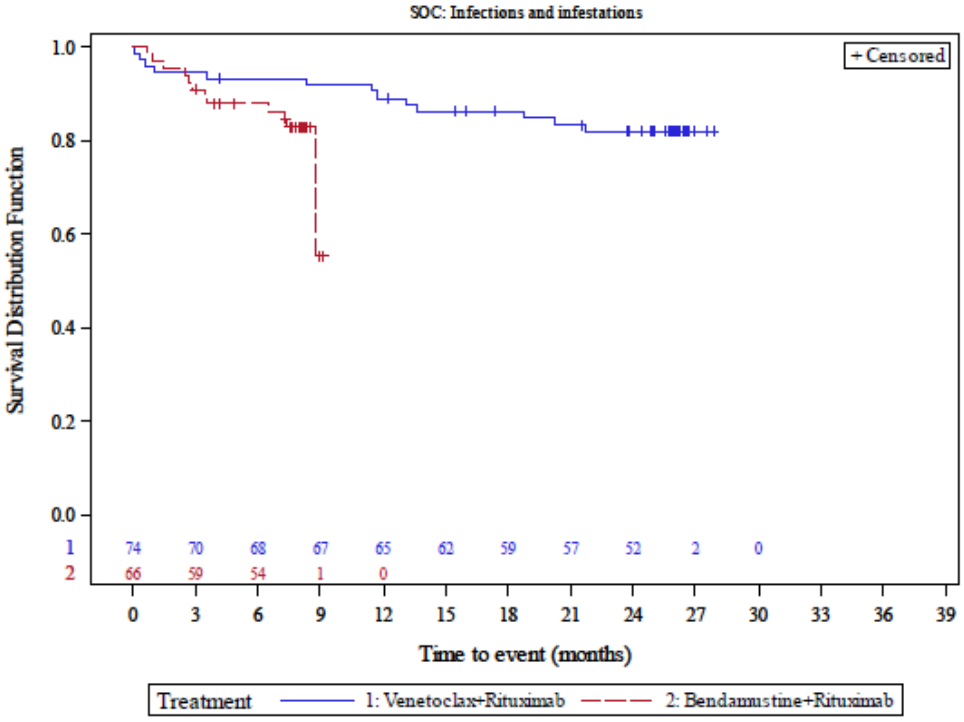

Figure 12: Kaplan-Meier curves for the time to first occurrence of infections and infestations (SOC, SAE) from the MURANO study

Appendix D – Results on PFS and MRD negativity

Table 10: Results (morbidity – supplementary presentation on the outcomes PFS and MRD negativity) – RCT, direct comparison: venetoclax + rituximab vs. bendamustine + rituximab

Study Outcome category Outcome	Venetoclax + rituximab N	Venetoclax + rituximab Median time to event in months [95% CI] Patients with event n (%)	Bendamustine + rituximab N	Bendamustine + rituximab Median time to event in months [95% CI] Patients with event n (%)	Venetoclax + rituximab vs. bendamustine + rituximab HR [95% CI]; p-value[a]
MURANO					
Morbidity					
PFS (investigator's assessment)	74	44.3 [44.3; NC] 16 (21.6)	66	24.2 [16.4; 29.6] 47 (71.2)	0.13 [0.07; 0.23]; < 0.001
PFS (IRC assessment; data cut-off: 8 May 2017)[b]	74	NA 7 (9.5)	66	22.8 [16.2; 33.0] 34 (51.5)	0.11 [0.05; 0.25]; < 0.001
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value[c]**
MRD negativity in the blood[d, e]	74	64 (86.5)	66	19 (28.8)	3.00 [2.03; 4.44]; < 0.001
MRD negativity in the bone marrow[f, g]	74	17 (23.0)	66	1 (1.5)	15.16 [2.07;110.84]; < 0.001

a: HR and CI: Cox proportional hazards model, p-value: log-rank test, model and test stratified by geographical region.
b: There is no analysis available for the data cut-off of 8 May 2018; the data cut-off of 8 May 2017 is a pre-specified data cut-off.
c: Institute's calculation (unconditional exact test [CSZ] method according to [4]).
d: Recorded using allele-specific oligonucleotide PCR and flow cytometry; MRD negativity was determined when there was less than one CLL cell among 10 000 leukocytes (< 1/10 000) at any time point; recordings were made at several time points during and after the combination therapy.
e: Patients without MRD recording after the start of the study were imputed as non-responders. According to the company, patients whose follow-up observation period was too short to enable the documentation of an MRD investigation at this time point were an exception. It remained unclear whether or how these patients were included in the analysis.
f: Recorded using flow cytometry; MRD negativity was determined when there was less than one CLL cell among 10 000 leukocytes (< 1/10 000) at the EOCTR visit; recordings were only made in patients with complete or partial response exclusively at the EOCTR visit.
g: As the company's analysis is based on all patients of the subpopulation formed by it, but apparently not all patients experienced complete or partial response, those patients were presumably also imputed as non-responders. However, the company presented no information on this.

CI: confidence interval; CLL: chronic lymphocytic leukaemia; EOCTR: end of combination treatment response; HR: hazard ratio; IRC: independent review committee; MRD: minimal residual disease; n: number of patients with event; N: number of analysed patients; PCR: polymerase chain reaction; PFS: progression-free survival; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Appendix E: Further results on EQ-5D VAS

Table 11: Results (morbidity – further results on the outcome EQ-5D VAS) – RCT, direct comparison: venetoclax + rituximab vs. bendamustine + rituximab

Study Outcome category Outcome	Venetoclax + rituximab N	Venetoclax + rituximab Median time to event in months [95% CI] Patients with event n (%)	Bendamustine + rituximab N	Bendamustine + rituximab Median time to event in months [95% CI] Patients with event n (%)	Venetoclax + rituximab vs. bendamustine + rituximab HR [95% CI]; p-value[a]
MURANO					
Morbidity					
Health status – time to improvement of symptoms by ≥ 7 points[b]					
EQ-5D VAS	30	11.0 [2.7; NC] 19 (63.3)	62	3.0 [1.9; 6.9] 41 (66.1)	0.66 [0.37; 1.16]; 0.142
Health status – time to improvement of symptoms by ≥ 12 points[b]					
EQ-5D VAS	30	NA [8.3; NC] 13 (43.3)	62	15.6 [5.6; NC] 30 (48.4)	0.63 [0.33; 1.23]; 0.171
Health status – time to deterioration of symptoms by ≥ 7 points[b]					
EQ-5D VAS	30	31.4 [6.8; NC] 15 (50.0)	62	12.4 [4.7; 25.6] 37 (59.7)	0.66 [0.36; 1.23]; 0.186
Health status – time to deterioration of symptoms by ≥ 12 points[b]					
EQ-5D VAS	30	NA [22.5; NC] 11 (36.7)	62	NA [21.6; NC] 24 (38.7)	0.79 [0.38; 1.67]; 0.542

a: HR and CI: Cox proportional hazards model, p-value: log-rank test, each stratified by geographical region
b: Change in comparison with the baseline value; operationalization not prespecified.

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