



A Randomised Investigation of Alternative Ofatumumab-containing regimens in less fit patients with CLL

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Final Statistical Analysis 2.0 Report

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2 Recruitment

Section 3 details the recruitment of participants throughout the course of the study.

2.1 Screening Summary

Table 2-1 Recruitment Summary by Site

The table below shows recruitment summaries sorted by best recruiting sites. Due to high number of centres, the table only reports the sites with at least 10 patients recruited.

Site Name	Date of Green Light*	Date of First Randomisation	Date of Last Randomisation	No. Screened	No. Randomised	Site Open to Revised Design?
Kent and Canterbury Hospital	01JUN2012	06JUN2012	05MAR2018	31	30	Yes
Royal Liverpool University Hospital	07DEC2011	14DEC2011	26FEB2018	22	20	Yes
Russells Hall Hospital (Dudley)	05DEC2012	21JAN2013	26APR2018	18	18	Yes
Nottingham City Hospital	25JUN2013	18SEP2013	23FEB2018	16	16	Yes
Sandwell Hospital (Birmingham)	09JAN2013	10MAY2013	27APR2018	16	16	Yes
Churchill Hospital (Oxford)	10JAN2013	07FEB2013	16FEB2015	15	14	Yes
Heartlands Hospital (Birmingham)	21DEC2012	09AUG2013	20MAR2017	14	13	Yes
Maidstone Hospital	05OCT2012	14FEB2013	01MAR2017	18	13	Yes
Royal United Hospital (Bath)	20FEB2012	24APR2012	22JUN2017	14	13	Yes
Southend Hospital (Westcliff-on-Sea)	26FEB2013	27FEB2013	20MAR2017	13	13	Yes
Colchester General Hospital	03JUL2012	29AUG2012	05MAR2018	21	12	Yes
Southampton General Hospital	08MAR2012	27APR2012	13JAN2015	17	12	Yes
Torbay Hospital (Torquay)	24FEB2012	11MAY2012	19MAR2018	40	12	Yes
Medway Maritime Hospital (Gillingham)	12JUN2013	23JUL2013	09AUG2016	13	11	Yes
St. James's University Hospital (Leeds)	24APR2012	23MAY2012	07APR2015	14	11	Yes
Blackpool Victoria Hospital	07OCT2013	31MAR2014	14NOV2017	15	10	Yes
The Royal Bournemouth Hospital	04MAY2012	12OCT2012	17JAN2018	12	10	Yes
Worthing Hospital	27JAN2014	14JAN2015	02DEC2016	14	10	Yes
Wrexham Maelor Hospital	16APR2014	28MAY2014	27MAR2018	11	10	Yes
Subtotal				334	264	
Total				939	521	

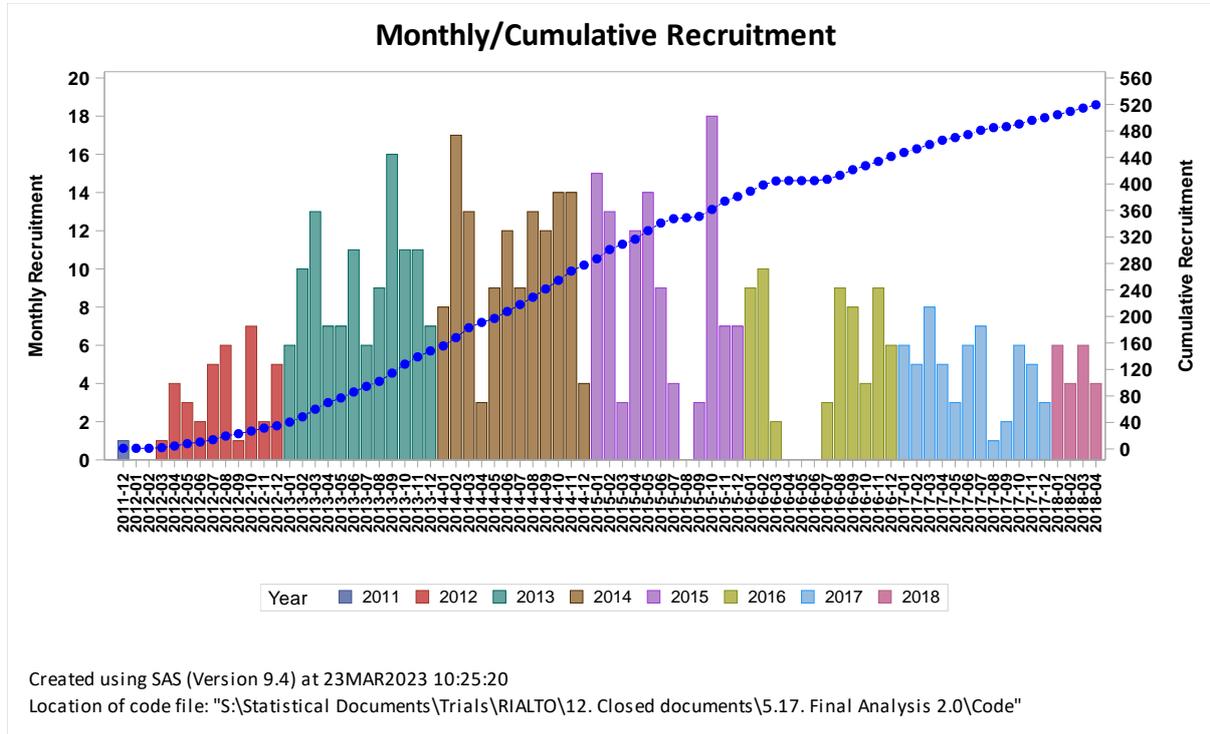
*The Trial Coordinator and/or Chief Investigator have completed the initiation visit at site. Research staff including research nurses has been fully initiated and have signed the delegation log and initiation log. All staff have been fully trained by the Chief Investigator and/or Trial Coordinator; All regulatory and ethical approvals are in place; All signatures are complete, and all documentation is in place; The Research Site Agreement is signed by all parties; The CRFs are at site; The drug has been released to site.

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2.2 Recruitment Graph

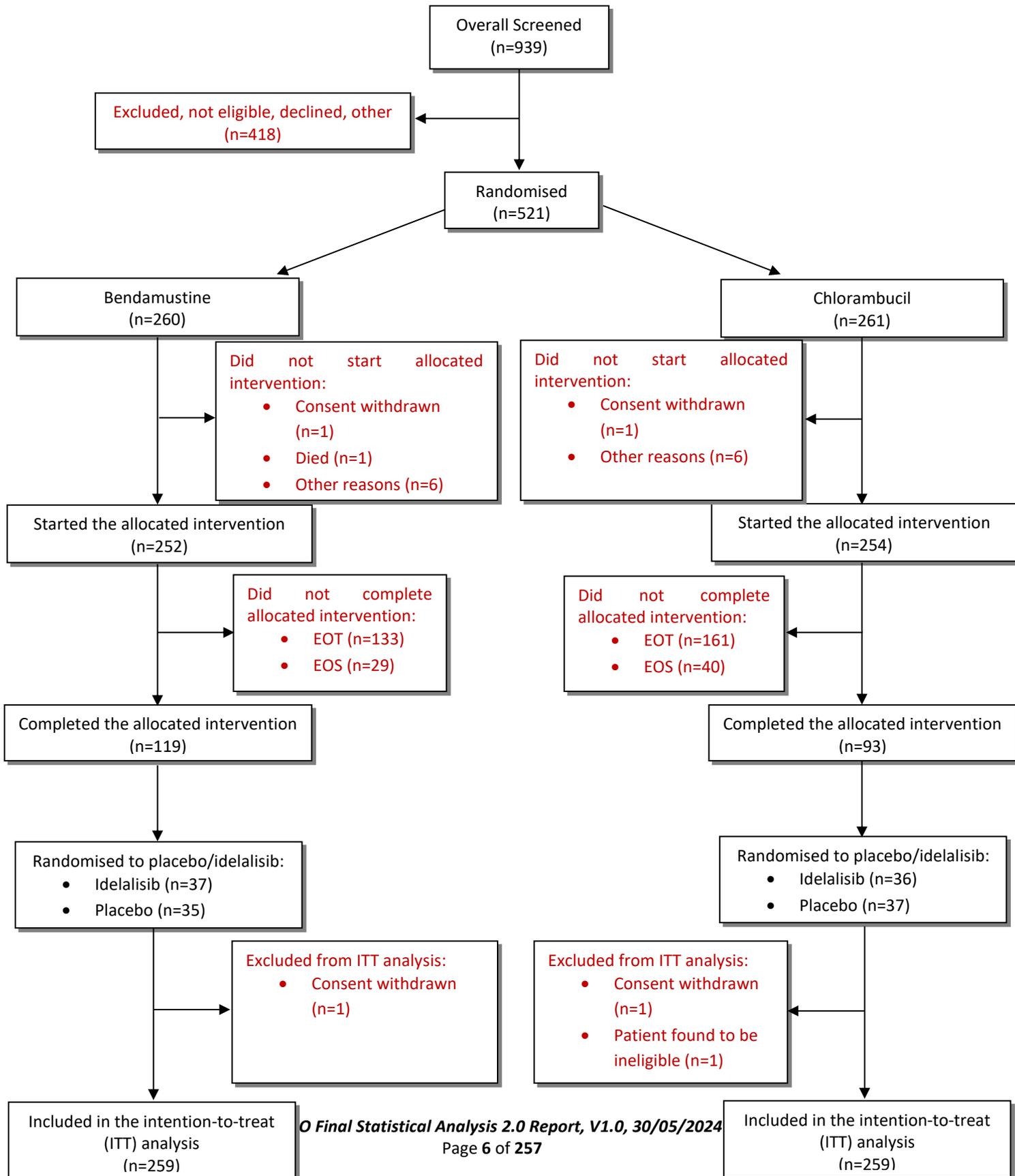
Figure 2-1 Recruitment Graph



3 Completeness of Follow-Up

Figure 3-1 CONSORT Diagram

Figure 4-1 gives a CONSORT diagram to show patient disposition throughout the study.



4 Baseline Characteristics

Section 4 details the demographics of the patient's population as they were recruited into the study. Please note that patients randomised to receive Idelalisib do not contribute towards the primary analyses included within this report.

Table 4-1 Baseline Characteristics

	Bendamustine* (N=223)	Chlorambucil* (N=225)	Idelalisib (N=73)	Placebo (N=72)
Demographic Characteristics				
Age, Median (IQR)	76.0 (72.0;80.0)	76.0 (72.0;79.0)	76.0 (71.0;80.0)	76.0 (72.0;80.0)
Age Group, n (%)				
<=70	41 (18.4%)	47 (20.9%)	16 (21.9%)	13 (18.1%)
>70	182 (81.6%)	178 (79.1%)	57 (78.1%)	59 (81.9%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gender, n (%)				
Male	144 (64.6%)	143 (63.6%)	56 (76.7%)	53 (73.6%)
Female	79 (35.4%)	82 (36.4%)	17 (23.3%)	19 (26.4%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Days to treatment since registration, Median (IQR)	9.0 (6.0;17.0)	7.0 (5.0;15.0)	8.5 (6.0;19.5)	8.0 (6.0;14.5)
Physical Findings				
Who Performance Status, n (%)				
0/1	186 (83.4%)	187 (83.1%)	65 (89.0%)	65 (90.3%)
2/3	37 (16.6%)	38 (16.9%)	8 (11.0%)	7 (9.7%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cumulative Illness Rating Score, Median (IQR)	4.0 (2.0;6.0)	4.0 (2.0;6.0)	4.0 (2.0;5.0)	4.0 (1.0;6.0)
Cumulative Illness Rating Score, n (%)				
≤6	173 (77.6%)	174 (77.3%)	59 (80.8%)	57 (79.2%)
>6	50 (22.4%)	51 (22.7%)	14 (19.2%)	15 (20.8%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Disease Stage, n (%)				
A	28 (12.6%)	26 (11.6%)	13 (17.8%)	10 (13.9%)
B	73 (32.7%)	73 (32.4%)	20 (27.4%)	25 (34.7%)
C	116 (52.0%)	123 (54.7%)	40 (54.8%)	37 (51.4%)
Missing	6 (2.7%)	3 (1.3%)	0 (0.0%)	0 (0.0%)
VES-13 Assessment, Median (IQR)	1.0 (1.0;4.0)	1.0 (1.0;3.0)	1.0 (1.0;3.0)	1.0 (1.0;3.0)
VES-13 Assessment, n (%)				
<3	124 (55.6%)	131 (58.2%)	41 (56.2%)	48 (66.7%)

	Bendamustine* (N=223)	Chlorambucil* (N=225)	Idelalisib (N=73)	Placebo (N=72)
≥3	72 (32.3%)	77 (34.2%)	24 (32.9%)	18 (25.0%)
Missing	27 (12.1%)	17 (7.6%)	8 (11.0%)	6 (8.3%)
GFI Assessment, Median (IQR)	3.0 (1.0;5.0)	2.0 (1.0;4.0)	3.0 (2.0;4.0)	2.0 (1.0;5.0)
GFI Assessment, n (%)				
<4	121 (54.3%)	137 (60.9%)	37 (50.7%)	40 (55.6%)
≥4	72 (32.3%)	71 (31.6%)	28 (38.4%)	24 (33.3%)
Missing	30 (13.5%)	17 (7.6%)	8 (11.0%)	8 (11.1%)
Timed Up & Go Assessment, Median (IQR)	10.0 (8.2;14.4)	10.5 (8.2;16.0)	10.0 (7.5;12.7)	10.4 (8.5;14.6)
Timed Up & Go Assessment, n (%)				
<10	84 (37.7%)	73 (32.4%)	29 (39.7%)	27 (37.5%)
≥10	92 (41.3%)	105 (46.7%)	30 (41.1%)	33 (45.8%)
Missing	47 (21.1%)	47 (20.9%)	14 (19.2%)	12 (16.7%)
IGHV Status, n (%)				
Mutated	67 (30.0%)	73 (32.4%)	19 (26.0%)	20 (27.8%)
Unmutated	71 (31.8%)	79 (35.1%)	30 (41.1%)	27 (37.5%)
Missing	85 (38.1%)	73 (32.4%)	24 (32.9%)	25 (34.7%)
FISH Status, n (%)				
17p-	12 (5.4%)	6 (2.7%)	3 (4.1%)	3 (4.2%)
11q-	23 (10.3%)	29 (12.9%)	11 (15.1%)	6 (8.3%)
+12	46 (20.6%)	55 (24.4%)	15 (20.5%)	18 (25.0%)
13q-	69 (30.9%)	64 (28.4%)	19 (26.0%)	23 (31.9%)
No FISH defect	53 (23.8%)	51 (22.7%)	20 (27.4%)	17 (23.6%)
Missing	20 (9.0%)	20 (8.9%)	5 (6.8%)	5 (6.9%)

*Data for Bendamustine & Chlorambucil include patients who received placebo to match the primary analysis objectives.

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4.1 Baseline Characteristics Summary

There is no evidence of any imbalance between treatment groups. The study population is as expected from the entry criteria.

5 Study Population

Section 6 details the numbers of patient to be included in each analysis.

Table 5-1 Data Sets Analysed

Population	Bendamustine*	Chlorambucil*	Idelalisib	Placebo
Randomised, n (%)	223	225	73	72
Intention-to-treat, n (%)	222	223	73	70
Per protocol, n (%)	134	158	45	53
Safety, n (%)	215	219	72	67

*Data for Bendamustine & Chlorambucil include patients who received placebo to match the primary analysis objectives.

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6 Protocol Deviations

Protocol deviations are listed in table 7-1. Please note that any patient with a 'major' protocol deviation are removed from the per-protocol treatment groups.

Table 6-1 Summary of Deviations

Type	Description of Deviation	Category	Total No.
Major	Violation of entry criteria	1	41
	Administration of wrong treatment or incorrect dose etc	3	10
	Major protocol deviation in patient management and/or assessment	5	50
	Other major protocol deviation	6	96
	Other - Source Data	8	1
	Other - Delegation Issues	9	1
	Other - Registration Issues	10	2
	Other - Consent Issue	11	1
	Other - IMP Issue	12	1
	Patient Management/Assessment - Translational	14	6
	Patient Management/Assessment - PV	15	6
	Patient Management/Assessment - Visit Timepoint	16	3
	Patient Management/Assessment - Patient examination/Test	17	1
Minor	Protocol Deviations not expected to have an impact on defined endpoints of the trial	7	3706
Other	COVID-19 Patient Safety/Feasibility	33	28

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7 Treatment Overview

7.1 Treatment Cycles

Treatment overview is shown by the number of patients completing each cycle (Table 8-1), the total dose received at each cycle (Table 8-2) and the number of dose omissions, reductions and delays (Table 8-3).

Table 7-1 Number of Patients Completing Each Cycle

Cycle	Bendamustine (N=252)		Chlorambucil (N=254)	
	Bendamustine	Ofatumumab	Chlorambucil	Ofatumumab
1	252 (100.0%)	252 (100.0%)	251 (98.8%)	253 (99.6%)
2	232 (92.1%)	232 (92.1%)	225 (88.6%)	226 (89.0%)
3	211 (83.7%)	209 (82.9%)	204 (80.3%)	201 (79.1%)
4	186 (73.8%)	182 (72.2%)	189 (74.4%)	188 (74.0%)
5	161 (63.9%)	161 (63.9%)	172 (67.7%)	172 (67.7%)
6	145 (57.5%)	146 (57.9%)	148 (58.3%)	153 (60.2%)
7	NA	NA	61 (24.0%)	63 (24.8%)
8	NA	NA	53 (20.9%)	57 (22.4%)
9	NA	NA	42 (16.5%)	44 (17.3%)
10	NA	NA	11 (4.3%)	12 (4.7%)
11	NA	NA	6 (2.4%)	8 (3.1%)
12	NA	NA	6 (2.4%)	6 (2.4%)

Percentage calculations based on patients who started treatment.

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Table 7-2 Total Dose Received at Each Cycle

Cycle	Bendamustine (N=252)		Chlorambucil (N=254)	
	Bendamustine	Ofatumumab	Chlorambucil	Ofatumumab
1	64346.6	293201.6	32563.0	289613.4
2	54246.8	226460.0	26679.0	219958.5
3	48174.4	208187.0	24224.0	200000.0
4	42424.4	181500.0	21898.0	186119.0
5	37200.4	161000.0	19435.0	182000.0
6	33488.7	146000.0	16342.0	153000.0
7	NA	NA	6482.0	63000.0
8	NA	NA	5538.0	57000.0
9	NA	NA	4584.0	44000.0
10	NA	NA	1282.0	12000.0
11	NA	NA	742.0	8000.0
12	NA	NA	742.0	6000.0

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Table 7-3 Number of Patients with Reductions and Delays at Each Cycle

Cycle	Reductions		Delays	
	Bendamustine	Chlorambucil	Bendamustine	Chlorambucil
1	1	5	33	17
2	32	18	64	48
3	41	23	31	43
4	32	23	22	34
5	21	20	27	30
6	20	15	15	20
7	NA	12	NA	5
8	NA	10	NA	7
9	NA	9	NA	9
10	NA	3	NA	4
11	NA	1	NA	2
12	NA	1	NA	1

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7.2 Treatment Compliance

Table 8-4 Treatment Dose Administered (Secondary Outcome)

Arm	Drug	No. cycles received, Median (IQR)	% of planned cycles received, Median (IQR)	Cumulative dose received, Median (IQR)	% of planned dose received, Median (IQR)
O-B	Bendamustine	6.0 (4.0,6.0)	100.0 (66.7,100.0)	1210.0 (737.0,1500.0)	97.6 (82.3,100.0)
O-B	Ofatumumab	6.0 (3.0,6.0)	100.0 (66.7,100.0)	6300.0 (3300.0,6300.0)	100.0 (100.0,100.0)
O-Chl	Chlorambucil	6.0 (4.0,7.0)	100.0 (66.7,100.0)	672.0 (420.0,840.0)	96.6 (86.2,100.0)
O-Chl	Ofatumumab	6.0 (4.0,7.0)	100.0 (66.7,100.0)	6300.0 (4300.0,7900.0)	100.0 (100.0,100.0)

Cumulative cycles and doses were not statistically compared due to cycles and doses being different for each treatment arm.

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7.3 Treatment Overview Summary

Given the different schedules between the randomised groups, direct comparisons are difficult. There is no clear evidence that either regimen has better/worse compliance than the other. There is some evidence that patients randomised to Bendamustine had a greater number of reductions, conversely however, patients randomised to Chlorambucil may be more likely to have dose delays.

8 Protocol Treatment & Trial Dropouts

Table 9-1 details the patients who have discontinued trial treatment as well as those who have discontinued the study.

Table 8-1 Protocol Treatment & Trial Dropouts

Reason	Bendamustine* (N=223)	Chlorambucil* (N=225)	Idelalisib (N=73)
Total discontinued induction treatment [n (%)]			
Clinician decision (not adverse event)	13 (6%)	43 (20%)	5 (7%)
Completed protocol treatment	110 (51%)	87 (40%)	15 (22%)
Death	4 (2%)	2 (1%)	2 (3%)
Disease progression	1 (0%)	4 (2%)	0 (0%)
Inadequate Response	2 (1%)	13 (6%)	1 (1%)
Non-treatment-related (please specify reason)	5 (2%)	2 (1%)	3 (4%)
Other (please specify reason)	28 (13%)	19 (9%)	17 (25%)
Patient decision (not Adverse Event)	4 (2%)	3 (1%)	2 (3%)
Serious adverse event	1 (0%)	3 (1%)	0 (0%)
Treatment-related event (please specify reason)	33 (15%)	35 (16%)	21 (30%)
Unacceptable adverse event	7 (3%)	4 (2%)	0 (0%)
Withdrawal of consent	2 (1%)	1 (0%)	3 (4%)
Reason missing	4 (2%)	2 (1%)	0 (0%)
Total	214 (100%)	218 (100%)	69 (100%)
Days from recruitment to discontinuation of protocol treatment**			
Median	149.5	162	153
IQR	111, 168	123, 231	52, 202
Range	1, 886	2, 513	4, 481
Total discontinued trial [n (%)]			
Consent withdrawn	13 (9%)	19 (14%)	7 (16%)
Death	64 (44%)	54 (41%)	16 (36%)
Lost to follow up	2 (1%)	4 (3%)	0 (0%)
Other	65 (45%)	56 (42%)	22 (49%)
Total	144 (100%)	133 (100%)	45 (100%)
Days from recruitment to discontinuation of trial			
Median	1239.5	1243	1451
IQR	416, 1723	378, 1900	83, 1988
Range	2, 3039	0, 3293	14, 2346

*Data for Bendamustine & Chlorambucil include patients who received placebo to match the primary analysis objectives.

**Chlorambucil is administered in 3-12 treatment cycles while Bendamustine in 3-6 cycles (28 days/cycle).

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8.1 Protocol Treatment & Trial Dropouts Summary

In terms of withdrawing from study, the number of patients withdrawing consent or being lost to follow-up are rare across both treatment groups. In terms of ending treatment, there is some evidence that patients on Chlorambucil (n=43) are more likely to end treatment due to clinician's choice than patients on Bendamustine (n=13).

9 Primary Outcome – Progression Free Survival (PFS)

9.1 Primary Analysis – Bendamustine vs. Chlorambucil (Including Placebo)

Table 9-1 Progression Free Survival

Table 10-1 lists the results for PFS by Bendamustine and Chlorambucil patients (including Placebo patients). The 12-month PFS rate for the Bendamustine arm was 83% compared to the Chlorambucil arm with 85%. The hazard ratio between the two arms was 0.72 (0.57 – 0.90). Using the trial stratification factors for a stratified log rank test showed a statistically significant difference between the two treatment arms (p=0.004).

Treatment Arm	No. patients	No. PFS events (%)	Median PFS in months (95% CI)	12-month PFS rate (95% CI)	Hazard Ratio (95% CI)*	p-value**
Bendamustine	222	143 (64%)	37.71 (32.85;44.55)	83% (78%;88%)	0.72 (0.57;0.90)	0.004
Chlorambucil	223	165 (74%)	29.89 (26.38;34.66)	85% (80%;90%)	NA	NA
Total	445	308 (69%)	32.92 (28.78;36.79)	84% (81%;88%)	NA	NA

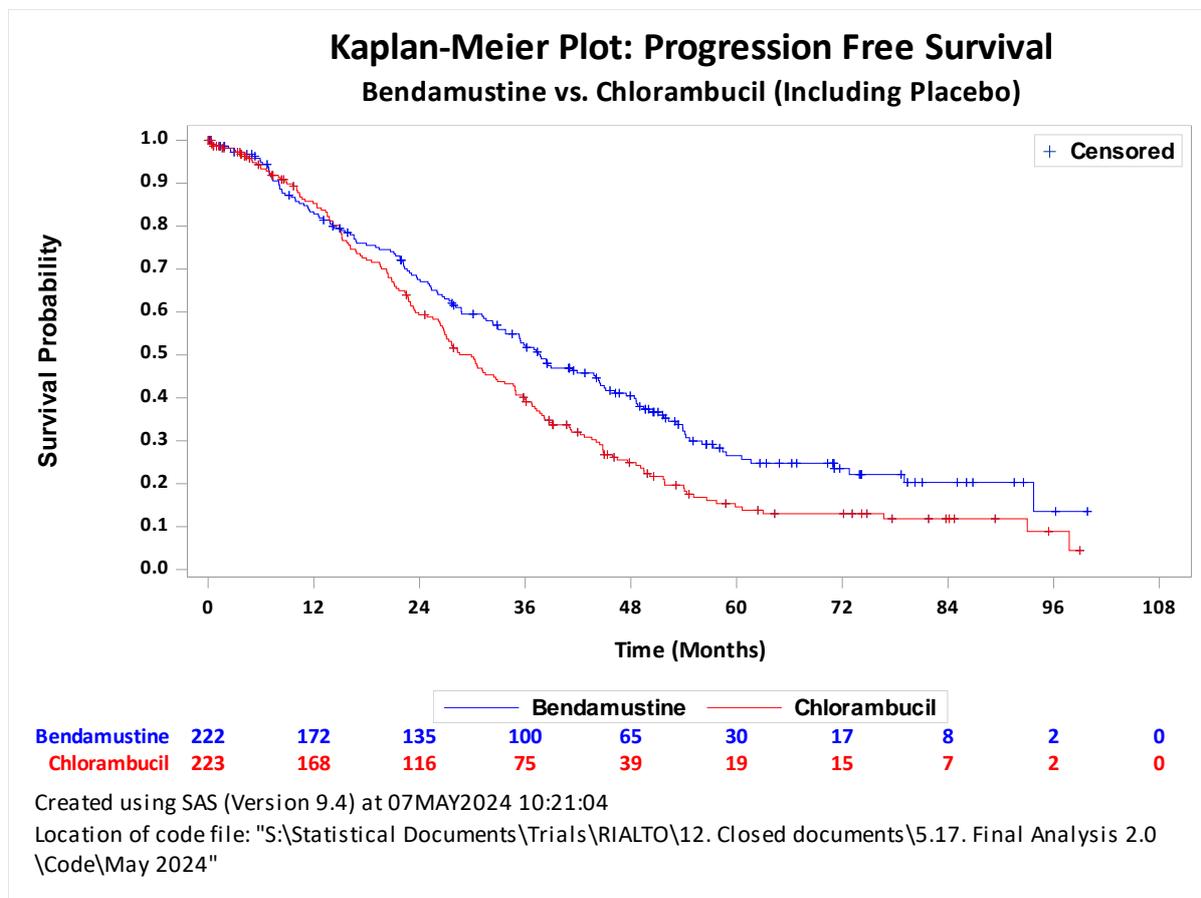
*Stratified Cox PH model

**Stratified log rank test

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Figure 9-1 Kaplan Meier Plot: Progression Free Survival



9.2 Secondary Analysis – Bendamustine vs. Chlorambucil (Including Placebo) Under Non-Proportional Hazards

A test for non-proportional hazards based on correlating Schoenfeld residuals against the rank of time gave a p-value=0.249. There is no evidence of non-proportionality and no analyses under restricted mean survival time is performed.

9.3 Exploratory Analysis – Idelalisib vs. Placebo

Table 9-2 Progression Free Survival

Table 10-3 lists the results for PFS by Idelalisib and Placebo patients. The 12-month PFS rate for the Idelalisib arm was 82% compared to the Placebo arm with 86%. The hazard ratio between the two arms was 0.69 (0.45 – 1.05). Using the trial stratification factors for a stratified log rank test showed no statistically significant difference between the two treatment arms (p>0.05).

Treatment Arm	No. patients	No. PFS events (%)	Median PFS in months (95% CI)	12-month PFS rate (95% CI)	Hazard Ratio (95% CI)*	p-value**
Idelalisib	73	44 (60%)	43.46 (32.42;59.92)	82% (73%;91%)	0.69 (0.45;1.05)	0.082
Placebo	70	53 (76%)	26.84 (22.34;39.13)	86% (78%;95%)	NA	NA
Total	143	97 (68%)	35.45 (26.61;43.99)	84% (78%;90%)	NA	NA

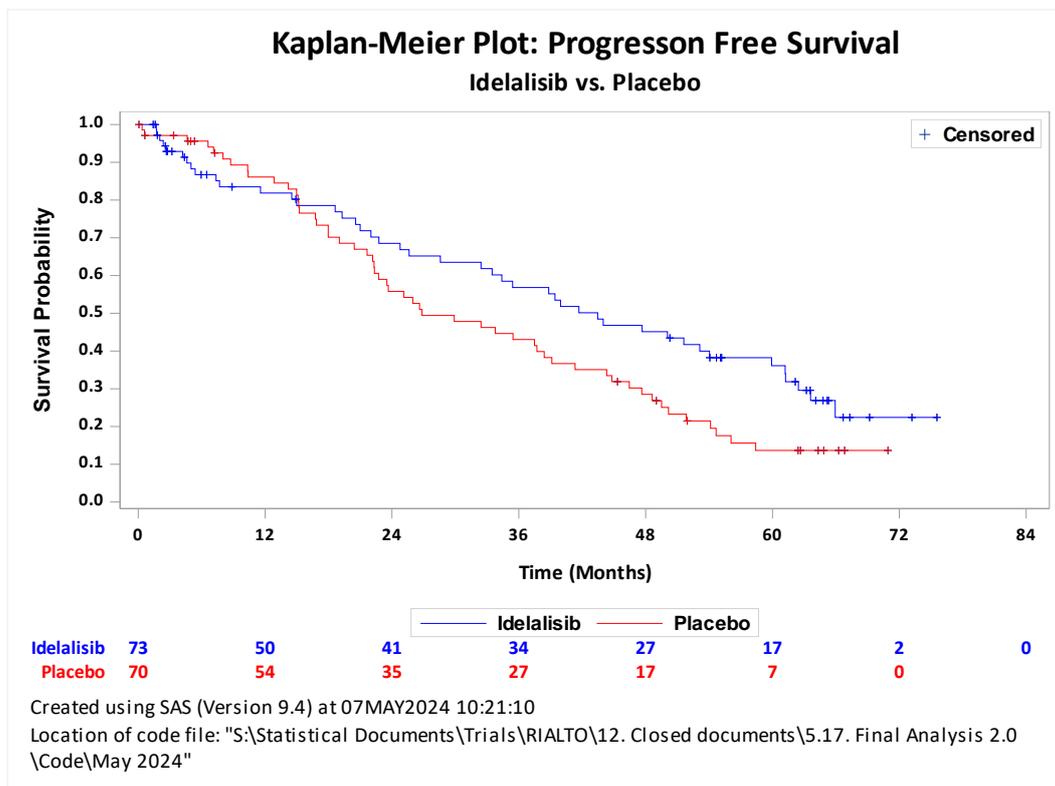
*Stratified Cox PH model

**Stratified log rank test

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Figure 9-2 Kaplan Meier Plot: Progression Free Survival



9.4 Sensitivity Analysis 1 – Per Protocol Set – Bendamustine vs. Chlorambucil (Including Placebo)

Table 9-3 Progression Free Survival

Table 10-4 lists the results for PFS by Bendamustine and Chlorambucil patients (including Placebo patients) within the Per Protocol Set. The 12-month PFS rate for the Bendamustine arm was 81% compared to the Chlorambucil arm with 84%. The hazard ratio between the two arms was 0.73 (0.55 – 0.99). Using the trial stratification factors for a stratified log rank test shown a statistically significant difference between the two treatment arms ($p=0.042$).

Treatment Arm	No. patients	No. PFS events (%)	Median PFS in months (95% CI)	12-month PFS rate (95% CI)	Hazard Ratio (95% CI)*	p-value**
Bendamustine	134	80 (60%)	37.71 (32.29;48.39)	81% (74%;88%)	0.73 (0.55;0.99)	0.042
Chlorambucil	158	111 (70%)	28.32 (25.53;34.86)	84% (78%;90%)	NA	NA
Total	292	191 (65%)	32.65 (27.76;37.09)	83% (78%;88%)	NA	NA

*Stratified Cox PH model

**Stratified log rank test

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9.5 Sensitivity Analysis 2 – All Randomised Patients – Bendamustine vs. Chlorambucil (Including Idelalisib & Placebo)

Table 10-5 lists the results for PFS for all randomised patients (including Idelalisib and Placebo patients). The 12-month PFS rate for both the Bendamustine and Chlorambucil arm was 84%. The hazard ratio between the two arms was 0.67 (0.54 – 0.83). Using the trial stratification factors for a stratified log rank test shown a statistically significant difference between the two treatment arms ($p<0.001$).

Table 9-4 Progression Free Survival

Treatment Arm	No. patients	No. PFS events (%)	Median PFS in months (95% CI)	12-month PFS rate (95% CI)	Hazard Ratio (95% CI)*	p-value**
Bendamustine	260	162 (62%)	41.33 (35.45;48.39)	84% (79%;89%)	0.67 (0.54;0.83)	<0.001
Chlorambucil	261	190 (73%)	28.58 (26.38;33.67)	84% (79%;88%)	NA	NA
Total	521	352 (68%)	34.86 (31.11;37.48)	84% (80%;87%)	NA	NA

*Stratified Cox PH model

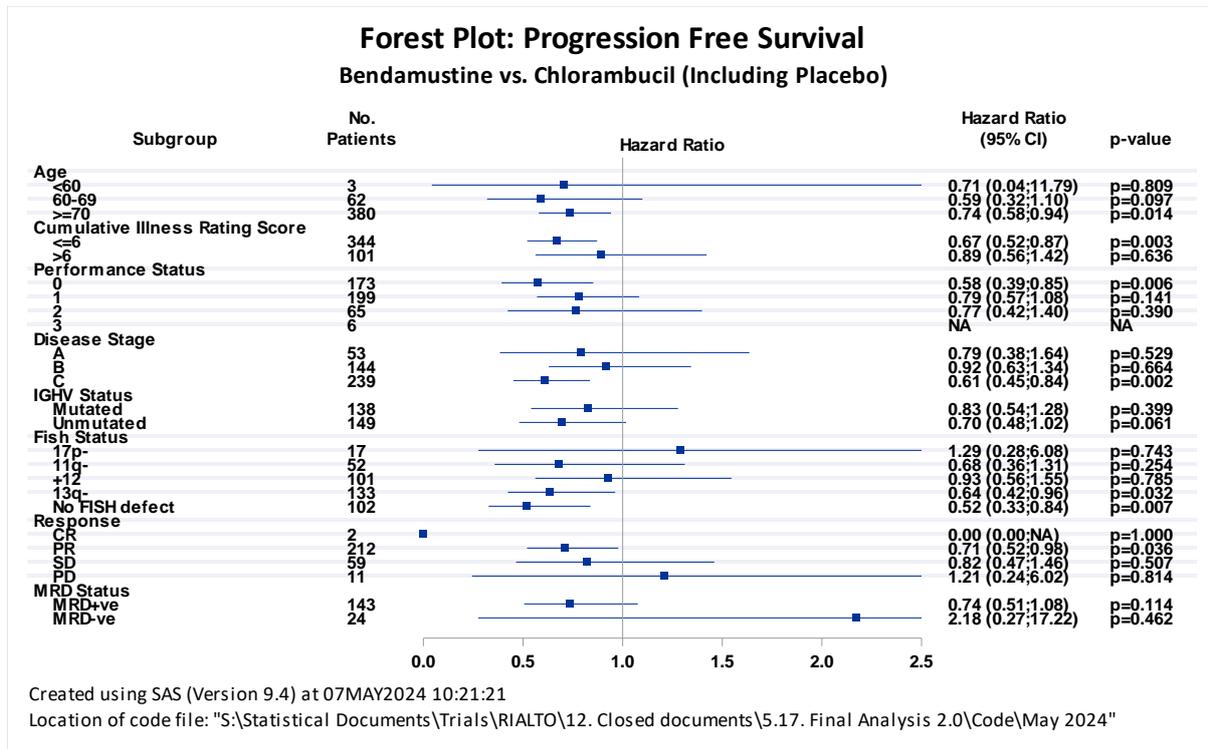
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9.6 Subgroup Analysis – Bendamustine vs. Chlorambucil (Including Placebo)

Figure 9-3 Forest Plot: Progression Free Survival



9.7 Progression Free Survival Summary

Analysis of the primary outcome shows that progression free survival is improved on Bendamustine compared to Chlorambucil [HR=0.72 (0.57;0.90); p=0.004]. The benefit is approximately 8 months [37.71 (32.85;44.55) vs. 29.89 (26.38;34.66)]. Results are consistent across in the subgroup and sensitivity analyses with the exception of the 17p- FISH status group, PD response & MRD-ve status group.

10 Secondary Outcome – Overall Survival (OS)

10.1 Primary Analysis – Bendamustine vs. Chlorambucil (Including Placebo)

Table 10-1 Overall Survival

Table 10-1 lists the results for OS by Bendamustine and Chlorambucil patients (including Placebo patients). The 12-month OS rate for the Bendamustine arm was 75% compared to the Chlorambucil arm with 70%. The hazard ratio between the two arms was 1.08 (0.78 – 1.48). Using the trial stratification factors for a stratified log rank test showed no statistically significant difference between the two treatment arms ($p > 0.05$).

Treatment Arm	No. patients	No. OS events (%)	Median OS in months (95% CI)	12-month OS rate (95% CI)	Hazard Ratio (95% CI)*	p-value**
Bendamustine	222	83 (37%)	75.03 (63.45;90.07)	92% (89%;96%)	1.08 (0.78;1.48)	0.650
Chlorambucil	223	76 (34%)	70.10 (59.93;93.13)	95% (92%;98%)	NA	NA
Total	445	159 (36%)	71.22 (63.72;82.99)	94% (91%;96%)	NA	NA

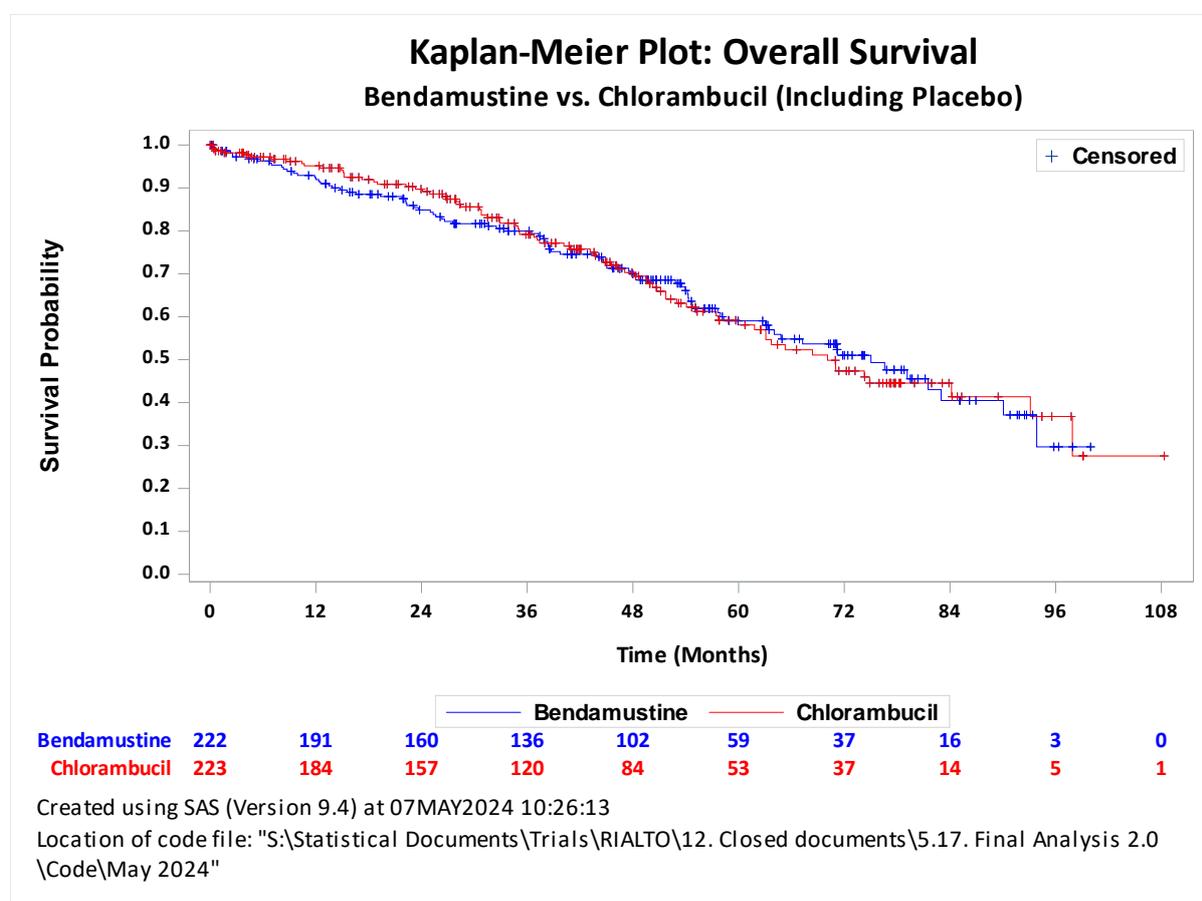
*Stratified Cox PH model

**Stratified log rank test

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Figure 10-1 Kaplan Meier Plot: Overall Survival



10.2 Exploratory Analysis – Idelalisib vs. Placebo

Table 10-2 Overall Survival

Table 11-2 lists the results for OS by Idelalisib and Placebo patients. The 12-month OS rate for the Idelalisib arm was 88% compared to the Placebo arm with 94%. The hazard ratio between the two arms was 0.70 (0.38 – 1.29). Using the trial stratification factors for a stratified log rank test showed no statistically significant difference between the two treatment arms (p=0.251).

Treatment Arm	No. patients	No. OS events (%)	Median OS in months (95% CI)	12-month OS rate (95% CI)	Hazard Ratio (95% CI)*	p-value**
Idelalisib	73	20 (27%)	NA (66.78;NA)	88% (81%;96%)	0.70 (0.38;1.29)	0.251
Placebo	70	26 (37%)	57.70 (52.83;NA)	94% (88%;100%)	NA	NA
Total	143	46 (32%)	75.03 (66.02;NA)	91% (86%;96%)	NA	NA

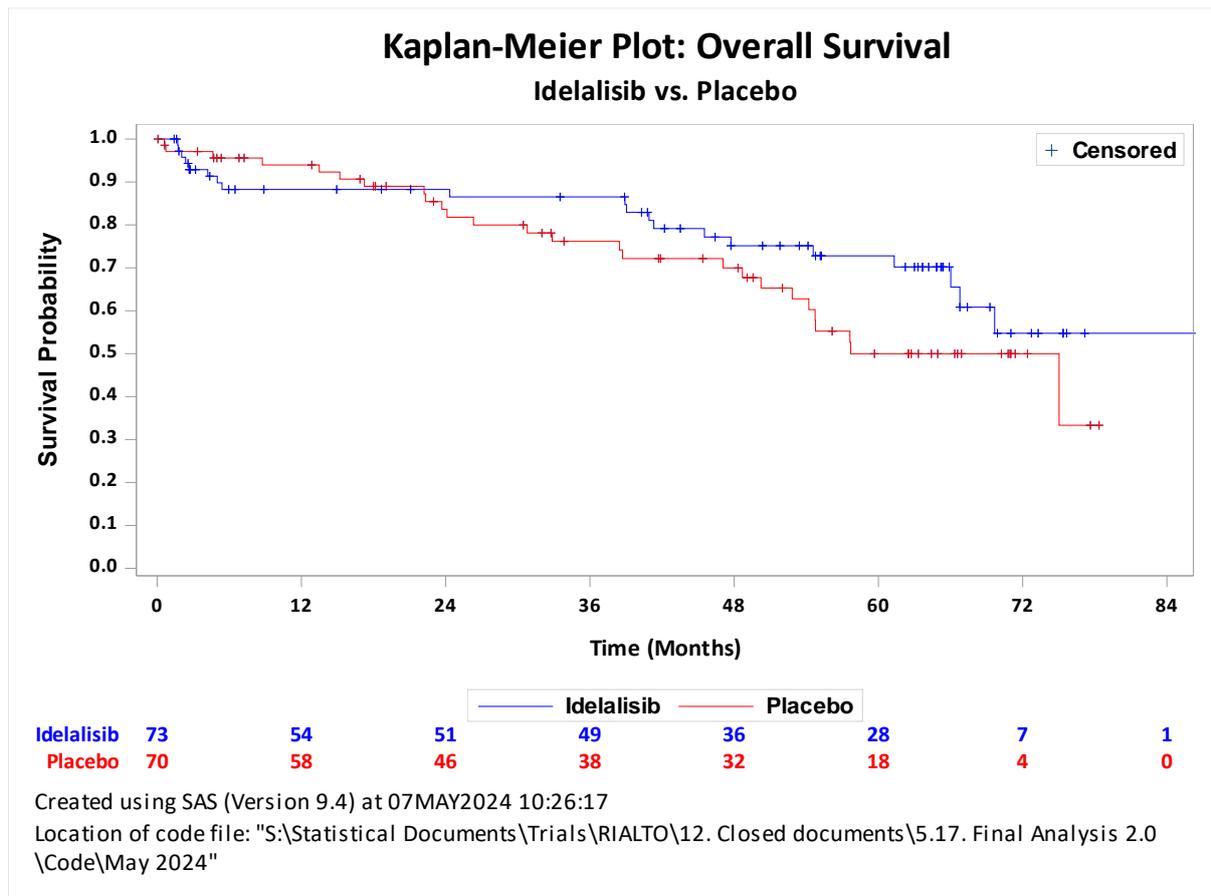
*Stratified Cox PH model

**Stratified log rank test

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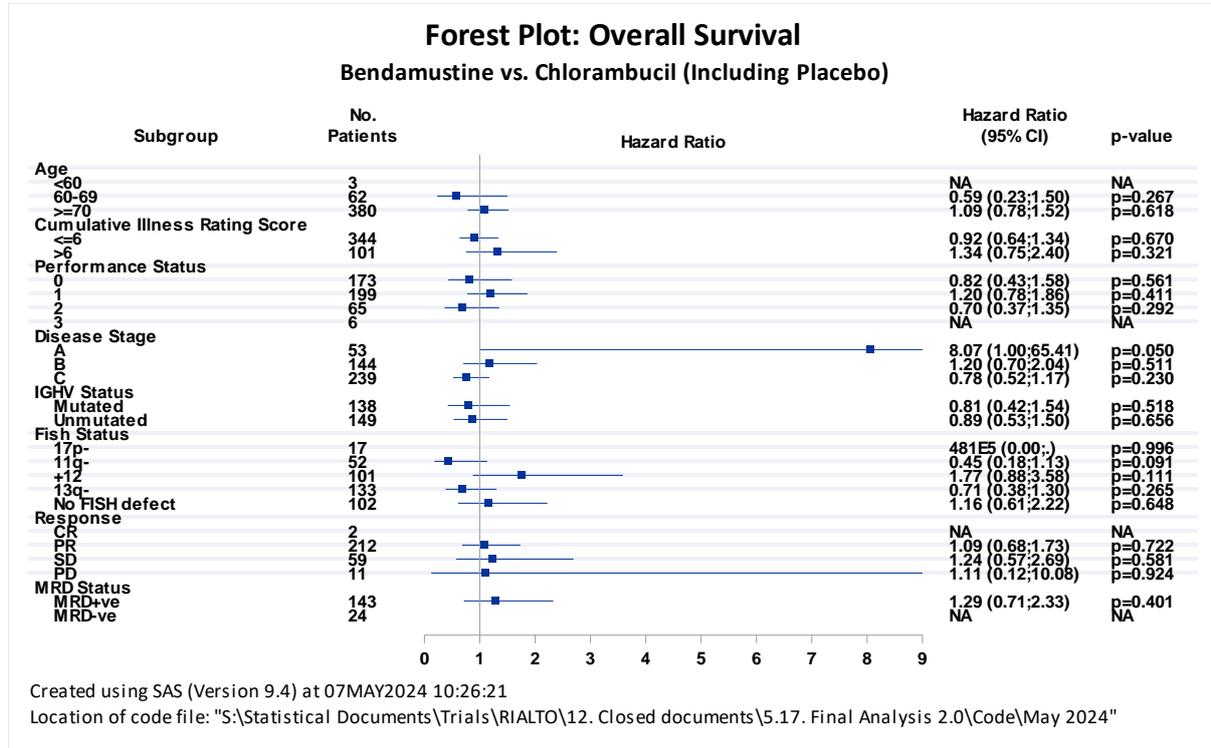
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Figure 10-2 Kaplan Meier Plot: Overall Survival



10.3 Subgroup Analysis – Bendamustine vs. Chlorambucil (Including Placebo)

Figure 10-3 Forest Plot: Overall Survival



10.4 Overall Survival Summary

There is no evidence of any difference between Bendamustine and Chlorambucil with respect to overall survival which is consistent across subgroup analyses.

11 Secondary Outcome – Response Including MRD Negativity

11.1 Primary Analysis – Bendamustine vs. Chlorambucil (Including Placebo)

Table 11-1 Response by MRD Status

Table 12-1 below shows disease responses split by bone marrow MRD.

MRD	CR	PR	SD	PD	Response Unknown
MRD data not available	2 (1%)	109 (39%)	30 (11%)	7 (3%)	130 (47%)
MRD data available	0 (0%)	103 (62%)	29 (17%)	4 (2%)	31 (19%)
MRD+ve	0 (0%)	88 (62%)	28 (20%)	4 (3%)	23 (16%)
MRD-ve	0 (0%)	15 (63%)	1 (4%)	0 (0%)	8 (33%)

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Table 11-2 Response and MRD by Treatment

Response/MRD	Bendamustine (N=223)	Chlorambucil (N=225)	Total (N=448)
Response, no. patients	143	141	284
Complete Remission	1 (1%)	1 (1%)	2 (1%)
Partial Remission	111 (78%)	101 (72%)	212 (75%)
Stable Disease	23 (16%)	36 (26%)	59 (21%)
Progressive Disease	8 (6%)	3 (2%)	11 (4%)
MRD, no. patients	79	88	167
MRD+ve	59 (75%)	84 (95%)	143 (86%)
MRD-ve	20 (25%)	4 (5%)	24 (14%)

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Table 12-3 Overall Response (Complete Remission & Partial Remission)

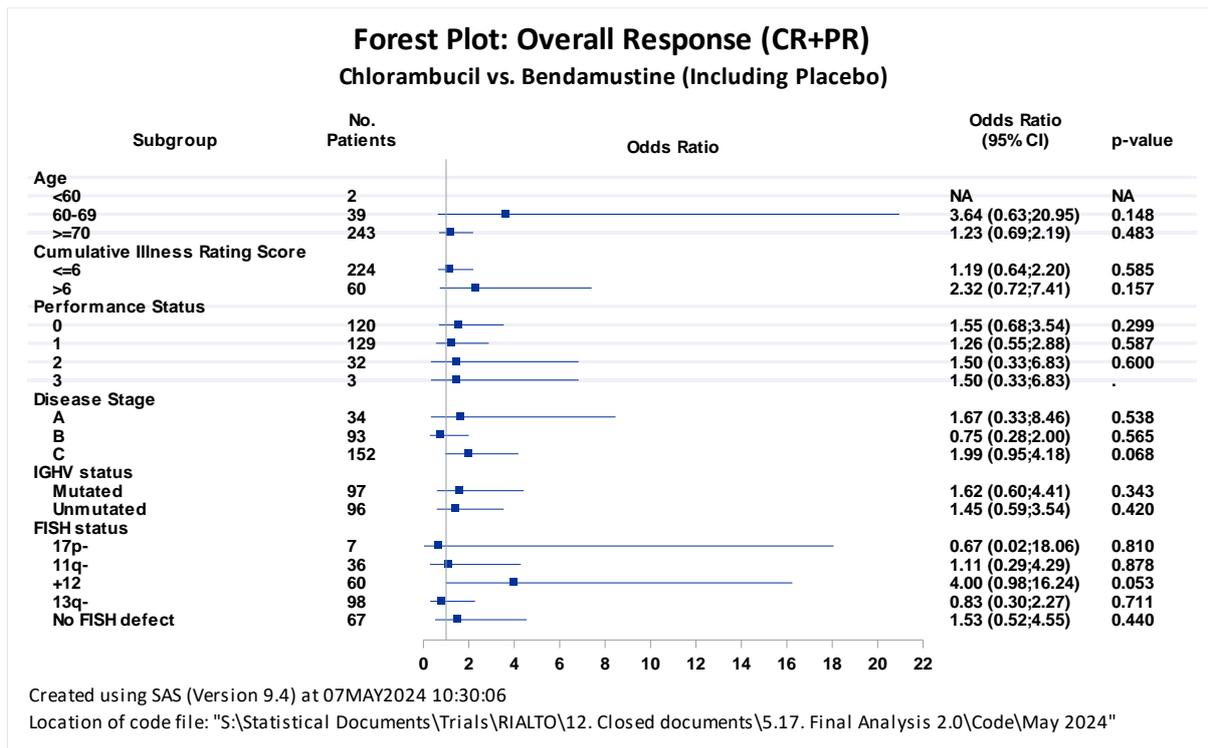
Treatment Arm	No. Patients	No. Events	Odds Ratio (95% CI)*	p-value*
Bendamustine	143	112	1.31 (0.76;2.26)	0.334
Chlorambucil	141	102	NA	NA

*Logistic regression model

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Figure 11-1 Forest Plot: Overall Response



11.2 Response Including MRD Negativity Summary

Sufficient information was available to assign end-of-treatment response and MRD status in 143/223 (64.1%) and 79/223 (35.4%) patients, respectively, in the bendamustine cohort, and 141/225 (62.7%) and 88/225 (39.1%) patients, respectively, in the chlorambucil cohort. Overall, MRD data was available in 0/2 (0%), 103/212 (48.6%), 29/59 (49.2%) and 4/11 (36.4%) patients who achieved a CR, PR, SD and PD, respectively, This indicates that, although response/MRD data was incomplete, there was no obvious association between treatment allocation and the availability of response and MRD data, nor between response achieved and the availability of MRD data. Although complete and partial response rates were similar for bendamustine and chlorambucil, MRD negative rates were higher for bendamustine (25% vs 5%).

12 Secondary Outcome – Duration of Response

12.1 Primary Analysis – Bendamustine vs. Chlorambucil (Including Placebo)

Table 13-1 Duration of Response

Treatment Arm	No. patients	No. relapse/progression events (%)	Median response duration in months (95% CI)	12-month response duration rate (95% CI)	Hazard Ratio (95% CI)*	p-value**
Bendamustine	112	54 (48%)	44.44 (32.57;49.80)	93% (88%;98%)	0.58 (0.40;0.84)	0.004
Chlorambucil	102	67 (66%)	30.20 (23.19;34.90)	81% (73%;88%)	NA	NA
Total	214	121 (57%)	34.90 (30.95;41.74)	87% (82%;91%)	NA	NA

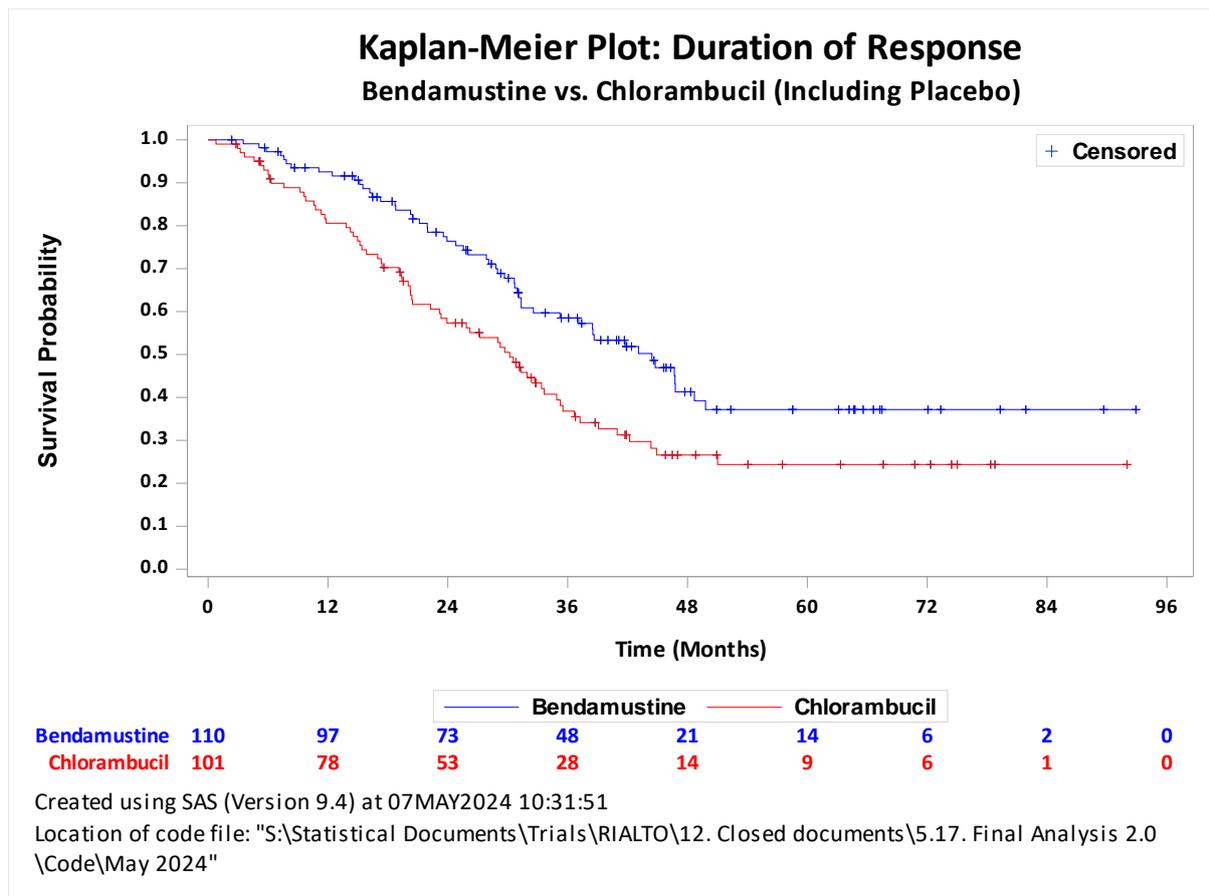
*Stratified Cox PH model

**Stratified log rank test

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Figure 13-1 Kaplan Meier Plot: Duration of Response



12.2 Duration of Response Summary

Duration of response is improved on Bendamustine compared to Chlorambucil [HR=0.58 (0.40;0.84); p=0.004]. The benefit is approximately 14 months [44.44 (32.57;49.80) vs. 30.20 (23.19;34.90)].

13 Secondary Outcome – Time to Treatment Failure (TTF)

13.1 Primary Analysis – Bendamustine vs. Chlorambucil (Including Placebo)

Table 14-1 Time to Treatment Failure

Treatment Arm	No. patients	No. TTF events (%)	Median TTF in months (95% CI)	12-month TTF rate (95% CI)	Hazard Ratio (95% CI)*	p-value**
Bendamustine	215	141 (66%)	37.73 (32.76;44.61)	84% (78%;89%)	0.68 (0.54;0.86)	0.001
Chlorambucil	219	168 (77%)	28.09 (26.18;33.59)	83% (78%;88%)	NA	NA
Total	434	309 (71%)	32.76 (28.68;35.92)	83% (80%;87%)	NA	NA

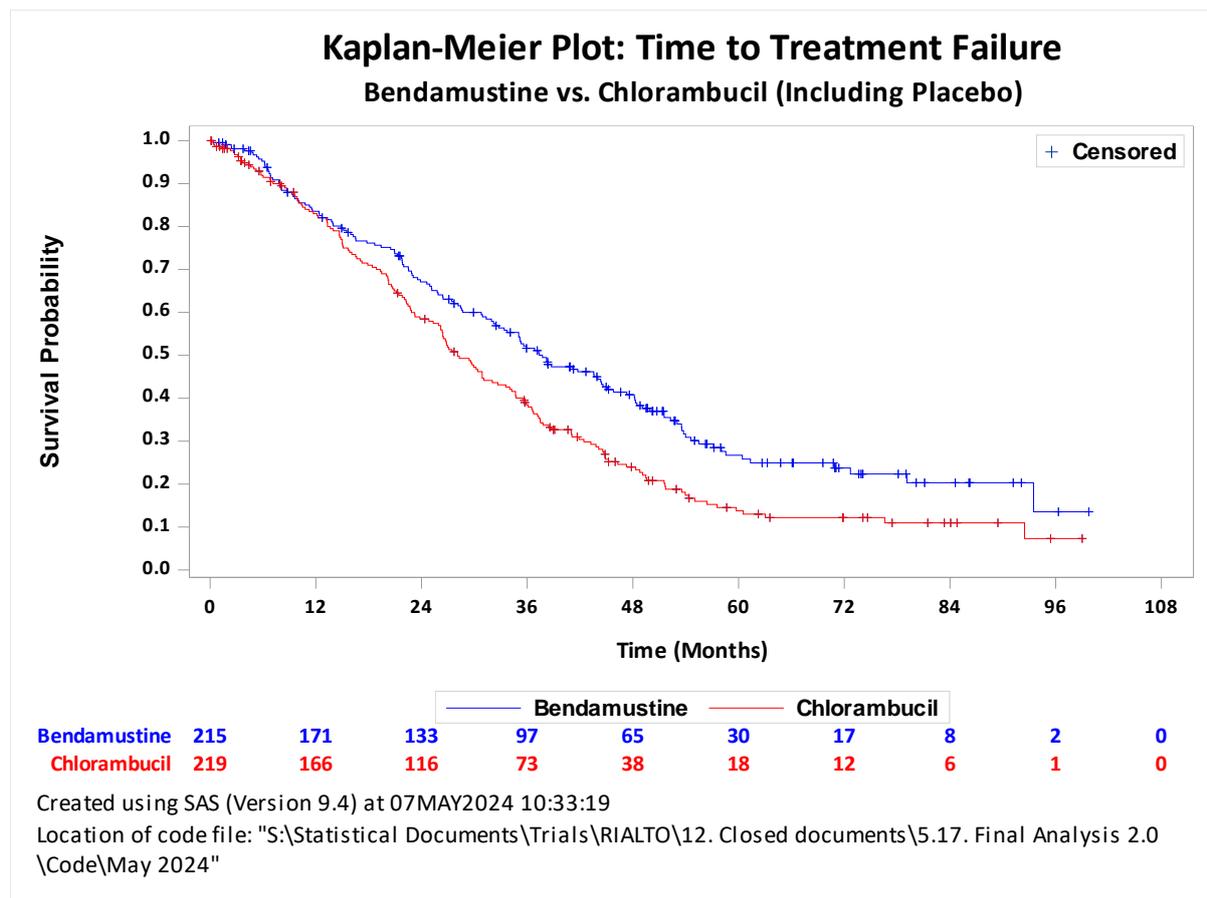
*Stratified Cox PH model

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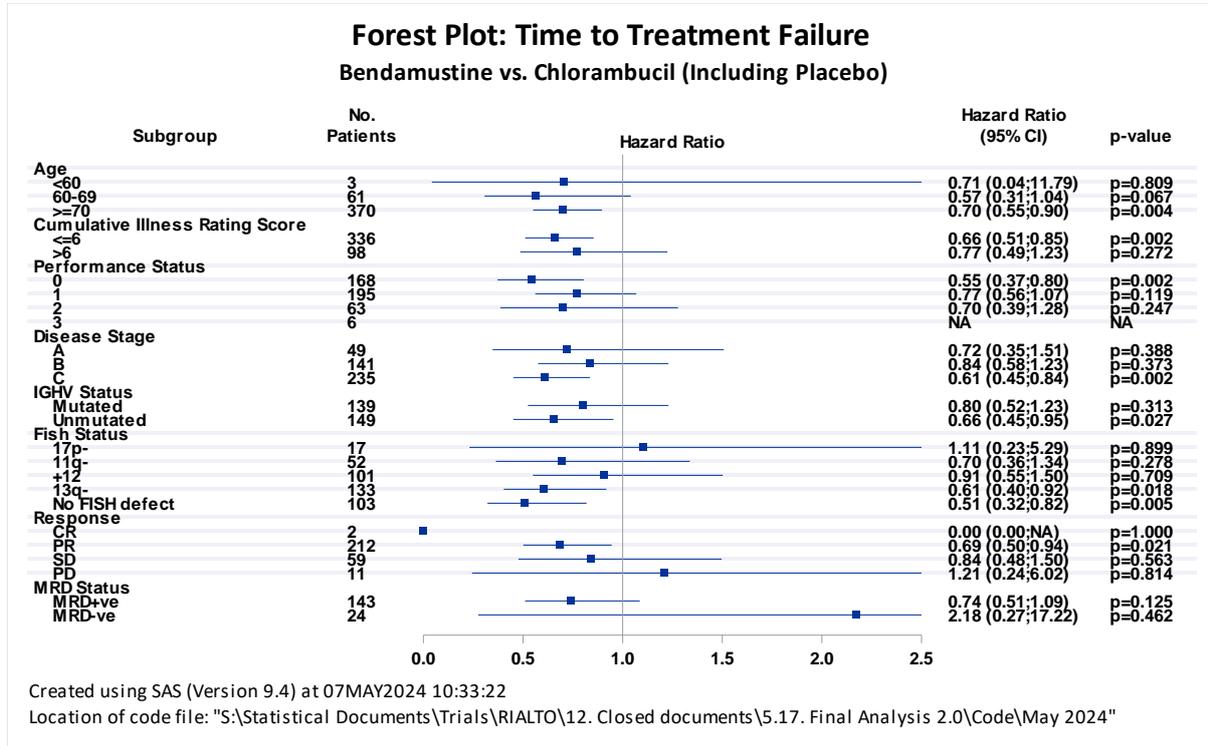
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Figure 14-1 Kaplan Meier Plot: Time to Treatment Failure



13.2 Subgroup Analysis – Bendamustine vs. Chlorambucil (Including Placebo)

Figure 14-2 Forest Plot: Time to Treatment Failure



13.3 Time to Treatment Failure Summary

Time to treatment failure is improved on Bendamustine compared to Chlorambucil [HR=0.68 (0.54;0.86); p=0.001]. The benefit is approximately 9 months [37.73 (32.76;44.61) vs. 28.09 (26.18;33.59)].

14 Secondary Outcome – Toxicity

Toxicity are reported in terms of Adverse Events (AEs), Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs). AEs and SAEs are mutually exclusive meaning that no one event will be reported in more than one section, however SUSARs will be within SAE tables. Analysis on toxicities will be done on the safety set (SS) which consists of all patients who received any trial treatment.

14.1 Primary Analysis – Bendamustine vs. Chlorambucil (Including Placebo)

An overview of toxicity is presented in terms of the number of patients to report a grade 3+ adverse event or a serious adverse event across treatment groups.

Table 15-1: Toxicity Summary – Bendamustine vs. Chlorambucil (Including Placebo)

Variable	Bendamustine (N=215)	Chlorambucil (N=219)	Total (N=434)
Grade 3+ AE	108 (50%)	102 (47%)	210 (48%)
SAE	139 (65%)	127 (58%)	266 (61%)
Either Grade 3+ AE or SAE	175 (81%)	166 (76%)	341 (79%)

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14.1.1 Adverse Events

Table 15-2: Adverse Events by Severity – Bendamustine vs. Chlorambucil (Including Placebo)

Severity	Bendamustine (N=215)	Chlorambucil (N=219)	Total (N=434)
1	1162 (54%)	1105 (53%)	2267 (54%)
2	694 (33%)	704 (34%)	1398 (33%)
3	219 (10%)	222 (11%)	441 (10%)
4	43 (2%)	32 (2%)	75 (2%)
5	0 (0%)	1 (0%)	1 (0%)
Missing	17 (1%)	19 (1%)	36 (1%)

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Table 15-3: Adverse Events by CTCAE Category Name and Event Name – Bendamustine vs. Chlorambucil (Including Placebo)

				Bendamustine (N=215)		Chlorambucil (N=219)		
Category Name		Event Name		Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Blood and disorders	lymphatic system	Anemia		1	57	34	42	25
Blood and disorders	lymphatic system	Anemia		2	39	26	25	20
Blood and disorders	lymphatic system	Anemia		3	16	11	18	13
Blood and disorders	lymphatic system	Blood and lymphatic system disorders - Other, specify		1	10	6	21	11
Blood and disorders	lymphatic system	Blood and lymphatic system disorders - Other, specify		2	8	4	13	10
Blood and disorders	lymphatic system	Blood and lymphatic system disorders - Other, specify		3	3	1	6	5
Blood and disorders	lymphatic system	Blood and lymphatic system disorders - Other, specify		4	1	1	0	0
Blood and disorders	lymphatic system	Blood and lymphatic system disorders - Other, specify		Missing	1	1	0	0
Blood and disorders	lymphatic system	Febrile neutropenia		1	0	0	1	1
Blood and disorders	lymphatic system	Febrile neutropenia		3	1	1	1	1
Blood and disorders	lymphatic system	Haemolysis		3	0	0	1	1
Blood and disorders	lymphatic system	Haemolytic uremic syndrome		2	0	0	1	1

				Bendamustine (N=215)		Chlorambucil (N=219)	
Category Name		Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Blood and lymphatic system disorders		Leukocytosis	1	3	2	0	0
Blood and lymphatic system disorders		Leukocytosis	2	1	1	0	0
Blood and lymphatic system disorders		Leukocytosis	3	1	1	2	2
Blood and lymphatic system disorders		Leukocytosis	4	1	1	0	0
Blood and lymphatic system disorders		Leukocytosis	Missing	1	1	0	0
Blood and lymphatic system disorders		Lymph node pain	1	1	1	0	0
Blood and lymphatic system disorders		Lymph node pain	Missing	0	0	1	1
Blood and lymphatic system disorders		Thrombotic thrombocytopenic purpura	1	2	1	3	3
Blood and lymphatic system disorders		Thrombotic thrombocytopenic purpura	2	2	1	6	4
Blood and lymphatic system disorders		Thrombotic thrombocytopenic purpura	3	4	3	2	2
Cardiac disorders		Aortic valve disease	1	1	1	0	0
Cardiac disorders		Atrial fibrillation	1	0	0	1	1
Cardiac disorders		Atrial fibrillation	2	3	3	2	2
Cardiac disorders		Atrial fibrillation	3	0	0	1	1

			Bendamustine (N=215)		Chlorambucil (N=219)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Cardiac disorders	Atrial fibrillation	Missing	1	1	1	1
Cardiac disorders	Atrial flutter	2	1	1	0	0
Cardiac disorders	Cardiac disorders - Other, specify	1	0	0	4	4
Cardiac disorders	Cardiac disorders - Other, specify	2	2	2	2	2
Cardiac disorders	Cardiac disorders - Other, specify	3	1	1	2	2
Cardiac disorders	Chest pain - cardiac	1	2	2	1	1
Cardiac disorders	Chest pain - cardiac	2	1	1	1	1
Cardiac disorders	Heart failure	3	1	1	1	1
Cardiac disorders	Palpitations	1	1	1	2	2
Cardiac disorders	Palpitations	2	2	2	1	1
Cardiac disorders	Sinus bradycardia	1	2	2	1	1
Cardiac disorders	Sinus tachycardia	1	2	2	1	1
Cardiac disorders	Sinus tachycardia	2	0	0	1	1
Cardiac disorders	Sinus tachycardia	3	0	0	1	1
Cardiac disorders	Ventricular tachycardia	2	1	1	0	0
Ear and labyrinth disorders	Ear and labyrinth disorders - Other, specify	1	1	1	3	2
Ear and labyrinth disorders	Ear and labyrinth disorders - Other, specify	2	0	0	2	2
Ear and labyrinth disorders	Ear pain	1	2	2	4	4
Ear and labyrinth disorders	Ear pain	2	1	1	0	0
Ear and labyrinth disorders	External ear inflammation	1	1	1	0	0
Ear and labyrinth disorders	Hearing impaired	1	0	0	1	1

			Bendamustine (N=215)		Chlorambucil (N=219)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Ear and labyrinth disorders	Hearing impaired	2	0	0	1	1
Ear and labyrinth disorders	Hearing impaired	3	0	0	1	1
Ear and labyrinth disorders	Vertigo	1	3	3	0	0
Ear and labyrinth disorders	Vertigo	2	1	1	1	1
Ear and labyrinth disorders	Vestibular disorder	2	3	3	0	0
Endocrine disorders	Endocrine disorders - Other, specify	1	0	0	1	1
Eye disorders	Blurred vision	1	0	0	1	1
Eye disorders	Blurred vision	2	1	1	2	2
Eye disorders	Cataract	1	0	0	1	1
Eye disorders	Cataract	3	1	1	0	0
Eye disorders	Conjunctivitis	1	1	1	1	1
Eye disorders	Conjunctivitis	2	3	3	1	1
Eye disorders	Dry eye	1	1	1	1	1
Eye disorders	Eye disorders - Other, specify	1	5	5	4	4
Eye disorders	Eye disorders - Other, specify	2	2	2	0	0
Eye disorders	Eye pain	1	0	0	1	1
Eye disorders	Eyelid function disorder	2	0	0	1	1
Eye disorders	Flashing lights	1	0	0	2	2
Eye disorders	Watering eyes	1	0	0	1	1
Gastrointestinal disorders	Abdominal distension	1	0	0	2	2
Gastrointestinal disorders	Abdominal distension	2	0	0	1	1

			Bendamustine (N=215)		Chlorambucil (N=219)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Gastrointestinal disorders	Abdominal pain	1	16	12	13	12
Gastrointestinal disorders	Abdominal pain	2	3	3	4	4
Gastrointestinal disorders	Abdominal pain	3	2	2	0	0
Gastrointestinal disorders	Anal pain	2	1	1	0	0
Gastrointestinal disorders	Anal ulcer	2	1	1	0	0
Gastrointestinal disorders	Bloating	1	3	3	2	1
Gastrointestinal disorders	Bloating	2	1	1	0	0
Gastrointestinal disorders	Colitis	2	1	1	0	0
Gastrointestinal disorders	Colonic hemorrhage	1	1	1	0	0
Gastrointestinal disorders	Colonic hemorrhage	2	0	0	1	1
Gastrointestinal disorders	Constipation	1	54	39	34	27
Gastrointestinal disorders	Constipation	2	17	12	9	7
Gastrointestinal disorders	Constipation	3	3	2	0	0
Gastrointestinal disorders	Constipation	Missing	1	1	0	0
Gastrointestinal disorders	Dental caries	2	1	1	0	0
Gastrointestinal disorders	Diarrhea	1	44	30	49	32
Gastrointestinal disorders	Diarrhea	2	20	17	18	12
Gastrointestinal disorders	Diarrhea	3	9	5	2	2
Gastrointestinal disorders	Dry mouth	1	12	11	5	4
Gastrointestinal disorders	Dry mouth	3	0	0	1	1
Gastrointestinal disorders	Dyspepsia	1	1	1	2	2

			Bendamustine (N=215)		Chlorambucil (N=219)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Gastrointestinal disorders	Dyspepsia	2	0	0	2	2
Gastrointestinal disorders	Dysphagia	1	0	0	1	1
Gastrointestinal disorders	Esophageal pain	2	1	1	0	0
Gastrointestinal disorders	Flatulence	1	2	2	0	0
Gastrointestinal disorders	Gastroesophageal reflux disease	1	2	2	1	1
Gastrointestinal disorders	Gastroesophageal reflux disease	2	1	1	1	1
Gastrointestinal disorders	Gastrointestinal disorders - Other, specify	1	10	9	3	3
Gastrointestinal disorders	Gastrointestinal disorders - Other, specify	2	8	6	3	3
Gastrointestinal disorders	Gastrointestinal disorders - Other, specify	3	0	0	1	1
Gastrointestinal disorders	Gastrointestinal pain	1	1	1	0	0
Gastrointestinal disorders	Gingival pain	1	0	0	1	1
Gastrointestinal disorders	Gingival pain	2	1	1	0	0
Gastrointestinal disorders	Haemorrhoids	1	1	1	0	0
Gastrointestinal disorders	Haemorrhoids	2	1	1	0	0
Gastrointestinal disorders	Mucositis oral	1	2	2	2	2
Gastrointestinal disorders	Mucositis oral	2	5	5	3	3
Gastrointestinal disorders	Nausea	1	72	53	80	55
Gastrointestinal disorders	Nausea	2	17	14	22	17
Gastrointestinal disorders	Nausea	3	4	2	2	2
Gastrointestinal disorders	Nausea	Missing	2	2	0	0
Gastrointestinal disorders	Oral dysesthesia	1	1	1	0	0

			Bendamustine (N=215)		Chlorambucil (N=219)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Gastrointestinal disorders	Oral pain	1	4	4	8	8
Gastrointestinal disorders	Oral pain	2	0	0	1	1
Gastrointestinal disorders	Rectal hemorrhage	1	1	1	0	0
Gastrointestinal disorders	Salivary duct inflammation	1	0	0	1	1
Gastrointestinal disorders	Stomach pain	1	0	0	3	3
Gastrointestinal disorders	Stomach pain	2	1	1	2	1
Gastrointestinal disorders	Toothache	2	0	0	3	3
Gastrointestinal disorders	Vomiting	1	29	23	39	31
Gastrointestinal disorders	Vomiting	2	9	7	11	8
Gastrointestinal disorders	Vomiting	Missing	1	1	0	0
General disorders and administration site conditions	Chills	1	16	13	18	15
General disorders and administration site conditions	Chills	2	1	1	3	3
General disorders and administration site conditions	Chills	Missing	1	1	0	0
General disorders and administration site conditions	Edema face	1	2	2	0	0
General disorders and administration site conditions	Edema limbs	1	16	15	13	12
General disorders and administration site conditions	Edema limbs	2	5	5	1	1

			Bendamustine (N=215)		Chlorambucil (N=219)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
General disorders and administration site conditions	Edema limbs	Missing	1	1	0	0
General disorders and administration site conditions	Fatigue	1	68	49	74	60
General disorders and administration site conditions	Fatigue	2	20	18	21	17
General disorders and administration site conditions	Fatigue	3	3	3	5	3
General disorders and administration site conditions	Fever	1	23	20	13	9
General disorders and administration site conditions	Fever	2	7	6	1	1
General disorders and administration site conditions	Flu like symptoms	1	8	8	3	3
General disorders and administration site conditions	Flu like symptoms	2	2	2	2	1
General disorders and administration site conditions	Flu like symptoms	3	1	1	1	1
General disorders and administration site conditions	Gait disturbance	2	1	1	0	0
General disorders and administration site conditions	Gait disturbance	3	0	0	1	1
General disorders and administration site conditions	General disorders and administration site conditions - Other, specify	1	19	13	21	15

			Bendamustine (N=215)		Chlorambucil (N=219)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
General disorders and administration site conditions	General disorders and administration site conditions - Other, specify	2	5	4	5	5
General disorders and administration site conditions	General disorders and administration site conditions - Other, specify	3	0	0	2	1
General disorders and administration site conditions	General disorders and administration site conditions - Other, specify	Missing	0	0	1	1
General disorders and administration site conditions	Infusion related reaction	1	16	13	22	17
General disorders and administration site conditions	Infusion related reaction	2	60	45	64	38
General disorders and administration site conditions	Infusion related reaction	3	6	4	11	7
General disorders and administration site conditions	Infusion related reaction	4	0	0	2	1
General disorders and administration site conditions	Infusion related reaction	Missing	2	1	2	2
General disorders and administration site conditions	Infusion site extravasation	2	1	1	0	0
General disorders and administration site conditions	Injection site reaction	1	0	0	1	1
General disorders and administration site conditions	Localized edema	1	1	1	1	1
General disorders and administration site conditions	Localized edema	2	0	0	1	1

			Bendamustine (N=215)		Chlorambucil (N=219)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
General disorders and administration site conditions	Malaise	1	2	1	1	1
General disorders and administration site conditions	Malaise	2	0	0	2	2
General disorders and administration site conditions	Neck edema	1	0	0	1	1
General disorders and administration site conditions	Non-cardiac chest pain	1	1	1	2	2
General disorders and administration site conditions	Non-cardiac chest pain	2	0	0	2	2
General disorders and administration site conditions	Oedema	1	15	13	9	8
General disorders and administration site conditions	Oedema	2	1	1	2	2
General disorders and administration site conditions	Oedema	3	1	1	0	0
General disorders and administration site conditions	Pain	1	24	22	19	11
General disorders and administration site conditions	Pain	2	7	7	7	4
General disorders and administration site conditions	Pain	3	1	1	3	2
Hepatobiliary disorders	Hepatic pain	3	1	1	0	0
Hepatobiliary disorders	Portal vein thrombosis	2	1	1	0	0
Immune system disorders	Allergic reaction	1	7	7	5	5

			Bendamustine (N=215)		Chlorambucil (N=219)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Immune system disorders	Allergic reaction	2	14	12	25	18
Immune system disorders	Allergic reaction	3	2	1	0	0
Immune system disorders	Allergic reaction	5	0	0	1	1
Immune system disorders	Allergic reaction	Missing	0	0	1	1
Immune system disorders	Anaphylaxis	3	1	1	0	0
Immune system disorders	Immune system disorders - Other, specify	1	1	1	0	0
Immune system disorders	Immune system disorders - Other, specify	2	0	0	1	1
Immune system disorders	Immune system disorders - Other, specify	3	1	1	0	0
Infections and infestations	Bladder infection	2	1	1	0	0
Infections and infestations	Bronchial infection	1	1	1	1	1
Infections and infestations	Bronchial infection	2	3	3	11	9
Infections and infestations	Bronchial infection	3	2	2	1	1
Infections and infestations	Device related infection	2	1	1	0	0
Infections and infestations	Eye infection	1	1	1	0	0
Infections and infestations	Eye infection	2	4	3	3	3
Infections and infestations	Hepatic infection	3	1	1	0	0
Infections and infestations	Infections and infestations - Other, specify	1	14	12	19	13
Infections and infestations	Infections and infestations - Other, specify	2	16	15	17	15
Infections and infestations	Infections and infestations - Other, specify	3	2	2	1	1
Infections and infestations	Lip infection	1	1	1	0	0
Infections and infestations	Lung infection	1	0	0	1	1

			Bendamustine (N=215)		Chlorambucil (N=219)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Infections and infestations	Lung infection	2	8	6	10	10
Infections and infestations	Lung infection	3	2	2	2	2
Infections and infestations	Mucosal infection	1	0	0	1	1
Infections and infestations	Mucosal infection	2	2	1	1	1
Infections and infestations	Otitis media	2	1	1	0	0
Infections and infestations	Papulopustular rash	1	1	1	0	0
Infections and infestations	Papulopustular rash	3	1	1	0	0
Infections and infestations	Penile infection	2	1	1	0	0
Infections and infestations	Pharyngitis	1	1	1	1	1
Infections and infestations	Pharyngitis	2	0	0	1	1
Infections and infestations	Phlebitis infective	2	0	0	1	1
Infections and infestations	Rash pustular	1	0	0	1	1
Infections and infestations	Rash pustular	2	0	0	1	1
Infections and infestations	Rhinitis infective	2	1	1	1	1
Infections and infestations	Sepsis	2	0	0	1	1
Infections and infestations	Sinusitis	1	0	0	1	1
Infections and infestations	Sinusitis	2	3	1	1	1
Infections and infestations	Skin infection	1	2	2	1	1
Infections and infestations	Skin infection	2	4	4	4	4
Infections and infestations	Skin infection	3	1	1	2	2
Infections and infestations	Soft tissue infection	2	2	2	0	0

			Bendamustine (N=215)		Chlorambucil (N=219)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Infections and infestations	Tooth infection	2	1	1	2	2
Infections and infestations	Tooth infection	3	1	1	0	0
Infections and infestations	Upper respiratory infection	1	5	5	3	3
Infections and infestations	Upper respiratory infection	2	9	8	8	7
Infections and infestations	Upper respiratory infection	3	0	0	1	1
Infections and infestations	Urinary tract infection	1	2	2	4	3
Infections and infestations	Urinary tract infection	2	7	5	12	8
Infections and infestations	Vaginal infection	1	1	1	0	0
Infections and infestations	Vaginal infection	2	1	1	1	1
Infections and infestations	Vulval infection	1	0	0	1	1
Infections and infestations	Vulval infection	2	1	1	0	0
Injury, poisoning and procedural complications	Bruising	1	3	3	4	3
Injury, poisoning and procedural complications	Fall	1	5	5	3	2
Injury, poisoning and procedural complications	Fall	2	2	2	2	2
Injury, poisoning and procedural complications	Fracture	2	0	0	2	2
Injury, poisoning and procedural complications	Fracture	Missing	0	0	1	1
Injury, poisoning and procedural complications	Injury, poisoning and procedural complications - Other, specify	1	2	2	0	0

			Bendamustine (N=215)		Chlorambucil (N=219)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Injury, poisoning and procedural complications	Injury, poisoning and procedural complications - Other, specify	2	1	1	2	2
Injury, poisoning and procedural complications	Injury, poisoning and procedural complications - Other, specify	3	1	1	0	0
Injury, poisoning and procedural complications	Wrist fracture	1	0	0	1	1
Investigations	Alanine aminotransferase increased	1	2	2	2	1
Investigations	Alanine aminotransferase increased	2	0	0	1	1
Investigations	Alanine aminotransferase increased	3	1	1	0	0
Investigations	Alkaline phosphatase increased	1	4	4	6	6
Investigations	Alkaline phosphatase increased	2	1	1	0	0
Investigations	Aspartate aminotransferase increased	1	0	0	1	1
Investigations	Aspartate aminotransferase increased	2	0	0	1	1
Investigations	Aspartate aminotransferase increased	3	0	0	1	1
Investigations	Blood bilirubin increased	1	4	2	1	1
Investigations	Blood bilirubin increased	2	2	2	1	1
Investigations	CPK increased	1	1	1	0	0
Investigations	Creatinine increased	1	6	3	5	5
Investigations	Creatinine increased	2	1	1	3	3
Investigations	Creatinine increased	3	1	1	0	0
Investigations	GGT increased	2	0	0	1	1
Investigations	GGT increased	3	1	1	0	0

			Bendamustine (N=215)		Chlorambucil (N=219)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Investigations	GGT increased	4	0	0	1	1
Investigations	Investigations - Other, specify	1	6	4	0	0
Investigations	Investigations - Other, specify	2	2	2	1	1
Investigations	Investigations - Other, specify	3	1	1	1	1
Investigations	Investigations - Other, specify	Missing	0	0	2	2
Investigations	Lymphocyte count decreased	1	2	2	1	1
Investigations	Lymphocyte count decreased	2	1	1	0	0
Investigations	Lymphocyte count increased	2	4	4	0	0
Investigations	Lymphocyte count increased	3	1	1	1	1
Investigations	Lymphocyte count increased	4	1	1	0	0
Investigations	Lymphocyte count increased	Missing	0	0	1	1
Investigations	Neutrophil count decreased	1	57	35	76	40
Investigations	Neutrophil count decreased	2	62	34	72	38
Investigations	Neutrophil count decreased	3	91	56	78	44
Investigations	Neutrophil count decreased	4	35	23	23	21
Investigations	Neutrophil count decreased	Missing	0	0	1	1
Investigations	Platelet count decreased	1	93	46	78	37
Investigations	Platelet count decreased	2	75	43	67	35
Investigations	Platelet count decreased	3	17	12	29	16
Investigations	Platelet count decreased	4	4	4	4	4
Investigations	Weight gain	1	2	2	0	0

			Bendamustine (N=215)		Chlorambucil (N=219)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Investigations	Weight loss	1	5	5	3	3
Investigations	Weight loss	2	2	2	2	2
Investigations	White blood cell decreased	1	2	2	4	3
Investigations	White blood cell decreased	2	2	2	4	3
Investigations	White blood cell decreased	3	2	2	0	0
Investigations	White blood cell decreased	4	0	0	1	1
Metabolism and nutrition disorders	Anorexia	1	15	15	8	6
Metabolism and nutrition disorders	Anorexia	2	11	10	5	5
Metabolism and nutrition disorders	Anorexia	3	0	0	3	3
Metabolism and nutrition disorders	Hypercalcemia	1	1	1	0	0
Metabolism and nutrition disorders	Hyperglycemia	1	3	1	1	1
Metabolism and nutrition disorders	Hyperglycemia	2	1	1	11	3
Metabolism and nutrition disorders	Hyperglycemia	3	1	1	4	3
Metabolism and nutrition disorders	Hyperkalemia	1	3	3	1	1
Metabolism and nutrition disorders	Hyperkalemia	2	1	1	2	2
Metabolism and nutrition disorders	Hyperkalemia	3	0	0	2	2
Metabolism and nutrition disorders	Hypernatremia	1	0	0	1	1
Metabolism and nutrition disorders	Hyperuricemia	1	1	1	8	6
Metabolism and nutrition disorders	Hypoalbuminemia	1	5	2	0	0
Metabolism and nutrition disorders	Hypoalbuminemia	2	2	1	0	0
Metabolism and nutrition disorders	Hypocalcemia	1	4	4	2	2

			Bendamustine (N=215)		Chlorambucil (N=219)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Metabolism and nutrition disorders	Hypocalcemia	2	1	1	0	0
Metabolism and nutrition disorders	Hypoglycemia	1	1	1	0	0
Metabolism and nutrition disorders	Hypoglycemia	2	1	1	0	0
Metabolism and nutrition disorders	Hypokalemia	1	5	4	5	3
Metabolism and nutrition disorders	Hypokalemia	2	0	0	2	2
Metabolism and nutrition disorders	Hypomagnesemia	1	2	2	0	0
Metabolism and nutrition disorders	Hypomagnesemia	2	0	0	2	1
Metabolism and nutrition disorders	Hyponatremia	1	7	2	5	3
Metabolism and nutrition disorders	Hyponatremia	2	0	0	2	1
Metabolism and nutrition disorders	Hyponatremia	3	0	0	1	1
Metabolism and nutrition disorders	Hyponatremia	Missing	1	1	0	0
Metabolism and nutrition disorders	Hypophosphatemia	2	1	1	0	0
Metabolism and nutrition disorders	Metabolism and nutrition disorders - Other, specify	1	5	3	1	1
Metabolism and nutrition disorders	Metabolism and nutrition disorders - Other, specify	2	1	1	1	1
Musculoskeletal and connective tissue disorders	Arthralgia	1	4	3	0	0
Musculoskeletal and connective tissue disorders	Arthralgia	2	1	1	1	1
Musculoskeletal and connective tissue disorders	Arthritis	1	1	1	0	0

				Bendamustine (N=215)		Chlorambucil (N=219)		
Category Name			Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Musculoskeletal tissue disorders	and	connective	Back pain	1	8	8	16	13
Musculoskeletal tissue disorders	and	connective	Back pain	2	4	4	9	9
Musculoskeletal tissue disorders	and	connective	Back pain	3	2	2	3	3
Musculoskeletal tissue disorders	and	connective	Back pain	Missing	1	1	0	0
Musculoskeletal tissue disorders	and	connective	Bone pain	1	1	1	0	0
Musculoskeletal tissue disorders	and	connective	Chest wall pain	1	1	1	1	1
Musculoskeletal tissue disorders	and	connective	Chest wall pain	2	1	1	2	2
Musculoskeletal tissue disorders	and	connective	Chest wall pain	Missing	0	0	1	1
Musculoskeletal tissue disorders	and	connective	Generalized muscle weakness	1	0	0	2	2
Musculoskeletal tissue disorders	and	connective	Joint effusion	1	1	1	0	0
Musculoskeletal tissue disorders	and	connective	Muscle weakness left-sided	1	0	0	1	1
Musculoskeletal tissue disorders	and	connective	Muscle weakness lower limb	1	1	1	1	1

			Bendamustine (N=215)		Chlorambucil (N=219)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Musculoskeletal and connective tissue disorders	Muscle weakness lower limb	2	1	1	2	2
Musculoskeletal and connective tissue disorders	Muscle weakness upper limb	1	1	1	0	0
Musculoskeletal and connective tissue disorders	Musculoskeletal and connective tissue disorder - Other, specify	1	5	4	8	7
Musculoskeletal and connective tissue disorders	Musculoskeletal and connective tissue disorder - Other, specify	2	5	4	3	3
Musculoskeletal and connective tissue disorders	Musculoskeletal and connective tissue disorder - Other, specify	3	1	1	3	2
Musculoskeletal and connective tissue disorders	Myalgia	1	3	3	0	0
Musculoskeletal and connective tissue disorders	Myalgia	2	0	0	1	1
Musculoskeletal and connective tissue disorders	Neck pain	1	2	2	2	2
Musculoskeletal and connective tissue disorders	Neck pain	2	0	0	1	1
Musculoskeletal and connective tissue disorders	Pain in extremity	1	4	3	5	5
Musculoskeletal and connective tissue disorders	Pain in extremity	2	1	1	0	0
Musculoskeletal and connective tissue disorders	Pain in extremity	3	1	1	0	0

			Bendamustine (N=215)		Chlorambucil (N=219)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify	1	1	1	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify	2	5	4	5	5
Nervous system disorders	Central nervous system necrosis	1	1	1	0	0
Nervous system disorders	Concentration impairment	1	1	1	1	1
Nervous system disorders	Dizziness	1	13	12	11	11
Nervous system disorders	Dizziness	2	2	2	3	3
Nervous system disorders	Dysarthria	2	0	0	1	1
Nervous system disorders	Dysesthesia	1	1	1	0	0
Nervous system disorders	Dysgeusia	1	7	7	4	4
Nervous system disorders	Extrapyramidal disorder	1	0	0	1	1
Nervous system disorders	Headache	1	16	12	14	8
Nervous system disorders	Headache	2	3	3	5	5
Nervous system disorders	Lethargy	1	9	8	14	12
Nervous system disorders	Lethargy	2	3	3	5	5
Nervous system disorders	Lethargy	3	1	1	0	0
Nervous system disorders	Lethargy	Missing	1	1	0	0
Nervous system disorders	Memory impairment	2	0	0	1	1
Nervous system disorders	Movements involuntary	2	0	0	1	1
Nervous system disorders	Nervous system disorders - Other, specify	1	6	5	7	6
Nervous system disorders	Nervous system disorders - Other, specify	2	1	1	1	1

			Bendamustine (N=215)		Chlorambucil (N=219)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Nervous system disorders	Olfactory nerve disorder	2	1	1	0	0
Nervous system disorders	Paresthesia	1	4	3	2	2
Nervous system disorders	Paresthesia	2	1	1	0	0
Nervous system disorders	Peripheral motor neuropathy	1	0	0	1	1
Nervous system disorders	Peripheral motor neuropathy	4	1	1	0	0
Nervous system disorders	Peripheral sensory neuropathy	1	4	4	11	8
Nervous system disorders	Peripheral sensory neuropathy	2	0	0	3	2
Nervous system disorders	Presyncope	1	1	1	0	0
Nervous system disorders	Presyncope	2	1	1	0	0
Nervous system disorders	Sinus pain	1	1	1	0	0
Nervous system disorders	Somnolence	1	0	0	1	1
Nervous system disorders	Somnolence	Missing	1	1	0	0
Nervous system disorders	Syncope	1	0	0	2	2
Nervous system disorders	Syncope	3	0	0	2	1
Nervous system disorders	Syncope	Missing	1	1	0	0
Nervous system disorders	Transient ischemic attacks	1	0	0	1	1
Nervous system disorders	Transient ischemic attacks	2	1	1	0	0
Nervous system disorders	Tremor	1	1	1	3	3
Nervous system disorders	Tremor	2	1	1	3	3
Nervous system disorders	Vasovagal reaction	3	1	1	1	1
Psychiatric disorders	Anxiety	1	2	2	5	3

			Bendamustine (N=215)		Chlorambucil (N=219)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Psychiatric disorders	Anxiety	2	1	1	1	1
Psychiatric disorders	Confusion	1	2	2	0	0
Psychiatric disorders	Confusion	2	1	1	0	0
Psychiatric disorders	Delirium	2	0	0	1	1
Psychiatric disorders	Depression	1	1	1	3	3
Psychiatric disorders	Depression	2	3	3	0	0
Psychiatric disorders	Depression	Missing	0	0	1	1
Psychiatric disorders	Hallucinations	1	1	1	1	1
Psychiatric disorders	Hallucinations	2	0	0	1	1
Psychiatric disorders	Insomnia	1	2	2	6	4
Psychiatric disorders	Insomnia	2	5	5	9	7
Psychiatric disorders	Insomnia	3	1	1	0	0
Psychiatric disorders	Libido decreased	1	0	0	1	1
Psychiatric disorders	Psychiatric disorders - Other, specify	Missing	0	0	1	1
Renal and urinary disorders	Acute kidney injury	1	1	1	1	1
Renal and urinary disorders	Acute kidney injury	2	0	0	1	1
Renal and urinary disorders	Cystitis noninfective	2	1	1	0	0
Renal and urinary disorders	Haematuria	1	1	1	1	1
Renal and urinary disorders	Renal and urinary disorders - Other, specify	1	1	1	0	0
Renal and urinary disorders	Renal calculi	3	0	0	1	1
Renal and urinary disorders	Urinary frequency	1	5	5	6	6

			Bendamustine (N=215)		Chlorambucil (N=219)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Renal and urinary disorders	Urinary frequency	2	0	0	1	1
Renal and urinary disorders	Urinary retention	1	0	0	1	1
Renal and urinary disorders	Urinary tract obstruction	2	1	1	0	0
Renal and urinary disorders	Urinary tract pain	1	0	0	1	1
Reproductive system and breast disorders	Genital edema	2	1	1	0	0
Reproductive system and breast disorders	Reproductive system and breast disorders - Other, specify	1	0	0	2	2
Reproductive system and breast disorders	Reproductive system and breast disorders - Other, specify	2	0	0	1	1
Respiratory, thoracic and mediastinal disorders	Allergic rhinitis	1	1	1	0	0
Respiratory, thoracic and mediastinal disorders	Cough	1	39	35	28	21
Respiratory, thoracic and mediastinal disorders	Cough	2	21	17	17	13
Respiratory, thoracic and mediastinal disorders	Dyspnea	1	19	17	21	19
Respiratory, thoracic and mediastinal disorders	Dyspnea	2	7	7	9	9
Respiratory, thoracic and mediastinal disorders	Dyspnea	3	1	1	4	4
Respiratory, thoracic and mediastinal disorders	Epistaxis	1	3	3	2	2

			Bendamustine (N=215)		Chlorambucil (N=219)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Respiratory, thoracic and mediastinal disorders	Epistaxis	2	0	0	1	1
Respiratory, thoracic and mediastinal disorders	Hoarseness	1	2	1	0	0
Respiratory, thoracic and mediastinal disorders	Hoarseness	2	0	0	4	3
Respiratory, thoracic and mediastinal disorders	Hypoxia	2	0	0	1	1
Respiratory, thoracic and mediastinal disorders	Laryngeal inflammation	1	1	1	2	2
Respiratory, thoracic and mediastinal disorders	Nasal congestion	1	2	2	1	1
Respiratory, thoracic and mediastinal disorders	Pleural effusion	1	1	1	0	0
Respiratory, thoracic and mediastinal disorders	Pleural effusion	2	2	1	0	0
Respiratory, thoracic and mediastinal disorders	Pneumonitis	2	2	2	1	1
Respiratory, thoracic and mediastinal disorders	Pneumonitis	3	0	0	1	1
Respiratory, thoracic and mediastinal disorders	Postnasal drip	1	1	1	2	2
Respiratory, thoracic and mediastinal disorders	Productive cough	1	6	5	1	1

			Bendamustine (N=215)		Chlorambucil (N=219)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Respiratory, thoracic and mediastinal disorders	Productive cough	2	2	2	2	2
Respiratory, thoracic and mediastinal disorders	Respiratory, thoracic and mediastinal disorders - Other, specify	1	5	5	1	1
Respiratory, thoracic and mediastinal disorders	Respiratory, thoracic and mediastinal disorders - Other, specify	2	11	10	6	6
Respiratory, thoracic and mediastinal disorders	Respiratory, thoracic and mediastinal disorders - Other, specify	3	2	2	0	0
Respiratory, thoracic and mediastinal disorders	Sinus disorder	2	0	0	1	1
Respiratory, thoracic and mediastinal disorders	Sneezing	1	1	1	0	0
Respiratory, thoracic and mediastinal disorders	Sore throat	1	11	11	13	10
Respiratory, thoracic and mediastinal disorders	Sore throat	2	2	2	2	2
Respiratory, thoracic and mediastinal disorders	Voice alteration	1	1	1	0	0
Respiratory, thoracic and mediastinal disorders	Wheezing	1	2	1	1	1
Skin and subcutaneous tissue disorders	Alopecia	1	4	4	11	9
Skin and subcutaneous tissue disorders	Body odor	1	1	1	0	0

				Bendamustine (N=215)		Chlorambucil (N=219)		
Category Name			Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Skin and disorders	subcutaneous	tissue	Dry skin	1	11	9	7	6
Skin and disorders	subcutaneous	tissue	Dry skin	2	3	3	1	1
Skin and disorders	subcutaneous	tissue	Dry skin	3	1	1	1	1
Skin and disorders	subcutaneous	tissue	Erythema multiforme	1	2	2	0	0
Skin and disorders	subcutaneous	tissue	Erythema multiforme	2	2	2	0	0
Skin and disorders	subcutaneous	tissue	Erythema multiforme	3	0	0	1	1
Skin and disorders	subcutaneous	tissue	Hyperhidrosis	1	2	2	3	3
Skin and disorders	subcutaneous	tissue	Hyperhidrosis	2	2	2	2	2
Skin and disorders	subcutaneous	tissue	Hyperhidrosis	3	0	0	1	1
Skin and disorders	subcutaneous	tissue	Hypohidrosis	2	1	1	0	0
Skin and disorders	subcutaneous	tissue	Palmar-plantar erythrodysesthesia syndrome	1	3	3	2	1
Skin and disorders	subcutaneous	tissue	Pruritus	1	17	14	10	10

				Bendamustine (N=215)		Chlorambucil (N=219)		
Category Name			Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Skin and disorders	subcutaneous	tissue	Pruritus	2	8	8	3	3
Skin and disorders	subcutaneous	tissue	Pruritus	3	2	2	0	0
Skin and disorders	subcutaneous	tissue	Purpura	2	0	0	1	1
Skin and disorders	subcutaneous	tissue	Rash Macular	1	2	2	0	0
Skin and disorders	subcutaneous	tissue	Rash Macular	2	1	1	0	0
Skin and disorders	subcutaneous	tissue	Rash Macular	3	1	1	0	0
Skin and disorders	subcutaneous	tissue	Rash acneiform	1	1	1	1	1
Skin and disorders	subcutaneous	tissue	Rash acneiform	2	1	1	1	1
Skin and disorders	subcutaneous	tissue	Rash erythematous	1	2	2	1	1
Skin and disorders	subcutaneous	tissue	Rash erythematous	2	2	2	2	2
Skin and disorders	subcutaneous	tissue	Rash erythematous	3	1	1	2	2
Skin and disorders	subcutaneous	tissue	Rash generalized	1	5	5	7	6

				Bendamustine (N=215)		Chlorambucil (N=219)		
Category Name			Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Skin and disorders	subcutaneous	tissue	Rash generalized	2	9	6	3	2
Skin and disorders	subcutaneous	tissue	Rash generalized	3	1	1	0	0
Skin and disorders	subcutaneous	tissue	Rash generalized	Missing	0	0	1	1
Skin and disorders	subcutaneous	tissue	Rash maculo-papular	1	20	17	17	15
Skin and disorders	subcutaneous	tissue	Rash maculo-papular	2	9	8	11	10
Skin and disorders	subcutaneous	tissue	Rash maculo-papular	3	5	5	4	4
Skin and disorders	subcutaneous	tissue	Rash maculo-papular	Missing	1	1	0	0
Skin and disorders	subcutaneous	tissue	Rash pruritic	1	1	1	0	0
Skin and disorders	subcutaneous	tissue	Skin and subcutaneous tissue disorders - Other, specify	1	31	21	30	15
Skin and disorders	subcutaneous	tissue	Skin and subcutaneous tissue disorders - Other, specify	2	26	16	23	16
Skin and disorders	subcutaneous	tissue	Skin and subcutaneous tissue disorders - Other, specify	3	4	4	1	1
Skin and disorders	subcutaneous	tissue	Skin and subcutaneous tissue disorders - Other, specify	Missing	0	0	2	2

			Bendamustine (N=215)		Chlorambucil (N=219)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Skin and subcutaneous tissue disorders	Skin ulceration	1	1	1	0	0
Skin and subcutaneous tissue disorders	Skin ulceration	2	1	1	3	3
Skin and subcutaneous tissue disorders	Urticaria	1	0	0	2	2
Skin and subcutaneous tissue disorders	Urticaria	2	1	1	2	2
Skin and subcutaneous tissue disorders	Urticaria	3	0	0	1	1
Skin and subcutaneous tissue disorders	Urticaria	Missing	0	0	1	1
Vascular disorders	Flushing	1	1	1	1	1
Vascular disorders	Flushing	2	1	1	1	1
Vascular disorders	Haematoma	1	1	1	0	0
Vascular disorders	Haematoma	3	1	1	0	0
Vascular disorders	Hot flashes	1	1	1	0	0
Vascular disorders	Hypertension	1	0	0	3	3
Vascular disorders	Hypertension	2	2	2	1	1
Vascular disorders	Hypertension	3	1	1	1	1
Vascular disorders	Hypotension	1	2	2	2	2
Vascular disorders	Hypotension	2	4	4	4	4
Vascular disorders	Hypotension	3	0	0	2	2

			Bendamustine (N=215)		Chlorambucil (N=219)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Vascular disorders	Hypotension	4	0	0	1	1
Vascular disorders	Phlebitis	2	2	1	0	0
Vascular disorders	Thromboembolic event	2	0	0	3	1
Vascular disorders	Thromboembolic event	3	2	2	1	1
Vascular disorders	Vascular disorders - Other, specify	2	2	2	0	0
Vascular disorders	Vascular disorders - Other, specify	Missing	0	0	1	1

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Table 15-4: Adverse Events by CTCAE Category Name – Bendamustine vs. Chlorambucil (Including Placebo)

Category Name	Severity	Bendamustine (N=215)		Chlorambucil (N=219)	
		No. Incidences	No. Patients	No. Incidences	No. Patients
Blood and lymphatic system disorders	1	73	38	67	33
Blood and lymphatic system disorders	2	50	29	45	31
Blood and lymphatic system disorders	3	25	16	30	20
Blood and lymphatic system disorders	4	2	2	0	0
Blood and lymphatic system disorders	Missing	2	1	1	1
Cardiac disorders	1	8	8	10	10
Cardiac disorders	2	10	9	7	7
Cardiac disorders	3	2	2	5	5
Cardiac disorders	Missing	1	1	1	1
Ear and labyrinth disorders	1	7	7	8	7
Ear and labyrinth disorders	2	5	4	4	4
Ear and labyrinth disorders	3	0	0	1	1
Endocrine disorders	1	0	0	1	1
Eye disorders	1	7	7	12	10
Eye disorders	2	6	6	4	4
Eye disorders	3	1	1	0	0
Gastrointestinal disorders	1	256	108	246	94
Gastrointestinal disorders	2	89	49	81	43
Gastrointestinal disorders	3	18	8	6	6
Gastrointestinal disorders	Missing	4	4	0	0

Category Name	Severity	Bendamustine (N=215)		Chlorambucil (N=219)	
		No. Incidences	No. Patients	No. Incidences	No. Patients
General disorders and administration site conditions	1	211	102	198	98
General disorders and administration site conditions	2	110	68	111	63
General disorders and administration site conditions	3	12	10	23	14
General disorders and administration site conditions	4	0	0	2	1
General disorders and administration site conditions	Missing	4	2	3	3
Hepatobiliary disorders	2	1	1	0	0
Hepatobiliary disorders	3	1	1	0	0
Immune system disorders	1	8	8	5	5
Immune system disorders	2	14	12	26	19
Immune system disorders	3	4	3	0	0
Immune system disorders	5	0	0	1	1
Immune system disorders	Missing	0	0	1	1
Infections and infestations	1	29	25	34	26
Infections and infestations	2	66	47	75	51
Infections and infestations	3	10	10	7	7
Injury, poisoning and procedural complications	1	10	10	8	6
Injury, poisoning and procedural complications	2	3	3	6	6
Injury, poisoning and procedural complications	3	1	1	0	0
Injury, poisoning and procedural complications	Missing	0	0	1	1
Investigations	1	184	63	177	63
Investigations	2	152	68	153	63

Category Name	Severity	Bendamustine (N=215)		Chlorambucil (N=219)	
		No. Incidences	No. Patients	No. Incidences	No. Patients
Investigations	3	115	67	110	53
Investigations	4	40	26	29	22
Investigations	Missing	0	0	4	3
Metabolism and nutrition disorders	1	52	31	32	20
Metabolism and nutrition disorders	2	19	14	25	13
Metabolism and nutrition disorders	3	1	1	10	8
Metabolism and nutrition disorders	Missing	1	1	0	0
Musculoskeletal and connective tissue disorders	1	32	26	36	25
Musculoskeletal and connective tissue disorders	2	13	10	19	16
Musculoskeletal and connective tissue disorders	3	4	3	6	5
Musculoskeletal and connective tissue disorders	Missing	1	1	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	1	1	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	5	4	5	5
Nervous system disorders	1	65	46	73	51
Nervous system disorders	2	14	14	23	20
Nervous system disorders	3	2	2	3	2
Nervous system disorders	4	1	1	0	0
Nervous system disorders	Missing	3	3	0	0
Psychiatric disorders	1	8	8	16	12
Psychiatric disorders	2	10	9	12	10
Psychiatric disorders	3	1	1	0	0

Category Name	Severity	Bendamustine (N=215)		Chlorambucil (N=219)	
		No. Incidences	No. Patients	No. Incidences	No. Patients
Psychiatric disorders	Missing	0	0	2	2
Renal and urinary disorders	1	8	8	10	9
Renal and urinary disorders	2	2	2	2	2
Renal and urinary disorders	3	0	0	1	1
Reproductive system and breast disorders	1	0	0	2	2
Reproductive system and breast disorders	2	1	1	1	1
Respiratory, thoracic and mediastinal disorders	1	95	60	72	44
Respiratory, thoracic and mediastinal disorders	2	47	31	44	32
Respiratory, thoracic and mediastinal disorders	3	3	3	5	5
Skin and subcutaneous tissue disorders	1	103	63	91	51
Skin and subcutaneous tissue disorders	2	66	39	52	35
Skin and subcutaneous tissue disorders	3	15	13	11	10
Skin and subcutaneous tissue disorders	Missing	1	1	4	4
Vascular disorders	1	5	4	6	5
Vascular disorders	2	11	8	9	7
Vascular disorders	3	4	3	4	4
Vascular disorders	4	0	0	1	1
Vascular disorders	Missing	0	0	1	1

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14.1.2 Serious Adverse Events

Table 15-5: Serious Adverse Events by Severity – Bendamustine vs. Chlorambucil (Including Placebo)

Severity	Bendamustine (N=215)	Chlorambucil (N=219)	Total (N=434)
1	58 (19%)	41 (18%)	99 (18%)
2	89 (29%)	69 (29%)	158 (29%)
3	93 (30%)	85 (36%)	178 (33%)
4	18 (6%)	18 (8%)	36 (7%)
5	9 (3%)	3 (1%)	12 (2%)
Missing	40 (13%)	18 (8%)	58 (11%)

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Table 15-6: Serious Adverse Events by MedDRA SOC and PT – Bendamustine vs. Chlorambucil (Including Placebo)

			Bendamustine (N=215)		Chlorambucil (N=219)	
SOC	PT	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Blood and lymphatic system disorders	Anaemia	1	2	1	3	3
Blood and lymphatic system disorders	Anaemia	2	0	0	3	3
Blood and lymphatic system disorders	Anaemia	3	3	3	1	1
Blood and lymphatic system disorders	Anaemia	4	1	1	2	2
Blood and lymphatic system disorders	Aplasia pure red cell	4	1	1	0	0
Blood and lymphatic system disorders	Bone marrow failure	4	1	1	0	0
Blood and lymphatic system disorders	Febrile neutropenia	1	1	1	0	0
Blood and lymphatic system disorders	Febrile neutropenia	2	0	0	1	1
Blood and lymphatic system disorders	Febrile neutropenia	3	5	5	6	5
Blood and lymphatic system disorders	Febrile neutropenia	4	1	1	1	1
Blood and lymphatic system disorders	Febrile neutropenia	Missing	2	2	0	0
Blood and lymphatic system disorders	Neutropenia	4	0	0	2	1
Blood and lymphatic system disorders	Neutropenia	Missing	1	1	1	1
Cardiac disorders	Acute myocardial infarction	1	0	0	1	1
Cardiac disorders	Acute myocardial infarction	3	2	2	0	0
Cardiac disorders	Angina pectoris	1	0	0	1	1
Cardiac disorders	Atrial fibrillation	3	0	0	1	1
Cardiac disorders	Atrial fibrillation	4	1	1	0	0
Cardiac disorders	Bundle branch block right	1	0	0	1	1
Cardiac disorders	Cardiac failure	3	1	1	0	0

			Bendamustine (N=215)		Chlorambucil (N=219)	
SOC	PT	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Cardiac disorders	Cardiac failure	5	1	1	0	0
Cardiac disorders	Cardiac failure	Missing	0	0	1	1
Cardiac disorders	Coronary artery disease	3	0	0	1	1
Cardiac disorders	Left ventricular dysfunction	2	1	1	0	0
Cardiac disorders	Myocardial infarction	1	1	1	0	0
Cardiac disorders	Myocardial infarction	4	1	1	0	0
Cardiac disorders	Myocardial ischaemia	3	0	0	1	1
Cardiac disorders	Myocardial ischaemia	5	1	1	0	0
Cardiac disorders	Right ventricular failure	4	0	0	1	1
Cardiac disorders	Supraventricular extrasystoles	2	1	1	0	0
Gastrointestinal disorders	Abdominal pain	2	0	0	3	3
Gastrointestinal disorders	Abdominal pain	Missing	0	0	1	1
Gastrointestinal disorders	Constipation	2	0	0	2	2
Gastrointestinal disorders	Constipation	3	1	1	0	0
Gastrointestinal disorders	Diarrhoea	2	0	0	1	1
Gastrointestinal disorders	Diarrhoea	3	0	0	2	2
Gastrointestinal disorders	Gastric ulcer	3	1	1	0	0
Gastrointestinal disorders	Gastritis	2	1	1	0	0
Gastrointestinal disorders	Nausea	3	1	1	0	0
Gastrointestinal disorders	Vomiting	1	1	1	1	1
Gastrointestinal disorders	Vomiting	2	0	0	1	1

			Bendamustine (N=215)		Chlorambucil (N=219)	
SOC	PT	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
General disorders and administration site conditions	Chest pain	3	0	0	1	1
General disorders and administration site conditions	Chills	2	2	2	0	0
General disorders and administration site conditions	General physical health deterioration	1	0	0	1	1
General disorders and administration site conditions	Influenza like illness	3	1	1	0	0
General disorders and administration site conditions	Malaise	1	0	0	1	1
General disorders and administration site conditions	Pyrexia	1	5	5	5	4
General disorders and administration site conditions	Pyrexia	2	3	3	1	1
General disorders and administration site conditions	Pyrexia	3	3	3	0	0
Hepatobiliary disorders	Cholecystitis acute	2	0	0	1	1
Hepatobiliary disorders	Cholecystitis acute	3	0	0	1	1
Hepatobiliary disorders	Cholecystitis acute	Missing	2	1	0	0
Hepatobiliary disorders	Cholelithiasis	3	1	1	0	0
Hepatobiliary disorders	Hepatic cirrhosis	2	0	0	1	1
Immune system disorders	Amyloidosis senile	2	1	1	0	0
Immune system disorders	Anaphylactic reaction	2	1	1	0	0
Immune system disorders	Anaphylactoid reaction	3	1	1	0	0

			Bendamustine (N=215)		Chlorambucil (N=219)	
SOC	PT	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Immune system disorders	Contrast media allergy	3	0	0	1	1
Immune system disorders	Drug hypersensitivity	3	1	1	0	0
Immune system disorders	Drug hypersensitivity	Missing	1	1	0	0
Immune system disorders	Hypersensitivity	1	2	2	0	0
Immune system disorders	Hypersensitivity	2	2	1	3	2
Infections and infestations	Abdominal infection	3	1	1	0	0
Infections and infestations	Anorectal infection	3	1	1	0	0
Infections and infestations	Atypical pneumonia	1	0	0	1	1
Infections and infestations	Bronchitis	3	1	1	1	1
Infections and infestations	COVID-19	2	0	0	1	1
Infections and infestations	COVID-19	3	0	0	1	1
Infections and infestations	COVID-19	Missing	2	1	0	0
Infections and infestations	Campylobacter infection	2	1	1	0	0
Infections and infestations	Candida infection	2	0	0	1	1
Infections and infestations	Cellulitis	2	1	1	0	0
Infections and infestations	Cellulitis	3	0	0	1	1
Infections and infestations	Cytomegalovirus colitis	1	1	1	0	0
Infections and infestations	Encephalitis	3	1	1	0	0
Infections and infestations	Encephalitis viral	4	1	1	0	0
Infections and infestations	Escherichia infection	3	0	0	1	1
Infections and infestations	Gastroenteritis viral	1	1	1	0	0

SOC	PT	Severity	Bendamustine (N=215)		Chlorambucil (N=219)	
			No. Incidences	No. Patients	No. Incidences	No. Patients
Infections and infestations	Gastroenteritis viral	2	1	1	0	0
Infections and infestations	Hepatitis B	3	1	1	0	0
Infections and infestations	Herpes zoster	3	0	0	1	1
Infections and infestations	Herpes zoster	Missing	0	0	1	1
Infections and infestations	Herpes zoster oticus	3	0	0	1	1
Infections and infestations	Infection	1	4	4	1	1
Infections and infestations	Infection	2	1	1	1	1
Infections and infestations	Infection	3	1	1	3	3
Infections and infestations	Infection	Missing	1	1	0	0
Infections and infestations	Infective exacerbation of bronchiectasis	2	1	1	0	0
Infections and infestations	Large intestine infection	1	1	1	0	0
Infections and infestations	Lower respiratory tract infection	1	5	5	1	1
Infections and infestations	Lower respiratory tract infection	2	8	7	5	5
Infections and infestations	Lower respiratory tract infection	3	7	7	8	7
Infections and infestations	Lower respiratory tract infection	4	2	2	0	0
Infections and infestations	Lower respiratory tract infection	Missing	1	1	0	0
Infections and infestations	Neutropenic sepsis	1	8	7	4	3
Infections and infestations	Neutropenic sepsis	2	2	2	3	3
Infections and infestations	Neutropenic sepsis	3	6	6	4	4
Infections and infestations	Neutropenic sepsis	4	3	3	1	1

SOC	PT	Severity	Bendamustine (N=215)		Chlorambucil (N=219)	
			No. Incidences	No. Patients	No. Incidences	No. Patients
Infections and infestations	Neutropenic sepsis	Missing	1	1	2	2
Infections and infestations	Oral candidiasis	1	0	0	1	1
Infections and infestations	Pneumocystis jirovecii pneumonia	3	1	1	0	0
Infections and infestations	Pneumonia	1	5	5	3	3
Infections and infestations	Pneumonia	3	4	4	0	0
Infections and infestations	Pneumonia	5	3	3	0	0
Infections and infestations	Pneumonia	Missing	1	1	2	2
Infections and infestations	Pneumonia pneumococcal	2	0	0	1	1
Infections and infestations	Progressive multifocal leukoencephalopathy	4	0	0	1	1
Infections and infestations	Pulmonary sepsis	2	1	1	0	0
Infections and infestations	Respiratory tract infection	2	0	0	2	2
Infections and infestations	Salmonellosis	3	0	0	1	1
Infections and infestations	Sepsis	1	4	4	0	0
Infections and infestations	Sepsis	2	1	1	0	0
Infections and infestations	Sepsis	3	2	2	2	2
Infections and infestations	Sepsis	4	0	0	2	2
Infections and infestations	Sepsis	5	1	1	0	0
Infections and infestations	Sepsis	Missing	1	1	0	0
Infections and infestations	Septic shock	2	0	0	1	1
Infections and infestations	Upper respiratory tract infection	2	0	0	1	1

SOC	PT	Severity	Bendamustine (N=215)		Chlorambucil (N=219)	
			No. Incidences	No. Patients	No. Incidences	No. Patients
Infections and infestations	Upper respiratory tract infection	3	0	0	2	2
Infections and infestations	Upper respiratory tract infection	Missing	0	0	1	1
Infections and infestations	Urinary tract infection	1	1	1	1	1
Infections and infestations	Urinary tract infection	Missing	0	0	2	2
Infections and infestations	Urosepsis	1	1	1	1	1
Infections and infestations	Urosepsis	3	0	0	1	1
Infections and infestations	Viral infection	2	0	0	1	1
Infections and infestations	Viral infection	3	0	0	1	1
Infections and infestations	Viral upper respiratory tract infection	2	1	1	0	0
Infections and infestations	Wound infection	3	1	1	0	0
Injury, poisoning and procedural complications	Expired product administered	Missing	1	1	0	0
Injury, poisoning and procedural complications	Infusion related reaction	1	5	5	10	9
Injury, poisoning and procedural complications	Infusion related reaction	2	6	6	8	7
Injury, poisoning and procedural complications	Infusion related reaction	3	11	9	4	4
Injury, poisoning and procedural complications	Infusion related reaction	4	1	1	0	0
Injury, poisoning and procedural complications	Infusion related reaction	Missing	4	4	2	1
Injury, poisoning and procedural complications	Post procedural haematuria	2	0	0	1	1
Injury, poisoning and procedural complications	Spinal compression fracture	2	1	1	0	0
Injury, poisoning and procedural complications	Subdural haematoma	2	0	0	1	1
Injury, poisoning and procedural complications	Subdural haematoma	3	0	0	1	1

			Bendamustine (N=215)		Chlorambucil (N=219)	
SOC	PT	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Injury, poisoning and procedural complications	Traumatic haematoma	3	1	1	0	0
Investigations	Neutrophil count decreased	Missing	0	0	1	1
Investigations	Weight decreased	2	0	0	1	1
Investigations	X-ray with contrast upper gastrointestinal tract	Missing	1	1	0	0
Metabolism and nutrition disorders	Alcohol intolerance	3	0	0	1	1
Metabolism and nutrition disorders	Dehydration	1	1	1	0	0
Metabolism and nutrition disorders	Dehydration	3	0	0	1	1
Metabolism and nutrition disorders	Hyperglycaemia	3	0	0	1	1
Metabolism and nutrition disorders	Hyperglycaemia	4	0	0	1	1
Metabolism and nutrition disorders	Hyperkalaemia	3	1	1	1	1
Metabolism and nutrition disorders	Hyperkalaemia	5	0	0	1	1
Metabolism and nutrition disorders	Hypokalaemic syndrome	4	1	1	0	0
Metabolism and nutrition disorders	Tumour Lysis syndrome	2	1	1	0	0
Metabolism and nutrition disorders	Tumour lysis syndrome	3	1	1	0	0
Musculoskeletal and connective tissue disorders	Back pain	3	0	0	2	2
Musculoskeletal and connective tissue disorders	Back pain	Missing	1	1	0	0
Musculoskeletal and connective tissue disorders	Musculoskeletal chest pain	3	1	1	0	0
Musculoskeletal and connective tissue disorders	Spinal osteoarthritis	3	1	1	0	0

SOC	PT	Severity	Bendamustine (N=215)		Chlorambucil (N=219)	
			No. Incidences	No. Patients	No. Incidences	No. Patients
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Basal cell carcinoma	2	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Bladder transitional cell carcinoma stage I	2	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Cholangiocarcinoma	3	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Colon cancer stage II	3	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Hepatic cancer	Missing	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lentigo maligna	3	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lung neoplasm malignant	2	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Acute myeloid leukaemia	3	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Adenocarcinoma	Missing	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Adenocarcinoma of colon	2	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Basal cell carcinoma	2	2	2	4	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Basal cell carcinoma	3	0	0	3	3

SOC	PT	Severity	Bendamustine (N=215)		Chlorambucil (N=219)	
			No. Incidences	No. Patients	No. Incidences	No. Patients
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Basal cell carcinoma	Missing	2	2	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Bladder cancer	2	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Bowen's disease	1	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Bowen's disease	2	4	3	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Bowen's disease	3	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Bowen's disease	Missing	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Cancer fatigue	2	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Chronic lymphocytic leukaemia transformation	3	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Colon cancer	1	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Colorectal adenocarcinoma	3	0	0	2	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Diffuse large B-cell lymphoma	4	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	External ear neoplasm malignant	2	2	2	1	1

SOC	PT	Severity	Bendamustine (N=215)		Chlorambucil (N=219)	
			No. Incidences	No. Patients	No. Incidences	No. Patients
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	External ear neoplasm malignant	3	1	1	2	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Gallbladder cancer	4	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Gastric cancer	1	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Hepatocellular carcinoma	3	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Hepatocellular carcinoma	Missing	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Hodgkin's disease	2	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Intraductal proliferative breast lesion	3	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Invasive ductal breast carcinoma	3	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Invasive ductal breast carcinoma	4	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Invasive ductal breast carcinoma	Missing	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lung cancer metastatic	2	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lung neoplasm malignant	5	0	0	1	1

SOC	PT	Severity	Bendamustine (N=215)		Chlorambucil (N=219)	
			No. Incidences	No. Patients	No. Incidences	No. Patients
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lymphoma	2	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Malignant melanoma	2	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Malignant melanoma	Missing	2	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Meningioma	3	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastatic malignant melanoma	Missing	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Myeloproliferative neoplasm	3	1	1	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neuroendocrine carcinoma	2	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neuroendocrine carcinoma	3	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neuroendocrine carcinoma	5	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Pancreatic carcinoma	4	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Pancreatic carcinoma	5	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Pleomorphic malignant fibrous histiocytoma	3	1	1	0	0

SOC	PT	Severity	Bendamustine (N=215)		Chlorambucil (N=219)	
			No. Incidences	No. Patients	No. Incidences	No. Patients
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Prostate cancer	2	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Prostate cancer	3	1	1	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Prostate cancer	Missing	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Rectal adenocarcinoma	Missing	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Second primary malignancy	3	1	1	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Second primary malignancy	4	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Second primary malignancy	Missing	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Skin cancer	2	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Squamous cell carcinoma	2	6	2	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Squamous cell carcinoma	3	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Squamous cell carcinoma	4	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Squamous cell carcinoma	Missing	3	2	1	1

			Bendamustine (N=215)		Chlorambucil (N=219)	
SOC	PT	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Squamous cell carcinoma of skin	1	3	2	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Squamous cell carcinoma of skin	2	14	7	3	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Squamous cell carcinoma of skin	3	1	1	7	6
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Squamous cell carcinoma of skin	Missing	2	2	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Urethral neoplasm	3	0	0	1	1
Nervous system disorders	Cerebrovascular accident	2	1	1	1	1
Nervous system disorders	Cerebrovascular accident	3	0	0	1	1
Nervous system disorders	Encephalopathy	Missing	1	1	0	0
Nervous system disorders	Headache	2	1	1	0	0
Nervous system disorders	Lethargy	1	1	1	0	0
Nervous system disorders	Leukoencephalopathy	5	0	0	1	1
Nervous system disorders	Loss of consciousness	2	1	1	0	0
Nervous system disorders	Presyncope	2	0	0	1	1
Nervous system disorders	Presyncope	3	2	2	0	0
Nervous system disorders	Seizure	2	0	0	1	1
Nervous system disorders	Syncope	2	0	0	1	1
Nervous system disorders	Syncope	3	1	1	0	0
Nervous system disorders	Transient ischaemic attack	1	1	1	0	0

			Bendamustine (N=215)		Chlorambucil (N=219)	
SOC	PT	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Psychiatric disorders	Confusional state	2	1	1	0	0
Renal and urinary disorders	Acute kidney injury	3	1	1	0	0
Renal and urinary disorders	Acute kidney injury	Missing	2	2	0	0
Renal and urinary disorders	Renal impairment	3	0	0	1	1
Renal and urinary disorders	Urinary retention	1	0	0	1	1
Renal and urinary disorders	Urinary retention	2	0	0	2	2
Renal and urinary disorders	Urinary retention	Missing	1	1	0	0
Reproductive system and breast disorders	Testicular swelling	1	0	0	1	1
Respiratory, thoracic and mediastinal disorders	Chronic obstructive pulmonary disease	2	3	1	0	0
Respiratory, thoracic and mediastinal disorders	Chronic obstructive pulmonary disease	3	2	2	0	0
Respiratory, thoracic and mediastinal disorders	Dyspnoea	2	0	0	1	1
Respiratory, thoracic and mediastinal disorders	Dyspnoea	3	1	1	1	1
Respiratory, thoracic and mediastinal disorders	Epistaxis	4	0	0	1	1
Respiratory, thoracic and mediastinal disorders	Interstitial lung disease	3	0	0	1	1
Respiratory, thoracic and mediastinal disorders	Pleural effusion	2	2	2	0	0
Respiratory, thoracic and mediastinal disorders	Pleural effusion	3	1	1	0	0
Respiratory, thoracic and mediastinal disorders	Pneumonitis	5	1	1	0	0
Respiratory, thoracic and mediastinal disorders	Pneumothorax	2	0	0	1	1
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	1	2	2	0	0
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	3	1	1	1	1

			Bendamustine (N=215)		Chlorambucil (N=219)	
SOC	PT	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Respiratory, thoracic and mediastinal disorders	Respiratory distress	4	0	0	1	1
Skin and subcutaneous tissue disorders	Angioedema	3	1	1	0	0
Skin and subcutaneous tissue disorders	Dermatitis allergic	2	1	1	0	0
Skin and subcutaneous tissue disorders	Dermatitis exfoliative generalised	3	1	1	0	0
Skin and subcutaneous tissue disorders	Drug eruption	2	2	1	0	0
Skin and subcutaneous tissue disorders	Drug eruption	3	1	1	1	1
Skin and subcutaneous tissue disorders	Drug eruption	Missing	0	0	1	1
Skin and subcutaneous tissue disorders	Hyperhidrosis	1	0	0	1	1
Skin and subcutaneous tissue disorders	Lichen planus	3	1	1	0	0
Skin and subcutaneous tissue disorders	Psoriasis	4	1	1	0	0
Skin and subcutaneous tissue disorders	Rash	2	1	1	1	1
Skin and subcutaneous tissue disorders	Rash maculo-papular	2	0	0	2	2
Skin and subcutaneous tissue disorders	Rash maculo-papular	3	0	0	2	2
Skin and subcutaneous tissue disorders	Skin ulcer	3	1	1	0	0
Vascular disorders	Deep vein thrombosis	2	1	1	0	0
Vascular disorders	Femoral artery embolism	4	0	0	1	1
Vascular disorders	Haematoma	3	1	1	0	0
Vascular disorders	Hypertension	3	0	0	1	1
Vascular disorders	Hypotension	2	0	0	1	1
Vascular disorders	Hypotension	4	1	1	0	0

			Bendamustine (N=215)		Chlorambucil (N=219)	
SOC	PT	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients

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Table 15-7: Serious Adverse Events by MedDRA SOC – Bendamustine vs. Chlorambucil (Including Placebo)

SOC	Severity	Bendamustine (N=215)		Chlorambucil (N=219)	
		No. Incidences	No. Patients	No. Incidences	No. Patients
Blood and lymphatic system disorders	1	3	2	3	3
Blood and lymphatic system disorders	2	0	0	4	4
Blood and lymphatic system disorders	3	8	8	7	6
Blood and lymphatic system disorders	4	4	4	5	4
Blood and lymphatic system disorders	Missing	3	3	1	1
Cardiac disorders	1	1	1	3	3
Cardiac disorders	2	2	2	0	0
Cardiac disorders	3	3	3	3	3
Cardiac disorders	4	2	2	1	1
Cardiac disorders	5	2	2	0	0
Cardiac disorders	Missing	0	0	1	1
Gastrointestinal disorders	1	1	1	1	1
Gastrointestinal disorders	2	1	1	7	6
Gastrointestinal disorders	3	3	3	2	2
Gastrointestinal disorders	Missing	0	0	1	1
General disorders and administration site conditions	1	5	5	7	6
General disorders and administration site conditions	2	5	5	1	1
General disorders and administration site conditions	3	4	4	1	1
Hepatobiliary disorders	2	0	0	2	2
Hepatobiliary disorders	3	1	1	1	1

SOC	Severity	Bendamustine (N=215)		Chlorambucil (N=219)	
		No. Incidences	No. Patients	No. Incidences	No. Patients
Hepatobiliary disorders	Missing	2	1	0	0
Immune system disorders	1	2	2	0	0
Immune system disorders	2	4	3	3	2
Immune system disorders	3	2	2	1	1
Immune system disorders	Missing	1	1	0	0
Infections and infestations	1	31	26	13	12
Infections and infestations	2	18	16	17	16
Infections and infestations	3	27	25	28	24
Infections and infestations	4	6	6	4	4
Infections and infestations	5	4	4	0	0
Infections and infestations	Missing	7	5	8	8
Injury, poisoning and procedural complications	1	5	5	10	9
Injury, poisoning and procedural complications	2	7	7	10	9
Injury, poisoning and procedural complications	3	12	10	5	5
Injury, poisoning and procedural complications	4	1	1	0	0
Injury, poisoning and procedural complications	Missing	5	4	2	1
Investigations	2	0	0	1	1
Investigations	Missing	1	1	1	1
Metabolism and nutrition disorders	1	1	1	0	0
Metabolism and nutrition disorders	2	1	1	0	0
Metabolism and nutrition disorders	3	2	2	4	4

SOC	Severity	Bendamustine (N=215)		Chlorambucil (N=219)	
		No. Incidences	No. Patients	No. Incidences	No. Patients
Metabolism and nutrition disorders	4	1	1	1	1
Metabolism and nutrition disorders	5	0	0	1	1
Musculoskeletal and connective tissue disorders	3	2	2	2	2
Musculoskeletal and connective tissue disorders	Missing	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	3	3	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	2	2	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Missing	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	5	4	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	34	17	12	10
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	12	12	21	17
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4	2	2	4	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5	2	2	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Missing	15	10	3	3
Nervous system disorders	1	2	2	0	0
Nervous system disorders	2	3	3	4	4
Nervous system disorders	3	3	3	1	1
Nervous system disorders	5	0	0	1	1
Nervous system disorders	Missing	1	1	0	0
Psychiatric disorders	2	1	1	0	0
Renal and urinary disorders	1	0	0	1	1
Renal and urinary disorders	2	0	0	2	2

SOC	Severity	Bendamustine (N=215)		Chlorambucil (N=219)	
		No. Incidences	No. Patients	No. Incidences	No. Patients
Renal and urinary disorders	3	1	1	1	1
Renal and urinary disorders	Missing	3	3	0	0
Reproductive system and breast disorders	1	0	0	1	1
Respiratory, thoracic and mediastinal disorders	1	2	2	0	0
Respiratory, thoracic and mediastinal disorders	2	5	3	2	2
Respiratory, thoracic and mediastinal disorders	3	5	4	3	3
Respiratory, thoracic and mediastinal disorders	4	0	0	2	2
Respiratory, thoracic and mediastinal disorders	5	1	1	0	0
Skin and subcutaneous tissue disorders	1	0	0	1	1
Skin and subcutaneous tissue disorders	2	4	3	3	3
Skin and subcutaneous tissue disorders	3	5	5	3	3
Skin and subcutaneous tissue disorders	4	1	1	0	0
Skin and subcutaneous tissue disorders	Missing	0	0	1	1
Vascular disorders	2	1	1	1	1
Vascular disorders	3	1	1	1	1
Vascular disorders	4	1	1	1	1

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Table 15-8: Serious Adverse Event Outcomes – Bendamustine vs. Chlorambucil (Including Placebo)

SAE Outcome	Bendamustine (N=215)	Chlorambucil (N=219)	Total (N=434)
Resolved	221 (72%)	179 (76%)	400 (74%)
Resolved with sequelae	35 (11%)	22 (9%)	57 (11%)
Not resolved	20 (7%)	9 (4%)	29 (5%)
Ongoing at death	17 (6%)	9 (4%)	26 (5%)
Fatal	14 (5%)	14 (6%)	28 (5%)
Missing	0 (0%)	1 (0%)	1 (0%)

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14.2 Exploratory Analysis – Idelalisib vs. Placebo

Table 15-9: Toxicity Summary – Idelalisib vs. Placebo

Variable	Idelalisib (N=72)	Placebo (N=67)	Total (N=139)
Grade 3+ AE	41 (57%)	37 (55%)	78 (56%)
SAE	60 (83%)	38 (57%)	98 (71%)
Either Grade 3+ AE or SAE	69 (96%)	56 (84%)	125 (90%)

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14.2.1 Adverse Events

Table 15-10: Adverse Events by Severity – Idelalisib vs. Placebo

Severity	Idelalisib (N=72)	Placebo (N=67)	Total (N=139)
1	460 (54%)	493 (57%)	953 (56%)
2	259 (30%)	278 (32%)	537 (31%)
3	114 (13%)	80 (9%)	194 (11%)
4	14 (2%)	7 (1%)	21 (1%)
5	1 (0%)	0 (0%)	1 (0%)
Missing	2 (0%)	6 (1%)	8 (0%)

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Table 15-11: Adverse Events by CTCAE Category Name and Event Name – Idelalisib vs. Placebo

				Idelalisib (N=72)		Placebo (N=67)		
Category Name			Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Blood and disorders	lymphatic	system	Anemia	1	15	12	20	14
Blood and disorders	lymphatic	system	Anemia	2	12	8	11	7
Blood and disorders	lymphatic	system	Anemia	3	10	7	5	5
Blood and disorders	lymphatic	system	Anemia	4	1	1	0	0
Blood and disorders	lymphatic	system	Blood and lymphatic system disorders - Other, specify	1	5	1	5	4
Blood and disorders	lymphatic	system	Blood and lymphatic system disorders - Other, specify	2	4	2	4	4
Blood and disorders	lymphatic	system	Blood and lymphatic system disorders - Other, specify	3	4	3	0	0
Blood and disorders	lymphatic	system	Blood and lymphatic system disorders - Other, specify	4	1	1	0	0
Blood and disorders	lymphatic	system	Febrile neutropenia	1	1	1	0	0
Blood and disorders	lymphatic	system	Febrile neutropenia	2	2	1	0	0
Blood and disorders	lymphatic	system	Febrile neutropenia	3	1	1	0	0
Blood and disorders	lymphatic	system	Febrile neutropenia	4	1	1	0	0

			Idelalisib (N=72)		Placebo (N=67)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Blood and lymphatic system disorders	Haemolytic uremic syndrome	2	0	0	1	1
Blood and lymphatic system disorders	Thrombotic thrombocytopenic purpura	1	0	0	4	3
Blood and lymphatic system disorders	Thrombotic thrombocytopenic purpura	2	0	0	1	1
Cardiac disorders	Atrial fibrillation	1	1	1	0	0
Cardiac disorders	Atrial fibrillation	3	1	1	0	0
Cardiac disorders	Atrial flutter	2	1	1	0	0
Cardiac disorders	Cardiac disorders - Other, specify	1	1	1	1	1
Cardiac disorders	Cardiac disorders - Other, specify	2	1	1	1	1
Cardiac disorders	Chest pain - cardiac	1	0	0	1	1
Cardiac disorders	Heart failure	3	0	0	1	1
Cardiac disorders	Palpitations	1	1	1	1	1
Cardiac disorders	Palpitations	2	0	0	3	3
Cardiac disorders	Sinus bradycardia	1	0	0	1	1
Cardiac disorders	Sinus tachycardia	2	1	1	0	0
Cardiac disorders	Sinus tachycardia	3	0	0	1	1
Ear and labyrinth disorders	Ear and labyrinth disorders - Other, specify	1	1	1	2	1
Ear and labyrinth disorders	Ear pain	1	1	1	0	0
Ear and labyrinth disorders	Ear pain	2	1	1	0	0
Ear and labyrinth disorders	External ear inflammation	1	0	0	1	1

			Idelalisib (N=72)		Placebo (N=67)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Ear and labyrinth disorders	Hearing impaired	3	0	0	1	1
Ear and labyrinth disorders	Tinnitus	1	1	1	0	0
Ear and labyrinth disorders	Vestibular disorder	2	1	1	1	1
Eye disorders	Blurred vision	1	3	3	0	0
Eye disorders	Blurred vision	2	1	1	0	0
Eye disorders	Dry eye	1	0	0	1	1
Eye disorders	Eye disorders - Other, specify	1	2	2	2	2
Eye disorders	Eye disorders - Other, specify	2	1	1	1	1
Eye disorders	Eye pain	1	0	0	1	1
Eye disorders	Flashing lights	1	0	0	1	1
Gastrointestinal disorders	Abdominal distension	1	1	1	1	1
Gastrointestinal disorders	Abdominal pain	1	3	3	6	3
Gastrointestinal disorders	Abdominal pain	2	0	0	3	3
Gastrointestinal disorders	Colitis	2	0	0	1	1
Gastrointestinal disorders	Constipation	1	13	12	24	16
Gastrointestinal disorders	Constipation	2	4	3	5	4
Gastrointestinal disorders	Diarrhea	1	21	16	36	19
Gastrointestinal disorders	Diarrhea	2	9	9	5	4
Gastrointestinal disorders	Diarrhea	3	0	0	6	2
Gastrointestinal disorders	Dry mouth	1	1	1	5	4
Gastrointestinal disorders	Dry mouth	2	1	1	0	0

			Idelalisib (N=72)		Placebo (N=67)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Gastrointestinal disorders	Dry mouth	3	0	0	1	1
Gastrointestinal disorders	Dyspepsia	1	1	1	0	0
Gastrointestinal disorders	Dyspepsia	2	2	1	0	0
Gastrointestinal disorders	Dysphagia	1	1	1	0	0
Gastrointestinal disorders	Dysphagia	2	1	1	0	0
Gastrointestinal disorders	Dysphagia	3	1	1	0	0
Gastrointestinal disorders	Flatulence	1	2	2	1	1
Gastrointestinal disorders	Gastroesophageal reflux disease	1	1	1	1	1
Gastrointestinal disorders	Gastroesophageal reflux disease	2	0	0	1	1
Gastrointestinal disorders	Gastrointestinal disorders - Other, specify	1	8	6	3	3
Gastrointestinal disorders	Gastrointestinal disorders - Other, specify	2	1	1	2	2
Gastrointestinal disorders	Gastrointestinal pain	1	0	0	1	1
Gastrointestinal disorders	Gingival pain	1	0	0	1	1
Gastrointestinal disorders	Haemorrhoids	1	1	1	0	0
Gastrointestinal disorders	Lip pain	2	1	1	0	0
Gastrointestinal disorders	Mucositis oral	1	6	5	1	1
Gastrointestinal disorders	Mucositis oral	2	3	3	0	0
Gastrointestinal disorders	Mucositis oral	3	4	3	0	0
Gastrointestinal disorders	Nausea	1	30	20	35	22
Gastrointestinal disorders	Nausea	2	8	6	7	5
Gastrointestinal disorders	Oral dysesthesia	1	0	0	1	1

			Idelalisib (N=72)		Placebo (N=67)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Gastrointestinal disorders	Oral pain	1	2	2	1	1
Gastrointestinal disorders	Oral pain	2	1	1	0	0
Gastrointestinal disorders	Proctitis	2	1	1	0	0
Gastrointestinal disorders	Rectal hemorrhage	1	0	0	1	1
Gastrointestinal disorders	Vomiting	1	12	8	14	13
Gastrointestinal disorders	Vomiting	2	3	3	0	0
General disorders and administration site conditions	Chills	1	7	6	1	1
General disorders and administration site conditions	Chills	2	1	1	0	0
General disorders and administration site conditions	Edema limbs	1	3	3	4	4
General disorders and administration site conditions	Edema limbs	2	4	3	2	2
General disorders and administration site conditions	Fatigue	1	27	21	32	22
General disorders and administration site conditions	Fatigue	2	7	7	10	9
General disorders and administration site conditions	Fatigue	3	0	0	5	3
General disorders and administration site conditions	Fever	1	14	9	4	3
General disorders and administration site conditions	Fever	2	3	2	0	0

			Idelalisib (N=72)		Placebo (N=67)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
General disorders and administration site conditions	Flu like symptoms	1	2	2	2	2
General disorders and administration site conditions	Flu like symptoms	2	1	1	1	1
General disorders and administration site conditions	Gait disturbance	2	0	0	1	1
General disorders and administration site conditions	General disorders and administration site conditions - Other, specify	1	15	8	10	7
General disorders and administration site conditions	General disorders and administration site conditions - Other, specify	2	6	6	2	1
General disorders and administration site conditions	General disorders and administration site conditions - Other, specify	3	4	3	0	0
General disorders and administration site conditions	Infusion related reaction	1	5	4	5	4
General disorders and administration site conditions	Infusion related reaction	2	20	17	30	15
General disorders and administration site conditions	Infusion related reaction	3	0	0	1	1
General disorders and administration site conditions	Infusion related reaction	Missing	0	0	1	1
General disorders and administration site conditions	Localized edema	2	0	0	1	1
General disorders and administration site conditions	Malaise	1	1	1	0	0

			Idelalisib (N=72)		Placebo (N=67)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
General disorders and administration site conditions	Malaise	2	0	0	1	1
General disorders and administration site conditions	Oedema	1	10	9	5	4
General disorders and administration site conditions	Oedema	2	2	1	1	1
General disorders and administration site conditions	Oedema	3	0	0	1	1
General disorders and administration site conditions	Pain	1	5	3	7	7
General disorders and administration site conditions	Pain	2	3	2	1	1
Hepatobiliary disorders	Portal vein thrombosis	2	0	0	1	1
Immune system disorders	Allergic reaction	1	1	1	3	3
Immune system disorders	Allergic reaction	2	1	1	6	4
Immune system disorders	Allergic reaction	Missing	0	0	1	1
Immune system disorders	Immune system disorders - Other, specify	2	1	1	1	1
Infections and infestations	Bronchial infection	2	2	1	4	4
Infections and infestations	Eye infection	1	0	0	1	1
Infections and infestations	Eye infection	2	0	0	2	2
Infections and infestations	Infections and infestations - Other, specify	1	4	4	12	6
Infections and infestations	Infections and infestations - Other, specify	2	10	6	8	6
Infections and infestations	Infections and infestations - Other, specify	3	1	1	0	0

			Idelalisib (N=72)		Placebo (N=67)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Infections and infestations	Infections and infestations - Other, specify	Missing	1	1	0	0
Infections and infestations	Kidney infection	3	1	1	0	0
Infections and infestations	Lip infection	2	1	1	0	0
Infections and infestations	Lung infection	2	4	3	1	1
Infections and infestations	Lung infection	3	1	1	0	0
Infections and infestations	Mucosal infection	2	2	2	3	2
Infections and infestations	Otitis externa	2	1	1	0	0
Infections and infestations	Pharyngitis	1	1	1	0	0
Infections and infestations	Rash pustular	3	2	1	0	0
Infections and infestations	Rhinitis infective	2	0	0	1	1
Infections and infestations	Sepsis	3	1	1	0	0
Infections and infestations	Sepsis	4	1	1	0	0
Infections and infestations	Sinusitis	1	1	1	0	0
Infections and infestations	Sinusitis	2	1	1	0	0
Infections and infestations	Skin infection	2	1	1	1	1
Infections and infestations	Tooth infection	3	0	0	1	1
Infections and infestations	Upper respiratory infection	1	0	0	2	2
Infections and infestations	Upper respiratory infection	2	1	1	4	4
Infections and infestations	Urinary tract infection	1	1	1	0	0
Infections and infestations	Urinary tract infection	2	2	2	1	1
Infections and infestations	Wound infection	2	1	1	0	0

			Idelalisib (N=72)		Placebo (N=67)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Injury, poisoning and procedural complications	Bruising	1	2	2	2	1
Injury, poisoning and procedural complications	Fall	1	2	2	2	1
Injury, poisoning and procedural complications	Fall	2	0	0	2	2
Injury, poisoning and procedural complications	Fall	3	1	1	0	0
Injury, poisoning and procedural complications	Fracture	1	1	1	0	0
Injury, poisoning and procedural complications	Spinal fracture	3	1	1	0	0
Injury, poisoning and procedural complications	Wrist fracture	1	1	1	0	0
Investigations	Alanine aminotransferase increased	1	6	5	1	1
Investigations	Alanine aminotransferase increased	3	7	5	0	0
Investigations	Alanine aminotransferase increased	4	1	1	0	0
Investigations	Alkaline phosphatase increased	1	4	3	2	2
Investigations	Alkaline phosphatase increased	3	1	1	0	0
Investigations	Aspartate aminotransferase increased	1	2	2	0	0
Investigations	Aspartate aminotransferase increased	2	1	1	0	0
Investigations	Aspartate aminotransferase increased	3	1	1	0	0
Investigations	Blood bilirubin increased	1	8	5	3	1

			Idelalisib (N=72)		Placebo (N=67)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Investigations	Blood bilirubin increased	2	1	1	2	2
Investigations	Creatinine increased	1	4	2	5	2
Investigations	Creatinine increased	2	0	0	1	1
Investigations	Investigations - Other, specify	1	1	1	3	1
Investigations	Investigations - Other, specify	2	2	2	0	0
Investigations	Investigations - Other, specify	5	1	1	0	0
Investigations	Lymphocyte count decreased	1	2	1	1	1
Investigations	Lymphocyte count decreased	2	2	2	1	1
Investigations	Lymphocyte count decreased	3	2	2	0	0
Investigations	Neutrophil count decreased	1	17	9	22	13
Investigations	Neutrophil count decreased	2	21	14	22	12
Investigations	Neutrophil count decreased	3	32	23	37	19
Investigations	Neutrophil count decreased	4	8	8	6	6
Investigations	Neutrophil count decreased	Missing	0	0	1	1
Investigations	Platelet count decreased	1	16	12	44	18
Investigations	Platelet count decreased	2	15	7	35	19
Investigations	Platelet count decreased	3	4	3	9	5
Investigations	Platelet count decreased	4	1	1	1	1
Investigations	Weight loss	1	3	3	3	3
Investigations	Weight loss	2	0	0	1	1
Investigations	White blood cell decreased	2	0	0	2	2

			Idelalisib (N=72)		Placebo (N=67)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Metabolism and nutrition disorders	Anorexia	1	3	3	4	4
Metabolism and nutrition disorders	Anorexia	2	3	3	1	1
Metabolism and nutrition disorders	Anorexia	3	1	1	1	1
Metabolism and nutrition disorders	Dehydration	3	1	1	0	0
Metabolism and nutrition disorders	Hyperglycemia	3	2	2	0	0
Metabolism and nutrition disorders	Hyperkalemia	1	1	1	2	2
Metabolism and nutrition disorders	Hypernatremia	1	2	2	0	0
Metabolism and nutrition disorders	Hypernatremia	2	2	2	0	0
Metabolism and nutrition disorders	Hyperuricemia	1	3	3	1	1
Metabolism and nutrition disorders	Hypoalbuminemia	1	1	1	2	1
Metabolism and nutrition disorders	Hypoalbuminemia	2	3	1	2	1
Metabolism and nutrition disorders	Hypoalbuminemia	3	2	2	0	0
Metabolism and nutrition disorders	Hypocalcemia	1	1	1	2	2
Metabolism and nutrition disorders	Hypocalcemia	2	1	1	0	0
Metabolism and nutrition disorders	Hypocalcemia	3	1	1	0	0
Metabolism and nutrition disorders	Hypokalemia	1	0	0	2	2
Metabolism and nutrition disorders	Hypokalemia	2	1	1	1	1
Metabolism and nutrition disorders	Hypomagnesemia	1	1	1	1	1
Metabolism and nutrition disorders	Hypomagnesemia	2	1	1	0	0
Metabolism and nutrition disorders	Hyponatremia	1	3	2	7	2
Metabolism and nutrition disorders	Hyponatremia	Missing	0	0	1	1

			Idelalisib (N=72)		Placebo (N=67)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Metabolism and nutrition disorders	Metabolism and nutrition disorders - Other, specify	1	0	0	1	1
Musculoskeletal and connective tissue disorders	Arthralgia	1	1	1	0	0
Musculoskeletal and connective tissue disorders	Arthralgia	2	1	1	0	0
Musculoskeletal and connective tissue disorders	Arthritis	1	1	1	1	1
Musculoskeletal and connective tissue disorders	Arthritis	2	1	1	0	0
Musculoskeletal and connective tissue disorders	Back pain	1	2	2	7	6
Musculoskeletal and connective tissue disorders	Back pain	2	1	1	2	2
Musculoskeletal and connective tissue disorders	Bone pain	2	1	1	0	0
Musculoskeletal and connective tissue disorders	Chest wall pain	1	1	1	0	0
Musculoskeletal and connective tissue disorders	Joint effusion	1	0	0	1	1
Musculoskeletal and connective tissue disorders	Muscle weakness lower limb	2	1	1	1	1
Musculoskeletal and connective tissue disorders	Muscle weakness lower limb	3	1	1	0	0

			Idelalisib (N=72)		Placebo (N=67)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Musculoskeletal and connective tissue disorders	Musculoskeletal and connective tissue disorder - Other, specify	1	4	4	3	3
Musculoskeletal and connective tissue disorders	Musculoskeletal and connective tissue disorder - Other, specify	2	3	3	3	3
Musculoskeletal and connective tissue disorders	Musculoskeletal and connective tissue disorder - Other, specify	3	0	0	1	1
Musculoskeletal and connective tissue disorders	Myalgia	1	0	0	1	1
Musculoskeletal and connective tissue disorders	Neck pain	1	0	0	2	2
Musculoskeletal and connective tissue disorders	Pain in extremity	1	3	3	3	3
Musculoskeletal and connective tissue disorders	Pain in extremity	2	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify	2	2	2	2	1
Nervous system disorders	Dizziness	1	10	10	3	3
Nervous system disorders	Dizziness	2	2	2	3	3
Nervous system disorders	Dysgeusia	1	2	2	3	3
Nervous system disorders	Headache	1	6	6	13	8
Nervous system disorders	Headache	2	0	0	1	1
Nervous system disorders	Lethargy	1	4	4	1	1
Nervous system disorders	Lethargy	2	2	2	2	2
Nervous system disorders	Lethargy	Missing	1	1	0	0

			Idelalisib (N=72)		Placebo (N=67)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Nervous system disorders	Movements involuntary	2	0	0	1	1
Nervous system disorders	Nervous system disorders - Other, specify	1	0	0	5	3
Nervous system disorders	Olfactory nerve disorder	2	0	0	1	1
Nervous system disorders	Paresthesia	1	0	0	1	1
Nervous system disorders	Peripheral sensory neuropathy	1	1	1	3	3
Nervous system disorders	Peripheral sensory neuropathy	2	0	0	2	1
Nervous system disorders	Sinus pain	1	1	1	0	0
Nervous system disorders	Syncope	Missing	0	0	1	1
Nervous system disorders	Tremor	1	2	2	0	0
Nervous system disorders	Tremor	2	0	0	1	1
Nervous system disorders	Tremor	3	1	1	0	0
Nervous system disorders	Vasovagal reaction	3	0	0	1	1
Psychiatric disorders	Agitation	3	1	1	0	0
Psychiatric disorders	Anxiety	1	0	0	1	1
Psychiatric disorders	Depression	1	2	2	0	0
Psychiatric disorders	Depression	2	0	0	1	1
Psychiatric disorders	Hallucinations	1	1	1	1	1
Psychiatric disorders	Hallucinations	2	1	1	0	0
Psychiatric disorders	Hallucinations	3	1	1	0	0
Psychiatric disorders	Insomnia	1	2	2	1	1
Psychiatric disorders	Insomnia	2	2	2	0	0

			Idelalisib (N=72)		Placebo (N=67)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Psychiatric disorders	Libido decreased	1	0	0	1	1
Psychiatric disorders	Psychiatric disorders - Other, specify	1	1	1	0	0
Psychiatric disorders	Psychiatric disorders - Other, specify	2	1	1	0	0
Psychiatric disorders	Suicidal ideation	2	1	1	0	0
Renal and urinary disorders	Acute kidney injury	1	1	1	1	1
Renal and urinary disorders	Acute kidney injury	2	1	1	0	0
Renal and urinary disorders	Acute kidney injury	3	1	1	0	0
Renal and urinary disorders	Chronic kidney disease	2	1	1	0	0
Renal and urinary disorders	Urinary frequency	1	1	1	2	2
Renal and urinary disorders	Urinary tract obstruction	3	1	1	0	0
Renal and urinary disorders	Urinary tract pain	1	0	0	1	1
Reproductive system and breast disorders	Breast pain	1	1	1	0	0
Reproductive system and breast disorders	Gynecomastia	1	1	1	0	0
Respiratory, thoracic and mediastinal disorders	Cough	1	15	10	13	11
Respiratory, thoracic and mediastinal disorders	Cough	2	5	5	9	7
Respiratory, thoracic and mediastinal disorders	Dyspnea	1	8	8	2	2
Respiratory, thoracic and mediastinal disorders	Dyspnea	2	5	4	3	3

			Idelalisib (N=72)		Placebo (N=67)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Respiratory, thoracic and mediastinal disorders	Dyspnea	3	4	3	0	0
Respiratory, thoracic and mediastinal disorders	Epistaxis	1	0	0	1	1
Respiratory, thoracic and mediastinal disorders	Epistaxis	2	0	0	1	1
Respiratory, thoracic and mediastinal disorders	Laryngeal hemorrhage	2	1	1	0	0
Respiratory, thoracic and mediastinal disorders	Laryngeal inflammation	1	3	2	1	1
Respiratory, thoracic and mediastinal disorders	Nasal congestion	1	1	1	0	0
Respiratory, thoracic and mediastinal disorders	Pneumonitis	2	1	1	0	0
Respiratory, thoracic and mediastinal disorders	Productive cough	1	1	1	3	2
Respiratory, thoracic and mediastinal disorders	Pulmonary edema	2	1	1	0	0
Respiratory, thoracic and mediastinal disorders	Respiratory, thoracic and mediastinal disorders - Other, specify	1	2	1	1	1
Respiratory, thoracic and mediastinal disorders	Respiratory, thoracic and mediastinal disorders - Other, specify	2	2	2	1	1
Respiratory, thoracic and mediastinal disorders	Respiratory, thoracic and mediastinal disorders - Other, specify	3	3	2	0	0

			Idelalisib (N=72)		Placebo (N=67)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Respiratory, thoracic and mediastinal disorders	Sore throat	1	6	5	4	4
Respiratory, thoracic and mediastinal disorders	Wheezing	1	1	1	0	0
Skin and subcutaneous tissue disorders	Alopecia	1	0	0	3	3
Skin and subcutaneous tissue disorders	Dry skin	1	6	6	10	7
Skin and subcutaneous tissue disorders	Dry skin	2	1	1	3	3
Skin and subcutaneous tissue disorders	Dry skin	3	0	0	2	2
Skin and subcutaneous tissue disorders	Erythema multiforme	1	2	2	1	1
Skin and subcutaneous tissue disorders	Erythema multiforme	2	0	0	1	1
Skin and subcutaneous tissue disorders	Hyperhidrosis	1	1	1	0	0
Skin and subcutaneous tissue disorders	Hyperhidrosis	2	0	0	1	1
Skin and subcutaneous tissue disorders	Hyperhidrosis	3	0	0	1	1
Skin and subcutaneous tissue disorders	Nail ridging	1	1	1	0	0

				Idelalisib (N=72)		Placebo (N=67)		
Category Name			Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Skin and disorders	subcutaneous	tissue	Pain of skin	1	1	1	0	0
Skin and disorders	subcutaneous	tissue	Palmar-plantar erythrodysesthesia syndrome	1	0	0	1	1
Skin and disorders	subcutaneous	tissue	Pruritus	1	4	4	4	4
Skin and disorders	subcutaneous	tissue	Pruritus	2	2	2	2	2
Skin and disorders	subcutaneous	tissue	Pruritus	3	1	1	1	1
Skin and disorders	subcutaneous	tissue	Rash Exfoliative	2	1	1	0	0
Skin and disorders	subcutaneous	tissue	Rash Macular	1	2	2	0	0
Skin and disorders	subcutaneous	tissue	Rash Macular	3	0	0	1	1
Skin and disorders	subcutaneous	tissue	Rash acneiform	1	1	1	0	0
Skin and disorders	subcutaneous	tissue	Rash erythematous	1	1	1	1	1
Skin and disorders	subcutaneous	tissue	Rash erythematous	2	0	0	1	1
Skin and disorders	subcutaneous	tissue	Rash erythematous	3	0	0	1	1

				Idelalisib (N=72)		Placebo (N=67)		
Category Name			Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Skin and disorders	subcutaneous	tissue	Rash generalized	1	10	9	6	5
Skin and disorders	subcutaneous	tissue	Rash generalized	2	9	8	8	4
Skin and disorders	subcutaneous	tissue	Rash maculo-papular	1	12	8	5	5
Skin and disorders	subcutaneous	tissue	Rash maculo-papular	2	11	8	5	4
Skin and disorders	subcutaneous	tissue	Rash maculo-papular	3	7	6	0	0
Skin and disorders	subcutaneous	tissue	Rash maculo-papular	Missing	0	0	1	1
Skin and disorders	subcutaneous	tissue	Rash morbilliform	1	1	1	0	0
Skin and disorders	subcutaneous	tissue	Skin and subcutaneous tissue disorders - Other, specify	1	9	8	9	5
Skin and disorders	subcutaneous	tissue	Skin and subcutaneous tissue disorders - Other, specify	2	8	6	13	5
Skin and disorders	subcutaneous	tissue	Skin and subcutaneous tissue disorders - Other, specify	3	2	1	2	2
Skin and disorders	subcutaneous	tissue	Skin ulceration	1	2	1	0	0
Skin and disorders	subcutaneous	tissue	Skin ulceration	2	2	2	2	2

			Idelalisib (N=72)		Placebo (N=67)	
Category Name	Event Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Skin and subcutaneous tissue disorders	Urticaria	2	0	0	2	2
Vascular disorders	Haematoma	1	1	1	0	0
Vascular disorders	Hypertension	1	2	1	0	0
Vascular disorders	Hypertension	2	0	0	1	1
Vascular disorders	Hypertension	3	3	3	0	0
Vascular disorders	Hypotension	1	1	1	2	2
Vascular disorders	Hypotension	2	1	1	0	0
Vascular disorders	Hypotension	3	1	1	0	0
Vascular disorders	Lymphedema	1	1	1	0	0
Vascular disorders	Phlebitis	1	1	1	0	0
Vascular disorders	Phlebitis	2	0	0	2	1
Vascular disorders	Vascular disorders - Other, specify	2	0	0	2	2

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Table 15-12: Adverse Events by CTCAE Category Name – Idelalisib vs. Placebo

Category Name	Severity	Idelalisib (N=72)		Placebo (N=67)	
		No. Incidences	No. Patients	No. Incidences	No. Patients
Blood and lymphatic system disorders	1	21	13	29	16
Blood and lymphatic system disorders	2	18	11	17	13
Blood and lymphatic system disorders	3	15	9	5	5
Blood and lymphatic system disorders	4	3	2	0	0
Cardiac disorders	1	3	3	4	4
Cardiac disorders	2	3	3	4	4
Cardiac disorders	3	1	1	2	2
Ear and labyrinth disorders	1	3	3	3	2
Ear and labyrinth disorders	2	2	2	1	1
Ear and labyrinth disorders	3	0	0	1	1
Eye disorders	1	5	5	5	3
Eye disorders	2	2	2	1	1
Gastrointestinal disorders	1	103	39	132	40
Gastrointestinal disorders	2	35	21	24	12
Gastrointestinal disorders	3	5	3	7	3
General disorders and administration site conditions	1	89	43	70	36
General disorders and administration site conditions	2	47	27	50	25
General disorders and administration site conditions	3	4	3	7	5
General disorders and administration site conditions	Missing	0	0	1	1
Hepatobiliary disorders	2	0	0	1	1

Category Name	Severity	Idelalisib (N=72)		Placebo (N=67)	
		No. Incidences	No. Patients	No. Incidences	No. Patients
Immune system disorders	1	1	1	3	3
Immune system disorders	2	2	2	7	5
Immune system disorders	Missing	0	0	1	1
Infections and infestations	1	7	7	15	9
Infections and infestations	2	26	19	25	17
Infections and infestations	3	6	5	1	1
Infections and infestations	4	1	1	0	0
Infections and infestations	Missing	1	1	0	0
Injury, poisoning and procedural complications	1	6	5	4	2
Injury, poisoning and procedural complications	2	0	0	2	2
Injury, poisoning and procedural complications	3	2	1	0	0
Investigations	1	63	23	84	22
Investigations	2	42	21	64	28
Investigations	3	47	26	46	21
Investigations	4	10	9	7	6
Investigations	5	1	1	0	0
Investigations	Missing	0	0	1	1
Metabolism and nutrition disorders	1	15	7	22	9
Metabolism and nutrition disorders	2	11	7	4	3
Metabolism and nutrition disorders	3	7	4	1	1
Metabolism and nutrition disorders	Missing	0	0	1	1

Category Name	Severity	Idelalisib (N=72)		Placebo (N=67)	
		No. Incidences	No. Patients	No. Incidences	No. Patients
Musculoskeletal and connective tissue disorders	1	12	11	18	14
Musculoskeletal and connective tissue disorders	2	8	7	7	5
Musculoskeletal and connective tissue disorders	3	1	1	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	2	2	2	1
Nervous system disorders	1	26	21	29	18
Nervous system disorders	2	4	4	11	9
Nervous system disorders	3	1	1	1	1
Nervous system disorders	Missing	1	1	1	1
Psychiatric disorders	1	6	5	4	4
Psychiatric disorders	2	5	5	1	1
Psychiatric disorders	3	2	2	0	0
Renal and urinary disorders	1	2	2	4	4
Renal and urinary disorders	2	2	2	0	0
Renal and urinary disorders	3	2	2	0	0
Reproductive system and breast disorders	1	2	2	0	0
Respiratory, thoracic and mediastinal disorders	1	37	20	25	16
Respiratory, thoracic and mediastinal disorders	2	15	13	14	10
Respiratory, thoracic and mediastinal disorders	3	7	4	0	0
Skin and subcutaneous tissue disorders	1	53	30	40	20
Skin and subcutaneous tissue disorders	2	34	21	38	19
Skin and subcutaneous tissue disorders	3	10	7	8	7

		Idelalisib (N=72)		Placebo (N=67)	
Category Name	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Skin and subcutaneous tissue disorders	Missing	0	0	1	1
Vascular disorders	1	6	4	2	2
Vascular disorders	2	1	1	5	3
Vascular disorders	3	4	4	0	0

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14.2.2 Serious Adverse Events

Table 15-13: Serious Adverse Events by Severity – Idelalisib vs. Placebo

Severity	Idelalisib (N=72)	Placebo (N=67)	Total (N=139)
1	32 (23%)	15 (15%)	47 (20%)
2	42 (30%)	38 (38%)	80 (33%)
3	34 (24%)	23 (23%)	57 (24%)
4	9 (6%)	4 (4%)	13 (5%)
5	4 (3%)	1 (1%)	5 (2%)
Missing	20 (14%)	18 (18%)	38 (16%)

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Table 15-14: Serious Adverse Events by MedDRA SOC and PT – Idelalisib vs. Placebo

			Idelalisib (N=72)		Placebo (N=67)	
SOC	PT	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Blood and lymphatic system disorders	Anaemia	4	0	0	1	1
Blood and lymphatic system disorders	Febrile neutropenia	1	2	2	0	0
Blood and lymphatic system disorders	Febrile neutropenia	2	1	1	0	0
Blood and lymphatic system disorders	Febrile neutropenia	3	2	2	1	1
Blood and lymphatic system disorders	Neutropenia	4	1	1	0	0
Blood and lymphatic system disorders	Neutropenia	Missing	0	0	1	1
Cardiac disorders	Acute coronary syndrome	5	1	1	0	0
Cardiac disorders	Acute myocardial infarction	2	1	1	0	0
Cardiac disorders	Angina pectoris	1	0	0	1	1
Cardiac disorders	Bundle branch block right	1	0	0	1	1
Cardiac disorders	Myocardial infarction	1	0	0	1	1
Endocrine disorders	Inappropriate antidiuretic hormone secretion	2	1	1	0	0
Endocrine disorders	Inappropriate antidiuretic hormone secretion	4	1	1	0	0
Gastrointestinal disorders	Abdominal pain	2	0	0	1	1
Gastrointestinal disorders	Diarrhoea	2	1	1	0	0
Gastrointestinal disorders	Diarrhoea	3	0	0	1	1
Gastrointestinal disorders	Small intestinal obstruction	3	1	1	0	0
General disorders and administration site conditions	Chest pain	3	0	0	1	1

			Idelalisib (N=72)		Placebo (N=67)	
SOC	PT	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
General disorders and administration site conditions	Chest pain	Missing	1	1	0	0
General disorders and administration site conditions	General physical health deterioration	1	0	0	1	1
General disorders and administration site conditions	Oedema	3	1	1	0	0
General disorders and administration site conditions	Pyrexia	1	9	7	1	1
General disorders and administration site conditions	Pyrexia	2	4	4	0	0
General disorders and administration site conditions	Pyrexia	3	1	1	0	0
General disorders and administration site conditions	Pyrexia	4	1	1	0	0
General disorders and administration site conditions	Pyrexia	Missing	3	3	0	0
Hepatobiliary disorders	Cholecystitis acute	Missing	0	0	2	1
Hepatobiliary disorders	Hepatic cirrhosis	2	0	0	1	1
Immune system disorders	Hypersensitivity	1	1	1	0	0
Immune system disorders	Hypersensitivity	Missing	1	1	0	0
Infections and infestations	Arthritis infective	4	1	1	0	0
Infections and infestations	Bronchitis	3	1	1	0	0
Infections and infestations	COVID-19	Missing	0	0	2	1
Infections and infestations	Cellulitis	2	0	0	1	1

SOC	PT	Severity	Idelalisib (N=72)		Placebo (N=67)	
			No. Incidences	No. Patients	No. Incidences	No. Patients
Infections and infestations	Escherichia sepsis	1	1	1	0	0
Infections and infestations	Herpes virus infection	3	1	1	0	0
Infections and infestations	Infection	1	2	2	0	0
Infections and infestations	Infection	2	1	1	0	0
Infections and infestations	Infection	Missing	1	1	0	0
Infections and infestations	Influenza	2	1	1	0	0
Infections and infestations	Lower respiratory tract infection	1	0	0	2	2
Infections and infestations	Lower respiratory tract infection	2	1	1	3	3
Infections and infestations	Lower respiratory tract infection	3	0	0	1	1
Infections and infestations	Lower respiratory tract infection	4	0	0	1	1
Infections and infestations	Lower respiratory tract infection fungal	2	1	1	0	0
Infections and infestations	Mastoiditis	2	1	1	0	0
Infections and infestations	Neutropenic sepsis	1	1	1	0	0
Infections and infestations	Neutropenic sepsis	2	3	3	0	0
Infections and infestations	Neutropenic sepsis	3	6	6	0	0
Infections and infestations	Neutropenic sepsis	4	2	2	0	0
Infections and infestations	Neutropenic sepsis	5	1	1	0	0
Infections and infestations	Neutropenic sepsis	Missing	1	1	1	1
Infections and infestations	Otitis media	2	1	1	0	0
Infections and infestations	Peritonsillar abscess	2	1	1	0	0

			Idelalisib (N=72)		Placebo (N=67)	
SOC	PT	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Infections and infestations	Pneumocystis jirovecii pneumonia	1	1	1	0	0
Infections and infestations	Pneumocystis jirovecii pneumonia	2	1	1	0	0
Infections and infestations	Pneumonia	1	0	0	1	1
Infections and infestations	Pneumonia	2	4	4	0	0
Infections and infestations	Pneumonia	3	1	1	1	1
Infections and infestations	Pneumonia	4	1	1	0	0
Infections and infestations	Pneumonia	5	1	1	0	0
Infections and infestations	Pneumonia	Missing	2	2	0	0
Infections and infestations	Sepsis	1	5	5	2	2
Infections and infestations	Sepsis	2	2	2	0	0
Infections and infestations	Sepsis	3	3	3	1	1
Infections and infestations	Tonsillitis	3	1	1	0	0
Infections and infestations	Tooth infection	1	1	1	0	0
Infections and infestations	Upper respiratory tract infection	3	0	0	1	1
Infections and infestations	Urinary tract infection	1	1	1	0	0
Infections and infestations	Urinary tract infection	3	1	1	0	0
Infections and infestations	Viral upper respiratory tract infection	2	0	0	1	1
Injury, poisoning and procedural complications	Fall	3	1	1	0	0
Injury, poisoning and procedural complications	Infusion related reaction	1	2	2	2	2
Injury, poisoning and procedural complications	Infusion related reaction	2	2	2	1	1

			Idelalisib (N=72)		Placebo (N=67)	
SOC	PT	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Injury, poisoning and procedural complications	Infusion related reaction	3	1	1	0	0
Injury, poisoning and procedural complications	Infusion related reaction	Missing	0	0	1	1
Injury, poisoning and procedural complications	Spinal compression fracture	3	1	1	0	0
Injury, poisoning and procedural complications	Subdural haematoma	3	0	0	1	1
Investigations	Alanine aminotransferase increased	2	1	1	0	0
Investigations	Alanine aminotransferase increased	3	1	1	0	0
Metabolism and nutrition disorders	Dehydration	2	2	2	0	0
Metabolism and nutrition disorders	Hyperkalaemia	3	1	1	1	1
Metabolism and nutrition disorders	Hyperkalaemia	5	0	0	1	1
Metabolism and nutrition disorders	Hypoglycaemia	Missing	1	1	0	0
Musculoskeletal and connective tissue disorders	Back pain	Missing	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Bladder transitional cell carcinoma stage I	2	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Cholangiocarcinoma	3	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Chronic lymphocytic leukaemia	Missing	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Hepatic cancer	Missing	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Adenocarcinoma	Missing	1	1	1	1

			Idelalisib (N=72)		Placebo (N=67)	
SOC	PT	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Adenocarcinoma of colon	2	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Basal cell carcinoma	1	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Basal cell carcinoma	2	2	2	2	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Basal cell carcinoma	3	2	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Bowen's disease	2	0	0	2	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Burkitt's lymphoma	5	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Colon cancer	1	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Colon cancer	3	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Colorectal adenocarcinoma	1	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	External ear neoplasm malignant	2	1	1	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	External ear neoplasm malignant	3	1	1	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Gallbladder cancer	4	0	0	1	1

			Idelalisib (N=72)		Placebo (N=67)	
SOC	PT	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Gastric cancer	3	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Invasive ductal breast carcinoma	Missing	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Malignant melanoma	2	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Malignant melanoma	Missing	0	0	2	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastatic malignant melanoma	Missing	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Prostate cancer	3	2	2	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Prostate cancer	Missing	1	1	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Second primary malignancy	3	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Second primary malignancy	Missing	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Skin cancer	2	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Squamous cell carcinoma	2	0	0	5	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Squamous cell carcinoma	Missing	0	0	2	1

			Idelalisib (N=72)		Placebo (N=67)	
SOC	PT	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Squamous cell carcinoma of skin	1	0	0	2	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Squamous cell carcinoma of skin	2	0	0	11	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Squamous cell carcinoma of skin	3	0	0	2	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Squamous cell carcinoma of skin	Missing	0	0	1	1
Nervous system disorders	Cerebrovascular accident	2	1	1	0	0
Nervous system disorders	Cerebrovascular accident	3	0	0	1	1
Nervous system disorders	Presyncope	2	0	0	1	1
Nervous system disorders	Syncope	3	1	1	1	1
Nervous system disorders	Tremor	2	1	1	0	0
Psychiatric disorders	Confusional state	2	0	0	1	1
Psychiatric disorders	Suicidal ideation	3	1	1	0	0
Renal and urinary disorders	Acute Kidney Injury	2	1	1	0	0
Renal and urinary disorders	Acute kidney injury	1	1	1	0	0
Renal and urinary disorders	Acute kidney injury	2	1	1	0	0
Renal and urinary disorders	Acute kidney injury	3	1	1	0	0
Renal and urinary disorders	Renal impairment	3	0	0	1	1
Respiratory, thoracic and mediastinal disorders	Cough	1	1	1	0	0
Respiratory, thoracic and mediastinal disorders	Epistaxis	1	1	1	0	0

SOC	PT	Severity	Idelalisib (N=72)		Placebo (N=67)	
			No. Incidences	No. Patients	No. Incidences	No. Patients
Respiratory, thoracic and mediastinal disorders	Hypoxia	2	1	1	0	0
Respiratory, thoracic and mediastinal disorders	Pneumonitis	4	1	1	0	0
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	2	1	1	0	0
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	3	0	0	1	1
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	4	1	1	0	0
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	Missing	1	1	0	0
Skin and subcutaneous tissue disorders	Drug eruption	2	1	1	2	1
Skin and subcutaneous tissue disorders	Drug eruption	3	0	0	2	2
Skin and subcutaneous tissue disorders	Rash	Missing	1	1	0	0
Skin and subcutaneous tissue disorders	Rash erythematous	2	1	1	0	0
Skin and subcutaneous tissue disorders	Rash maculo-papular	1	1	1	0	0
Skin and subcutaneous tissue disorders	Rash maculo-papular	3	0	0	1	1
Skin and subcutaneous tissue disorders	Rash maculo-papular	Missing	2	2	0	0
Surgical and medical procedures	Tumour excision	Missing	1	1	0	0
Vascular disorders	Deep vein thrombosis	2	0	0	1	1
Vascular disorders	Haematoma	3	0	0	1	1
Vascular disorders	Hypertension	3	0	0	1	1
Vascular disorders	Hypotension	4	0	0	1	1
Vascular disorders	Hypotension	Missing	1	1	0	0
Vascular disorders	Orthostatic hypotension	2	1	1	0	0

			Idelalisib (N=72)		Placebo (N=67)	
SOC	PT	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients

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Table 15-15: Serious Adverse Events by MedDRA SOC – Idelalisib vs. Placebo

SOC	Severity	Idelalisib (N=72)		Placebo (N=67)	
		No. Incidences	No. Patients	No. Incidences	No. Patients
Blood and lymphatic system disorders	1	2	2	0	0
Blood and lymphatic system disorders	2	1	1	0	0
Blood and lymphatic system disorders	3	2	2	1	1
Blood and lymphatic system disorders	4	1	1	1	1
Blood and lymphatic system disorders	Missing	0	0	1	1
Cardiac disorders	1	0	0	3	3
Cardiac disorders	2	1	1	0	0
Cardiac disorders	5	1	1	0	0
Endocrine disorders	2	1	1	0	0
Endocrine disorders	4	1	1	0	0
Gastrointestinal disorders	2	1	1	1	1
Gastrointestinal disorders	3	1	1	1	1
General disorders and administration site conditions	1	9	7	2	2
General disorders and administration site conditions	2	4	4	0	0
General disorders and administration site conditions	3	2	2	1	1
General disorders and administration site conditions	4	1	1	0	0
General disorders and administration site conditions	Missing	4	4	0	0
Hepatobiliary disorders	2	0	0	1	1
Hepatobiliary disorders	Missing	0	0	2	1
Immune system disorders	1	1	1	0	0

SOC	Severity	Idelalisib (N=72)		Placebo (N=67)	
		No. Incidences	No. Patients	No. Incidences	No. Patients
Immune system disorders	Missing	1	1	0	0
Infections and infestations	1	12	11	5	5
Infections and infestations	2	17	13	5	5
Infections and infestations	3	14	12	4	4
Infections and infestations	4	4	3	1	1
Infections and infestations	5	2	2	0	0
Infections and infestations	Missing	4	4	3	1
Injury, poisoning and procedural complications	1	2	2	2	2
Injury, poisoning and procedural complications	2	2	2	1	1
Injury, poisoning and procedural complications	3	3	3	1	1
Injury, poisoning and procedural complications	Missing	0	0	1	1
Investigations	2	1	1	0	0
Investigations	3	1	1	0	0
Metabolism and nutrition disorders	2	2	2	0	0
Metabolism and nutrition disorders	3	1	1	1	1
Metabolism and nutrition disorders	5	0	0	1	1
Metabolism and nutrition disorders	Missing	1	1	0	0
Musculoskeletal and connective tissue disorders	Missing	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Missing	1	1	1	1

SOC	Severity	Idelalisib (N=72)		Placebo (N=67)	
		No. Incidences	No. Patients	No. Incidences	No. Patients
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	2	2	3	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	3	3	24	7
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	7	6	4	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Missing	3	3	9	4
Nervous system disorders	2	2	2	1	1
Nervous system disorders	3	1	1	2	2
Psychiatric disorders	2	0	0	1	1
Psychiatric disorders	3	1	1	0	0
Renal and urinary disorders	1	1	1	0	0
Renal and urinary disorders	2	2	2	0	0
Renal and urinary disorders	3	1	1	1	1
Respiratory, thoracic and mediastinal disorders	1	2	2	0	0
Respiratory, thoracic and mediastinal disorders	2	2	2	0	0
Respiratory, thoracic and mediastinal disorders	3	0	0	1	1
Respiratory, thoracic and mediastinal disorders	4	2	2	0	0
Respiratory, thoracic and mediastinal disorders	Missing	1	1	0	0
Skin and subcutaneous tissue disorders	1	1	1	0	0
Skin and subcutaneous tissue disorders	2	2	2	2	1
Skin and subcutaneous tissue disorders	3	0	0	3	3

		Idelalisib (N=72)		Placebo (N=67)	
SOC	Severity	No. Incidences	No. Patients	No. Incidences	No. Patients
Skin and subcutaneous tissue disorders	Missing	3	3	0	0
Surgical and medical procedures	Missing	1	1	0	0
Vascular disorders	2	1	1	1	1
Vascular disorders	3	0	0	2	2
Vascular disorders	4	0	0	1	1
Vascular disorders	Missing	1	1	0	0

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Table 15-16: Serious Adverse Event Outcomes – Idelalisib vs. Placebo

SAE Outcome	Idelalisib (N=72)	Placebo (N=67)	Total (N=139)
Resolved	108 (77%)	72 (73%)	180 (75%)
Resolved with sequelae	16 (11%)	6 (6%)	22 (9%)
Not resolved	5 (4%)	7 (7%)	12 (5%)
Ongoing at death	6 (4%)	9 (9%)	15 (6%)
Fatal	6 (4%)	5 (5%)	11 (5%)

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14.2.3 Suspected Unexpected Serious Adverse Reactions (SUSARs)

Table 15-17: Line Listing of SUSARs – All Randomised Patients

SAE Number	Randomisation Arm	SOC	PT	Severity	Randomisation Date	Onset Date	Related Drug
114-0005-1	Chlorambucil	Injury, poisoning and procedural complications	Infusion related reaction	1	27APR2012	03MAY2012	Ofatumumab
114-0006-1	Bendamustine	Skin and subcutaneous tissue disorders	Psoriasis	4	27APR2012	25JUL2012	Bendamustine & Ofatumumab
114-0006-2	Bendamustine	Infections and infestations	Encephalitis viral	4	27APR2012	07NOV2012	Bendamustine & Ofatumumab
124-0007-1	Chlorambucil	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Acute myeloid leukaemia	3	11MAY2012	03FEB2015	Chlorambucil
113-0008-1	Bendamustine	Blood and lymphatic system disorders	Febrile neutropenia	3	22MAY2012	07AUG2012	Bendamustine & Ofatumumab
113-0008-2	Bendamustine	Infections and infestations	Neutropenic sepsis	1	22MAY2012	14JAN2013	Bendamustine & Ofatumumab
003-0015-1	Bendamustine	Blood and lymphatic system disorders	Febrile neutropenia	3	19JUL2012	08AUG2012	Bendamustine & Ofatumumab
003-0015-3	Bendamustine	Gastrointestinal disorders	Constipation	3	19JUL2012	30SEP2012	Bendamustine
194-0016-1	Chlorambucil	Infections and infestations	Upper respiratory tract infection	Missing	24JUL2012	19FEB2013	Chlorambucil & Ofatumumab
046-0017-1	Chlorambucil	Skin and subcutaneous tissue disorders	Rash maculo-papular	3	03AUG2012	02NOV2012	Chlorambucil

SAE Number	Randomisation Arm	SOC	PT	Severity	Randomisation Date	Onset Date	Related Drug
130-0020-1	Chlorambucil	Injury, poisoning and procedural complications	Infusion related reaction	1	28AUG2012	10SEP2012	Ofatumumab
130-0020-2	Chlorambucil	Infections and infestations	Herpes zoster	Missing	28AUG2012	23NOV2012	Chlorambucil & Ofatumumab
178-0021-2	Bendamustine	Skin and subcutaneous tissue disorders	Skin ulcer	3	28AUG2012	05NOV2012	Bendamustine & Ofatumumab
178-0021-3	Bendamustine	Infections and infestations	Neutropenic sepsis	1	28AUG2012	22APR2013	Bendamustine & Ofatumumab
112-0025-1	Bendamustine	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Squamous cell carcinoma of skin	Missing	15OCT2012	05MAY2017	Bendamustine
115-0027-2	Bendamustine	Skin and subcutaneous tissue disorders	Rash	2	16OCT2012	29OCT2012	Ofatumumab
075-0031-5	Bendamustine	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Squamous cell carcinoma of skin	1	21NOV2012	15APR2013	Bendamustine
370-0032-2	Chlorambucil	Blood and lymphatic system disorders	Febrile neutropenia	3	30NOV2012	12DEC2012	Chlorambucil & Ofatumumab
050-0033-3	Bendamustine	Infections and infestations	Neutropenic sepsis	3	06DEC2012	09MAY2013	Bendamustine & Ofatumumab
113-0035-2	Chlorambucil	Blood and lymphatic system disorders	Febrile neutropenia	3	10DEC2012	23DEC2012	Chlorambucil & Ofatumumab
113-0035-3	Chlorambucil	Infections and infestations	Neutropenic sepsis	Missing	10DEC2012	17APR2013	Chlorambucil & Ofatumumab

SAE Number	Randomisation Arm	SOC	PT	Severity	Randomisation Date	Onset Date	Related Drug
113-0035-4	Chlorambucil	Infections and infestations	Neutropenic sepsis	3	10DEC2012	10JUN2013	Chlorambucil & Ofatumumab
112-0039-1	Chlorambucil	Skin and subcutaneous tissue disorders	Rash maculo-papular	2	07JAN2013	20JAN2013	Chlorambucil & Ofatumumab
112-0039-2	Chlorambucil	Infections and infestations	Upper respiratory tract infection	3	07JAN2013	20JAN2013	Chlorambucil & Ofatumumab
003-0040-1	Bendamustine	Blood and lymphatic system disorders	Febrile neutropenia	3	09JAN2013	04FEB2013	Bendamustine & Ofatumumab
124-0047-3	Bendamustine	Infections and infestations	Pneumocystis jirovecii pneumonia	3	14FEB2013	23OCT2013	Bendamustine & Ofatumumab
434-0050-1	Chlorambucil	Infections and infestations	Neutropenic sepsis	2	21FEB2013	26APR2013	Chlorambucil & Ofatumumab
049-0053-2	Chlorambucil	Infections and infestations	Atypical pneumonia	1	27FEB2013	20SEP2013	Chlorambucil & Ofatumumab
050-0054-1	Bendamustine	Blood and lymphatic system disorders	Febrile neutropenia	Missing	04MAR2013	19MAR2013	Bendamustine & Ofatumumab
092-0056-2	Bendamustine	Infections and infestations	Neutropenic sepsis	3	06MAR2013	29MAR2013	Bendamustine & Ofatumumab
092-0056-4	Bendamustine	Infections and infestations	Lower respiratory tract infection	1	06MAR2013	14JUN2013	Bendamustine & Ofatumumab
092-0056-5	Bendamustine	Infections and infestations	Pneumonia	3	06MAR2013	23JUN2013	Bendamustine & Ofatumumab
003-0062-1	Chlorambucil	Injury, poisoning and procedural complications	Infusion related reaction	1	13MAR2013	21MAR2013	Ofatumumab
255-0064-1	Bendamustine	Infections and infestations	Urinary tract infection	1	21MAR2013	25APR2013	Bendamustine & Ofatumumab

SAE Number	Randomisation Arm	SOC	PT	Severity	Randomisation Date	Onset Date	Related Drug
114-0066-1	Bendamustine	Infections and infestations	Lower respiratory tract infection	3	25MAR2013	02APR2013	Bendamustine & Ofatumumab
114-0066-4	Bendamustine	Nervous system disorders	Encephalopathy	Missing	25MAR2013	14SEP2013	Bendamustine & Ofatumumab
194-0068-2	Chlorambucil	Infections and infestations	Infection	1	09APR2013	08MAY2013	Chlorambucil & Ofatumumab
194-0068-3	Chlorambucil	Blood and lymphatic system disorders	Febrile neutropenia	3	09APR2013	21JUL2013	Chlorambucil & Ofatumumab
194-0068-4	Chlorambucil	Infections and infestations	Infection	3	09APR2013	19SEP2013	Chlorambucil & Ofatumumab
071-0071-1	Bendamustine	Infections and infestations	Campylobacter infection	2	12APR2013	03MAY2013	Bendamustine & Ofatumumab
370-0072-1	Bendamustine	Infections and infestations	Lower respiratory tract infection	2	18APR2013	25OCT2013	Bendamustine & Ofatumumab
370-0072-2	Bendamustine	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Pancreatic carcinoma	5	18APR2013	25APR2014	Ofatumumab
370-0072-3	Bendamustine	Infections and infestations	Hepatitis B	3	18APR2013	28JAN2014	Ofatumumab
153-0075-1	Bendamustine	Infections and infestations	Neutropenic sepsis	3	10MAY2013	05JUN2013	Bendamustine & Ofatumumab
319-0076-2	Chlorambucil	Infections and infestations	Escherichia infection	3	14MAY2013	08JUL2013	Chlorambucil & Ofatumumab
086-0087-1	Bendamustine	Infections and infestations	Sepsis	Missing	20JUN2013	05AUG2013	Bendamustine & Ofatumumab

SAE Number	Randomisation Arm	SOC	PT	Severity	Randomisation Date	Onset Date	Related Drug
095-0089-2	Bendamustine	Infections and infestations	Sepsis	5	25JUN2013	08JAN2014	Bendamustine & Ofatumumab
114-0098-2	Chlorambucil	Infections and infestations	Lower respiratory tract infection	3	01AUG2013	28FEB2014	Chlorambucil & Ofatumumab
114-0098-3	Chlorambucil	Infections and infestations	Lower respiratory tract infection	2	01AUG2013	28MAR2014	Chlorambucil & Ofatumumab
118-0101-2	Bendamustine	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Squamous cell carcinoma of skin	2	12AUG2013	05JUN2017	Bendamustine
118-0101-3	Bendamustine	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Bowen's disease	2	12AUG2013	08AUG2018	Bendamustine
175-0104-1	Chlorambucil	Metabolism and nutrition disorders	Dehydration	3	22AUG2013	22JAN2014	Chlorambucil & Ofatumumab
139-0106-1	Bendamustine	Infections and infestations	Lower respiratory tract infection	Missing	28AUG2013	03OCT2013	Bendamustine & Ofatumumab
179-0124-1	Chlorambucil	Infections and infestations	Lower respiratory tract infection	3	02OCT2013	08JAN2014	Chlorambucil & Ofatumumab
359-0125-1	Chlorambucil	Blood and lymphatic system disorders	Febrile neutropenia	4	02OCT2013	13FEB2014	Chlorambucil & Ofatumumab
218-0127-1	Bendamustine	Infections and infestations	Lower respiratory tract infection	3	08OCT2013	13MAR2014	Bendamustine & Ofatumumab
192-0129-1	Chlorambucil	Infections and infestations	Septic shock	2	15OCT2013	03NOV2013	Chlorambucil & Ofatumumab

SAE Number	Randomisation Arm	SOC	PT	Severity	Randomisation Date	Onset Date	Related Drug
187-0132-3	Bendamustine	Injury, poisoning and procedural complications	Infusion related reaction	2	23OCT2013	12NOV2013	Ofatumumab
198-0136-1	Chlorambucil	Musculoskeletal and connective tissue disorders	Back pain	3	08NOV2013	10JAN2014	Ofatumumab
179-0138-2	Bendamustine	Blood and lymphatic system disorders	Bone marrow failure	4	13NOV2013	08JAN2015	Bendamustine & Ofatumumab
124-0139-1	Chlorambucil	Infections and infestations	Lower respiratory tract infection	3	15NOV2013	03DEC2013	Chlorambucil & Ofatumumab
212-0147-1	Bendamustine	Blood and lymphatic system disorders	Anaemia	3	06DEC2013	24FEB2014	Bendamustine & Ofatumumab
370-0150-1	Chlorambucil	Infections and infestations	Sepsis	3	10DEC2013	10MAR2014	Chlorambucil & Ofatumumab
107-0151-1	Bendamustine	Respiratory, thoracic and mediastinal disorders	Pneumonitis	5	18DEC2013	14OCT2014	Bendamustine & Ofatumumab
361-0152-2	Chlorambucil	Infections and infestations	Herpes zoster	3	14JAN2014	10FEB2014	Ofatumumab
093-0156-1	Chlorambucil	Infections and infestations	Lower respiratory tract infection	2	17JAN2014	14MAY2014	Ofatumumab
172-0158-3	Bendamustine	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Hepatocellular carcinoma	Missing	29JAN2014	22NOV2017	Bendamustine & Ofatumumab
370-0161-1	Chlorambucil	Infections and infestations	Neutropenic sepsis	4	03FEB2014	20FEB2014	Chlorambucil & Ofatumumab

SAE Number	Randomisation Arm	SOC	PT	Severity	Randomisation Date	Onset Date	Related Drug
370-0161-2	Chlorambucil	Infections and infestations	Neutropenic sepsis	3	03FEB2014	12APR2014	Chlorambucil & Ofatumumab
370-0161-3	Chlorambucil	Respiratory, thoracic and mediastinal disorders	Interstitial lung disease	3	03FEB2014	12APR2014	Chlorambucil & Ofatumumab
098-0162-1	Bendamustine	Skin and subcutaneous tissue disorders	Dermatitis exfoliative generalised	3	04FEB2014	24APR2014	Bendamustine & Ofatumumab
003-0170-1	Bendamustine	General disorders and administration site conditions	Influenza like illness	3	19FEB2014	18APR2014	Bendamustine & Ofatumumab
102-0173-1	Chlorambucil	Investigations	Weight decreased	2	21FEB2014	11MAR2014	Chlorambucil & Ofatumumab
102-0173-2	Chlorambucil	Nervous system disorders	Leukoencephalopathy	5	21FEB2014	06AUG2015	Chlorambucil & Ofatumumab
511-0174-1	Bendamustine	Blood and lymphatic system disorders	Aplasia pure red cell	4	25FEB2014	26MAR2014	Bendamustine & Ofatumumab
075-0175-1	Chlorambucil	Infections and infestations	Neutropenic sepsis	1	26FEB2014	30MAY2014	Chlorambucil & Ofatumumab
075-0175-2	Chlorambucil	Infections and infestations	Neutropenic sepsis	1	26FEB2014	25JUN2014	Ofatumumab
112-0178-2	Chlorambucil	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Basal cell carcinoma	2	07MAR2014	.	Chlorambucil & Ofatumumab
085-0180-1	Bendamustine	Blood and lymphatic system disorders	Febrile neutropenia	Missing	13MAR2014	29MAR2014	Bendamustine & Ofatumumab
199-0182-1	Bendamustine	Infections and infestations	Neutropenic sepsis	2	14MAR2014	05APR2014	Bendamustine & Ofatumumab

SAE Number	Randomisation Arm	SOC	PT	Severity	Randomisation Date	Onset Date	Related Drug
364-0185-1	Chlorambucil	Infections and infestations	Lower respiratory tract infection	3	24MAR2014	22MAY2014	Chlorambucil & Ofatumumab
199-0188-1	Bendamustine	Infections and infestations	Neutropenic sepsis	1	28MAR2014	15MAY2014	Bendamustine & Ofatumumab
046-0190-1	Chlorambucil	Blood and lymphatic system disorders	Anaemia	3	02APR2014	19JUN2014	Ofatumumab
083-0193-1	Bendamustine	Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	1	07MAY2014	16JUN2014	Bendamustine & Ofatumumab
083-0193-2	Bendamustine	Cardiac disorders	Left ventricular dysfunction	2	07MAY2014	16JUN2014	Bendamustine
179-0194-1	Chlorambucil	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Pancreatic carcinoma	4	12MAY2014	29JUL2018	Chlorambucil
031-0195-1	Chlorambucil	Respiratory, thoracic and mediastinal disorders	Epistaxis	4	13MAY2014	30MAY2014	Chlorambucil & Ofatumumab
175-0196-1	Bendamustine	Metabolism and nutrition disorders	Hypokalaemic syndrome	4	19MAY2014	02JUN2014	Bendamustine & Ofatumumab
175-0196-2	Bendamustine	Infections and infestations	Bronchitis	3	19MAY2014	13AUG2014	Bendamustine & Ofatumumab
003-0204-1	Bendamustine	Cardiac disorders	Acute myocardial infarction	3	09JUN2014	26JUN2014	Bendamustine & Ofatumumab
046-0205-3	Chlorambucil	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Squamous cell carcinoma	4	11JUN2014	15MAY2017	Chlorambucil & Ofatumumab

SAE Number	Randomisation Arm	SOC	PT	Severity	Randomisation Date	Onset Date	Related Drug
168-0209-3	Bendamustine	Infections and infestations	Neutropenic sepsis	3	17JUN2014	04AUG2014	Bendamustine & Ofatumumab
202-0212-1	Chlorambucil	Injury, poisoning and procedural complications	Infusion related reaction	3	20JUN2014	02JUL2014	Ofatumumab
153-0218-1	Bendamustine	Blood and lymphatic system disorders	Febrile neutropenia	3	22JUL2014	25SEP2014	Bendamustine & Ofatumumab
153-0218-2	Bendamustine	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Squamous cell carcinoma of skin	2	22JUL2014	17FEB2017	Bendamustine & Ofatumumab
049-0219-1	Bendamustine	Respiratory, thoracic and mediastinal disorders	Chronic obstructive pulmonary disease	3	23JUL2014	27OCT2014	Bendamustine & Ofatumumab
049-0219-2	Bendamustine	Respiratory, thoracic and mediastinal disorders	Chronic obstructive pulmonary disease	2	23JUL2014	11JAN2015	Bendamustine & Ofatumumab
049-0219-3	Bendamustine	Respiratory, thoracic and mediastinal disorders	Chronic obstructive pulmonary disease	2	23JUL2014	27JAN2015	Bendamustine & Ofatumumab
049-0219-4	Bendamustine	Respiratory, thoracic and mediastinal disorders	Chronic obstructive pulmonary disease	2	23JUL2014	01MAR2015	Bendamustine & Ofatumumab
175-0220-1	Bendamustine	Infections and infestations	Lower respiratory tract infection	3	28JUL2014	08JAN2015	Bendamustine & Ofatumumab
175-0222-1	Bendamustine	Infections and infestations	Lower respiratory tract infection	3	30JUL2014	13MAR2015	Bendamustine & Ofatumumab

SAE Number	Randomisation Arm	SOC	PT	Severity	Randomisation Date	Onset Date	Related Drug
319-0229-1	Chlorambucil	Injury, poisoning and procedural complications	Infusion related reaction	1	19AUG2014	27AUG2014	Ofatumumab
319-0229-2	Chlorambucil	General disorders and administration site conditions	Malaise	1	19AUG2014	01SEP2014	Chlorambucil
319-0229-3	Chlorambucil	Injury, poisoning and procedural complications	Infusion related reaction	1	19AUG2014	03SEP2014	Ofatumumab
349-0232-2	Chlorambucil	Hepatobiliary disorders	Cholecystitis acute	2	21AUG2014	23OCT2014	Chlorambucil & Ofatumumab
349-0232-3	Chlorambucil	Infections and infestations	Lower respiratory tract infection	3	21AUG2014	16JAN2015	Chlorambucil & Ofatumumab
353-0235-3	Chlorambucil	Infections and infestations	Infection	3	29AUG2014	01OCT2013	Ofatumumab
178-0236-1	Chlorambucil	Infections and infestations	Neutropenic sepsis	2	03SEP2014	22FEB2015	Chlorambucil & Ofatumumab
045-0239-1	Bendamustine	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Invasive ductal breast carcinoma	4	11SEP2014	23MAR2015	Bendamustine
050-0240-2	Chlorambucil + Idelalisib	Infections and infestations	Tonsillitis	3	17SEP2014	30JAN2015	Chlorambucil & Ofatumumab
050-0240-3	Chlorambucil + Idelalisib	Infections and infestations	Lower respiratory tract infection	2	17SEP2014	31MAY2015	Chlorambucil, Ofatumumab & Idelalisib
050-0240-4	Chlorambucil + Idelalisib	Infections and infestations	Pneumocystis jirovecii pneumonia	1	17SEP2014	17AUG2015	Chlorambucil, Ofatumumab & Idelalisib

SAE Number	Randomisation Arm	SOC	PT	Severity	Randomisation Date	Onset Date	Related Drug
050-0241-1	Bendamustine + Placebo	Injury, poisoning and procedural complications	Infusion related reaction	1	23SEP2014	01OCT2014	Ofatumumab
050-0241-3	Bendamustine + Placebo	Infections and infestations	Lower respiratory tract infection	2	23SEP2014	13OCT2014	Bendamustine & Ofatumumab
212-0243-1	Chlorambucil	Immune system disorders	Hypersensitivity	2	24SEP2014	02OCT2014	Ofatumumab
132-0244-2	Bendamustine	Immune system disorders	Amyloidosis senile	2	25SEP2014	05DEC2014	Bendamustine & Ofatumumab
108-0246-1	Chlorambucil	Injury, poisoning and procedural complications	Infusion related reaction	2	26SEP2014	06OCT2014	Ofatumumab
039-0250-1	Bendamustine + Idelalisib	Renal and urinary disorders	Acute kidney injury	2	03OCT2014	18OCT2014	Bendamustine, Ofatumumab & Idelalisib
039-0250-10	Bendamustine + Idelalisib	Infections and infestations	Lower respiratory tract infection fungal	2	03OCT2014	27AUG2015	Bendamustine, Ofatumumab & Idelalisib
039-0250-11	Bendamustine + Idelalisib	Infections and infestations	Influenza	2	03OCT2014	22MAR2016	Bendamustine, Ofatumumab & Idelalisib
039-0250-2	Bendamustine + Idelalisib	Infections and infestations	Sepsis	3	03OCT2014	23OCT2014	Bendamustine, Ofatumumab & Idelalisib
039-0250-3	Bendamustine + Idelalisib	General disorders and administration site conditions	Pyrexia	2	03OCT2014	03NOV2014	Bendamustine & Ofatumumab
039-0250-4	Bendamustine + Idelalisib	General disorders and administration site conditions	Pyrexia	1	03OCT2014	28NOV2014	Bendamustine & Ofatumumab

SAE Number	Randomisation Arm	SOC	PT	Severity	Randomisation Date	Onset Date	Related Drug
039-0250-5	Bendamustine + Idelalisib	Infections and infestations	Tooth infection	1	03OCT2014	05APR2015	Bendamustine, Ofatumumab & Idelalisib
039-0250-6	Bendamustine + Idelalisib	Infections and infestations	Otitis media	2	03OCT2014	12JUN2015	Bendamustine, Ofatumumab & Idelalisib
039-0250-7	Bendamustine + Idelalisib	Infections and infestations	Mastoiditis	2	03OCT2014	22JUN2015	Bendamustine, Ofatumumab & Idelalisib
039-0250-9	Bendamustine + Idelalisib	Infections and infestations	Escherichia sepsis	1	03OCT2014	20JUL2015	Bendamustine, Ofatumumab & Idelalisib
434-0255-1	Bendamustine	Renal and urinary disorders	Acute kidney injury	Missing	13OCT2014	27JAN2015	Bendamustine & Ofatumumab
039-0260-1	Chlorambucil + Idelalisib	Endocrine disorders	Inappropriate antidiuretic hormone secretion	2	28OCT2014	07NOV2014	Chlorambucil & Idelalisib
039-0260-2	Chlorambucil + Idelalisib	Endocrine disorders	Inappropriate antidiuretic hormone secretion	4	28OCT2014	10DEC2014	Chlorambucil, Ofatumumab & Idelalisib
102-0261-1	Bendamustine + Placebo	Infections and infestations	Sepsis	3	29OCT2014	03DEC2014	Bendamustine & Ofatumumab
102-0261-2	Bendamustine + Placebo	Vascular disorders	Hypotension	4	29OCT2014	15JAN2015	Ofatumumab
082-0263-3	Bendamustine	Infections and infestations	Neutropenic sepsis	4	06NOV2014	22DEC2014	Bendamustine & Ofatumumab
075-0264-1	Chlorambucil	Infections and infestations	Neutropenic sepsis	1	11NOV2014	21NOV2014	Chlorambucil & Ofatumumab
046-0267-1	Bendamustine + Idelalisib	Infections and infestations	Neutropenic sepsis	3	14NOV2014	17DEC2014	Bendamustine, Ofatumumab & Idelalisib
194-0269-1	Bendamustine + Idelalisib	Infections and infestations	Neutropenic sepsis	3	20NOV2014	24DEC2014	Bendamustine, Ofatumumab & Idelalisib

SAE Number	Randomisation Arm	SOC	PT	Severity	Randomisation Date	Onset Date	Related Drug
194-0269-3	Bendamustine + Idelalisib	Infections and infestations	Sepsis	1	20NOV2014	15MAR2015	Bendamustine, Ofatumumab & Idelalisib
194-0269-4	Bendamustine + Idelalisib	Nervous system disorders	Syncope	3	20NOV2014	29MAR2015	Bendamustine, Ofatumumab & Idelalisib
194-0269-5	Bendamustine + Idelalisib	Infections and infestations	Pneumonia	5	20NOV2014	21APR2015	Bendamustine, Ofatumumab & Idelalisib
119-0278-1	Chlorambucil + Idelalisib	Nervous system disorders	Cerebrovascular accident	2	17DEC2014	04FEB2015	Chlorambucil, Ofatumumab & Idelalisib
098-0281-1	Bendamustine + Idelalisib	Respiratory, thoracic and mediastinal disorders	Cough	1	05JAN2015	19SEP2015	Bendamustine, Ofatumumab & Idelalisib
098-0281-2	Bendamustine + Idelalisib	Infections and infestations	Pneumonia	2	05JAN2015	29SEP2015	Bendamustine, Ofatumumab & Idelalisib
098-0281-3	Bendamustine + Idelalisib	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	External ear neoplasm malignant	2	05JAN2015	15FEB2016	Bendamustine
153-0285-1	Bendamustine + Placebo	Blood and lymphatic system disorders	Anaemia	4	07JAN2015	27JAN2015	Bendamustine & Ofatumumab
124-0287-1	Bendamustine + Idelalisib	Infections and infestations	Sepsis	1	12JAN2015	26JAN2015	Bendamustine, Ofatumumab & Idelalisib
124-0287-2	Bendamustine + Idelalisib	Infections and infestations	Infection	2	12JAN2015	13MAR2015	Bendamustine, Ofatumumab & Idelalisib
114-0288-1	Chlorambucil + Idelalisib	Respiratory, thoracic and mediastinal disorders	Pneumonitis	4	13JAN2015	10MAR2015	Chlorambucil, Ofatumumab & Idelalisib
363-0290-1	Chlorambucil + Placebo	Cardiac disorders	Angina pectoris	1	21JAN2015	26JAN2015	Ofatumumab

SAE Number	Randomisation Arm	SOC	PT	Severity	Randomisation Date	Onset Date	Related Drug
111-0291-1	Chlorambucil + Idelalisib	Nervous system disorders	Tremor	2	21JAN2015	02FEB2015	Chlorambucil, Ofatumumab & Idelalisib
111-0291-2	Chlorambucil + Idelalisib	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Prostate cancer	3	21JAN2015	15JUL2018	Chlorambucil & Ofatumumab
124-0292-1	Chlorambucil + Idelalisib	Infections and infestations	Pneumonia	2	21JAN2015	25MAY2015	Chlorambucil, Ofatumumab & Idelalisib
173-0293-1	Bendamustine + Idelalisib	Infections and infestations	Neutropenic sepsis	2	29JAN2015	21FEB2015	Bendamustine, Ofatumumab & Idelalisib
108-0295-1	Bendamustine + Placebo	Skin and subcutaneous tissue disorders	Drug eruption	2	04FEB2015	16MAR2015	Bendamustine & Ofatumumab
108-0295-2	Bendamustine + Placebo	Infections and infestations	Lower respiratory tract infection	1	04FEB2015	11APR2015	Bendamustine & Ofatumumab
082-0298-1	Chlorambucil + Idelalisib	Infections and infestations	Sepsis	1	11FEB2015	22MAR2015	Chlorambucil, Ofatumumab & Idelalisib
085-0300-1	Chlorambucil + Idelalisib	Metabolism and nutrition disorders	Dehydration	2	13FEB2015	24FEB2015	Chlorambucil
085-0300-2	Chlorambucil + Idelalisib	Infections and infestations	Neutropenic sepsis	3	13FEB2015	21APR2015	Chlorambucil, Ofatumumab & Idelalisib
178-0302-1	Chlorambucil + Idelalisib	Skin and subcutaneous tissue disorders	Rash maculo-papular	Missing	18FEB2015	27APR2015	Chlorambucil, Ofatumumab & Idelalisib
039-0304-1	Chlorambucil + Placebo	Nervous system disorders	Presyncope	2	23FEB2015	26FEB2015	Ofatumumab
093-0306-1	Bendamustine + Idelalisib	Infections and infestations	Pneumocystis jirovecii pneumonia	2	26FEB2015	30APR2015	Bendamustine, Ofatumumab & Idelalisib

SAE Number	Randomisation Arm	SOC	PT	Severity	Randomisation Date	Onset Date	Related Drug
168-0307-1	Bendamustine + Idelalisib	General disorders and administration site conditions	Pyrexia	1	27FEB2015	15MAR2015	Bendamustine & Ofatumumab
194-0308-1	Chlorambucil + Idelalisib	Infections and infestations	Neutropenic sepsis	5	12MAR2015	13MAY2015	Chlorambucil, Ofatumumab & Idelalisib
032-0311-1	Bendamustine + Idelalisib	Blood and lymphatic system disorders	Febrile neutropenia	1	02APR2015	22APR2015	Bendamustine, Ofatumumab & Idelalisib
032-0311-2	Bendamustine + Idelalisib	Infections and infestations	Sepsis	2	02APR2015	27MAR2016	Idelalisib
138-0314-1	Chlorambucil + Idelalisib	Infections and infestations	Neutropenic sepsis	1	09APR2015	23MAY2015	Chlorambucil, Ofatumumab & Idelalisib
138-0314-2	Chlorambucil + Idelalisib	Cardiac disorders	Acute myocardial infarction	2	09APR2015	28MAY2015	Chlorambucil, Ofatumumab & Idelalisib
138-0314-4	Chlorambucil + Idelalisib	Infections and infestations	Neutropenic sepsis	2	09APR2015	26JUL2015	Chlorambucil & Ofatumumab
138-0314-5	Chlorambucil + Idelalisib	Infections and infestations	Neutropenic sepsis	3	09APR2015	23AUG2015	Chlorambucil, Ofatumumab & Idelalisib
138-0314-6	Chlorambucil + Idelalisib	Infections and infestations	Neutropenic sepsis	4	09APR2015	13SEP2015	Chlorambucil, Ofatumumab & Idelalisib
119-0315-1	Bendamustine + Idelalisib	General disorders and administration site conditions	Pyrexia	2	09APR2015	16MAY2015	Bendamustine, Ofatumumab & Idelalisib
119-0315-2	Bendamustine + Idelalisib	Skin and subcutaneous tissue disorders	Rash erythematous	2	09APR2015	18MAY2015	Bendamustine, Ofatumumab & Idelalisib
119-0315-5	Bendamustine + Idelalisib	Renal and urinary disorders	Acute kidney injury	1	09APR2015	28AUG2015	Bendamustine & Ofatumumab

SAE Number	Randomisation Arm	SOC	PT	Severity	Randomisation Date	Onset Date	Related Drug
175-0316-1	Bendamustine + Idelalisib	Infections and infestations	Neutropenic sepsis	3	10APR2015	10JUL2015	Bendamustine, Ofatumumab & Idelalisib
175-0316-2	Bendamustine + Idelalisib	Metabolism and nutrition disorders	Dehydration	2	10APR2015	14JUL2015	Bendamustine, Ofatumumab & Idelalisib
175-0316-4	Bendamustine + Idelalisib	Infections and infestations	Sepsis	3	10APR2015	11JUN2015	Bendamustine & Ofatumumab
077-0318-2	Bendamustine + Idelalisib	Vascular disorders	Orthostatic hypotension	2	22APR2015	03JUN2015	Bendamustine & Idelalisib
373-0319-1	Bendamustine + Placebo	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Squamous cell carcinoma of skin	2	29APR2015	23DEC2015	Bendamustine & Ofatumumab
373-0319-2	Bendamustine + Placebo	Infections and infestations	Lower respiratory tract infection	4	29APR2015	21JAN2016	Bendamustine & Ofatumumab
434-0320-1	Bendamustine + Idelalisib	Infections and infestations	Infection	1	30APR2015	21MAY2015	Bendamustine, Ofatumumab & Idelalisib
434-0320-3	Bendamustine + Idelalisib	Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	4	30APR2015	26OCT2015	Bendamustine, Ofatumumab & Idelalisib
046-0321-1	Chlorambucil + Placebo	Skin and subcutaneous tissue disorders	Rash maculo-papular	3	30APR2015	19JUL2015	Chlorambucil & Ofatumumab
218-0322-1	Chlorambucil + Idelalisib	Metabolism and nutrition disorders	Hypoglycaemia	Missing	30APR2015	09JUN2015	Idelalisib
106-0325-1	Bendamustine + Idelalisib	Infections and infestations	Neutropenic sepsis	4	05MAY2015	03JUN2015	Bendamustine, Ofatumumab & Idelalisib
106-0325-2	Bendamustine + Idelalisib	Infections and infestations	Arthritis infective	4	05MAY2015	02AUG2015	Bendamustine, Ofatumumab & Idelalisib

SAE Number	Randomisation Arm	SOC	PT	Severity	Randomisation Date	Onset Date	Related Drug
276-0326-3	Chlorambucil + Idelalisib	Infections and infestations	Pneumonia	2	11MAY2015	25JUN2015	Chlorambucil, Ofatumumab & Idelalisib
039-0327-1	Chlorambucil + Idelalisib	Renal and urinary disorders	Acute Kidney Injury	2	11MAY2015	28MAY2015	Chlorambucil & Idelalisib
039-0329-1	Bendamustine + Idelalisib	Renal and urinary disorders	Acute kidney injury	3	15MAY2015	27MAY2015	Bendamustine, Ofatumumab & Idelalisib
039-0329-3	Bendamustine + Idelalisib	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	External ear neoplasm malignant	3	15MAY2015	01SEP2017	Bendamustine & Idelalisib
314-0333-3	Chlorambucil + Idelalisib	Infections and infestations	Sepsis	3	22MAY2015	05OCT2015	Chlorambucil, Ofatumumab & Idelalisib
098-0336-1	Bendamustine + Placebo	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Squamous cell carcinoma of skin	2	27MAY2015	15AUG2016	Bendamustine
098-0336-2	Bendamustine + Placebo	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Gallbladder cancer	4	27MAY2015	21AUG2018	Bendamustine
173-0339-1	Chlorambucil + Idelalisib	Injury, poisoning and procedural complications	Infusion related reaction	1	02JUN2015	10JUN2015	Ofatumumab
173-0339-2	Chlorambucil + Idelalisib	Respiratory, thoracic and mediastinal disorders	Hypoxia	2	02JUN2015	15SEP2015	Chlorambucil, Ofatumumab & Idelalisib

SAE Number	Randomisation Arm	SOC	PT	Severity	Randomisation Date	Onset Date	Related Drug
143-0340-2	Chlorambucil + Idelalisib	Investigations	Alanine aminotransferase increased	3	09JUN2015	16JUL2015	Idelalisib
098-0343-1	Bendamustine + Placebo	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Bowen's disease	2	23JUN2015	15NOV2019	Bendamustine
098-0343-1	Bendamustine + Placebo	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Malignant melanoma	2	23JUN2015	12MAY2020	Bendamustine
098-0343-1	Bendamustine + Placebo	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Squamous cell carcinoma	2	23JUN2015	12MAY2020	Bendamustine
098-0343-1	Bendamustine + Placebo	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Bowen's disease	2	23JUN2015	29JAN2016	Bendamustine
098-0343-11	Bendamustine + Placebo	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Malignant melanoma	Missing	23JUN2015	20MAY2020	Bendamustine
098-0343-12	Bendamustine + Placebo	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Squamous cell carcinoma	Missing	23JUN2015	17JUL2020	Bendamustine

SAE Number	Randomisation Arm	SOC	PT	Severity	Randomisation Date	Onset Date	Related Drug	
098-0343-14	Bendamustine + Placebo	Neoplasms malignant unspecified and polyps)	benign, and (incl cysts	Squamous carcinoma cell	2	23JUN2015	02NOV2020	Bendamustine
098-0343-15	Bendamustine + Placebo	Neoplasms malignant unspecified and polyps)	benign, and (incl cysts	Squamous carcinoma cell	2	23JUN2015	02NOV2020	Bendamustine
098-0343-16	Bendamustine + Placebo	Neoplasms malignant unspecified and polyps)	benign, and (incl cysts	Metastatic malignant melanoma	Missing	23JUN2015	04NOV2020	Bendamustine
098-0343-17	Bendamustine + Placebo	Neoplasms malignant unspecified and polyps)	benign, and (incl cysts	Squamous carcinoma cell	2	23JUN2015	02NOV2020	Bendamustine
098-0343-18	Bendamustine + Placebo	Neoplasms malignant unspecified and polyps)	benign, and (incl cysts	Squamous carcinoma cell	2	23JUN2015	02NOV2020	Bendamustine
098-0343-2	Bendamustine + Placebo	Neoplasms malignant unspecified and polyps)	benign, and (incl cysts	Squamous carcinoma of skin cell	2	23JUN2015	23SEP2016	Bendamustine & Ofatumumab
098-0343-20	Bendamustine + Placebo	Neoplasms malignant unspecified and polyps)	benign, and (incl cysts	Squamous carcinoma of skin cell	Missing	23JUN2015	16JAN2021	Bendamustine

SAE Number	Randomisation Arm	SOC	PT	Severity	Randomisation Date	Onset Date	Related Drug
098-0343-21	Bendamustine + Placebo	Neoplasms benign, and unspecified (incl cysts and polyps)	Squamous carcinoma of skin cell	2	23JUN2015	16JAN2021	Bendamustine
098-0343-3	Bendamustine + Placebo	Neoplasms benign, and unspecified (incl cysts and polyps)	Squamous carcinoma of skin cell	2	23JUN2015	05JAN2018	Bendamustine
098-0343-4	Bendamustine + Placebo	Neoplasms benign, and unspecified (incl cysts and polyps)	Squamous carcinoma of skin cell	2	23JUN2015	15MAR2018	Bendamustine
098-0343-5	Bendamustine + Placebo	Neoplasms benign, and unspecified (incl cysts and polyps)	External ear neoplasm malignant	2	23JUN2015	11MAY2018	Bendamustine
098-0343-6	Bendamustine + Placebo	Neoplasms benign, and unspecified (incl cysts and polyps)	Squamous carcinoma of skin cell	2	23JUN2015	07SEP2018	Bendamustine
098-0343-8	Bendamustine + Placebo	Neoplasms benign, and unspecified (incl cysts and polyps)	Squamous carcinoma of skin cell	2	23JUN2015	16NOV2018	Bendamustine
098-0343-9	Bendamustine + Placebo	Neoplasms benign, and unspecified (incl cysts and polyps)	Squamous carcinoma of skin cell	1	23JUN2015	12APR2019	Bendamustine

SAE Number	Randomisation Arm	SOC	PT	Severity	Randomisation Date	Onset Date	Related Drug
014-0344-2	Bendamustine + Idelalisib	Infections and infestations	Sepsis	1	25JUN2015	05FEB2016	Idelalisib
194-0345-1	Bendamustine + Placebo	Blood and lymphatic system disorders	Febrile neutropenia	3	26JUN2015	19JUL2015	Bendamustine & Ofatumumab
194-0345-2	Bendamustine + Placebo	Infections and infestations	Lower respiratory tract infection	2	26JUN2015	24JUL2015	Bendamustine & Ofatumumab
319-0348-1	Bendamustine + Idelalisib	Skin and subcutaneous tissue disorders	Rash maculo-papular	Missing	06JUL2015	01AUG2015	Bendamustine, Ofatumumab & Idelalisib
319-0348-2	Bendamustine + Idelalisib	Blood and lymphatic system disorders	Febrile neutropenia	3	06JUL2015	01AUG2015	Bendamustine, Ofatumumab & Idelalisib
319-0348-3	Bendamustine + Idelalisib	Immune system disorders	Hypersensitivity	1	06JUL2015	27AUG2015	Bendamustine, Ofatumumab & Idelalisib
194-0355-1	Chlorambucil + Idelalisib	Psychiatric disorders	Suicidal ideation	3	01OCT2015	01DEC2015	Idelalisib
071-0357-1	Bendamustine + Idelalisib	Infections and infestations	Neutropenic sepsis	Missing	08OCT2015	10MAR2016	Bendamustine, Ofatumumab & Idelalisib
106-0361-1	Bendamustine + Placebo	Cardiac disorders	Myocardial infarction	1	14OCT2015	25NOV2015	Bendamustine & Ofatumumab
106-0361-2	Bendamustine + Placebo	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Adenocarcinoma of colon	2	14OCT2015	26OCT2018	Bendamustine
138-0362-1	Chlorambucil + Idelalisib	Metabolism and nutrition disorders	Hyperkalaemia	3	15OCT2015	24NOV2015	Idelalisib
138-0362-2	Chlorambucil + Idelalisib	Gastrointestinal disorders	Small intestinal obstruction	3	15OCT2015	11DEC2015	Chlorambucil, Ofatumumab & Idelalisib
363-0363-3	Bendamustine + Idelalisib	Infections and infestations	Sepsis	1	15OCT2015	21JAN2016	Bendamustine & Ofatumumab

SAE Number	Randomisation Arm	SOC	PT	Severity	Randomisation Date	Onset Date	Related Drug
363-0363-4	Bendamustine + Idelalisib	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Basal cell carcinoma	3	15OCT2015	11OCT2018	Bendamustine & Idelalisib
130-0364-1	Chlorambucil + Idelalisib	Infections and infestations	Sepsis	2	15OCT2015	26FEB2016	Chlorambucil, Ofatumumab & Idelalisib
130-0365-1	Bendamustine + Idelalisib	Infections and infestations	Pneumonia	Missing	15OCT2015	31OCT2015	Bendamustine, Ofatumumab & Idelalisib
130-0365-2	Bendamustine + Idelalisib	Infections and infestations	Herpes virus infection	3	15OCT2015	30NOV2015	Bendamustine, Ofatumumab & Idelalisib
511-0367-1	Bendamustine + Placebo	Infections and infestations	Sepsis	1	19OCT2015	24NOV2015	Bendamustine & Ofatumumab
194-0371-1	Chlorambucil + Idelalisib	Infections and infestations	Pneumonia	2	05NOV2015	04DEC2015	Chlorambucil, Ofatumumab & Idelalisib
194-0371-2	Chlorambucil + Idelalisib	Infections and infestations	Neutropenic sepsis	2	05NOV2015	18DEC2015	Chlorambucil, Ofatumumab & Idelalisib
194-0371-3	Chlorambucil + Idelalisib	Blood and lymphatic system disorders	Febrile neutropenia	3	05NOV2015	09APR2016	Chlorambucil, Ofatumumab & Idelalisib
111-0373-1	Bendamustine + Idelalisib	Infections and infestations	Neutropenic sepsis	3	19NOV2015	27DEC2015	Bendamustine, Ofatumumab & Idelalisib
111-0373-2	Bendamustine + Idelalisib	Infections and infestations	Pneumonia	4	19NOV2015	06JAN2016	Bendamustine, Ofatumumab & Idelalisib
014-0378-1	Bendamustine + Placebo	Infections and infestations	Lower respiratory tract infection	2	04DEC2015	03AUG2016	Bendamustine
488-0380-1	Chlorambucil + Idelalisib	Blood and lymphatic system disorders	Febrile neutropenia	1	08DEC2015	05JAN2016	Chlorambucil, Ofatumumab & Idelalisib

SAE Number	Randomisation Arm	SOC	PT	Severity	Randomisation Date	Onset Date	Related Drug
488-0380-2	Chlorambucil + Idelalisib	Blood and lymphatic system disorders	Febrile neutropenia	2	08DEC2015	04APR2016	Chlorambucil, Ofatumumab & Idelalisib
488-0380-6	Chlorambucil + Idelalisib	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Basal cell carcinoma	2	08DEC2015	25SEP2017	Chlorambucil & Idelalisib
187-0381-1	Bendamustine + Placebo	Infections and infestations	Pneumonia	1	10DEC2015	12JAN2016	Bendamustine & Ofatumumab
187-0381-2	Bendamustine + Placebo	Infections and infestations	Neutropenic sepsis	Missing	10DEC2015	09FEB2016	Bendamustine & Ofatumumab
187-0381-3	Bendamustine + Placebo	Injury, poisoning and procedural complications	Infusion related reaction	Missing	10DEC2015	15DEC2015	Ofatumumab
187-0381-4	Bendamustine + Placebo	Infections and infestations	COVID-19	Missing	10DEC2015	05JUN2020	Bendamustine & Ofatumumab
009-0382-1	Bendamustine + Placebo	Infections and infestations	Lower respiratory tract infection	3	15DEC2015	18JAN2016	Bendamustine & Ofatumumab
009-0382-2	Bendamustine + Placebo	Infections and infestations	Sepsis	1	15DEC2015	18FEB2016	Chlorambucil & Ofatumumab
009-0382-3	Bendamustine + Placebo	Infections and infestations	Cellulitis	2	15DEC2015	28FEB2016	Bendamustine & Ofatumumab
102-0383-1	Bendamustine + Idelalisib	Injury, poisoning and procedural complications	Infusion related reaction	1	23DEC2015	11FEB2016	Ofatumumab
014-0386-1	Bendamustine + Idelalisib	General disorders and administration site conditions	Oedema	3	05JAN2016	24JAN2016	Bendamustine & Ofatumumab

SAE Number	Randomisation Arm	SOC	PT	Severity	Randomisation Date	Onset Date	Related Drug
032-0407-1	Chlorambucil	Infections and infestations	Sepsis	4	27JUL2016	15NOV2016	Chlorambucil & Ofatumumab
194-0408-1	Bendamustine	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Basal cell carcinoma	Missing	28JUL2016	19MAR2019	Bendamustine
194-0408-2	Bendamustine	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Basal cell carcinoma	2	28JUL2016	15APR2018	Bendamustine & Ofatumumab
098-0420-4	Chlorambucil	Infections and infestations	Urosepsis	1	09SEP2016	30AUG2017	Chlorambucil & Ofatumumab
098-0420-5	Chlorambucil	Infections and infestations	Urosepsis	3	09SEP2016	19OCT2017	Chlorambucil & Ofatumumab
102-0422-2	Bendamustine	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neuroendocrine carcinoma	2	19SEP2016	06MAY2020	Bendamustine
187-0427-2	Bendamustine	Injury, poisoning and procedural complications	Infusion related reaction	1	04OCT2016	13OCT2016	Ofatumumab
111-0430-1	Bendamustine	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neuroendocrine carcinoma	5	10NOV2016	14SEP2018	Bendamustine
644-0437-1	Chlorambucil	Infections and infestations	Cellulitis	3	29NOV2016	07NOV2017	Chlorambucil & Ofatumumab

SAE Number	Randomisation Arm	SOC	PT	Severity	Randomisation Date	Onset Date	Related Drug
644-0438-1	Chlorambucil	Infections and infestations	Respiratory tract infection	2	30NOV2016	11JAN2017	Chlorambucil
108-0452-1	Chlorambucil	Injury, poisoning and procedural complications	Infusion related reaction	2	09FEB2017	27FEB2017	Ofatumumab
108-0452-2	Chlorambucil	Injury, poisoning and procedural complications	Infusion related reaction	Missing	09FEB2017	27MAR2017	Ofatumumab
108-0452-4	Chlorambucil	Injury, poisoning and procedural complications	Infusion related reaction	Missing	09FEB2017	22MAY2017	Ofatumumab
194-0453-1	Chlorambucil	Nervous system disorders	Seizure	2	10FEB2017	02MAR2017	Chlorambucil
046-0460-1	Chlorambucil	Infections and infestations	Pneumonia pneumococcal	2	13MAR2017	07JUN2017	Chlorambucil & Ofatumumab
348-0467-2	Bendamustine	Infections and infestations	Lower respiratory tract infection	3	28APR2017	19MAY2017	Bendamustine & Ofatumumab
046-0470-1	Bendamustine	Infections and infestations	Neutropenic sepsis	3	12MAY2017	11AUG2017	Bendamustine & Ofatumumab
204-0475-3	Chlorambucil	Infections and infestations	Pneumonia	1	21JUN2017	27FEB2018	Chlorambucil & Ofatumumab
082-0477-1	Chlorambucil	Injury, poisoning and procedural complications	Infusion related reaction	3	30JUN2017	05JUL2017	Ofatumumab
082-0477-2	Chlorambucil	Injury, poisoning and procedural complications	Infusion related reaction	1	30JUN2017	12JUL2017	Ofatumumab

SAE Number	Randomisation Arm	SOC	PT	Severity	Randomisation Date	Onset Date	Related Drug
093-0478-1	Chlorambucil	Immune disorders	system Hypersensitivity	2	05JUL2017	20JUL2017	Ofatumumab
093-0478-2	Chlorambucil	Immune disorders	system Hypersensitivity	2	05JUL2017	27JUL2017	Ofatumumab
194-0492-2	Bendamustine	Infections and infestations	Lower respiratory tract infection	3	30OCT2017	17JAN2018	Bendamustine & Ofatumumab
194-0492-3	Bendamustine	Infections and infestations	Lower respiratory tract infection	4	30OCT2017	25JAN2018	Bendamustine & Ofatumumab
434-0493-1	Chlorambucil	Gastrointestinal disorders	Abdominal pain	2	30OCT2017	20MAY2018	Chlorambucil & Ofatumumab
039-0496-1	Chlorambucil	Infections and infestations	Sepsis	3	22NOV2017	02APR2018	Chlorambucil & Ofatumumab
194-0500-1	Chlorambucil	Infections and infestations	Lower respiratory tract infection	2	08DEC2017	02JAN2018	Chlorambucil & Ofatumumab
046-0502-1	Chlorambucil	Infections and infestations	Viral infection	2	05JAN2018	11FEB2018	Chlorambucil & Ofatumumab
126-0504-2	Bendamustine	Infections and infestations	Neutropenic sepsis	3	17JAN2018	05FEB2018	Bendamustine & Ofatumumab
124-0508-1	Bendamustine	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Hepatocellular carcinoma	3	13FEB2018	09AUG2018	Bendamustine & Ofatumumab
113-0509-2	Bendamustine	Infections and infestations	Neutropenic sepsis	1	14FEB2018	25MAR2018	Bendamustine & Ofatumumab
113-0509-3	Bendamustine	Infections and infestations	Pneumonia	1	14FEB2018	02APR2018	Bendamustine & Ofatumumab

SAE Number	Randomisation Arm	SOC	PT	Severity	Randomisation Date	Onset Date	Related Drug
039-0510-2	Bendamustine	Infections and infestations	Lower respiratory tract infection	2	23FEB2018	09JUL2018	Bendamustine & Ofatumumab
039-0510-5	Bendamustine	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Bowen's disease	1	23FEB2018	15AUG2018	Bendamustine & Ofatumumab
039-0510-7	Bendamustine	Infections and infestations	Lower respiratory tract infection	2	23FEB2018	27DEC2018	Bendamustine & Ofatumumab
039-0510-8	Bendamustine	Blood and lymphatic system disorders	Febrile neutropenia	4	23FEB2018	24AUG2018	Bendamustine & Ofatumumab
194-0514-1	Chlorambucil	Injury, poisoning and procedural complications	Infusion related reaction	3	05MAR2018	08MAR2018	Ofatumumab
124-0516-1	Bendamustine	Infections and infestations	Neutropenic sepsis	1	19MAR2018	05DEC2018	Bendamustine & Ofatumumab
124-0516-2	Bendamustine	Infections and infestations	Neutropenic sepsis	1	19MAR2018	11DEC2018	Bendamustine & Ofatumumab
175-0518-1	Chlorambucil	Infections and infestations	Neutropenic sepsis	2	13APR2018	11MAY2018	Chlorambucil & Ofatumumab
175-0518-2	Chlorambucil	Reproductive system and breast disorders	Testicular swelling	1	13APR2018	09AUG2018	Chlorambucil & Ofatumumab
175-0518-5	Chlorambucil	Cardiac disorders	Right ventricular failure	4	13APR2018	04MAR2019	Chlorambucil & Ofatumumab

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14.3 Subgroup Analysis – Bendamustine vs. Chlorambucil (Including Placebo)

Subgroup analysis is analysed on Bendamustine vs. Chlorambucil (Including Placebo) patients only.

14.3.1 Adverse Events

Table 15-18 Adverse Events by Age

Severity	<60 (N=4)	60-69 (N=75)	≥70 (N=427)	Total (N=506)
1	30 (63%)	247 (55%)	1990 (54%)	2267 (54%)
2	12 (25%)	150 (33%)	1236 (33%)	1398 (33%)
3	3 (6%)	46 (10%)	392 (11%)	441 (10%)
4	1 (2%)	7 (2%)	67 (2%)	75 (2%)
5	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Missing	2 (4%)	3 (1%)	31 (1%)	36 (1%)

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Table 15-19 Adverse Events by Cumulative Illness Rating Score

Severity	≤6 (N=394)	>6 (N=112)	Total (N=506)
1	1674 (53%)	593 (56%)	2267 (54%)
2	1073 (34%)	325 (31%)	1398 (33%)
3	339 (11%)	102 (10%)	441 (10%)
4	58 (2%)	17 (2%)	75 (2%)
5	0 (0%)	1 (0%)	1 (0%)
Missing	23 (1%)	13 (1%)	36 (1%)

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Table 15-20 Adverse Events by Performance Status

Severity	0 (N=194)	1 (N=233)	2 (N=70)	3 (N=7)	Total (N=504)
1	920 (58%)	923 (51%)	372 (53%)	52 (54%)	2267 (54%)
2	499 (31%)	641 (35%)	229 (32%)	29 (30%)	1398 (33%)
3	135 (8%)	204 (11%)	88 (12%)	14 (14%)	441 (10%)
4	26 (2%)	36 (2%)	12 (2%)	1 (1%)	75 (2%)
5	0 (0%)	1 (0%)	0 (0%)	0 (0%)	1 (0%)
Missing	10 (1%)	18 (1%)	7 (1%)	1 (1%)	36 (1%)

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Table 15-21 Adverse Events by Disease Stage

Severity	A (N=62)	B (N=161)	C (N=274)	Total (N=497)
1	236 (57%)	863 (57%)	1123 (51%)	2222 (54%)
2	143 (34%)	472 (31%)	762 (34%)	1377 (33%)
3	31 (7%)	129 (9%)	272 (12%)	432 (10%)
4	2 (0%)	28 (2%)	42 (2%)	72 (2%)
5	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Missing	5 (1%)	12 (1%)	19 (1%)	36 (1%)

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Table 15-22 Adverse Events by IGHV Status

Severity	Mutated (N=153)	Unmutated (N=177)	Total (N=330)
1	800 (55%)	727 (54%)	1527 (54%)
2	466 (32%)	470 (35%)	936 (33%)
3	161 (11%)	118 (9%)	279 (10%)
4	27 (2%)	16 (1%)	43 (2%)
5	1 (0%)	0 (0%)	1 (0%)
Missing	12 (1%)	10 (1%)	22 (1%)

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Table 15-23 Adverse Events by FISH Status

Severity	17p- (N=16)	11q- (N=63)	+12 (N=116)	13q- (N=149)	Np FISH Defect (N=120)	Total (N=464)
1	71 (53%)	175 (51%)	565 (57%)	776 (56%)	488 (50%)	2075 (54%)
2	48 (36%)	118 (35%)	313 (32%)	443 (32%)	346 (35%)	1268 (33%)
3	14 (11%)	40 (12%)	87 (9%)	140 (10%)	112 (11%)	393 (10%)
4	0 (0%)	6 (2%)	11 (1%)	24 (2%)	24 (2%)	65 (2%)
5	0 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)	1 (0%)
Missing	0 (0%)	1 (0%)	9 (1%)	11 (1%)	8 (1%)	29 (1%)

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14.3.2 Serious Adverse Events

Table 15-24 Serious Adverse Events by Age

Severity	<60 (N=4)	60-69 (N=75)	≥70 (N=427)	Total (N=506)
1	0 (0%)	20 (19%)	79 (18%)	99 (18%)
2	0 (0%)	30 (29%)	128 (29%)	158 (29%)
3	2 (100%)	33 (32%)	143 (33%)	178 (33%)
4	0 (0%)	6 (6%)	30 (7%)	36 (7%)
5	0 (0%)	2 (2%)	10 (2%)	12 (2%)
Missing	0 (0%)	12 (12%)	46 (11%)	58 (11%)

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Table 15-25 Serious Adverse Events by Cumulative Illness Rating Score

Severity	≤6 (N=394)	>6 (N=112)	Total (N=506)
1	77 (20%)	22 (15%)	99 (18%)
2	112 (29%)	46 (31%)	158 (29%)
3	131 (33%)	47 (32%)	178 (33%)
4	28 (7%)	8 (5%)	36 (7%)
5	7 (2%)	5 (3%)	12 (2%)
Missing	37 (9%)	21 (14%)	58 (11%)

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Table 15-26 Serious Adverse Events by Performance Status

Severity	0 (N=194)	1 (N=233)	2 (N=70)	3 (N=7)	Total (N=504)
1	23 (17%)	56 (21%)	18 (15%)	2 (17%)	99 (18%)
2	45 (32%)	68 (25%)	41 (34%)	4 (33%)	158 (29%)
3	46 (33%)	87 (33%)	38 (31%)	5 (42%)	176 (33%)
4	9 (6%)	18 (7%)	9 (7%)	0 (0%)	36 (7%)
5	2 (1%)	6 (2%)	3 (2%)	1 (8%)	12 (2%)
Missing	14 (10%)	32 (12%)	12 (10%)	0 (0%)	58 (11%)

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Table 15-27 Serious Adverse Events by Disease Stage

Severity	A (N=62)	B (N=161)	C (N=274)	Total (N=497)
1	6 (11%)	35 (23%)	57 (17%)	98 (18%)
2	22 (41%)	37 (24%)	98 (30%)	157 (29%)
3	18 (33%)	54 (35%)	104 (32%)	176 (33%)
4	4 (7%)	14 (9%)	18 (5%)	36 (7%)
5	1 (2%)	7 (5%)	4 (1%)	12 (2%)
Missing	3 (6%)	7 (5%)	47 (14%)	57 (11%)

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Location of code file: "S:\Statistical Documents\Trials\RIALTO\12. Closed documents\5.17. Final Analysis 2.0\Code\May 2024"

Table 15-28 Serious Adverse Events by IGHV Status

Severity	Mutated (N=153)	Unmutated (N=177)	Total (N=330)
1	32 (15%)	28 (18%)	60 (16%)
2	81 (37%)	38 (25%)	119 (32%)
3	73 (33%)	52 (34%)	125 (33%)
4	10 (5%)	14 (9%)	24 (6%)
5	5 (2%)	4 (3%)	9 (2%)
Missing	18 (8%)	19 (12%)	37 (10%)

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Table 15-29 Serious Adverse Events by FISH Status

Severity	17p- (N=16)	11q- (N=63)	+12 (N=116)	13q- (N=149)	No FISH Defect (N=120)	Total (N=464)
1	3 (19%)	10 (16%)	21 (18%)	27 (16%)	26 (21%)	87 (18%)
2	1 (6%)	14 (23%)	38 (33%)	62 (36%)	33 (26%)	148 (30%)
3	6 (38%)	22 (36%)	33 (28%)	53 (31%)	46 (37%)	160 (33%)
4	1 (6%)	3 (5%)	8 (7%)	12 (7%)	8 (6%)	32 (7%)
5	2 (13%)	3 (5%)	2 (2%)	4 (2%)	1 (1%)	12 (2%)
Missing	3 (19%)	9 (15%)	14 (12%)	15 (9%)	11 (9%)	52 (11%)

Created using SAS (Version 9.4) at 07MAY2024 9:49:57
 Location of code file: "S:\Statistical Documents\Trials\RIALTO\12. Closed documents\5.17. Final Analysis 2.0\Code\May 2024"

14.4 Toxicity Summary

Bendamustine vs. Chlorambucil

A similar number of AEs were reported in the bendamustine and chlorambucil arms (2143 and 2083) with no obvious difference in event categorisation or grading.

More SAEs were reported in more patients in the bendamustine arm compared to the chlorambucil arm (bendamustine: 307 SAEs in 139/215 (65%) patients; chlorambucil: 234 SAEs in 127/219 (58%) patients). Fatal SAEs were also more frequent in the bendamustine arm (9 vs 3).

More infection-related SAEs were reported in the bendamustine arm compared to the chlorambucil arm (93 vs 70, respectively). This was largely due to the more frequent occurrence of pneumonia/lower respiratory tract infection (39 vs 20, respectively).

More SAEs relating to neoplasms were reported in the bendamustine arm compared to the chlorambucil arm (74 vs 43, respectively). This was largely due to the more frequent occurrence of skin cancers (47 vs 24, respectively).

Idelalisib vs. Placebo

A similar number of AEs were reported in the idelalisib and placebo arms (850 and 864, respectively) with no obvious difference in event categorisation or grading.

More SAEs were reported in more patients in the idelalisib arm compared to the placebo arm (idelalisib: 141 SAEs in 60/72 (83%) patients; placebo: 99 SAEs in 38/69 (57%) patients). Fatal events were also more frequent in the idelalisib arm (5 vs 1, respectively).

More SAEs relating to general disorders were reported in the idelalisib arm compared to the placebo arm (20 vs 3, respectively). This was largely due to the more frequent occurrence of pyrexia (18 vs 1, respectively).

More infection-related SAEs were reported in the idelalisib arm compared to the placebo arm (53 vs 18, respectively). This was largely due to the more frequent occurrence of neutropenic sepsis/ febrile neutropenia (19 vs 2, respectively).

Fewer SAEs relating to neoplasms were reported in the idelalisib arm compared to the placebo arm (17 vs 44, respectively). This was largely due to the less frequent occurrence of skin cancers (7 vs 30, respectively).

The frequency of immune-mediated toxicity typically associated with idelalisib (dermatitis, hepatitis, colitis, pneumonitis) was low and similar in the idelalisib and placebo arms.

15 Secondary Outcome – Quality of Life

15.1 Primary Analysis – Bendamustine vs. Chlorambucil (Including Placebo)

Figure 16-1 EQ-5D-3L – Mobility

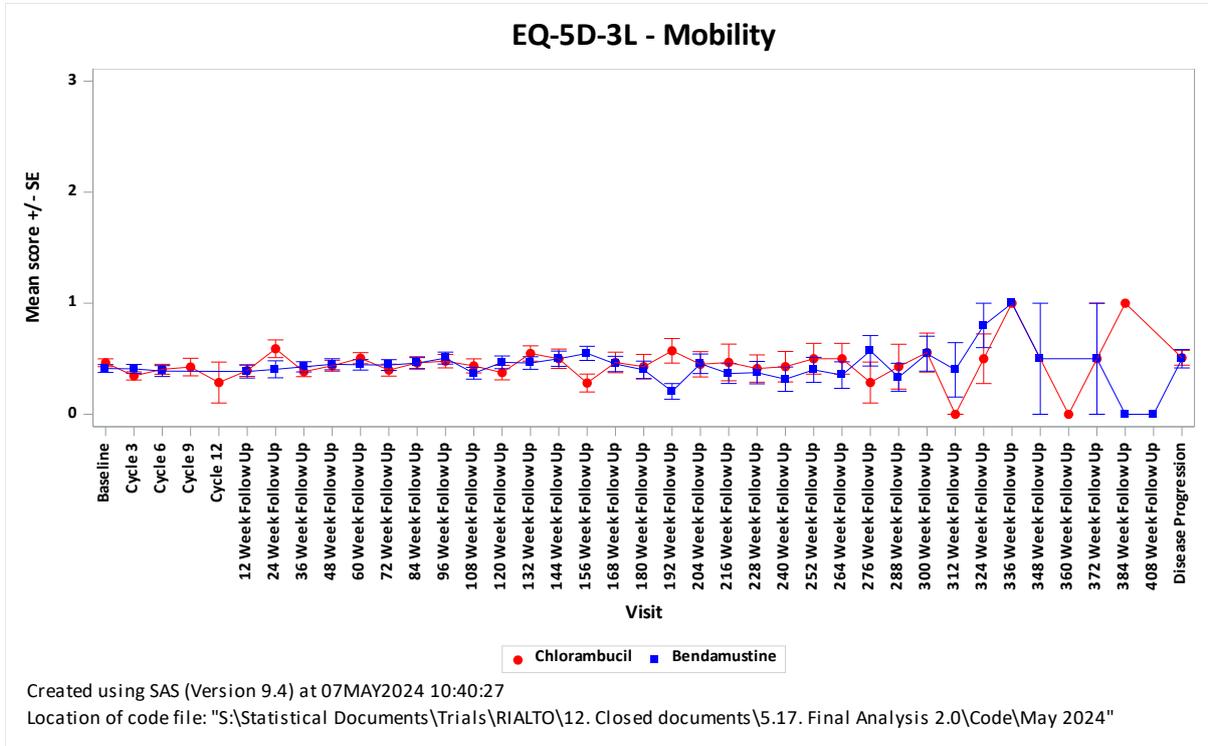


Figure 16-2 EQ-5D-3L – Self-Care

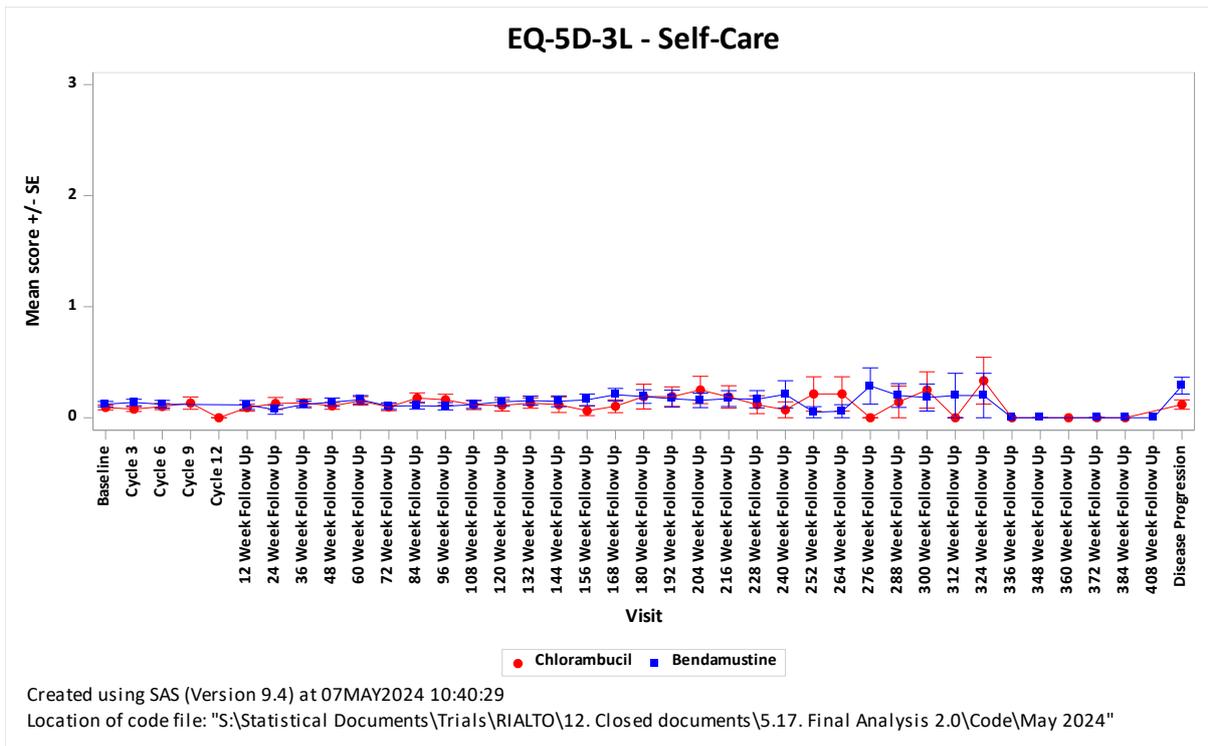


Figure 16-3 EQ-5D-3L – Usual Activities

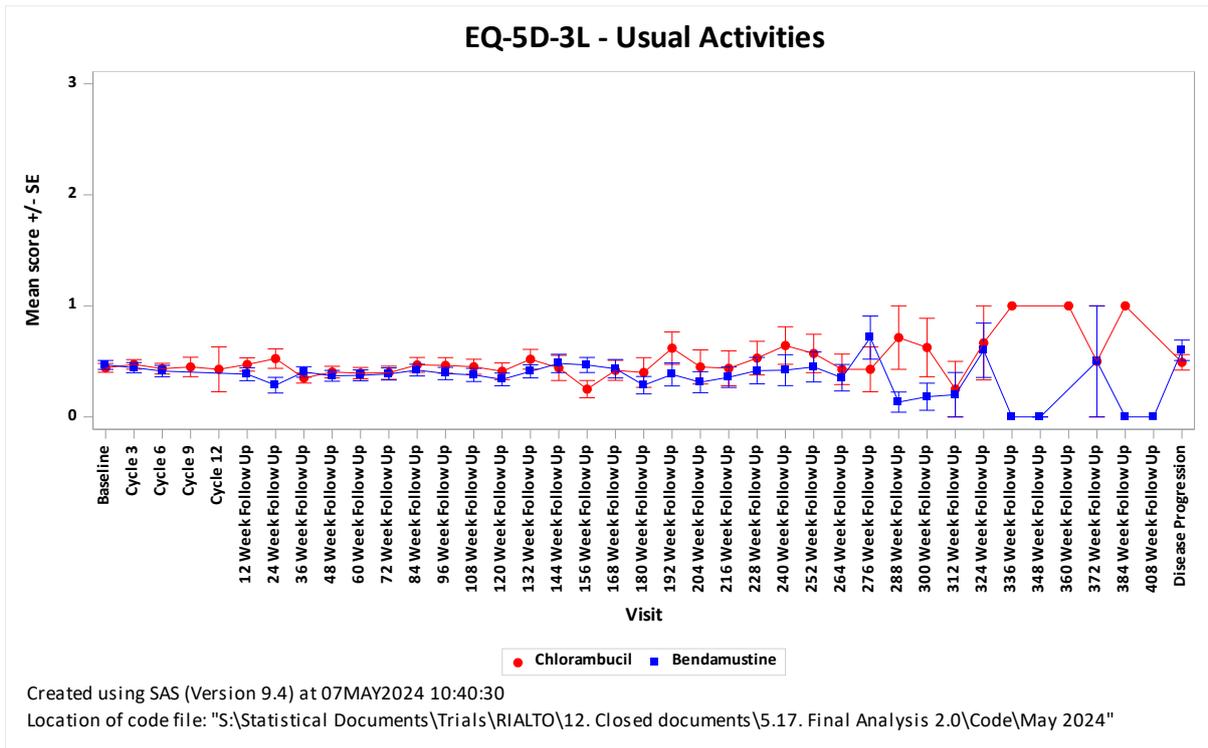


Figure 16-4 EQ-5D-3L – Pain/Discomfort

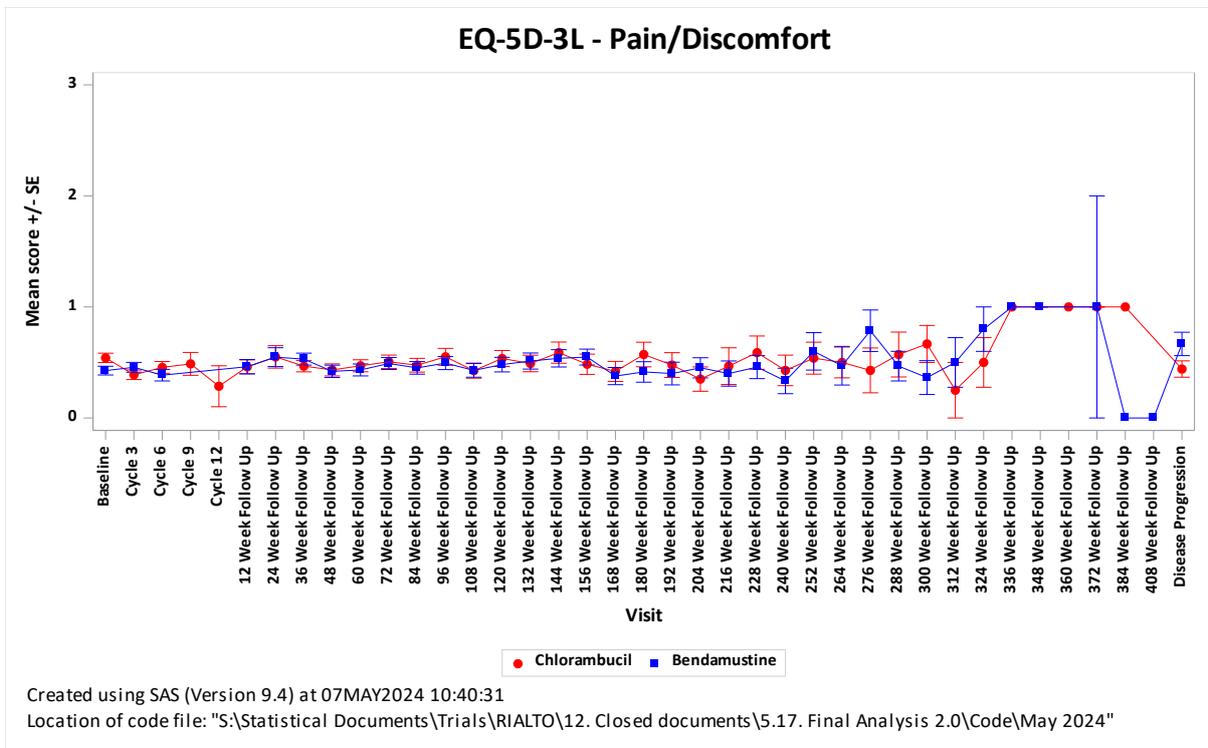


Figure 16-5 EQ-5D-3L – Anxiety/Depression

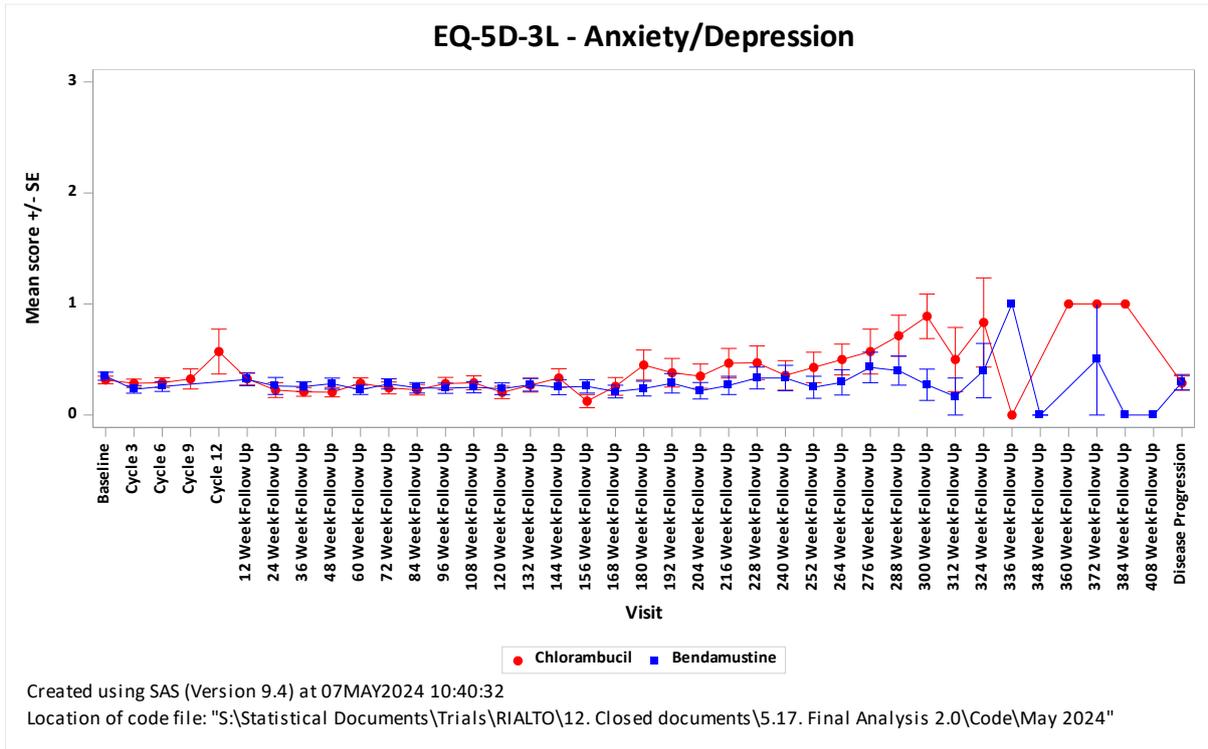


Figure 16-6 EQ-5D-3L – Index Scores

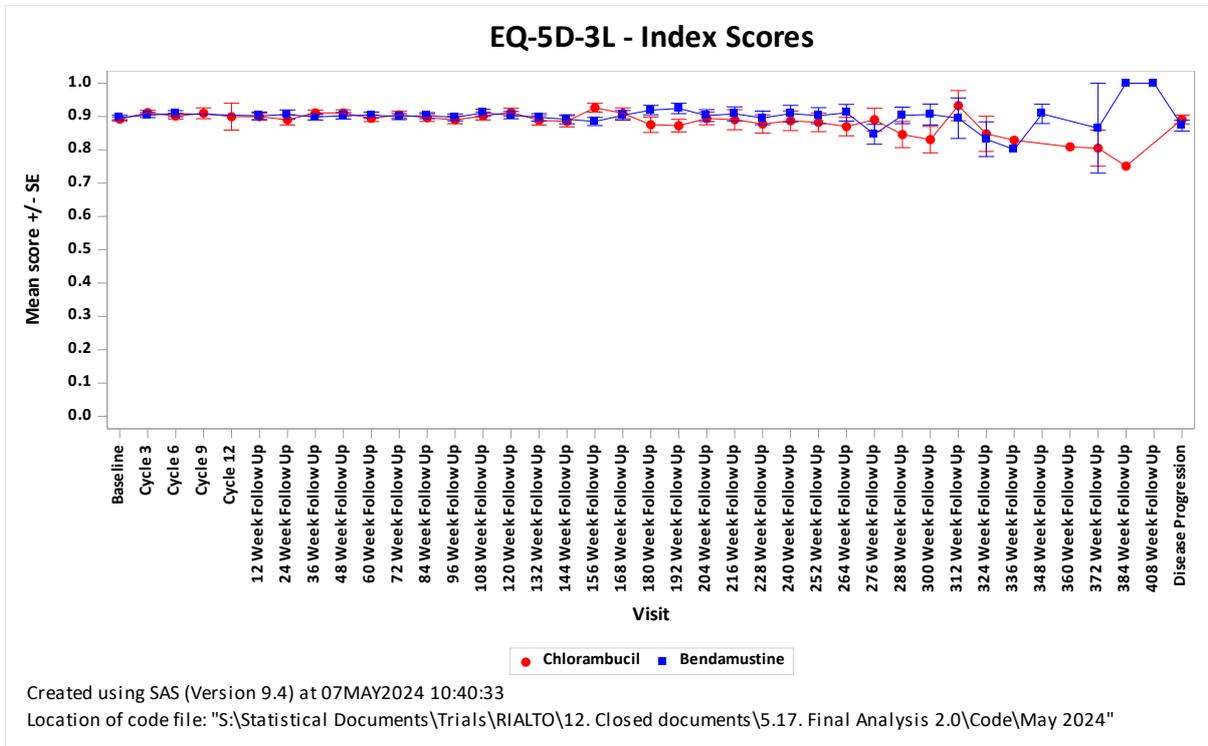


Figure 16-7 EQ-VAS – Health State

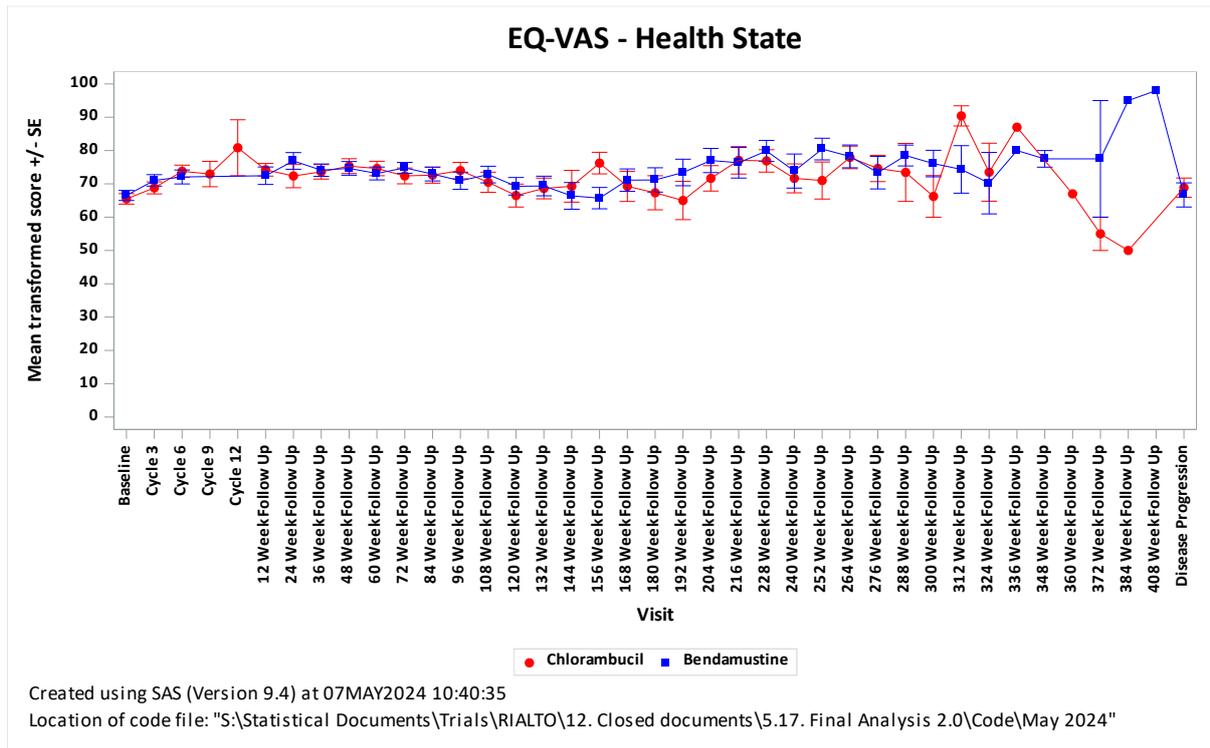


Figure 16-8 QLQ-C30 – Physical Functioning

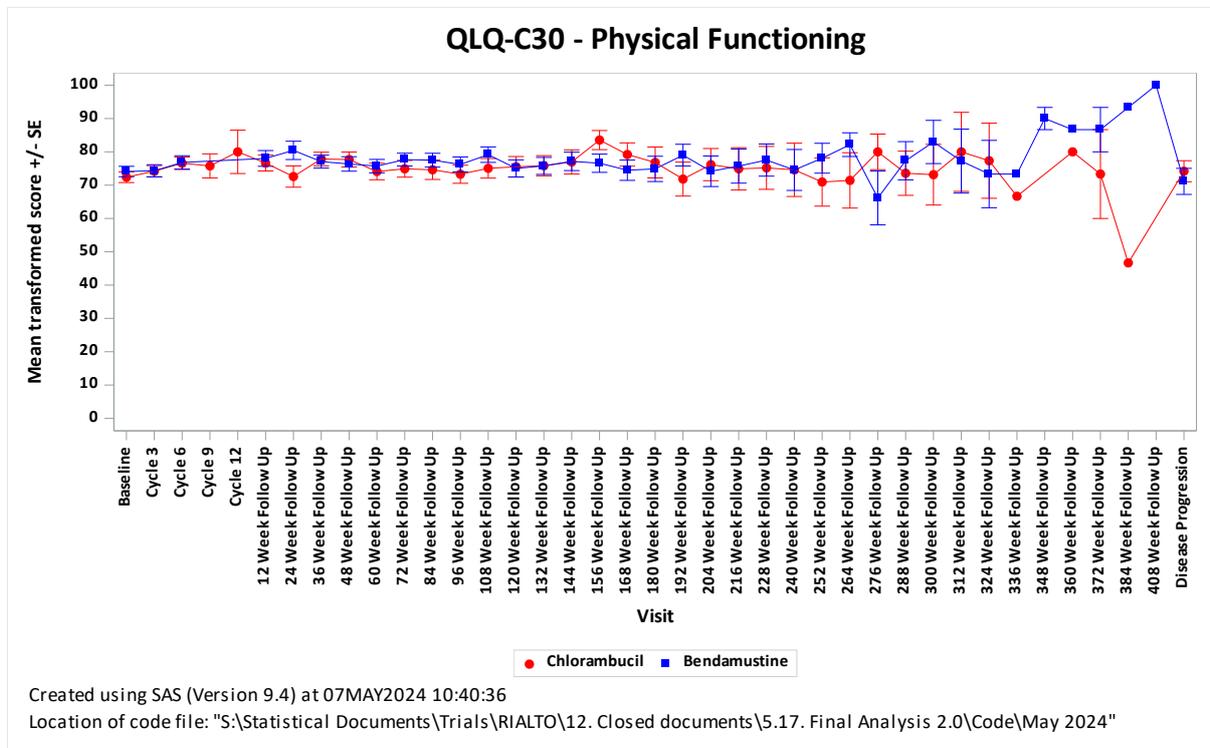


Figure 16-9 QLQ-C30 – Role Functioning

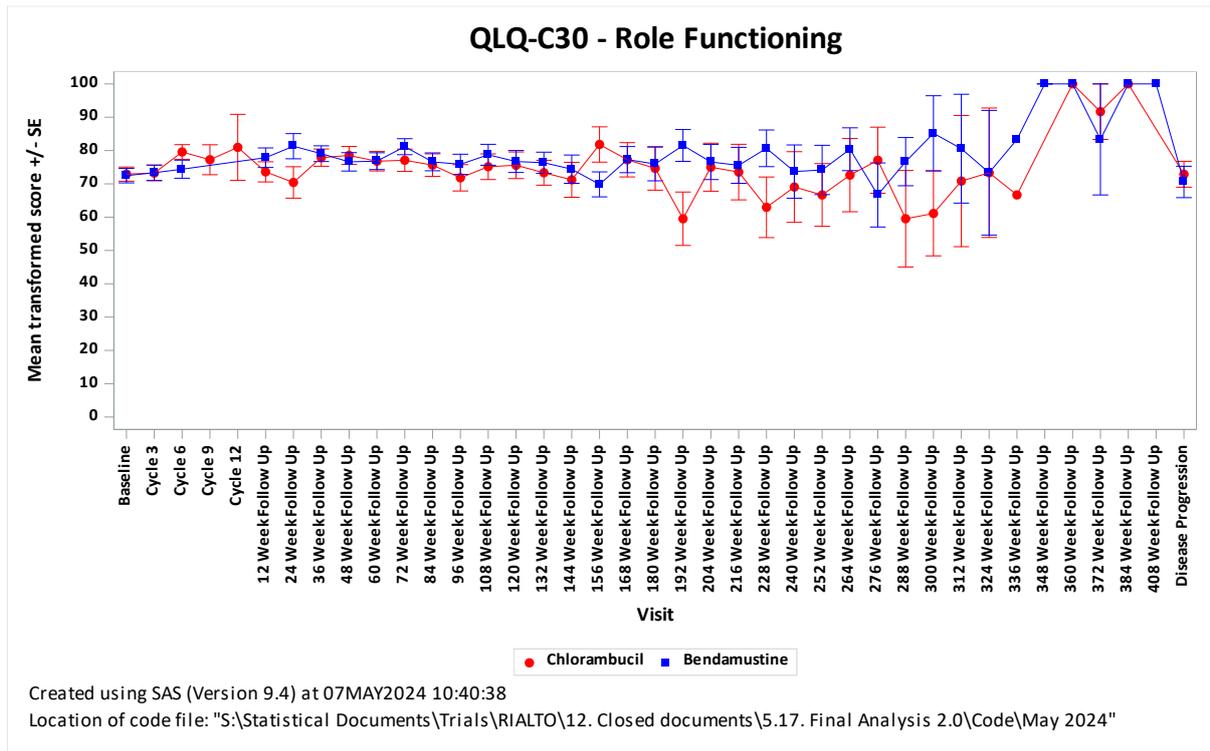


Figure 16-10 QLQ-C30 – Emotional Functioning

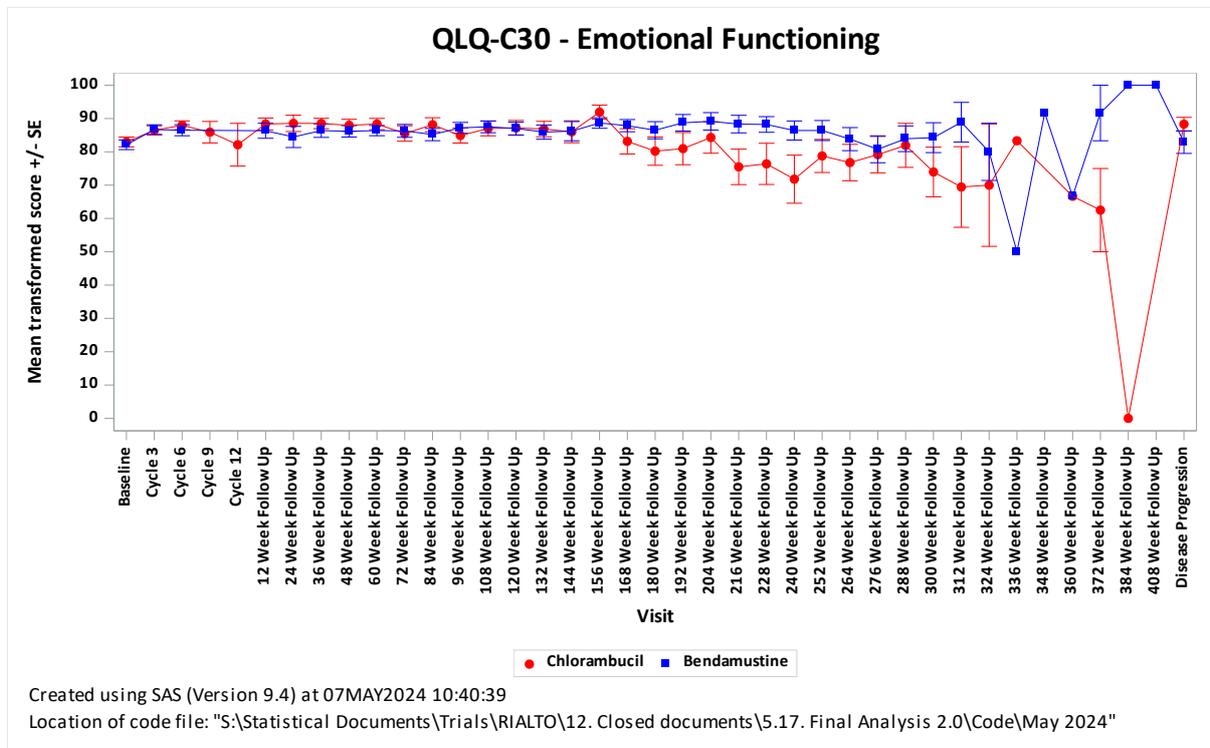


Figure 16-11 QLQ-C30 – Cognitive Functioning

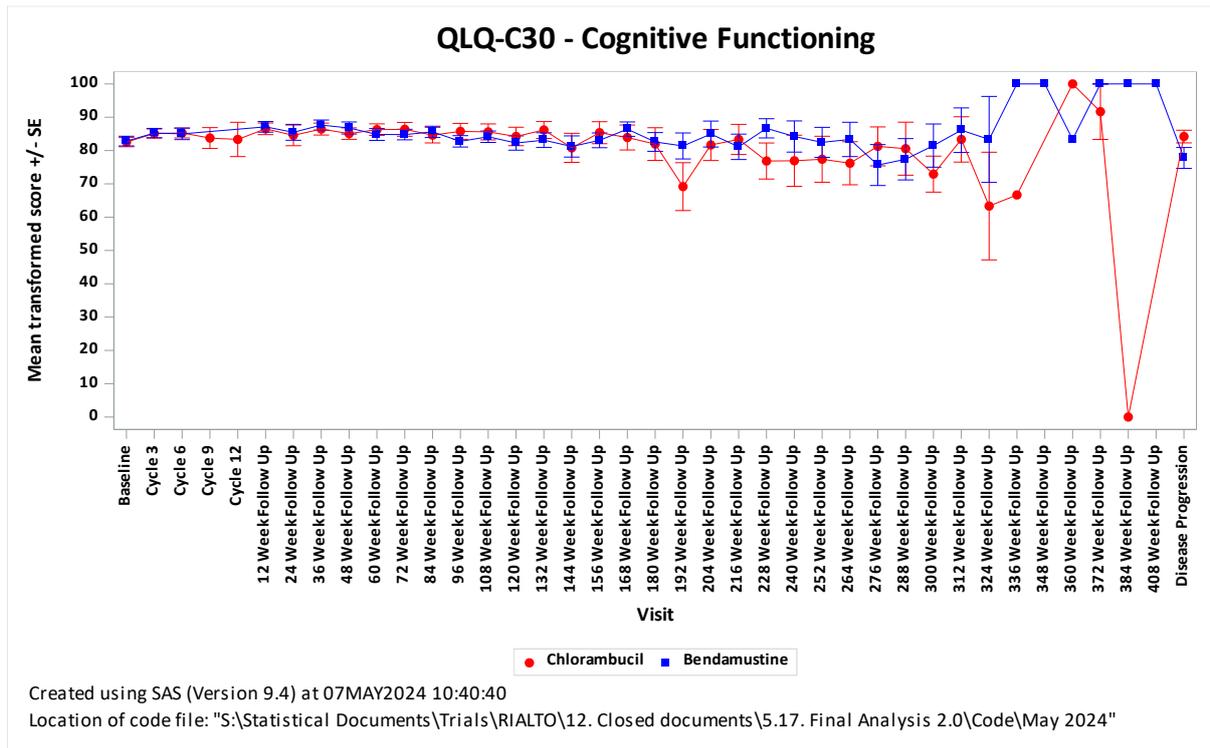


Figure 16-12 QLQ-C30 – Social Functioning

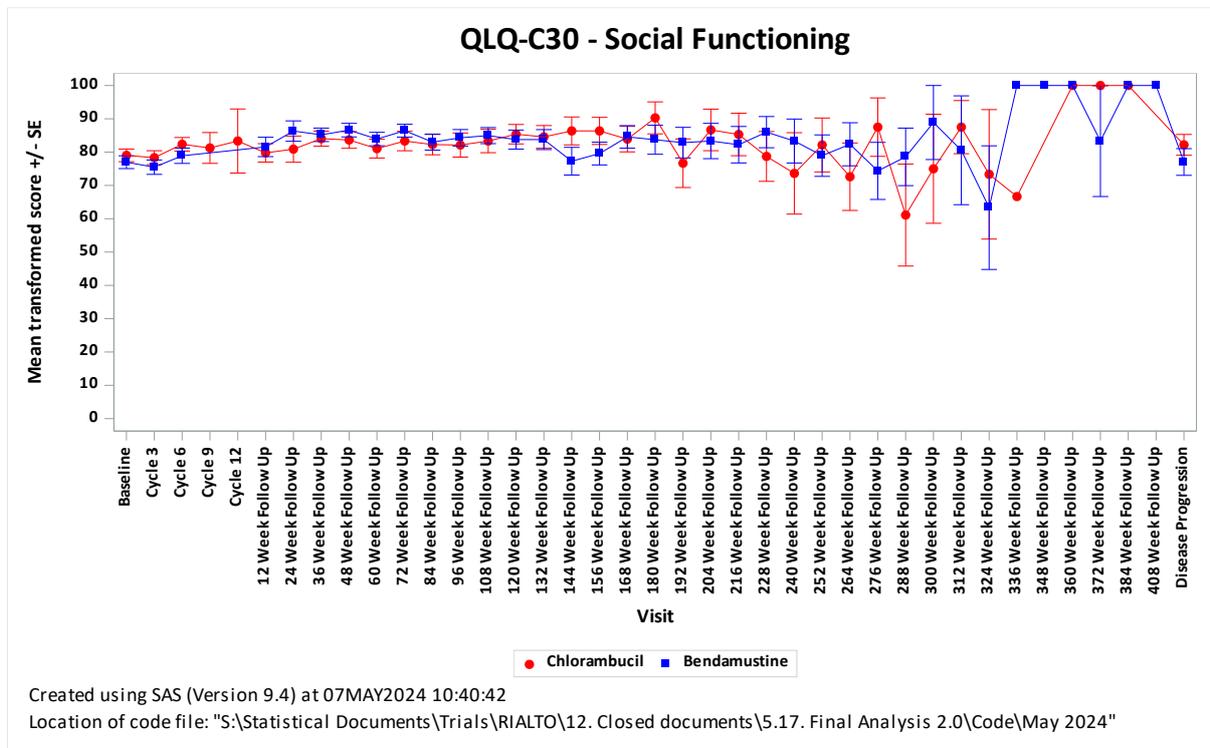


Figure 16-13 QLQ-C30 – Fatigue

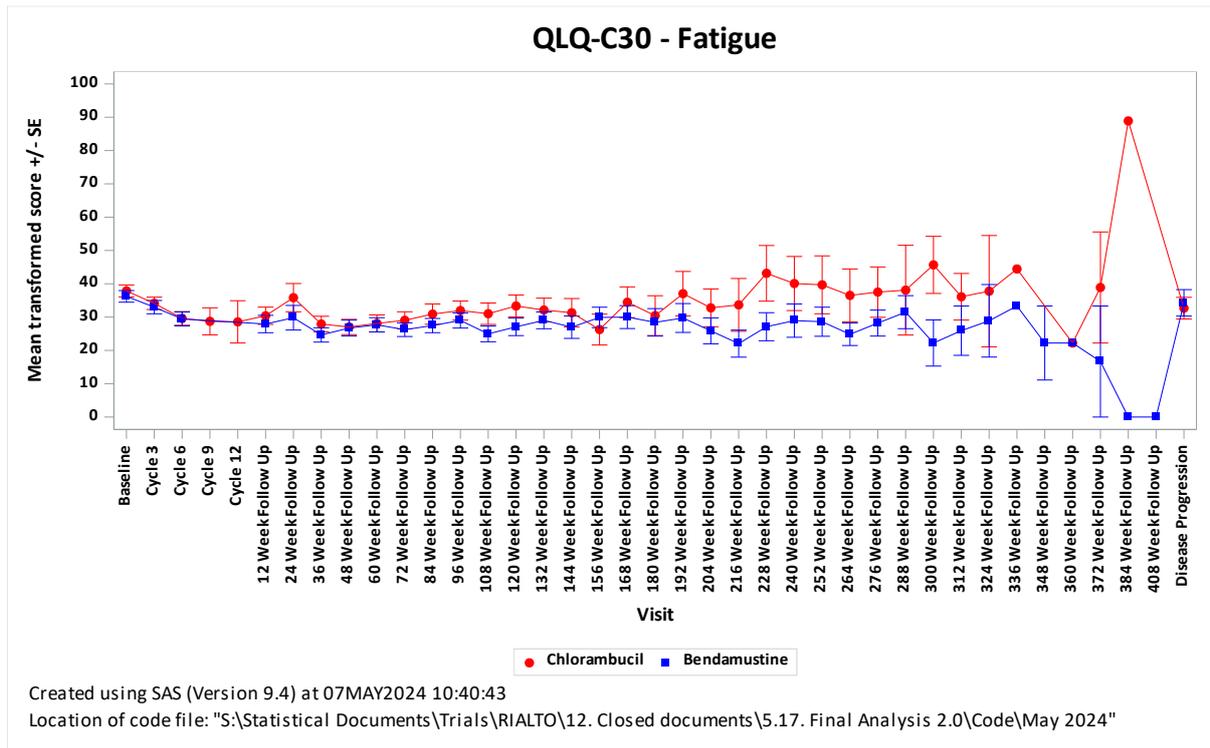


Figure 16-14 QLQ-C30 – Nausea and Vomiting

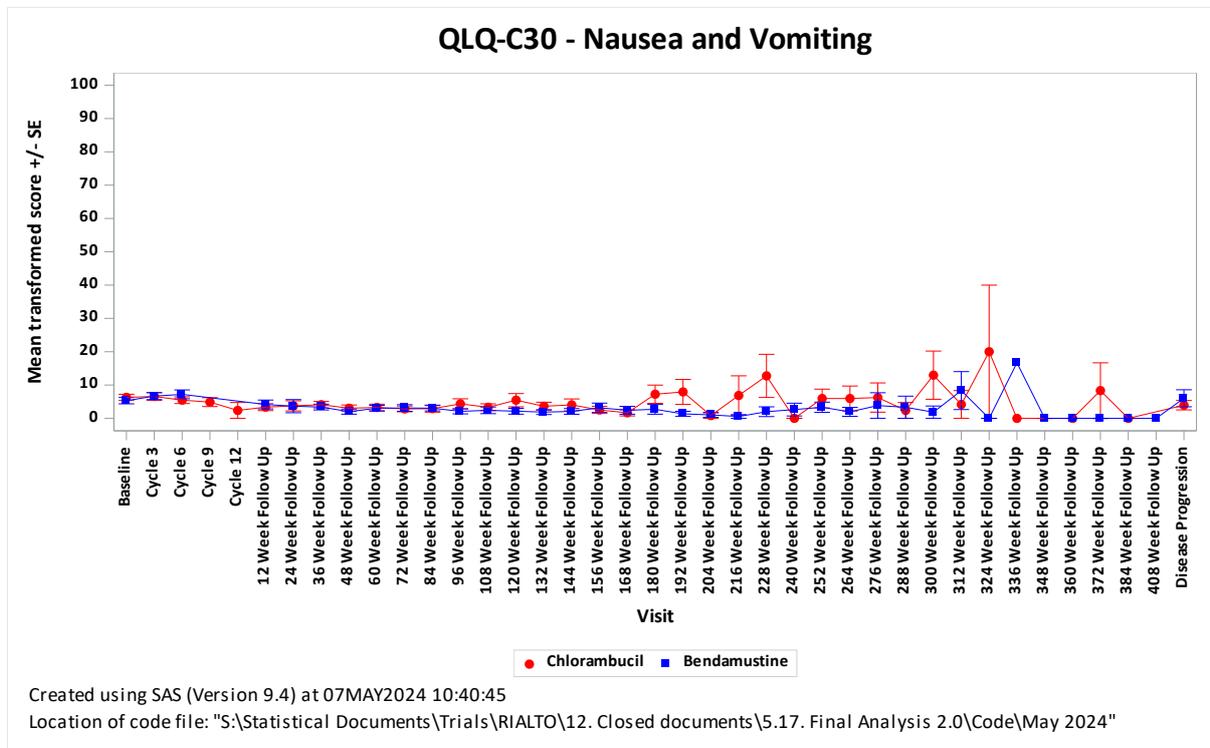


Figure 16-15 QLQ-C30 – Pain

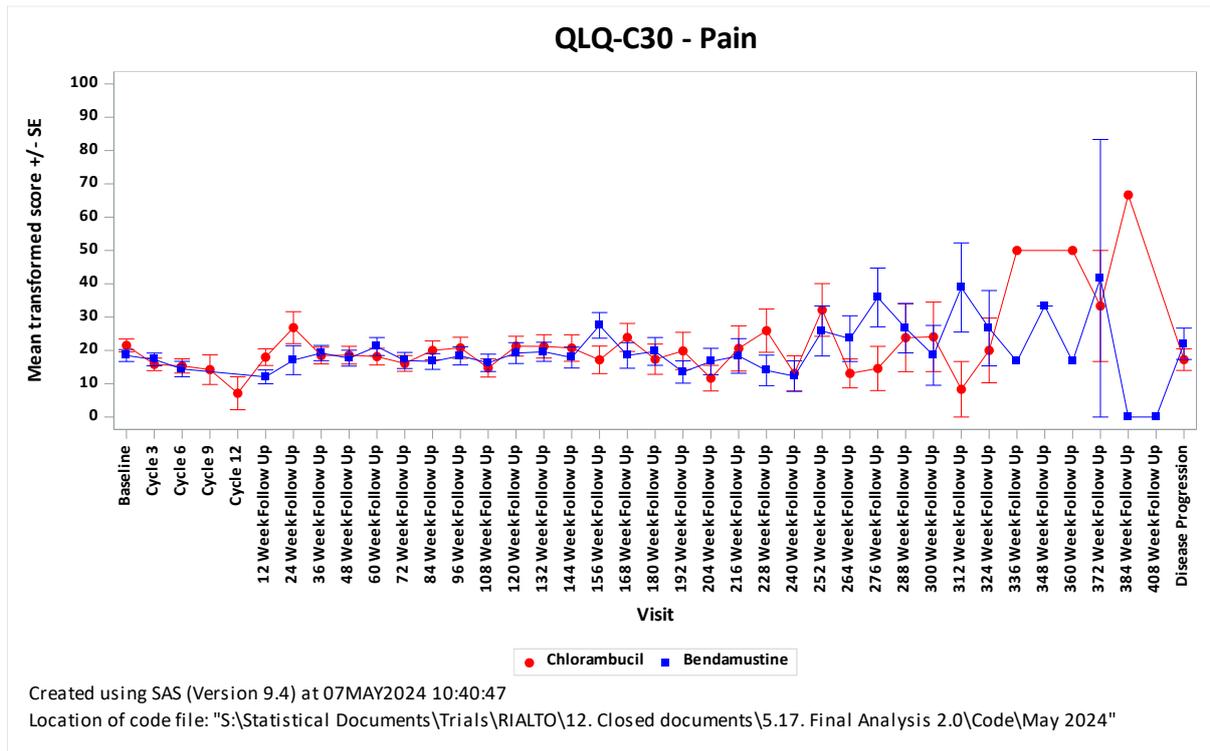


Figure 16-16 QLQ-C30 – Dyspnoea

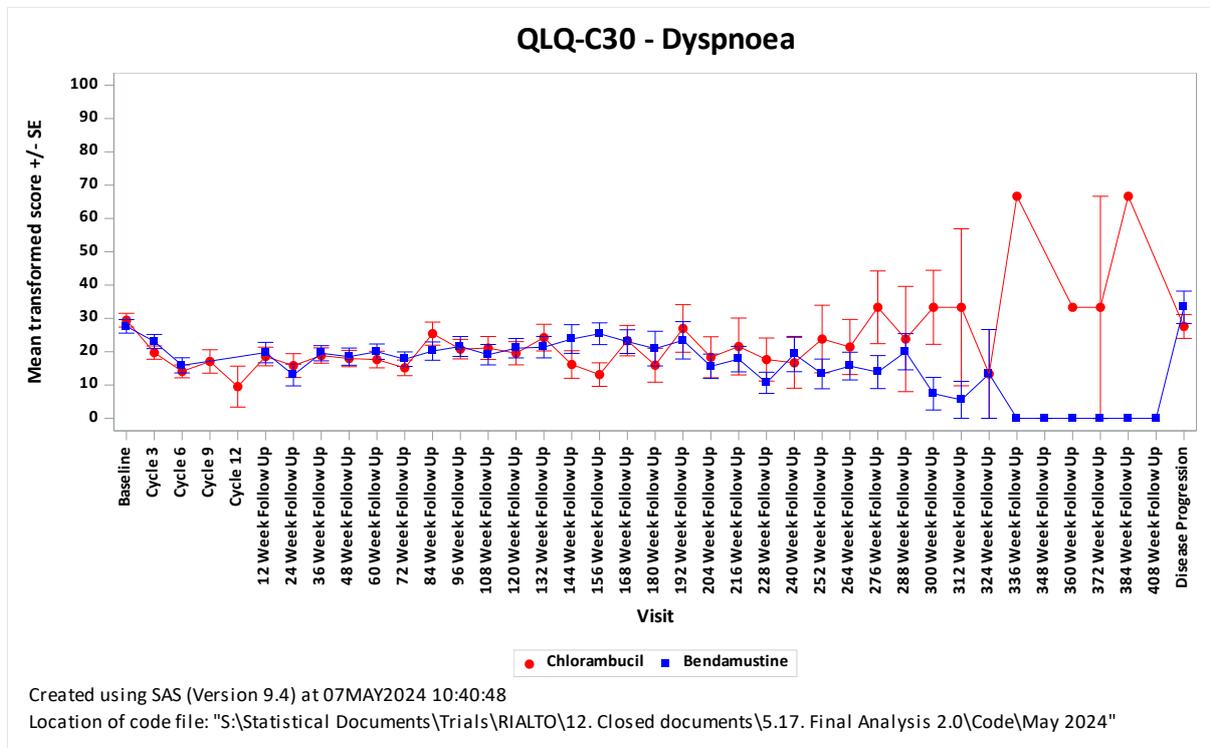


Figure 16-17 QLQ-C30 – Insomnia

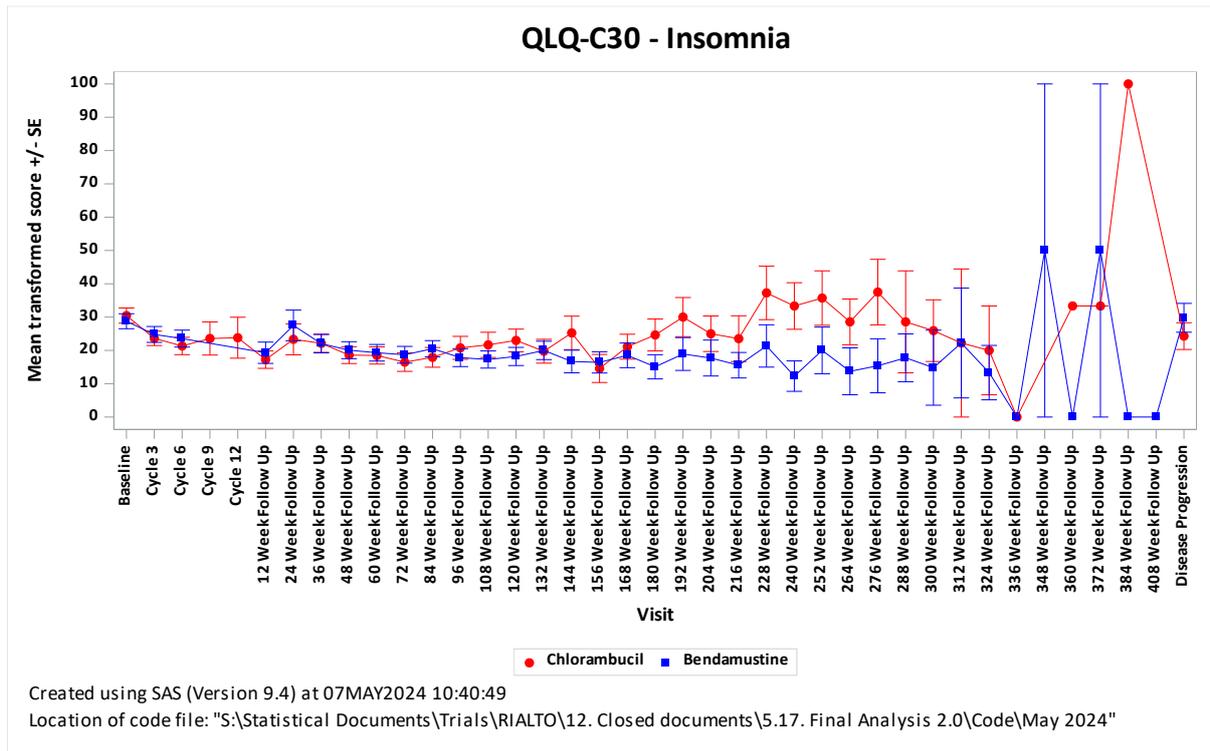


Figure 16-18 QLQ-C30 – Appetite Loss

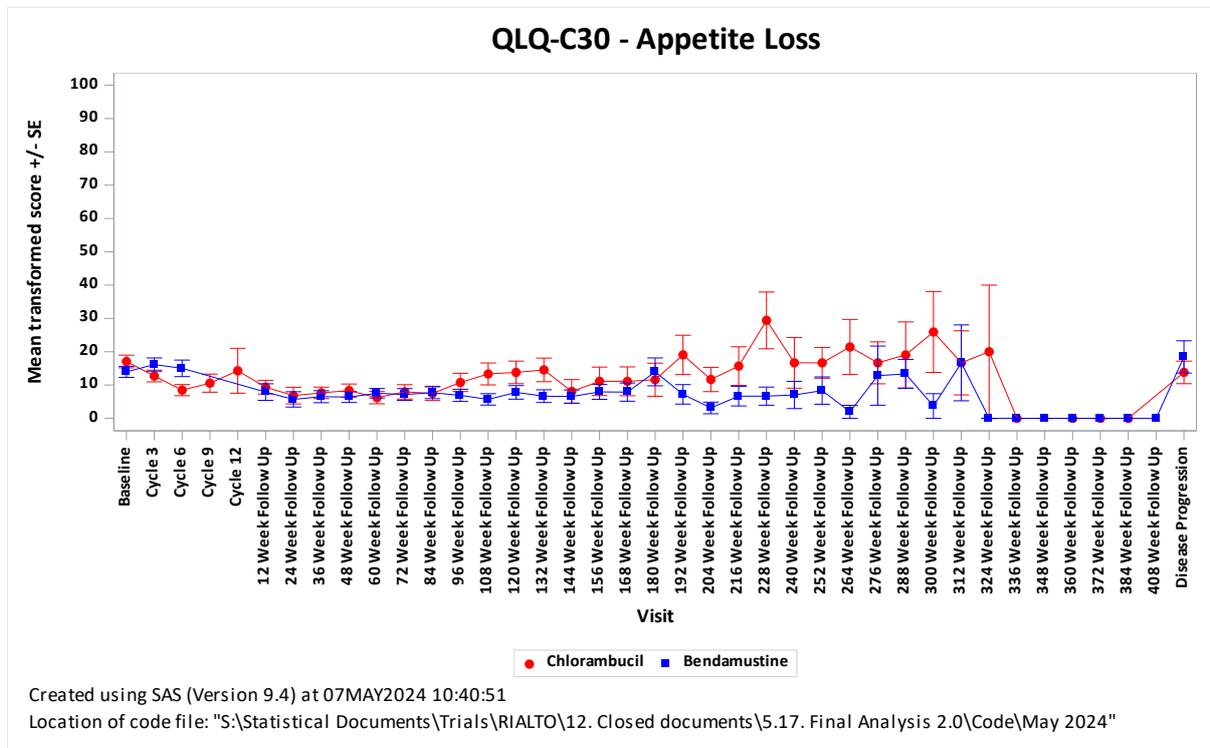


Figure 16-19 QLQ-C30 – Constipation

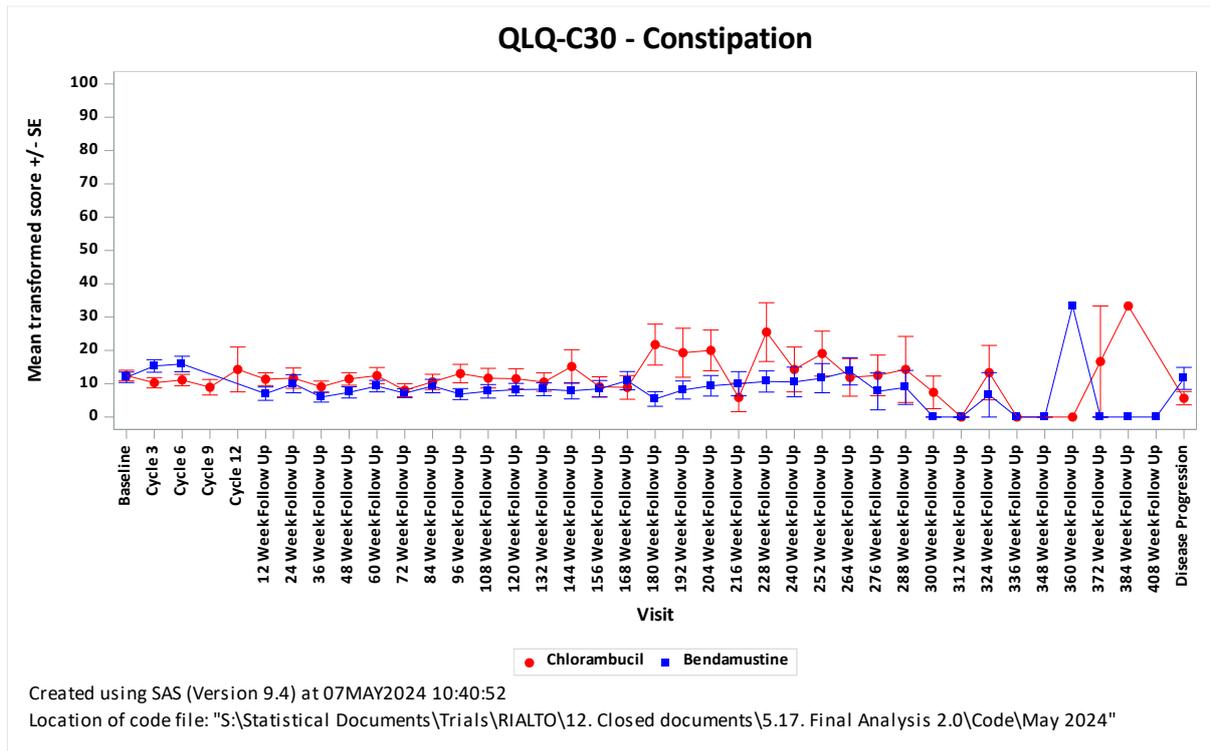


Figure 16-20 QLQ-C30 – Diarrhoea

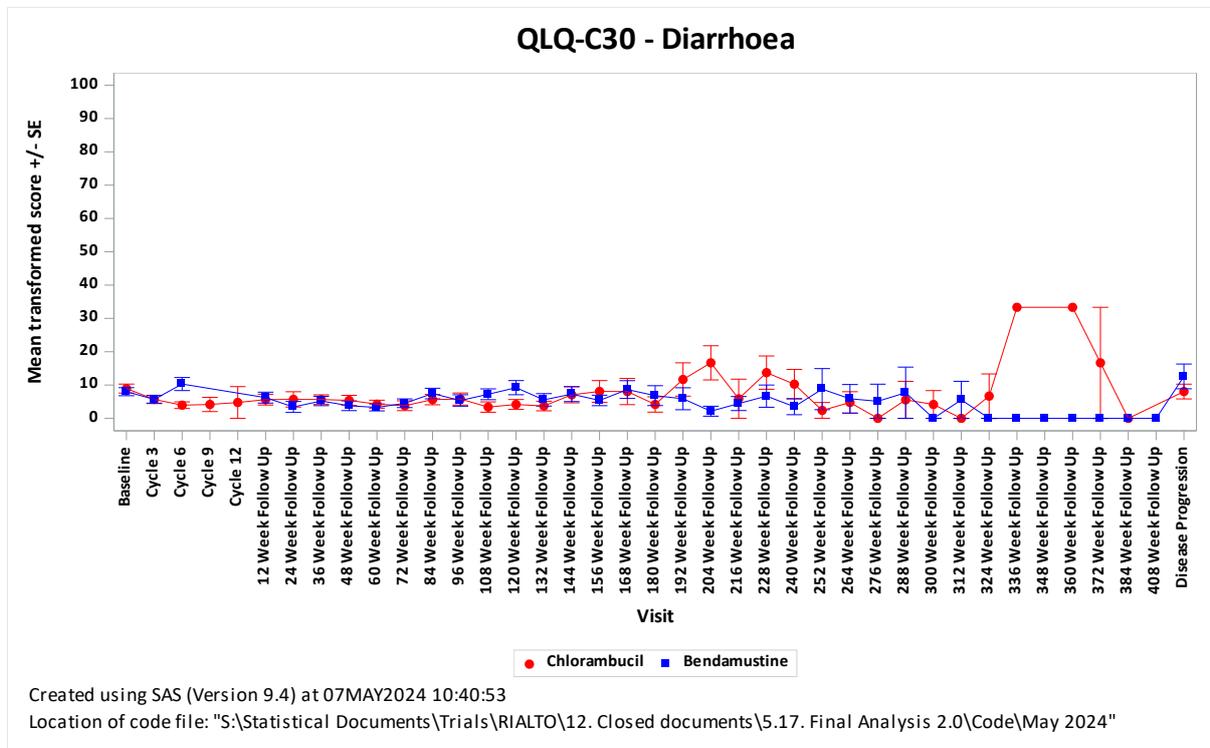


Figure 16-21 QLQ-C30 – Financial Difficulties

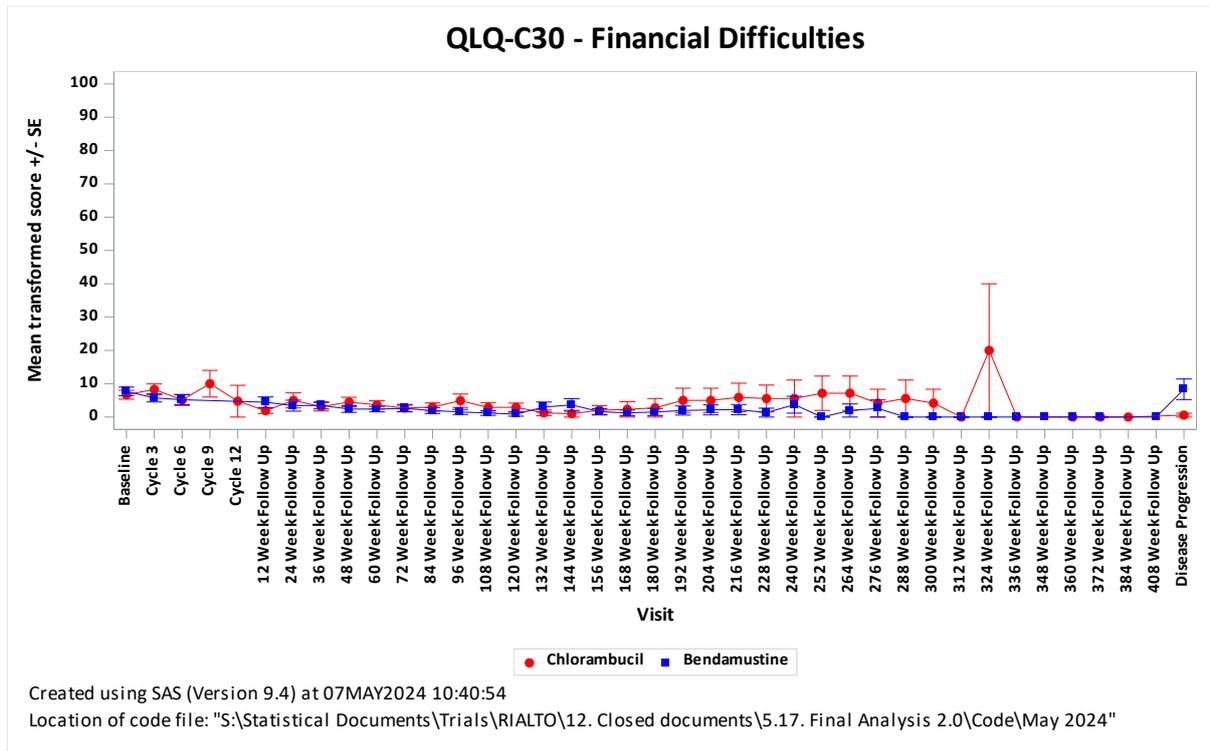


Figure 16-22 QLQ-C30 – Global Health Status/Quality of Life

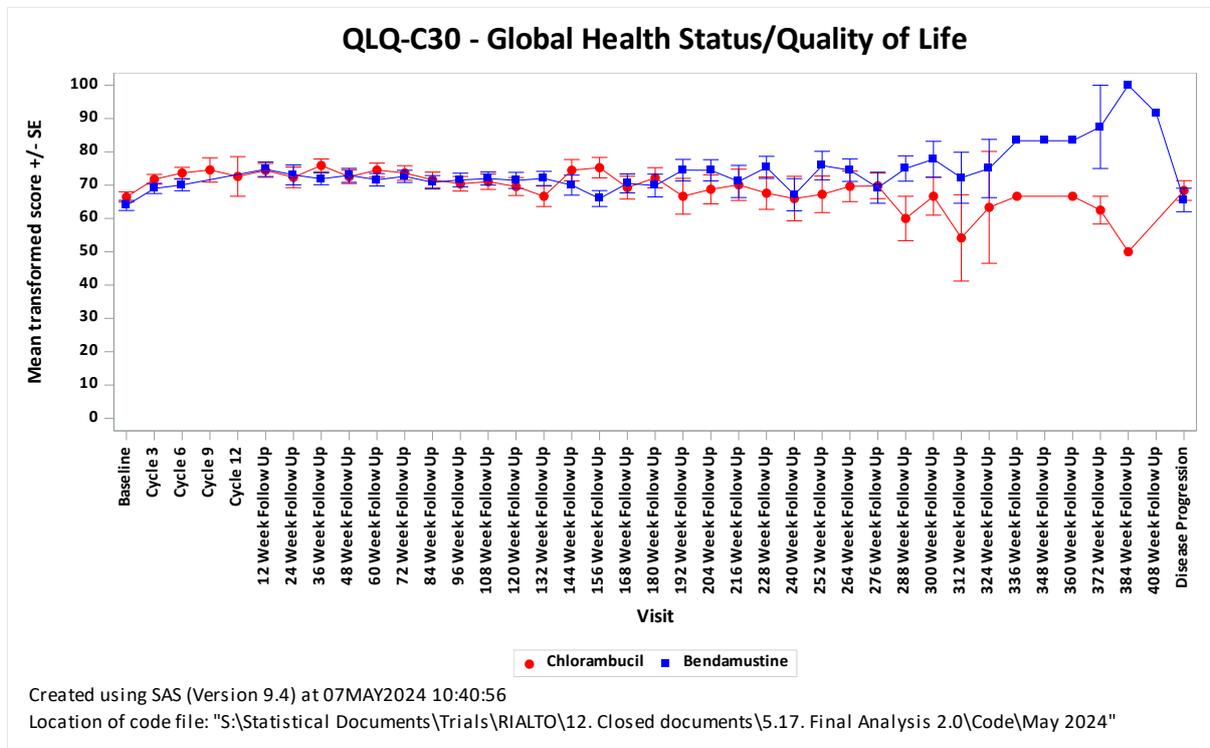


Figure 16-23 QLQ-CLL16 – Weight Loss

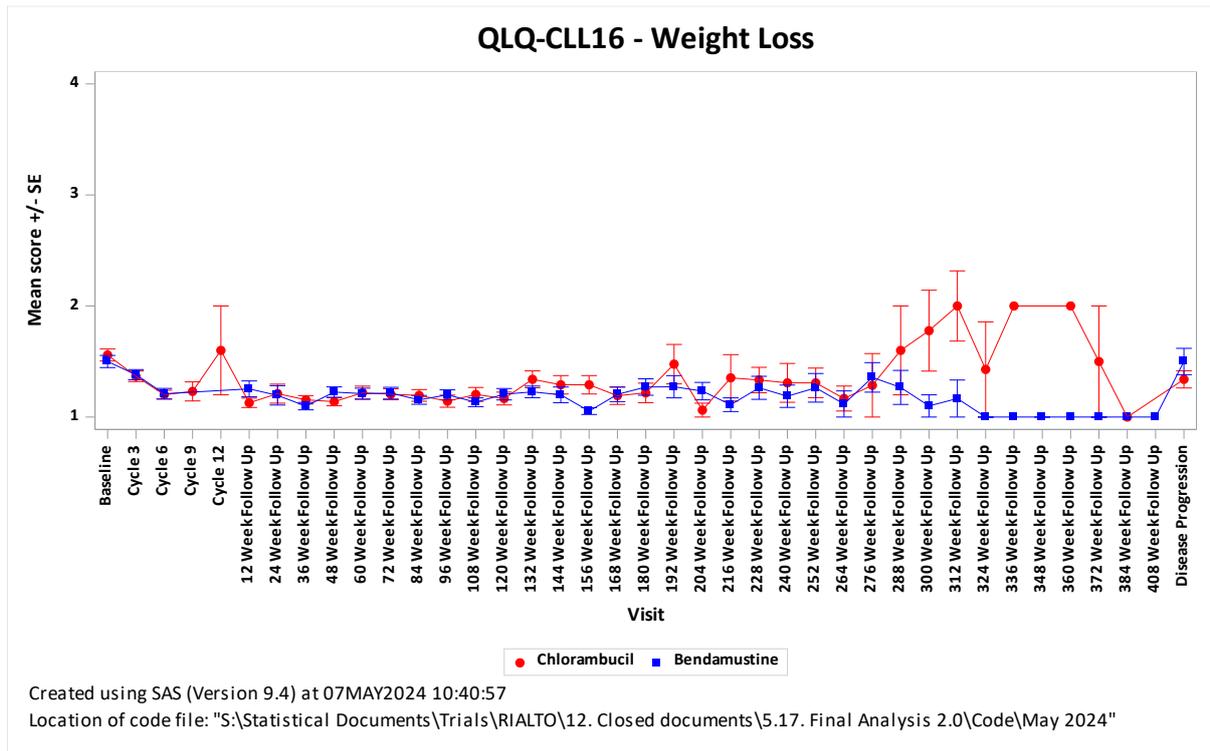


Figure 16-24 QLQ-CLL16 – Dry Mouth

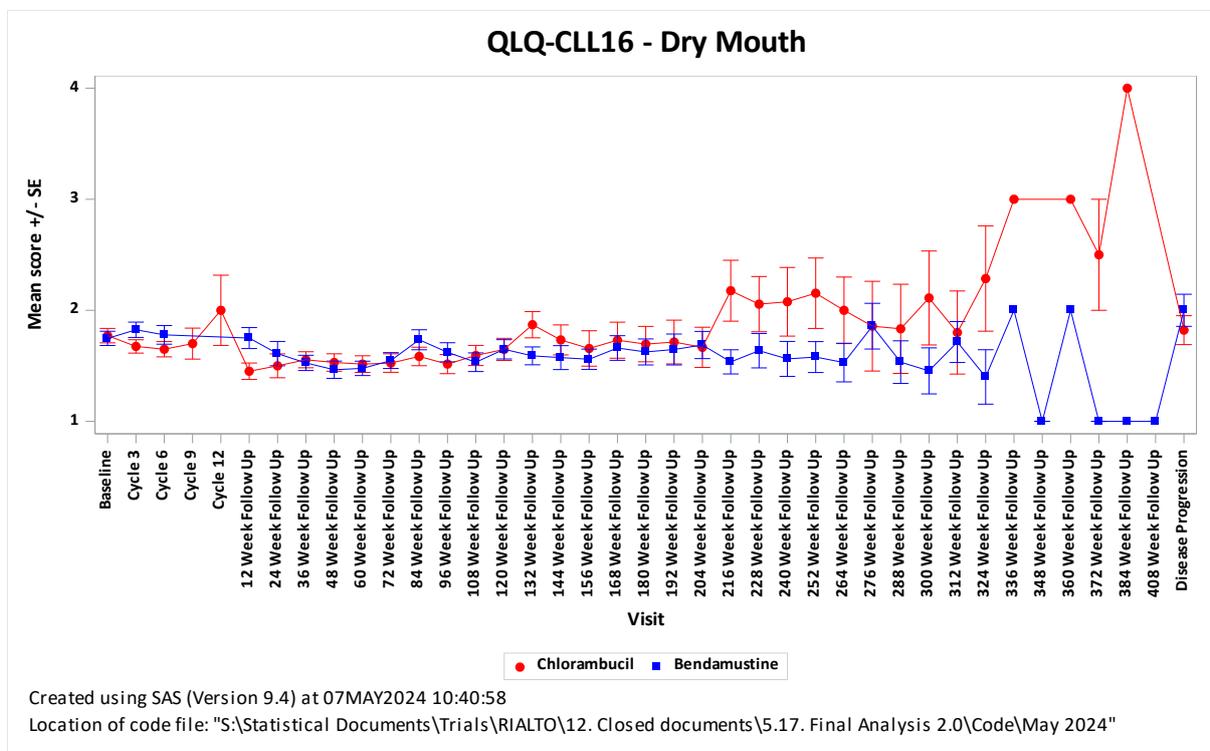


Figure 16-25 QLQ-CLL16 – Bruising

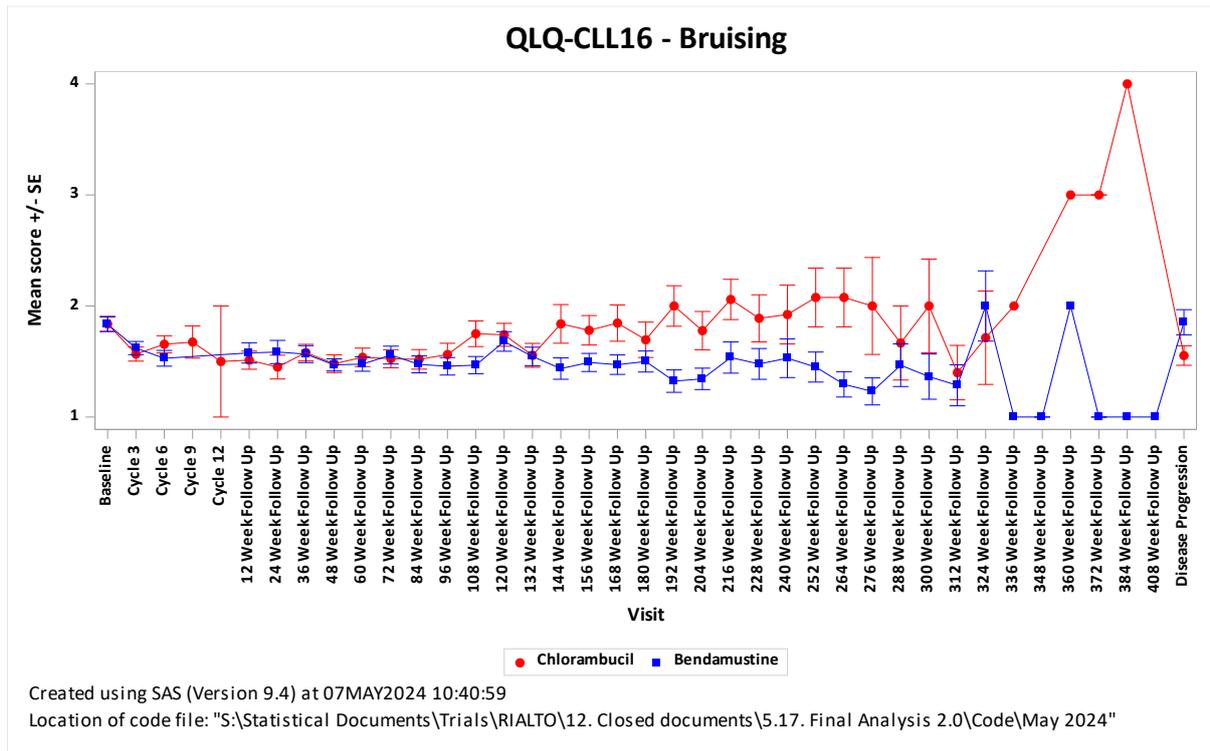


Figure 16-26 QLQ-CLL16 – Abdominal Discomfort

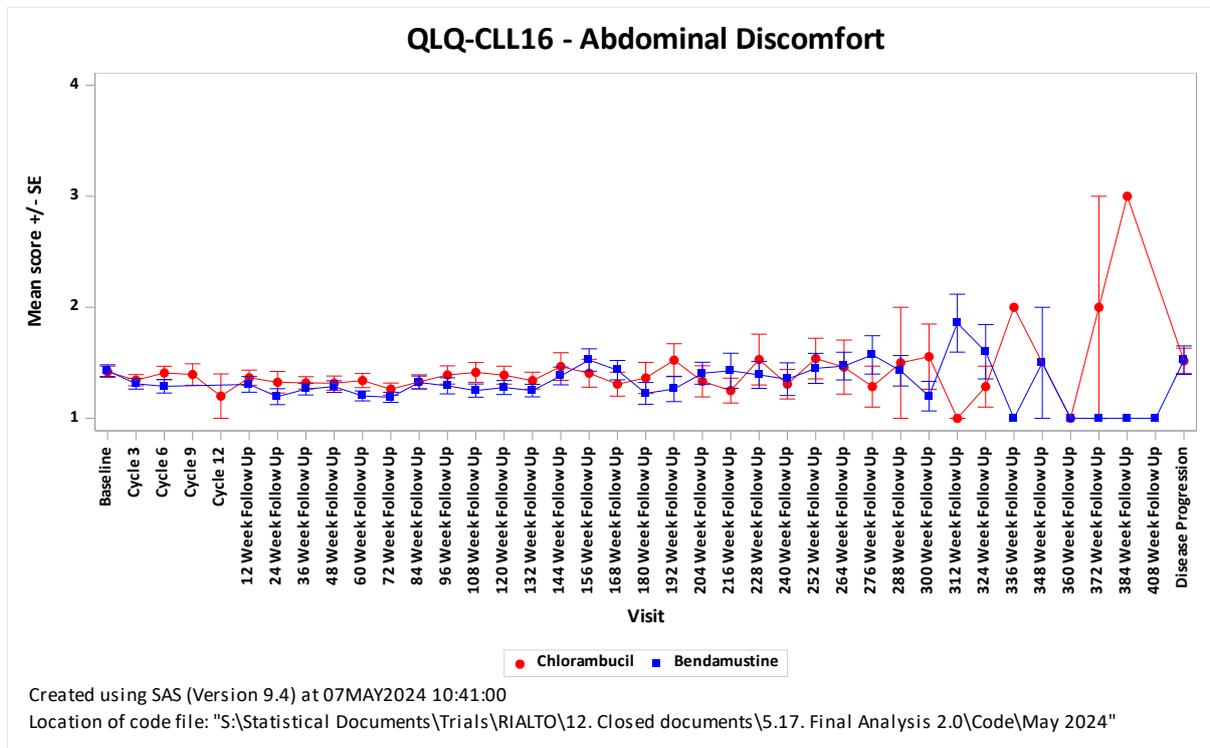


Figure 16-27 QLQ-CLL16 – Up and Down Temperature

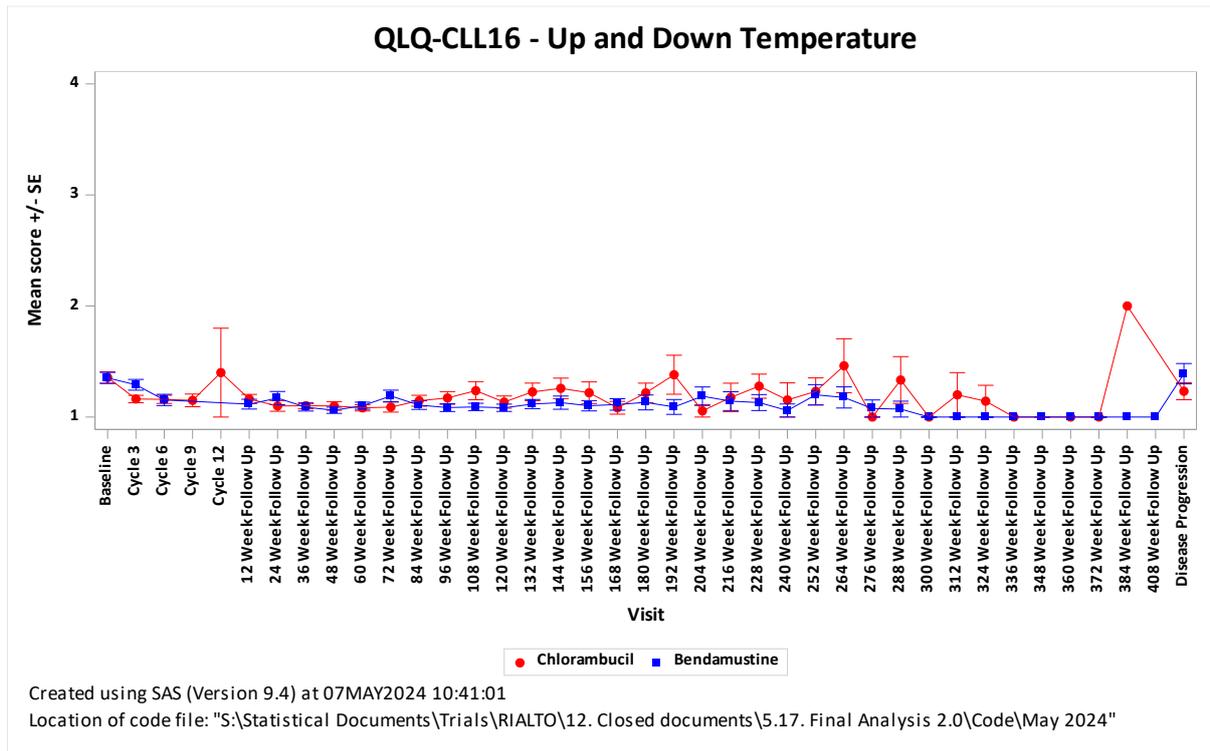


Figure 16-28 QLQ-CLL16 – Night Sweats

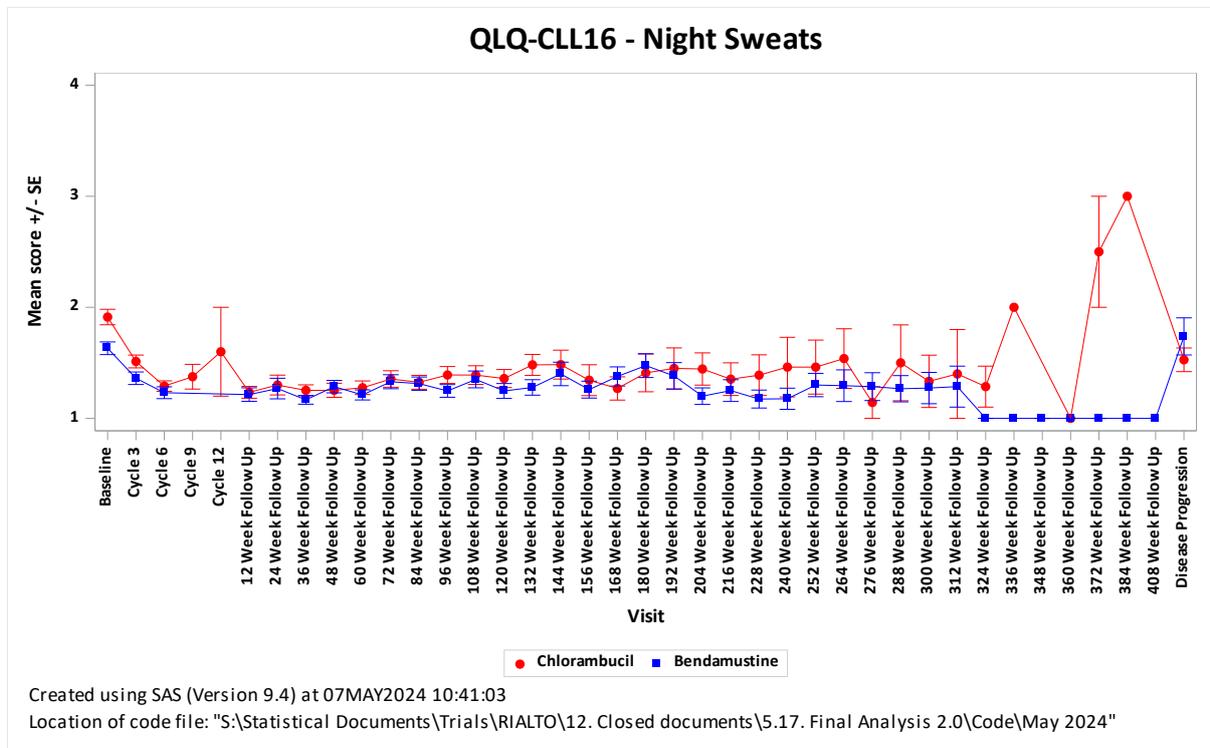


Figure 16-29 QLQ-CLL16 – Skin Problems

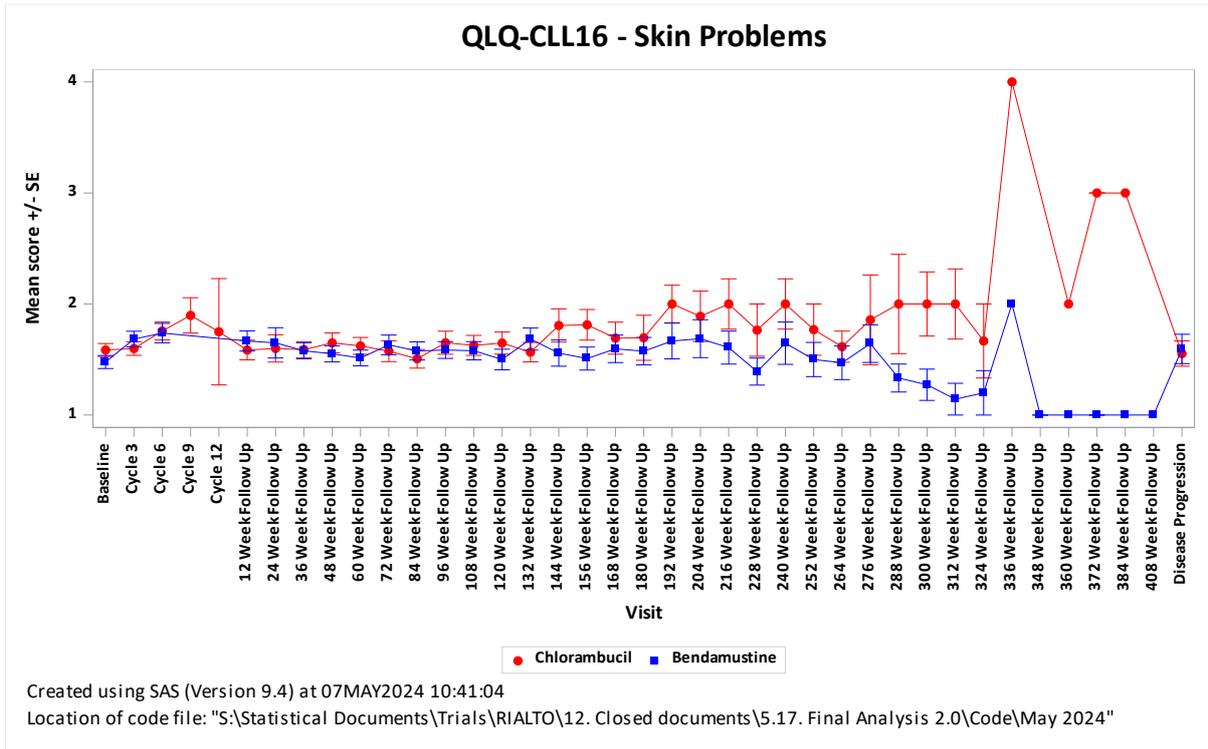


Figure 16-30 QLQ-CLL16 – Feeling Unwell

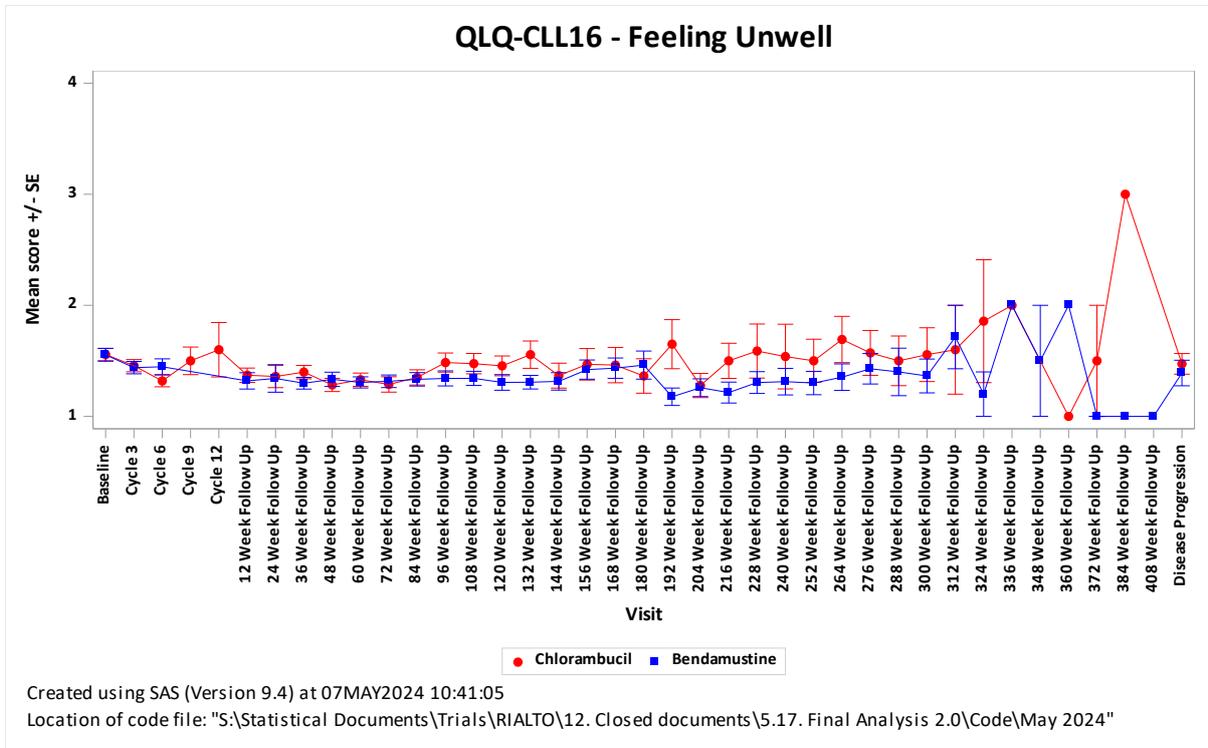


Figure 16-31 QLQ-CLL16 – Feeling Lethargic

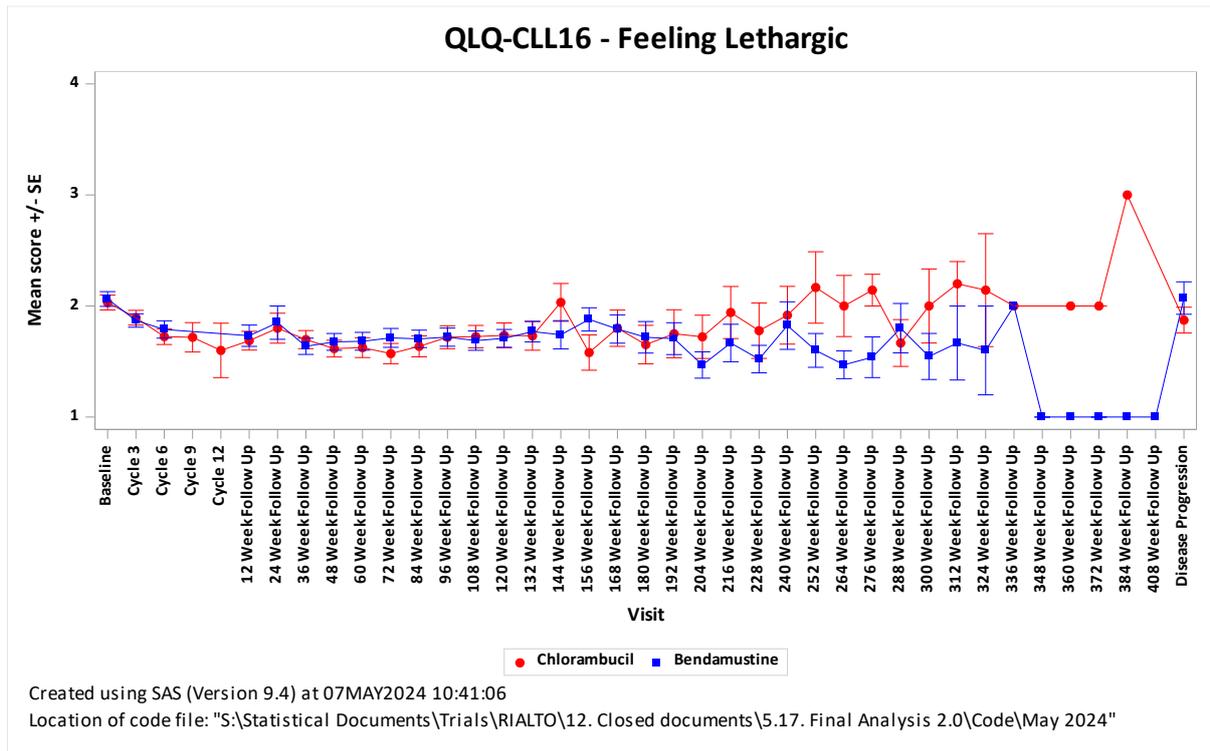


Figure 16-32 QLQ-CLL16 – Felt Slowed Down

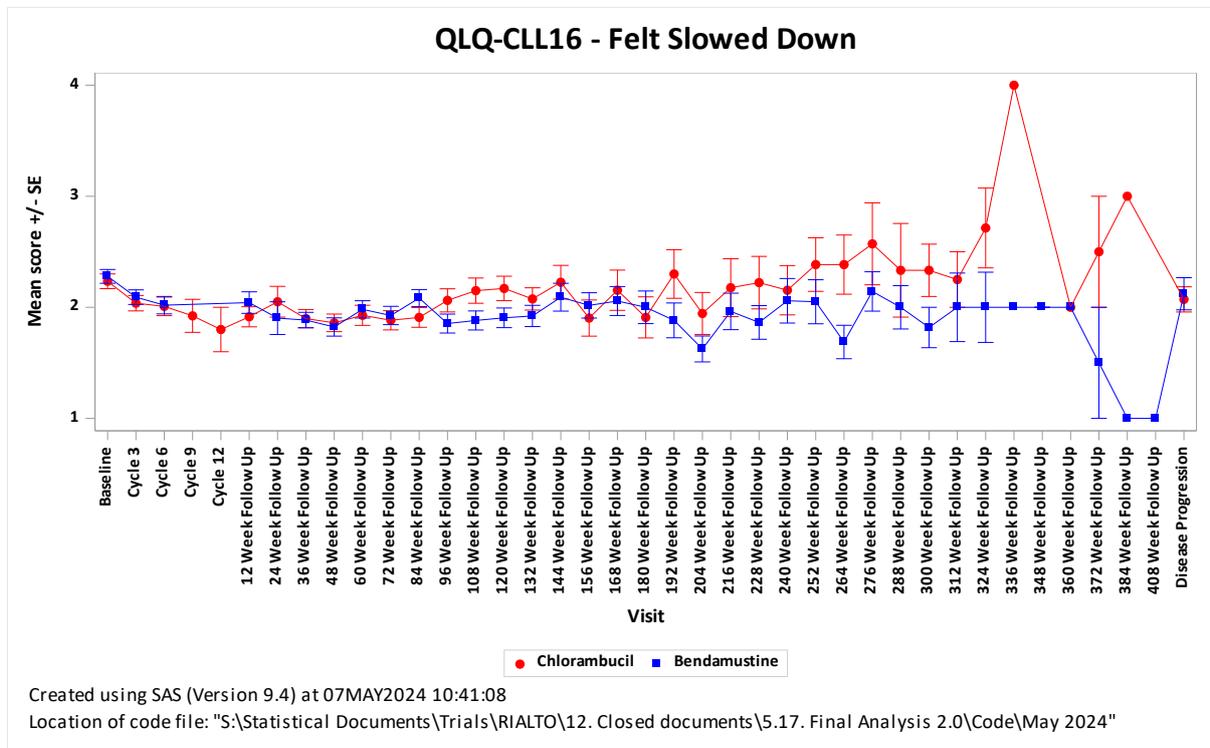


Figure 16-33 QLQ-CLL16 – Planning Activities

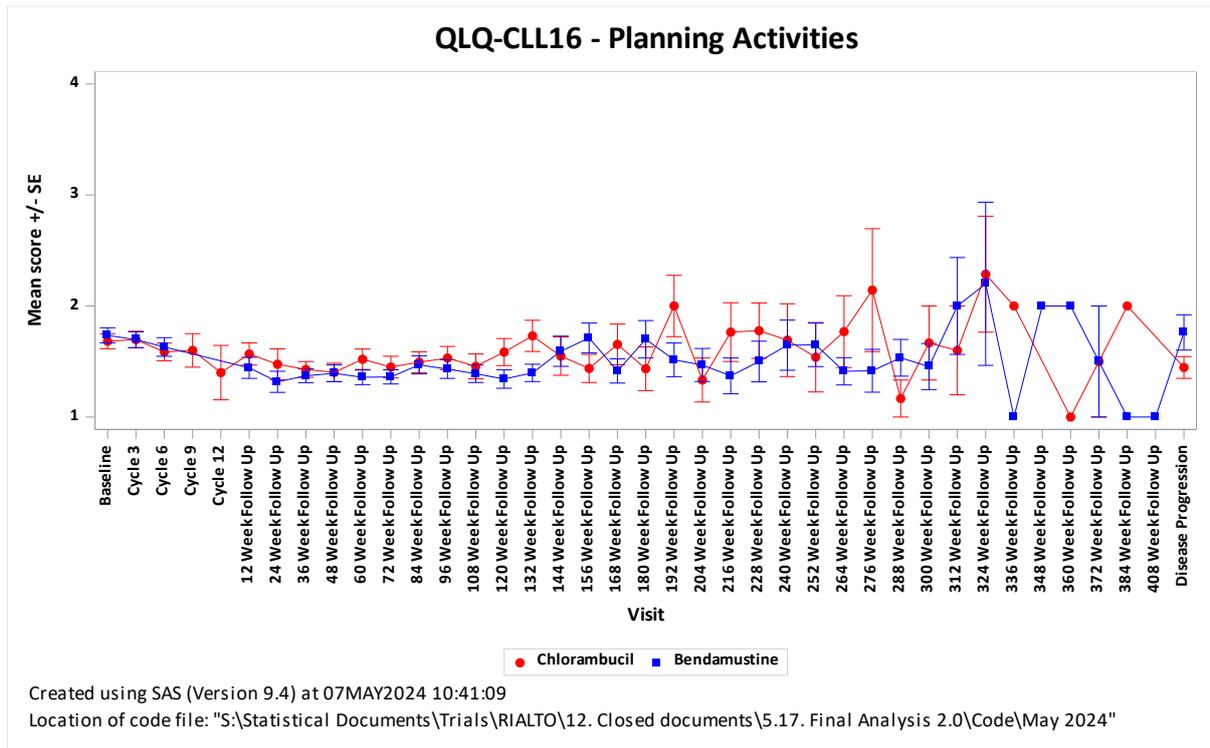


Figure 16-34 QLQ-CLL16 – Future Health Worries

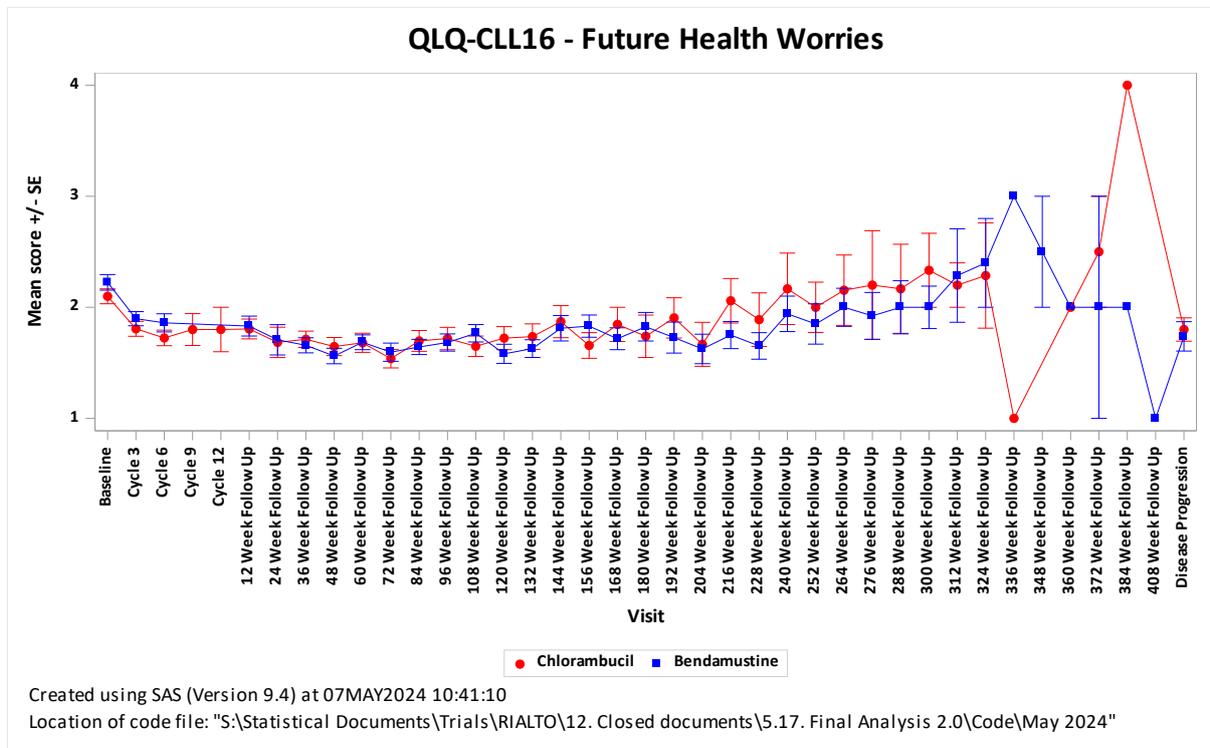


Figure 16-35 QLQ-CLL16 – Chest Infection

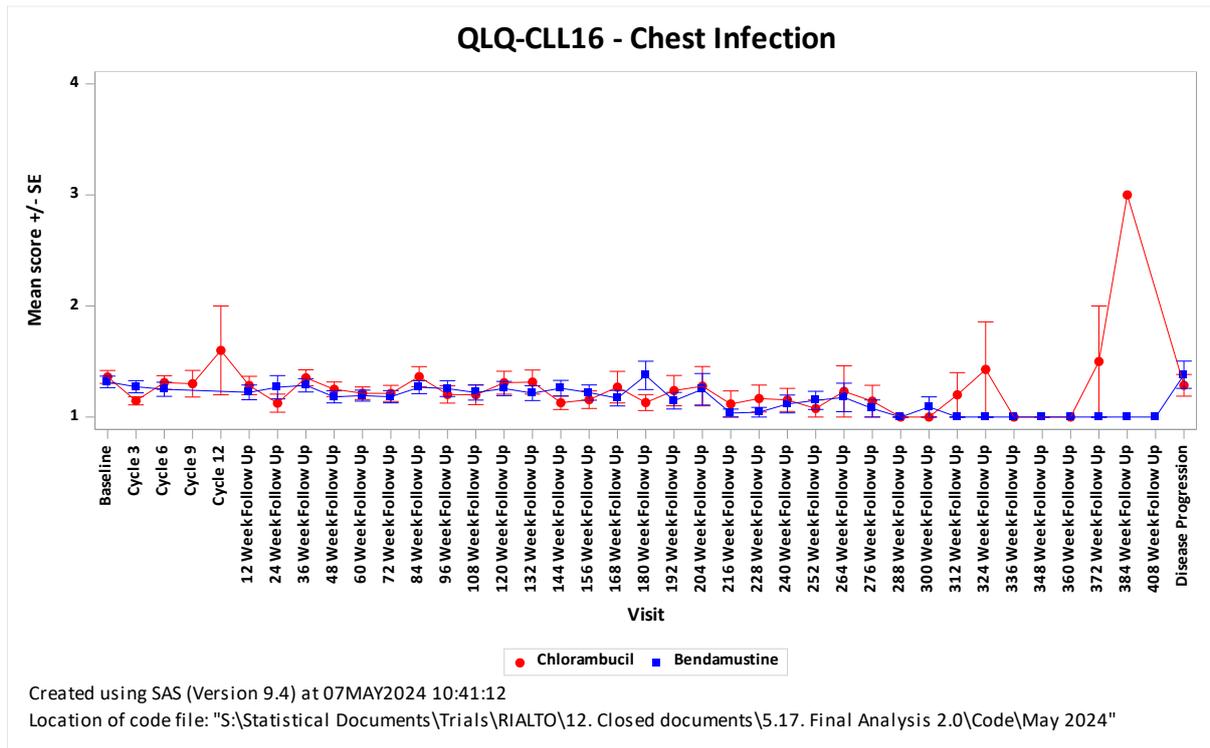


Figure 16-36 QLQ-CLL16 – Other Infection

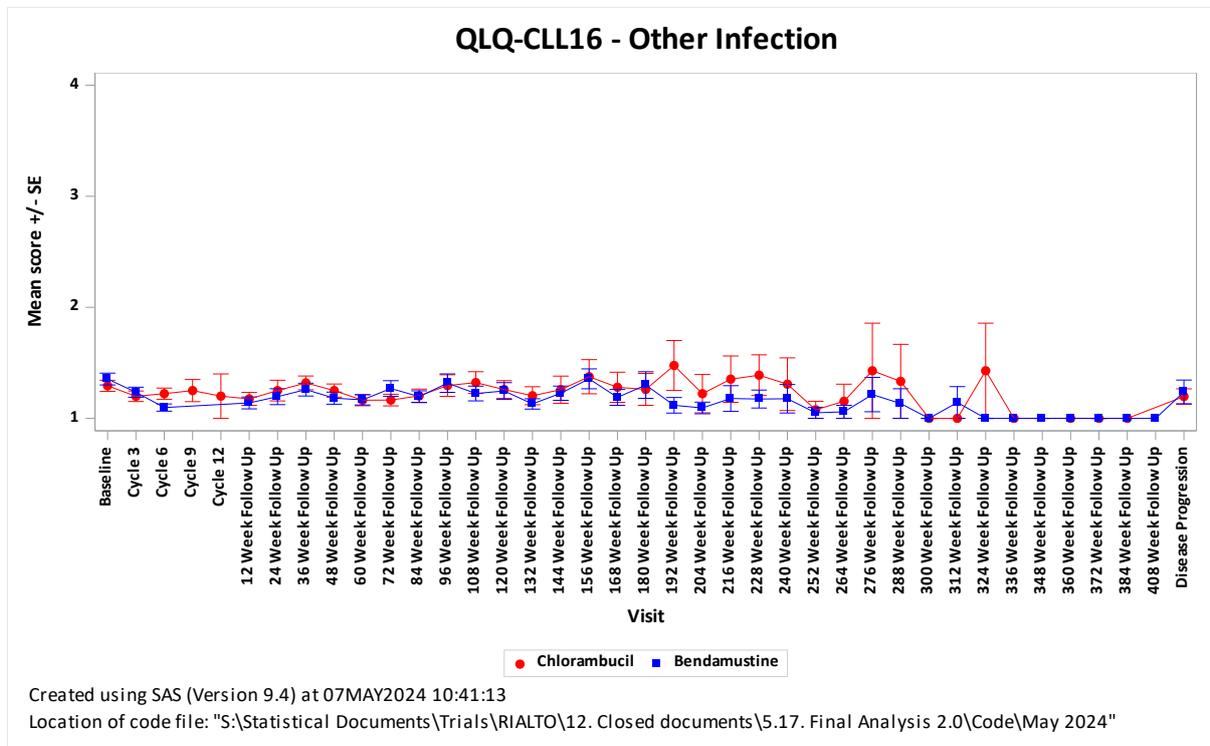


Figure 16-37 QLQ-CLL16 – Repeated Course of Antibiotics

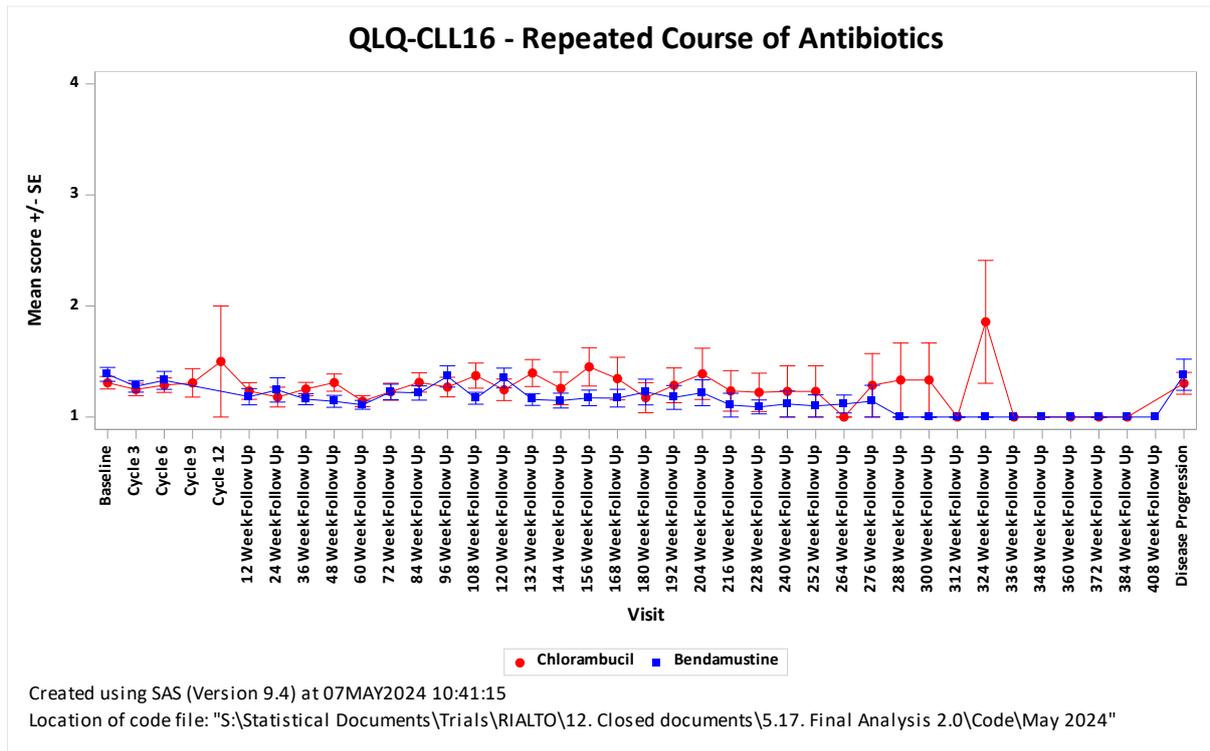
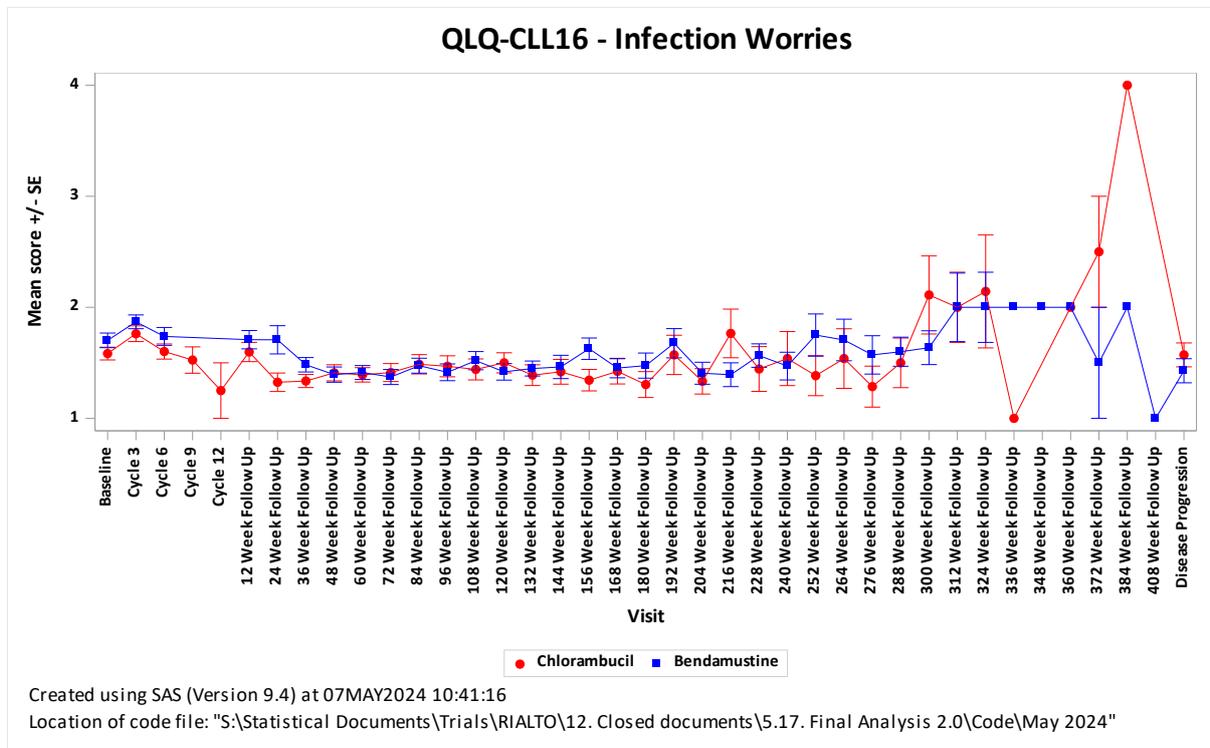


Figure 16-38 QLQ-CLL16 – Infection Worries



15.2 Quality of Life Summary

Differences in some Quality of Life measurements between the Chlorambucil and Bendamustine groups were apparent from approximately 3 years after the start of treatment. Compared to Bendamustine, Chlorambucil was associated with lower emotional functioning and more fatigue, insomnia and appetite loss in the QLQ-30 assessment, and more dry mouth, bruising, skin problems in the QLQ-CLL16 assessment. No differences between the two treatment arms was seen with the EQ-VAS assessment.

16 Secondary Outcome – Analysis of Frailty and Co-Morbidity

Frailty and co-morbidity analyses are undertaken to investigate the subgroup effects on progression free survival, overall survival and time to treatment failure. The subgroups being considered are:

- Cumulative Illness Rating Scale (≤ 6 vs. >6)
- Performance Status (0 vs. 1 vs. 2 vs. 3)
- VES-13 (<3 vs. ≥ 3)
- GFI (<4 vs. ≥ 4)
- Timed Up and Go (<10 vs. ≥ 10)

Results are presented in terms of the hazard ratios between each level of each subgroups as well as the difference between treatment arms within each group. For each analysis, results are presented in terms of hazard ratios and associated 95% confidence intervals. Kaplan Meier plots for each analysis are also provided.

16.1 Progression Free Survival

Table 16-1 Frailty and Comorbidity – Progression Free Survival – Subgroup Comparison

Frailty/Comorbidity	Comparison	Hazard Ratio (95% CI)*
Cumulative Illness Rating Score	≤ 6 vs. >6	0.96 (1.24;0.73)
Performance Status	0 vs. 1	0.73 (0.57;0.93)
	0 vs. 2	0.59 (0.42;0.85)
	0 vs. 3	0.60 (0.24;1.47)
	1 vs. 2	0.82 (0.58;1.14)
	1 vs. 3	0.83 (0.34;2.02)
	2 vs. 3	1.01 (0.40;2.55)
Vulnerable Elders Survey-13	<3 vs. ≥ 3	0.97 (0.76;1.23)
Groningen Frailty Index	<4 vs. ≥ 4	0.73 (0.57;0.93)
Timed Up and Go Test	<10 vs. ≥ 10	0.82 (0.64;1.04)

Created using SAS (Version 9.4) at 07MAY2024 10:43:18

*Cox PH model

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Table 16-2 Frailty and Comorbidity – Progression Free Survival – Treatment Comparison

Frailty/Comorbidity	Subgroup	Comparison	Hazard Ratio (95% CI)*
Cumulative Illness Rating Score	<=6	Bendamustine vs. Chlorambucil	0.67 (0.52;0.87)
	>6	Bendamustine vs. Chlorambucil	0.89 (0.56;1.42)
Performance Status	0	Bendamustine vs. Chlorambucil	0.58 (0.39;0.85)
	1	Bendamustine vs. Chlorambucil	0.79 (0.57;1.08)
	2	Bendamustine vs. Chlorambucil	0.77 (0.42;1.40)
	3	Bendamustine vs. Chlorambucil	NA (NA;NA)
VES-13	<3	Bendamustine vs. Chlorambucil	0.64 (0.48;0.86)
	>=3	Bendamustine vs. Chlorambucil	0.91 (0.62;1.34)
GFI	<4	Bendamustine vs. Chlorambucil	0.54 (0.40;0.74)
	>=4	Bendamustine vs. Chlorambucil	1.09 (0.75;1.60)
Timed Up and Go	<10	Bendamustine vs. Chlorambucil	0.66 (0.46;0.94)
	>=10	Bendamustine vs. Chlorambucil	0.75 (0.54;1.05)

Created using SAS (Version 9.4) at 07MAY2024 10:43:20

*Cox PH model

Location of code file: "S:\Statistical Documents\Trials\RIALTO\12. Closed documents\5.17. Final Analysis 2.0\Code\May 2024"

16.1.1 Kaplan Meier Plots – PFS

16.1.1.1 Cumulative Illness Rating Score

Figure 16-1 Kaplan Meier Plot: Progression Free Survival – Cumulative Illness Rating Score (≤ 6 vs. >6)

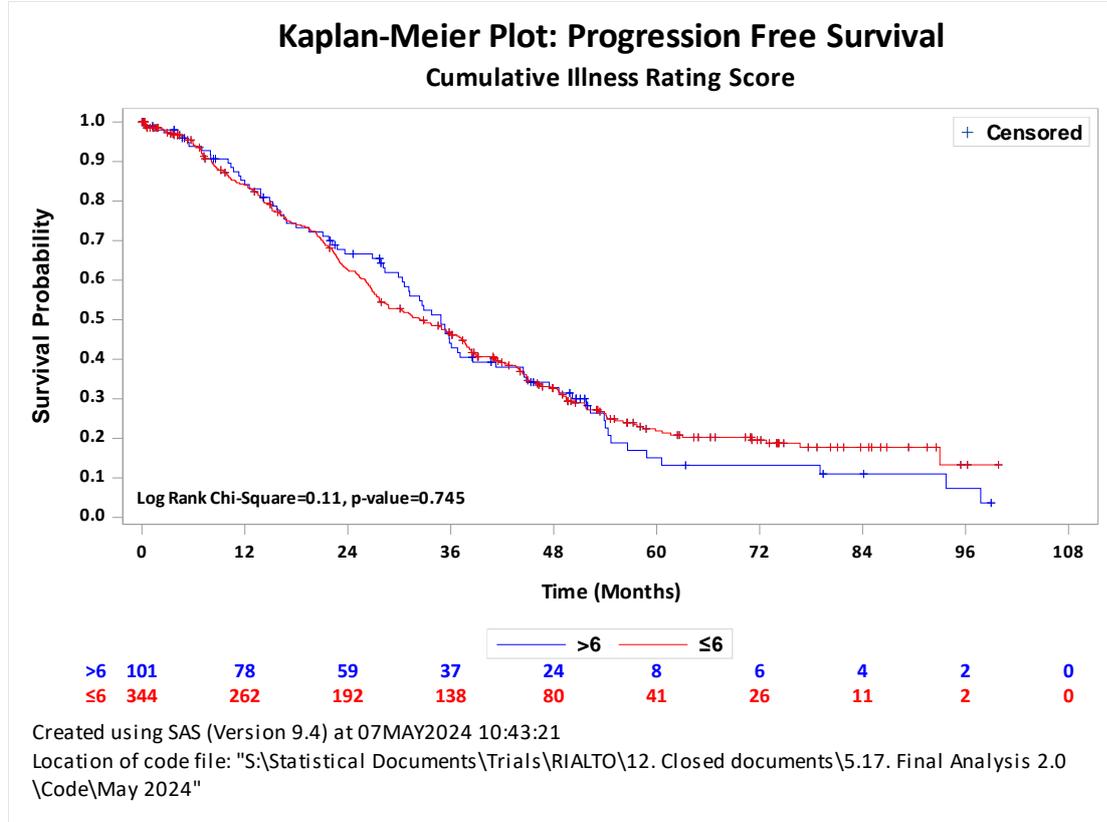


Figure 16-2 Kaplan Meier Plot: Progression Free Survival – Cumulative Illness Rating Score (≤ 6) – Treatment Comparison

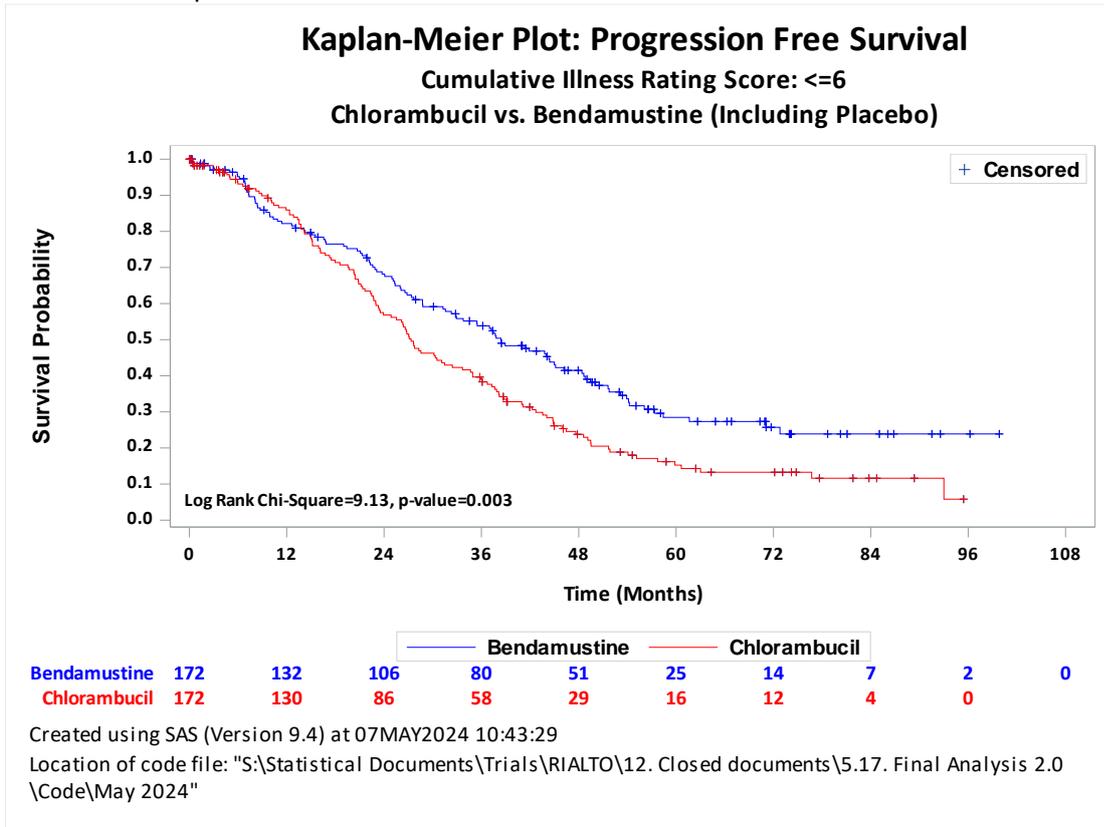
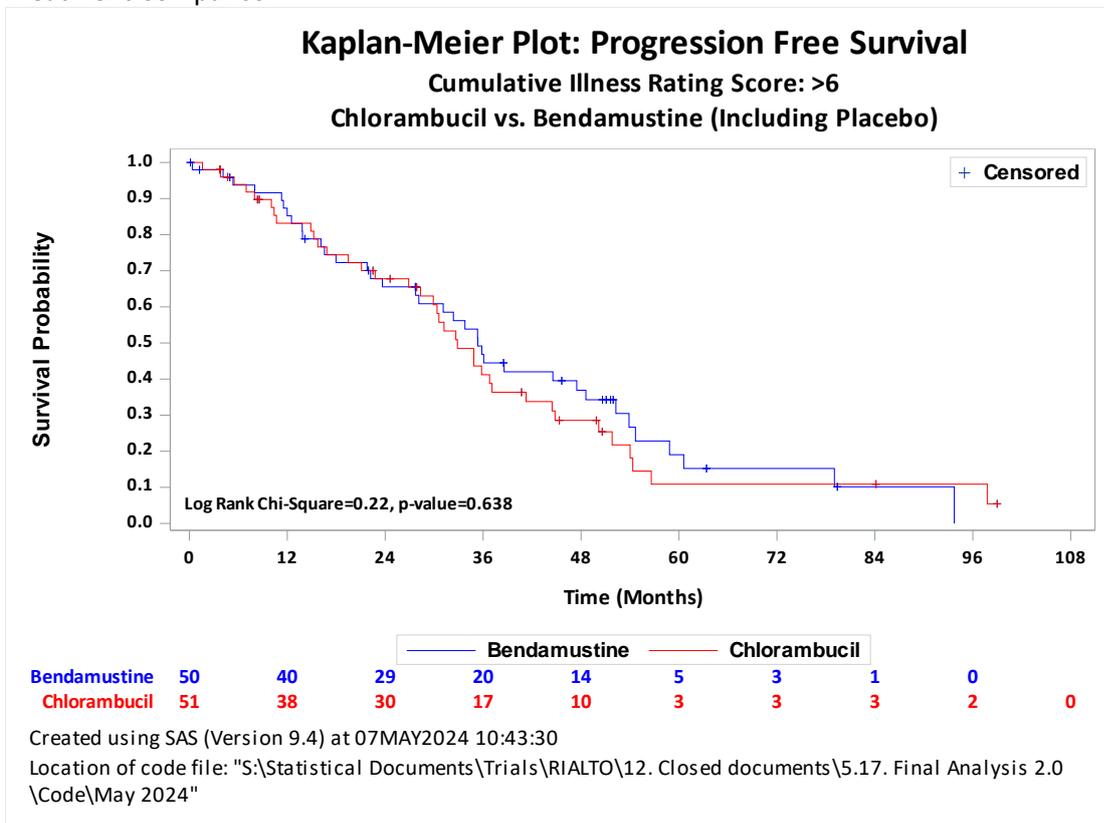


Figure 16-3 Kaplan Meier Plot: Progression Free Survival – Cumulative Illness Rating Score (> 6) – Treatment Comparison



16.1.1.2 Performance Status

Figure 16-4 Kaplan Meier Plot: Progression Free Survival – Performance Status (0 vs. 1 vs. 2 vs. 3)

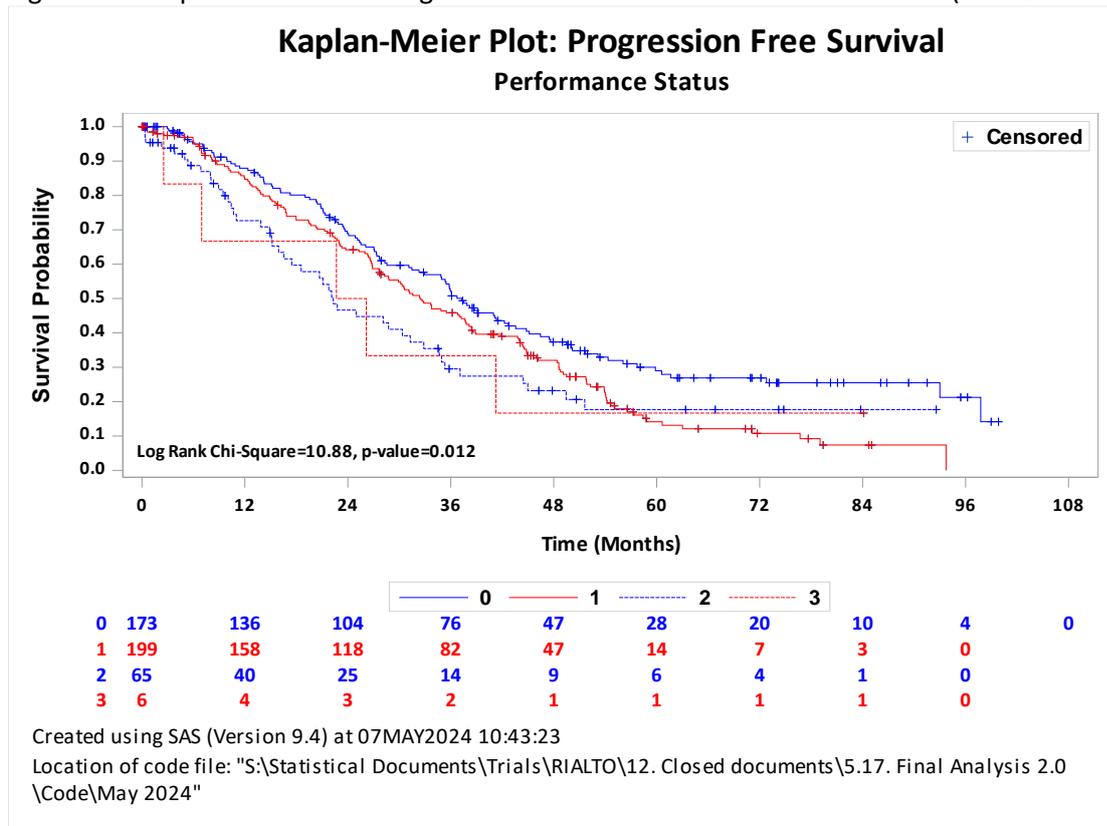


Figure 16-5 Kaplan Meier Plot: Progression Free Survival – Performance Status (0) – Treatment Comparison

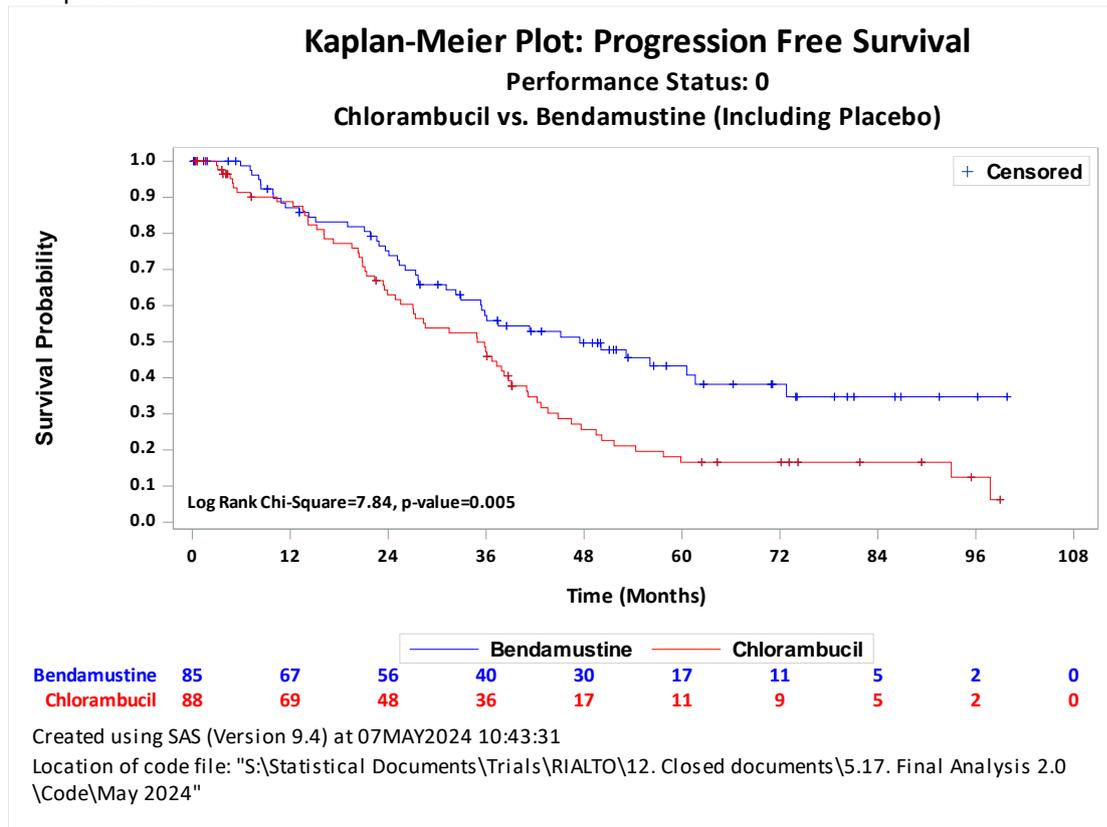


Figure 16-6 Kaplan Meier Plot: Progression Free Survival – Performance Status (1) – Treatment Comparison

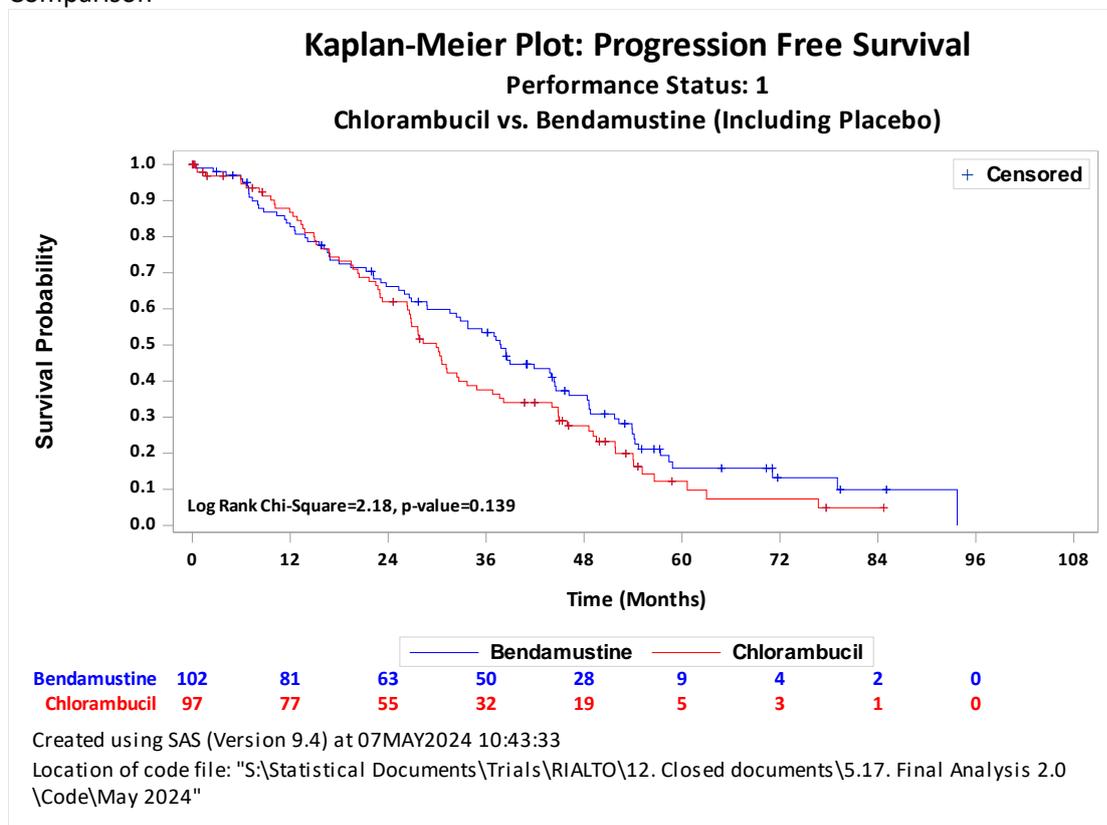


Figure 16-7 Kaplan Meier Plot: Progression Free Survival – Performance Status (2) – Treatment Comparison

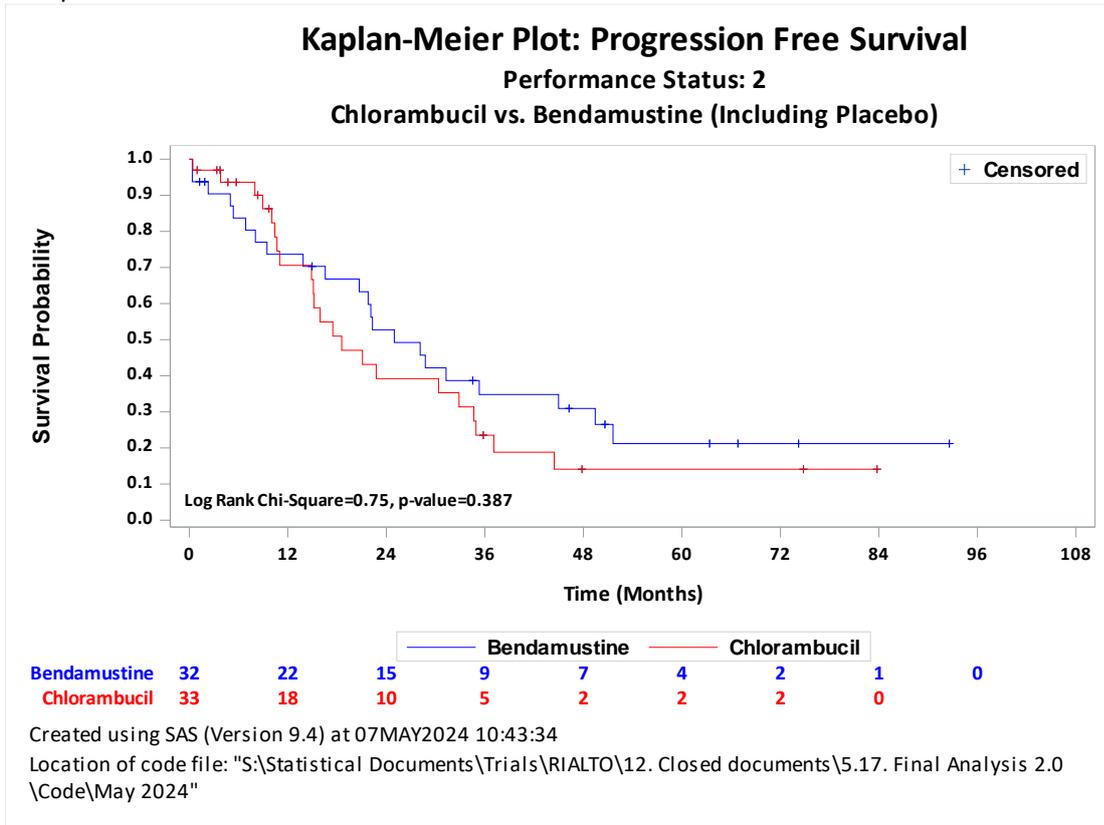
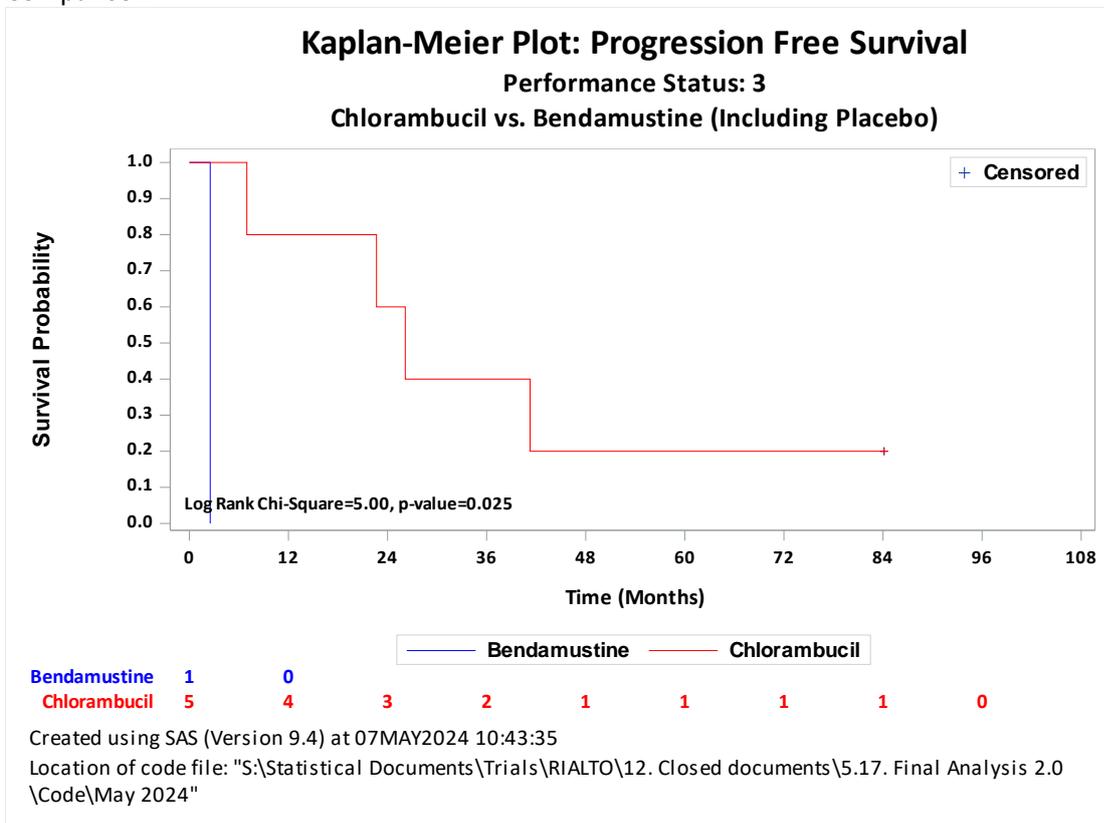


Figure 16-8 Kaplan Meier Plot: Progression Free Survival – Performance Status (3) – Treatment Comparison



16.1.1.3 VES-13

Figure 16-9 Kaplan Meier Plot: Progression Free Survival – VES-13 (<3 vs. ≥3)

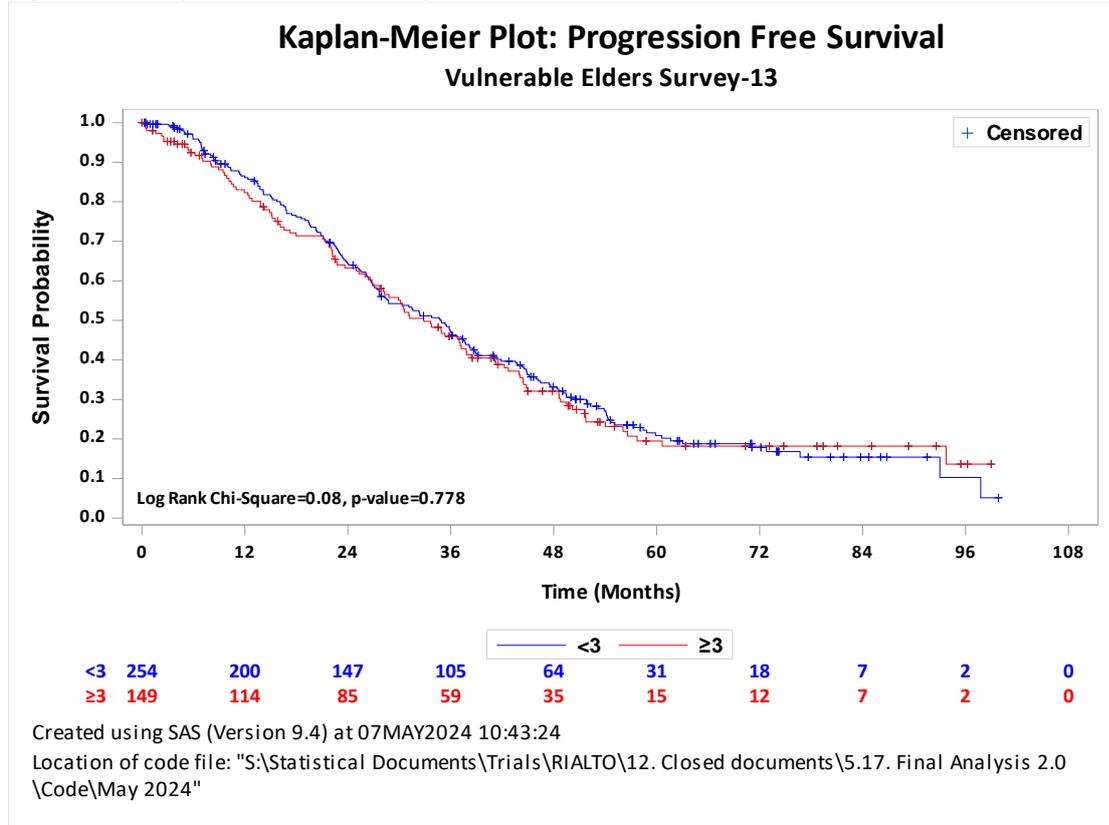


Figure 16-10 Kaplan Meier Plot: Progression Free Survival – VES-13 (<3) – Treatment Comparison

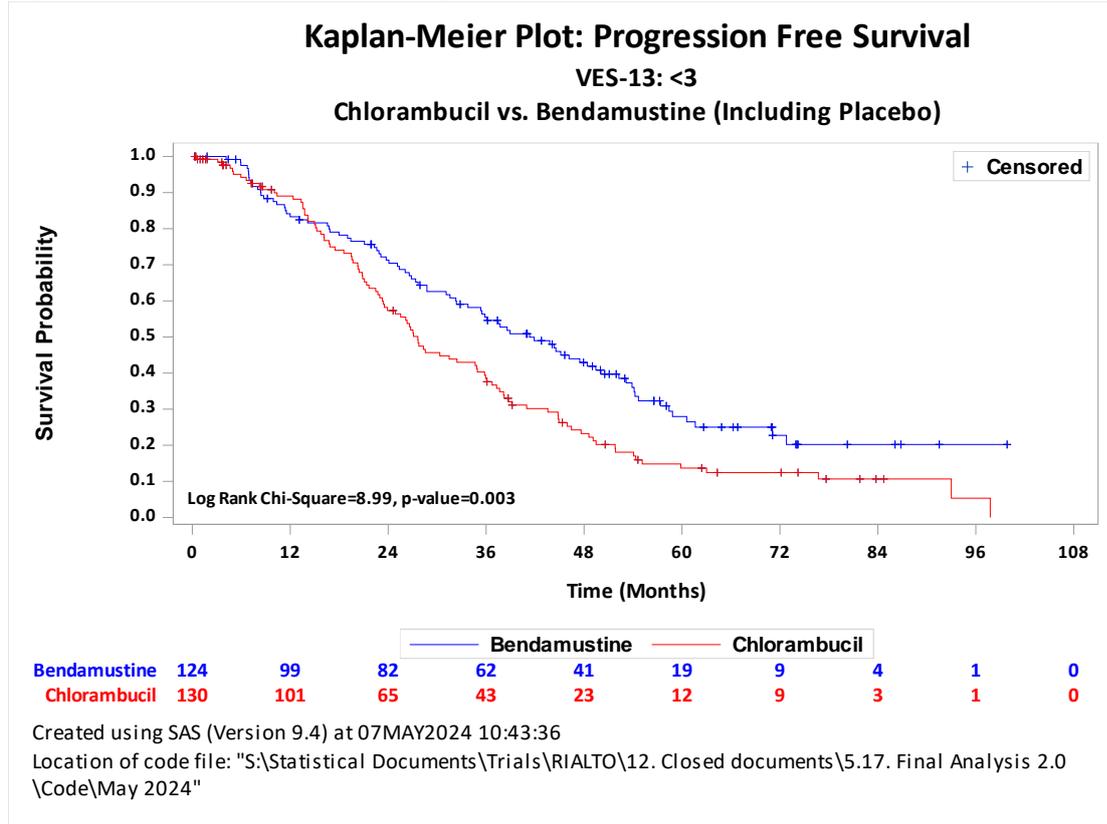
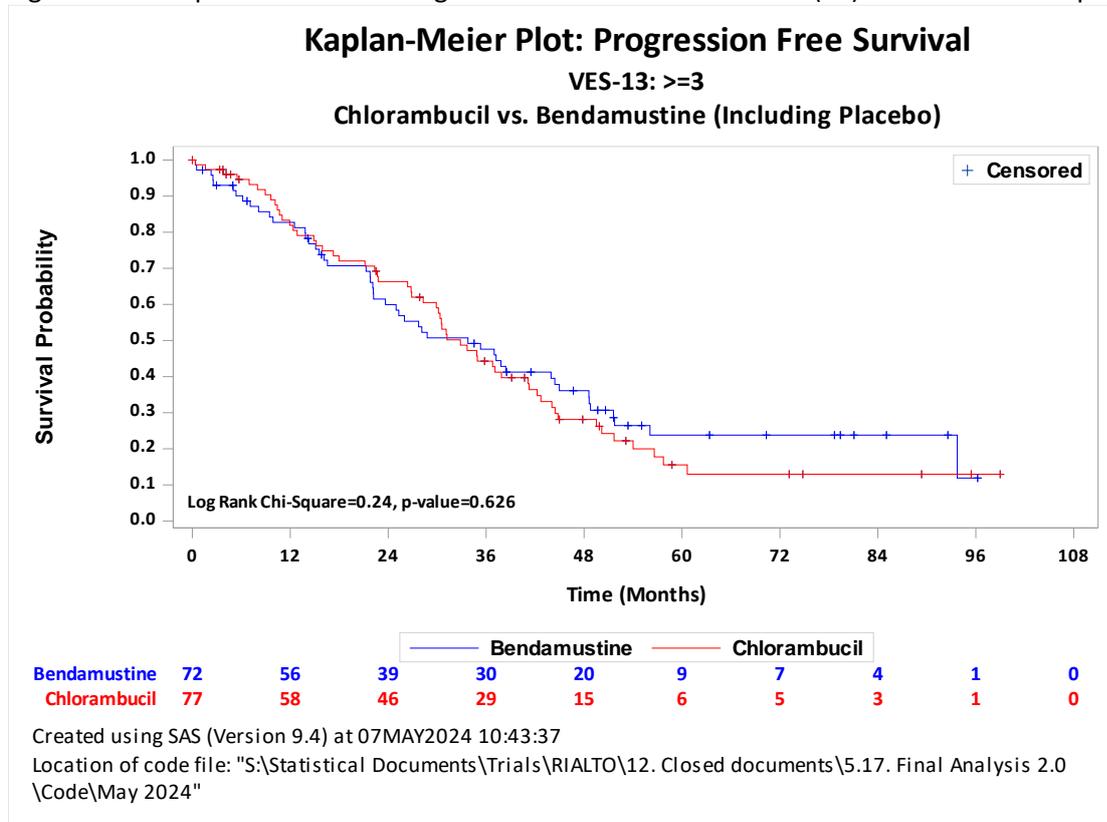


Figure 16-11 Kaplan Meier Plot: Progression Free Survival – VES-13 (≥3) – Treatment Comparison



16.1.1.4 GFI

Figure 16-12 Kaplan Meier Plot: Progression Free Survival – GFI (<4 vs. ≥4)

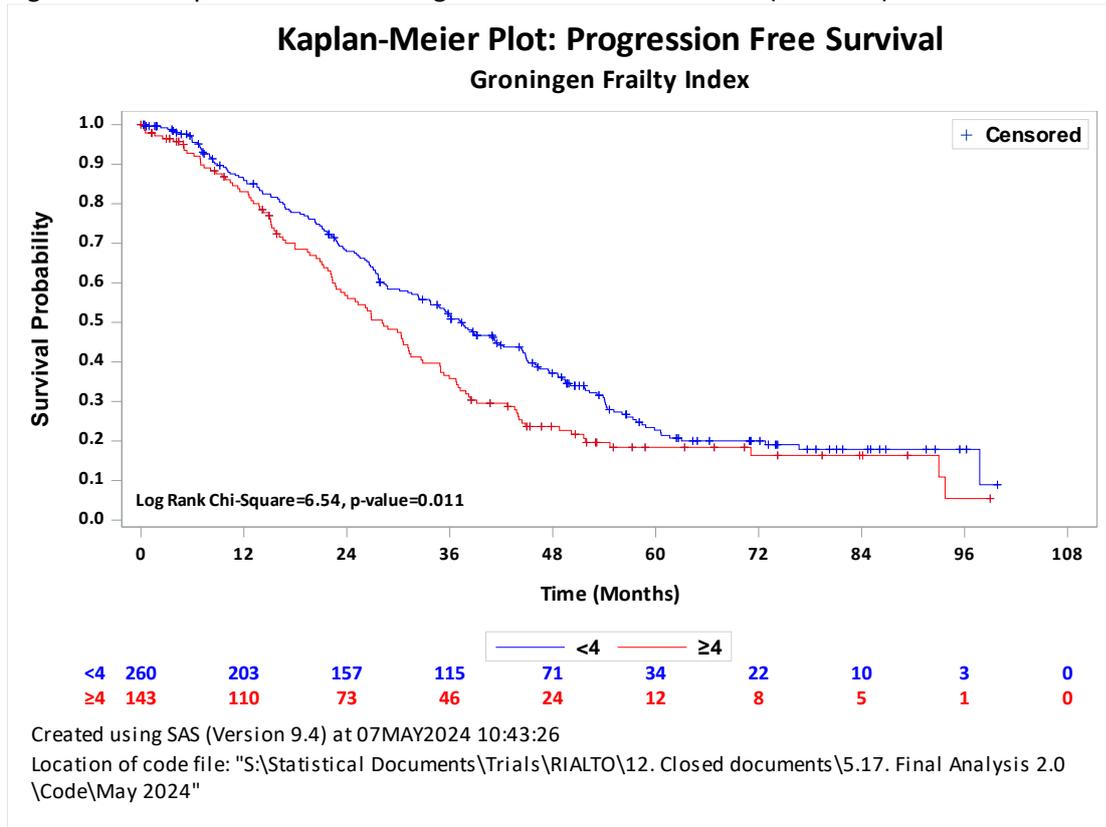


Figure 16-13 Kaplan Meier Plot: Progression Free Survival – GFI (<4) – Treatment Comparison

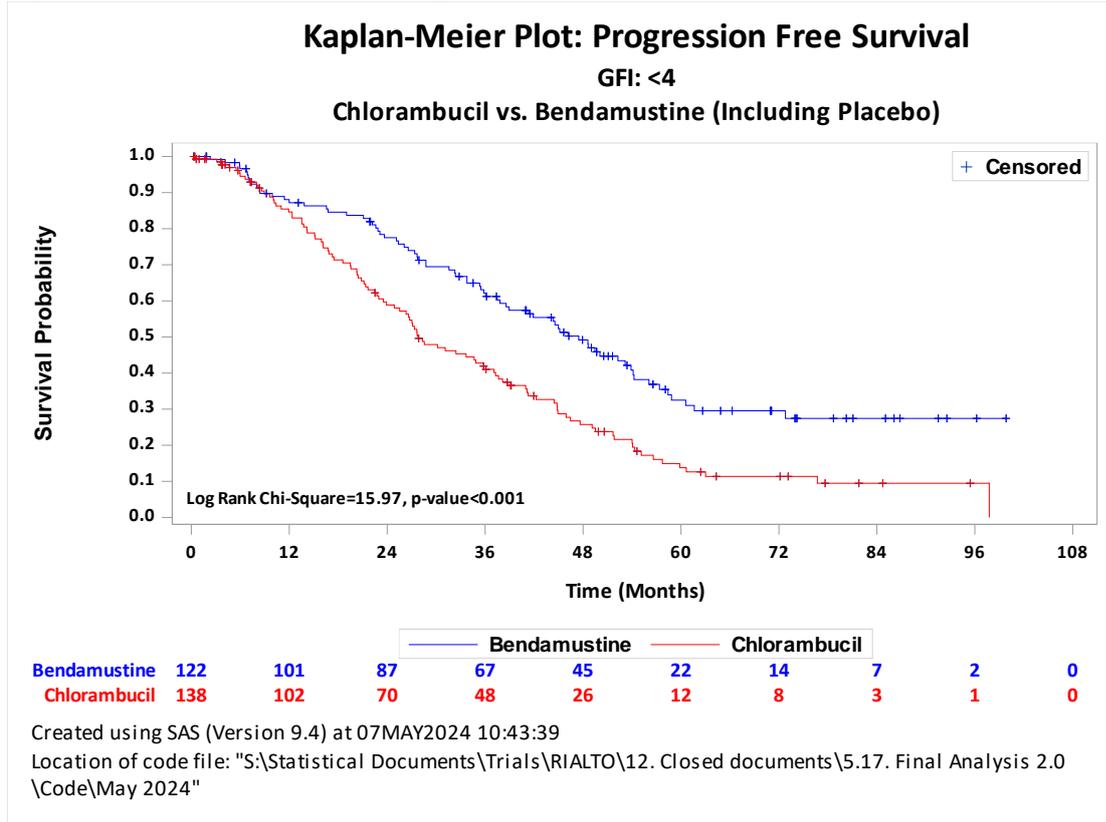
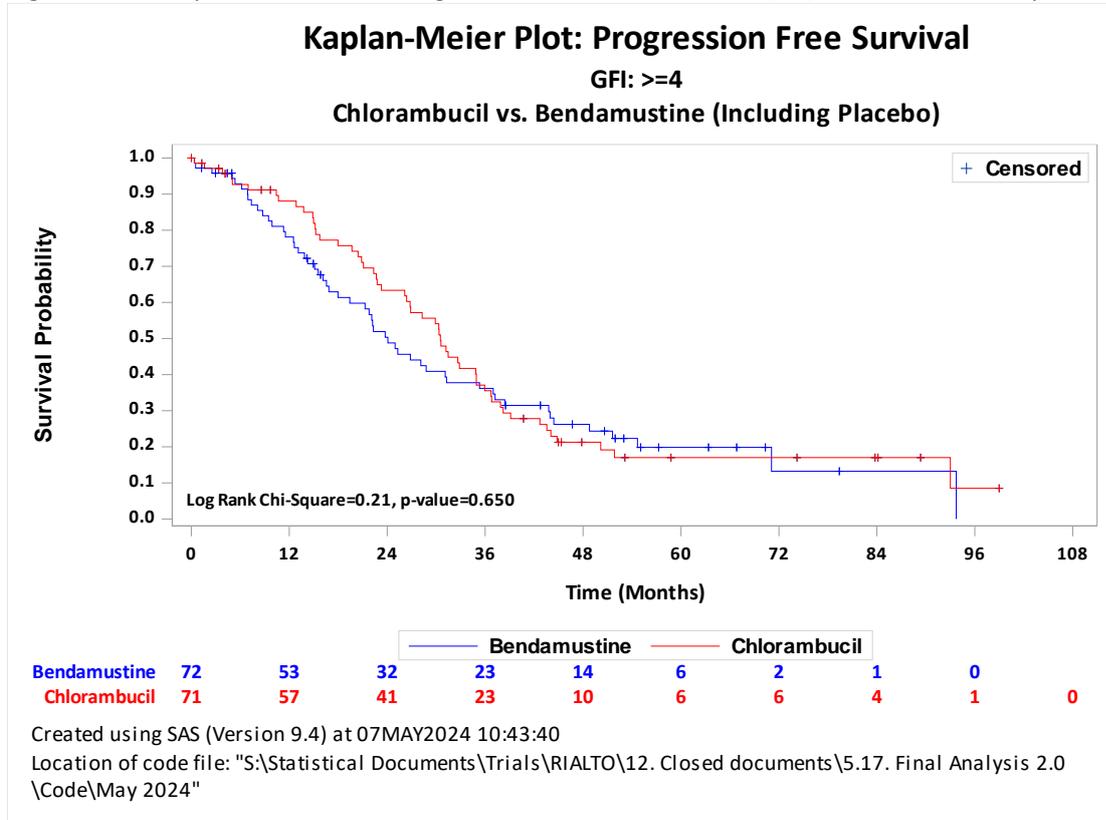


Figure 16-14 Kaplan Meier Plot: Progression Free Survival – GFI (≥4) – Treatment Comparison



16.1.1.5 Timed Up and Go

Figure 16-15 Kaplan Meier Plot: Progression Free Survival – Timed Up and Go (<10 vs. ≥10)

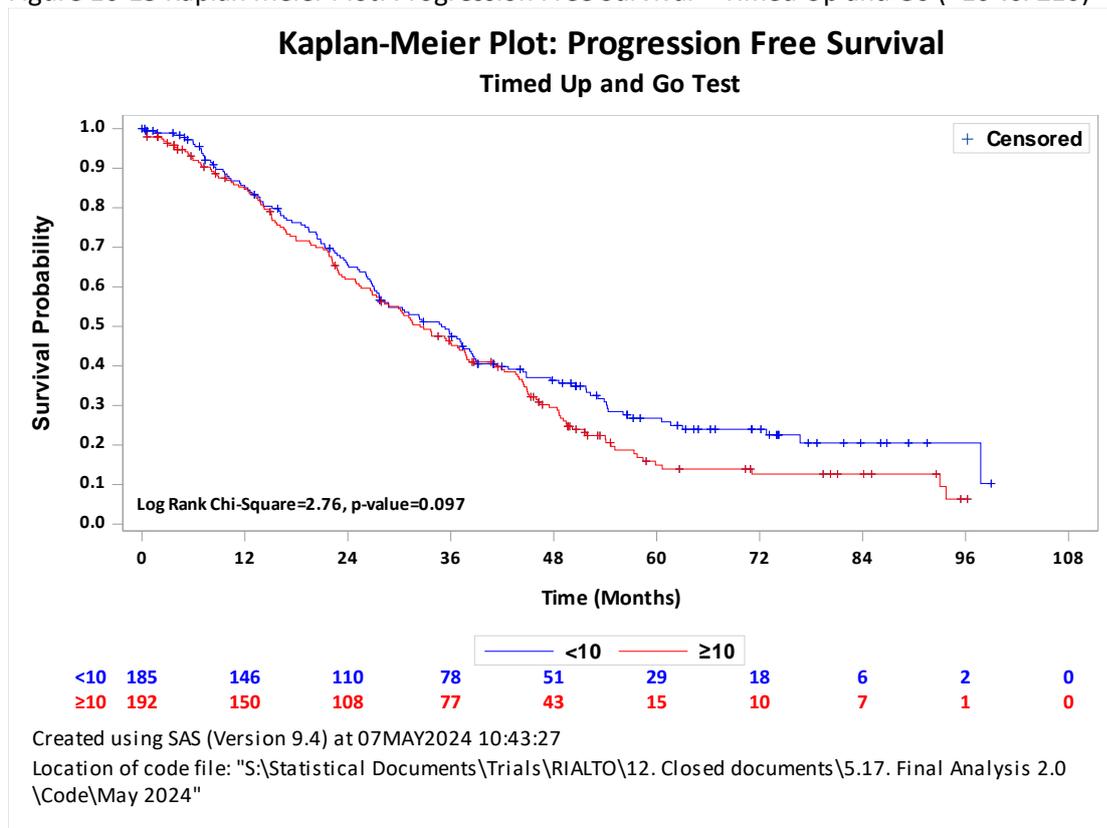


Figure 16-16 Kaplan Meier Plot: Progression Free Survival – Timed Up and Go (<10) – Treatment Comparison

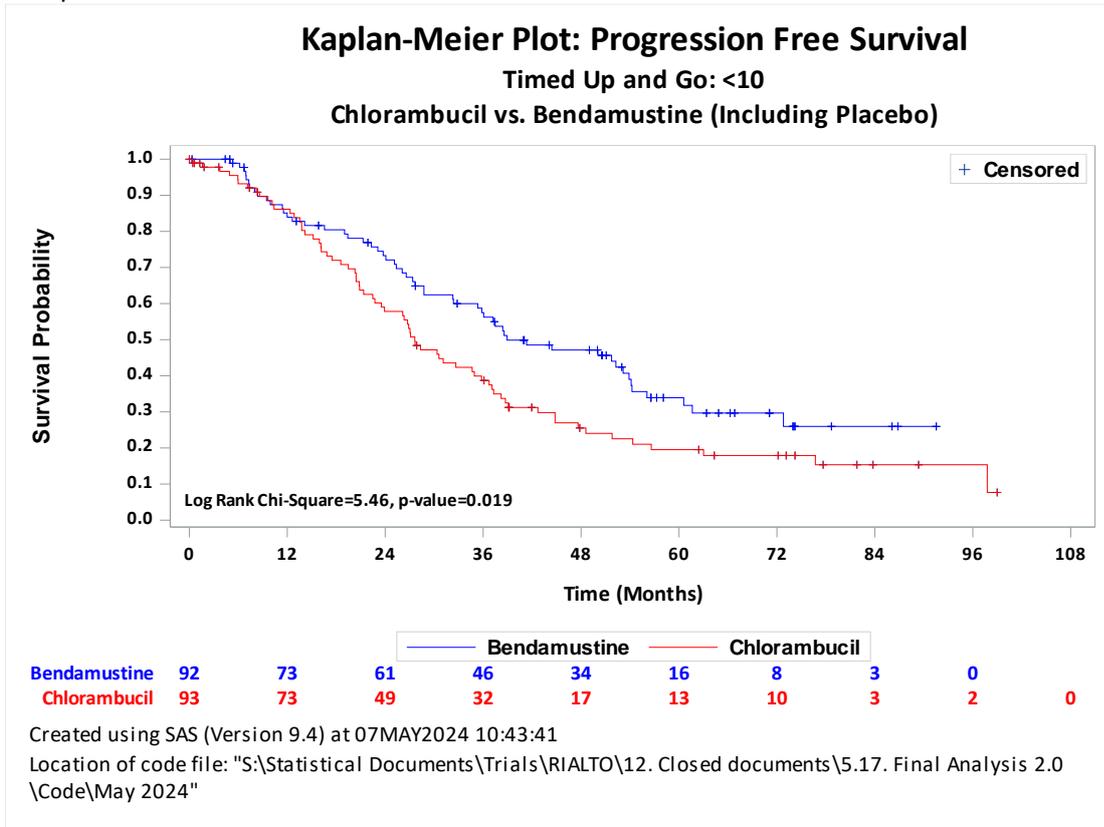
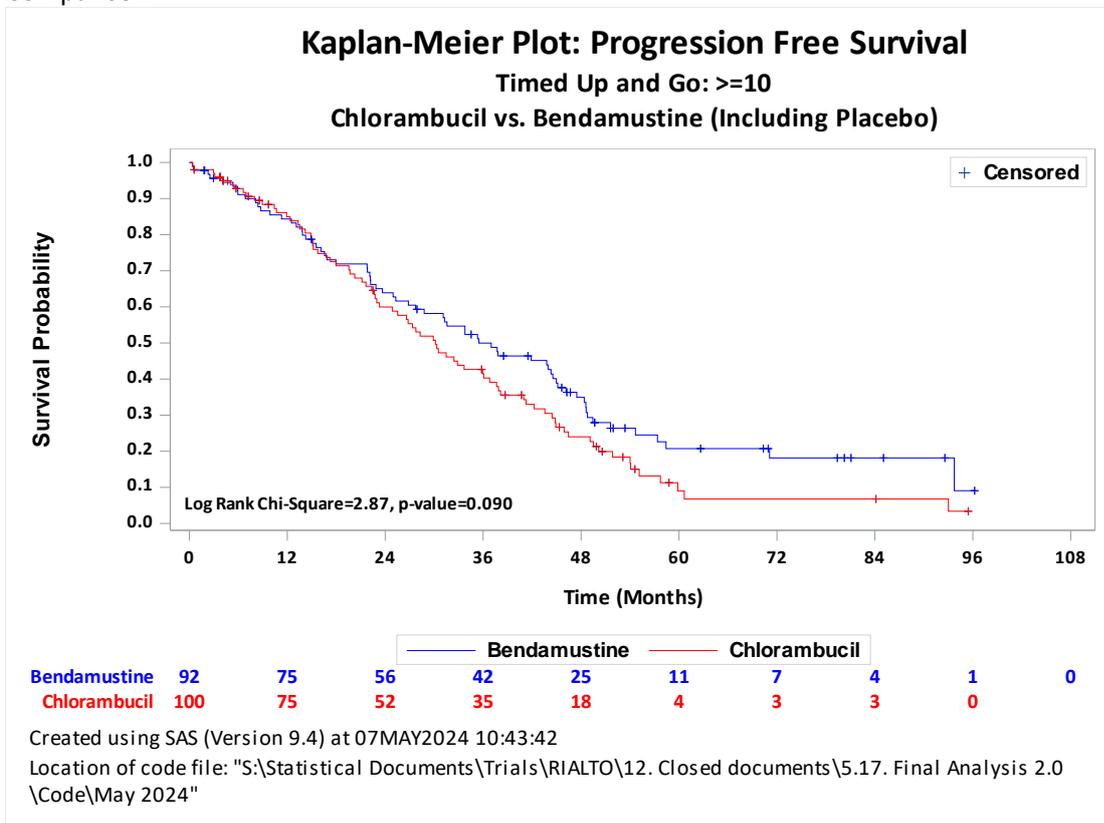


Figure 16-17 Kaplan Meier Plot: Progression Free Survival – Timed Up and Go (≥10) – Treatment Comparison



16.2 Secondary Analysis - Overall Survival

Table 16-3 Frailty and Comorbidity – Overall Survival – Subgroup Comparison

Frailty/Comorbidity	Comparison	Hazard Ratio (95% CI)*
Cumulative Illness Rating Score	≤6 vs. >6	0.62 (0.87;0.44)
Performance Status	0 vs. 1	0.44 (0.30;0.65)
	0 vs. 2	0.22 (0.14;0.35)
	0 vs. 3	0.41 (0.13;1.34)
	1 vs. 2	0.50 (0.34;0.73)
	1 vs. 3	0.93 (0.29;2.94)
	2 vs. 3	1.88 (0.58;6.10)
Vulnerable Elders Survey-13	<3 vs. ≥3	0.63 (0.46;0.87)
Groningen Frailty Index	<4 vs. ≥4	0.53 (0.38;0.73)
Timed Up and Go Test	<10 vs. ≥10	0.72 (0.51;1.00)

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*Cox PH model

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Table 16-4 Frailty and Comorbidity – Overall Survival – Treatment Comparison

Frailty/Comorbidity	Subgroup	Comparison	Hazard Ratio (95% CI)*
Cumulative Illness Rating Score	≤6	Bendamustine vs. Chlorambucil	0.92 (0.64;1.34)
	>6	Bendamustine vs. Chlorambucil	1.34 (0.75;2.40)
Performance Status	0	Bendamustine vs. Chlorambucil	0.82 (0.43;1.58)
	1	Bendamustine vs. Chlorambucil	1.20 (0.78;1.86)
	2	Bendamustine vs. Chlorambucil	0.71 (0.37;1.36)
	3	Bendamustine vs. Chlorambucil	NA (NA;NA)
VES-13	<3	Bendamustine vs. Chlorambucil	0.98 (0.63;1.51)
	≥3	Bendamustine vs. Chlorambucil	1.11 (0.69;1.79)
GFI	<4	Bendamustine vs. Chlorambucil	0.82 (0.53;1.27)
	≥4	Bendamustine vs. Chlorambucil	1.34 (0.83;2.17)
Timed Up and Go	<10	Bendamustine vs. Chlorambucil	1.00 (0.60;1.67)
	≥10	Bendamustine vs. Chlorambucil	1.26 (0.81;1.95)

*Cox PH model

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16.2.1 Kaplan Meier Plots – Overall Survival

16.2.1.1 Cumulative Illness Rating Score

Figure 16-18 Kaplan Meier Plot: Overall Survival – Cumulative Illness Rating Score (≤ 6 vs. >6)

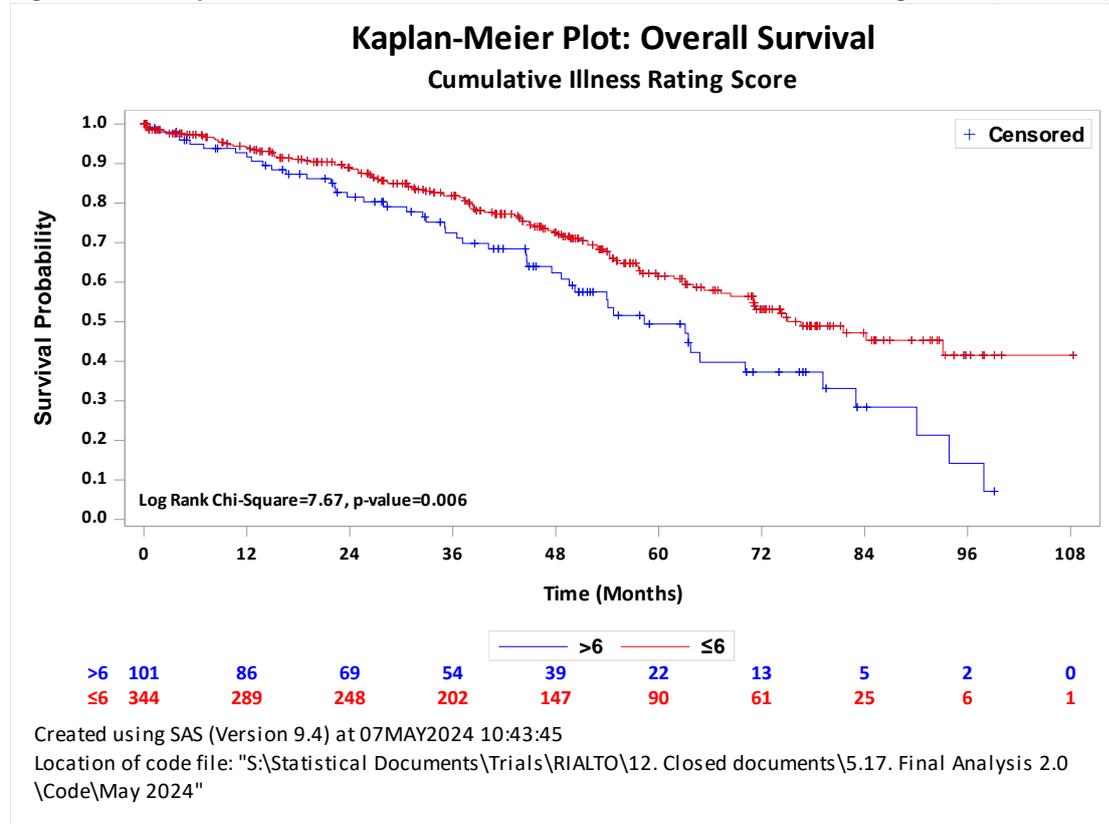


Figure 16-19 Kaplan Meier Plot: Overall Survival – Cumulative Illness Rating Score (≤6) – Treatment Comparison

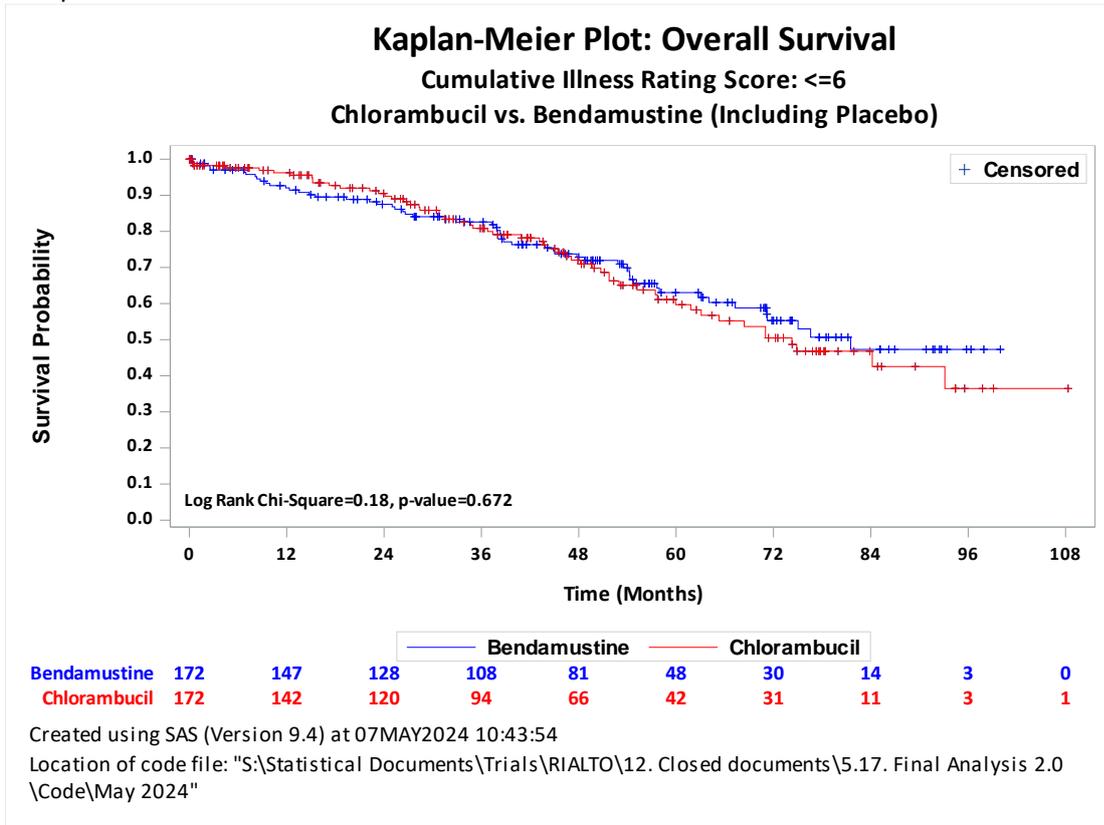
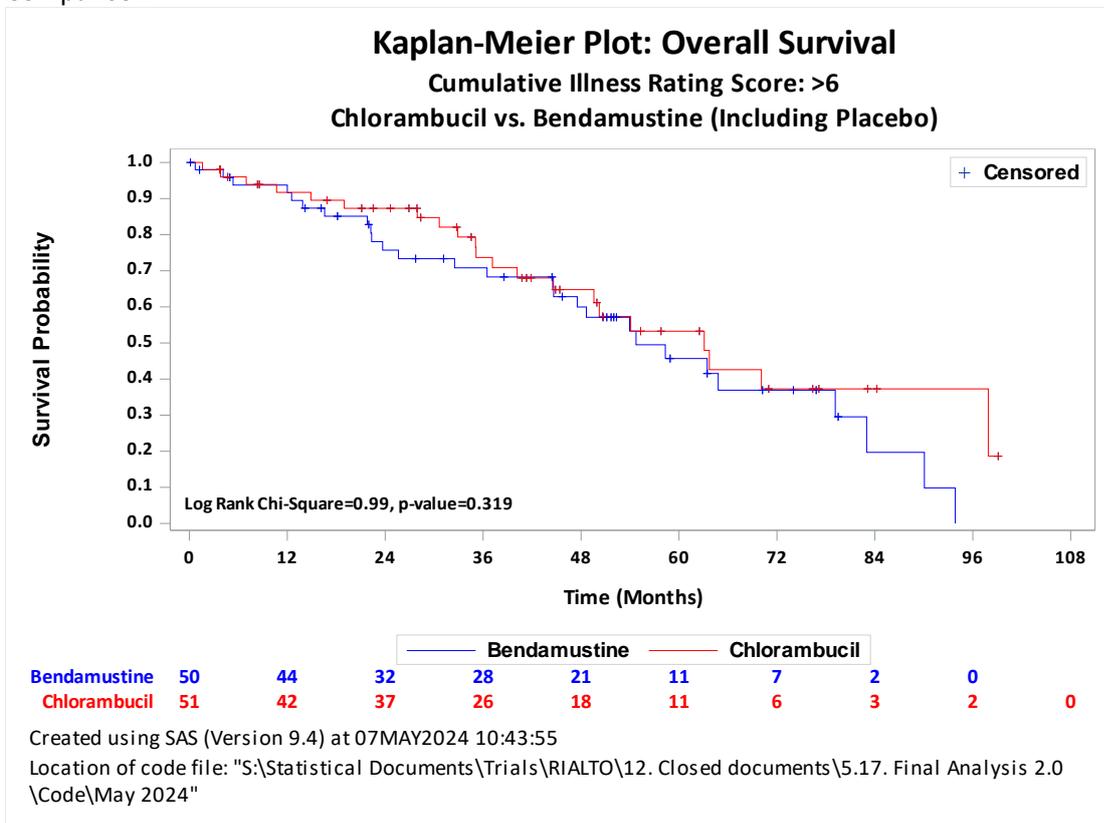


Figure 16-20 Kaplan Meier Plot: Overall Survival – Cumulative Illness Rating Score (>6) – Treatment Comparison



16.2.1.2 Performance Status

Figure 16-21 Kaplan Meier Plot: Overall Survival – Performance Status (0 vs. 1 vs. 2 vs. 3)

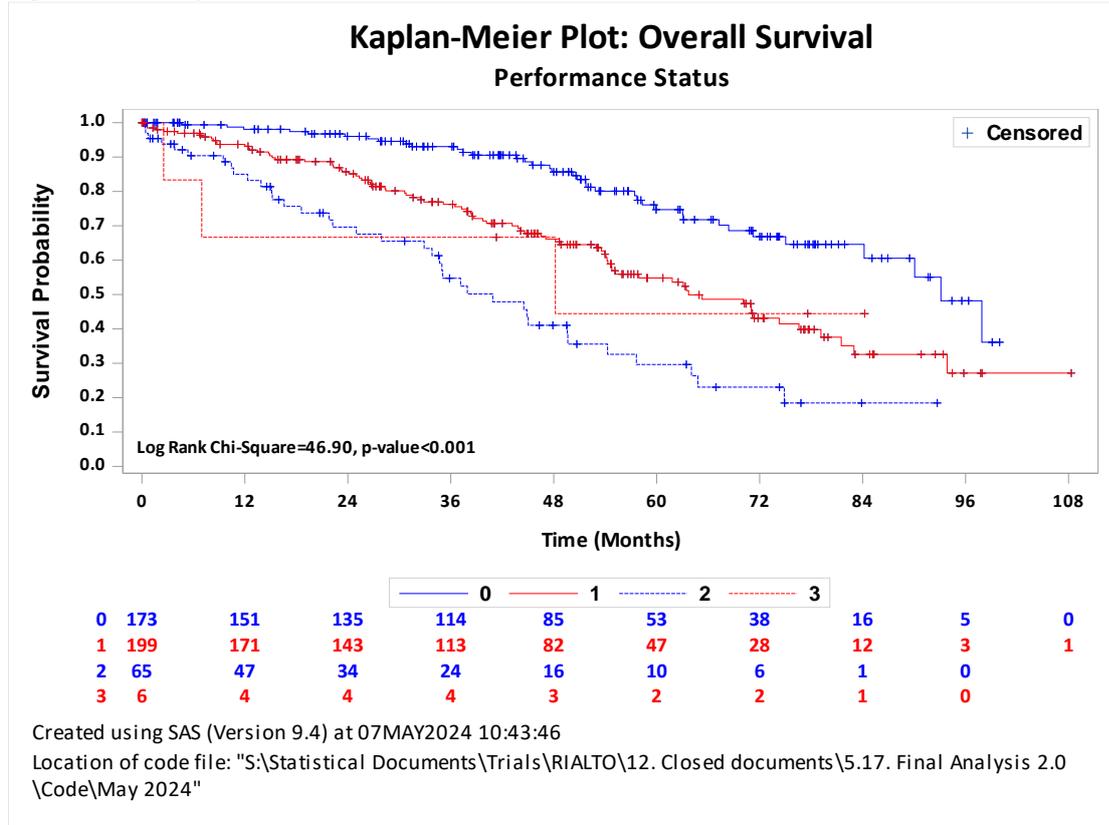


Figure 16-22 Kaplan Meier Plot: Overall Survival – Performance Status (0) – Treatment Comparison

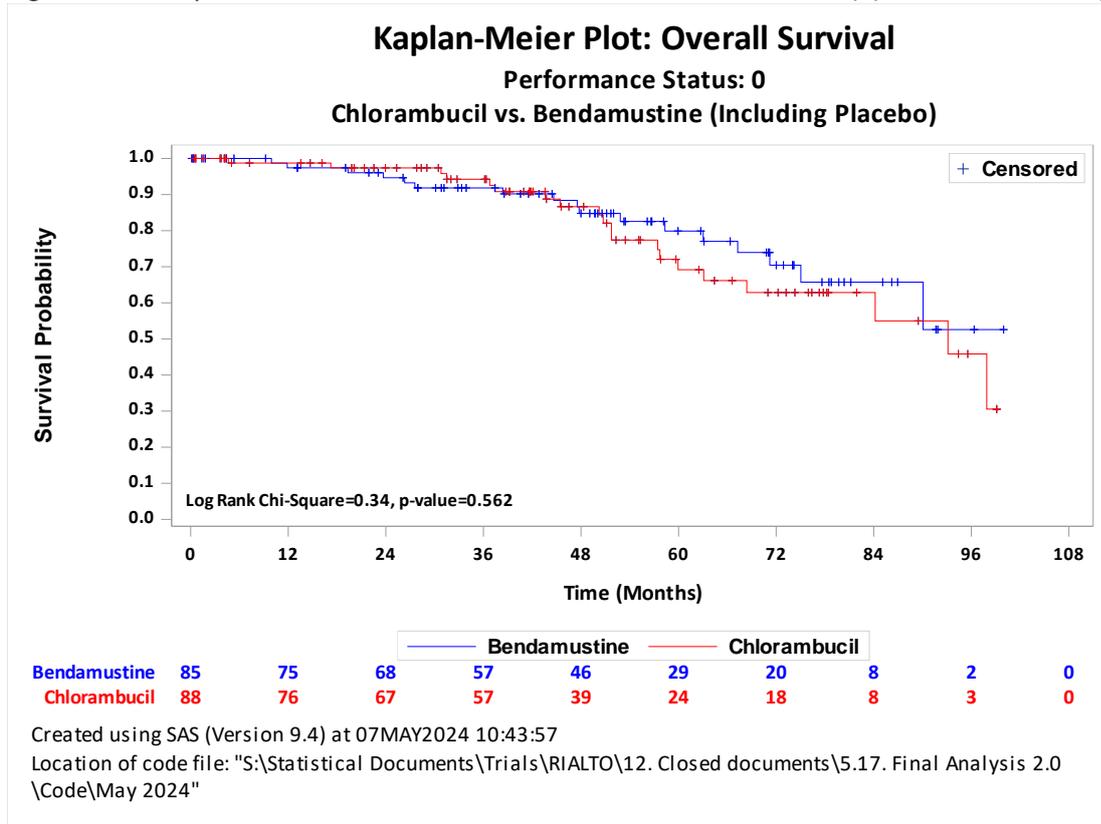


Figure 16-23 Kaplan Meier Plot: Overall Survival – Performance Status (1) – Treatment Comparison

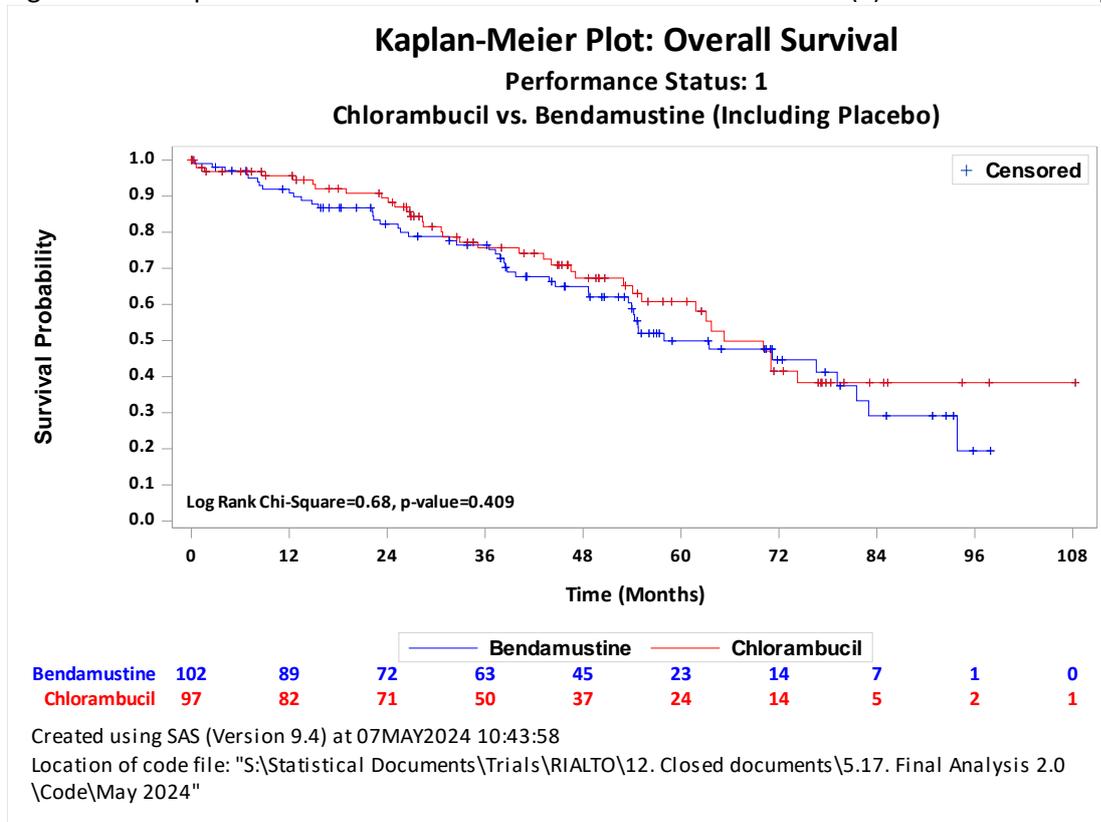


Figure 16-24 Kaplan Meier Plot: Overall Survival – Performance Status (2) – Treatment Comparison

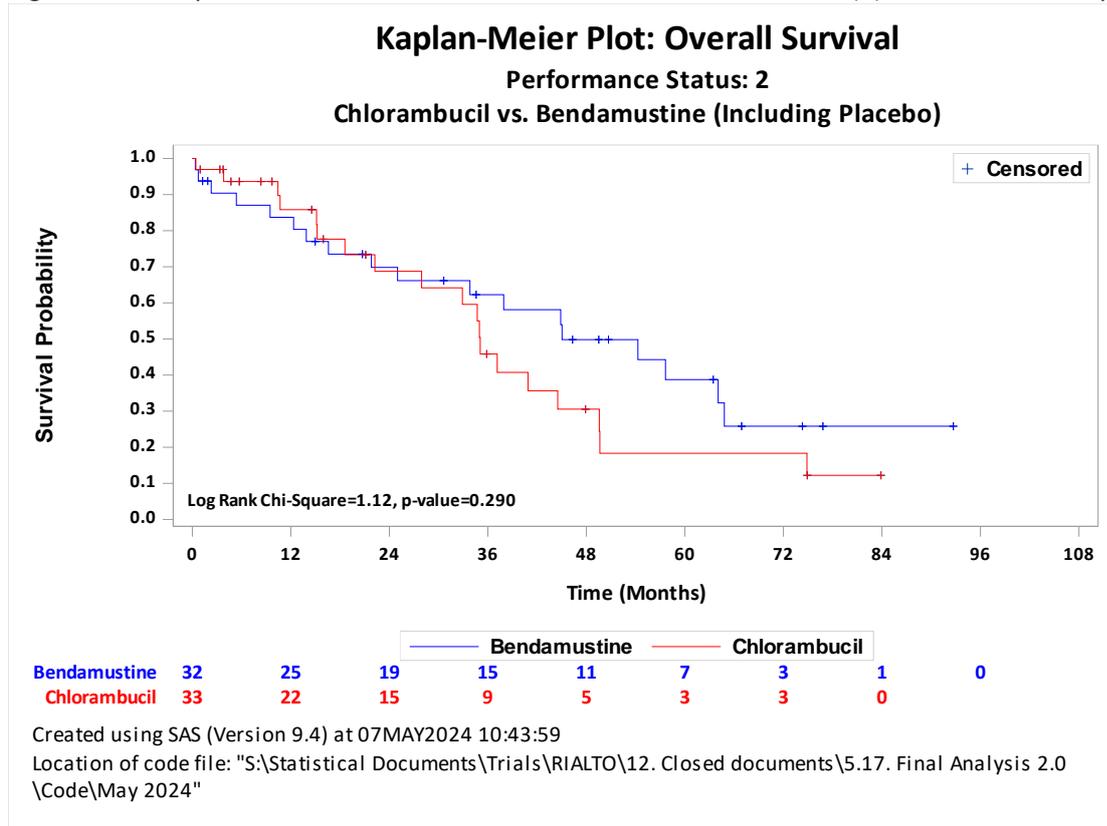
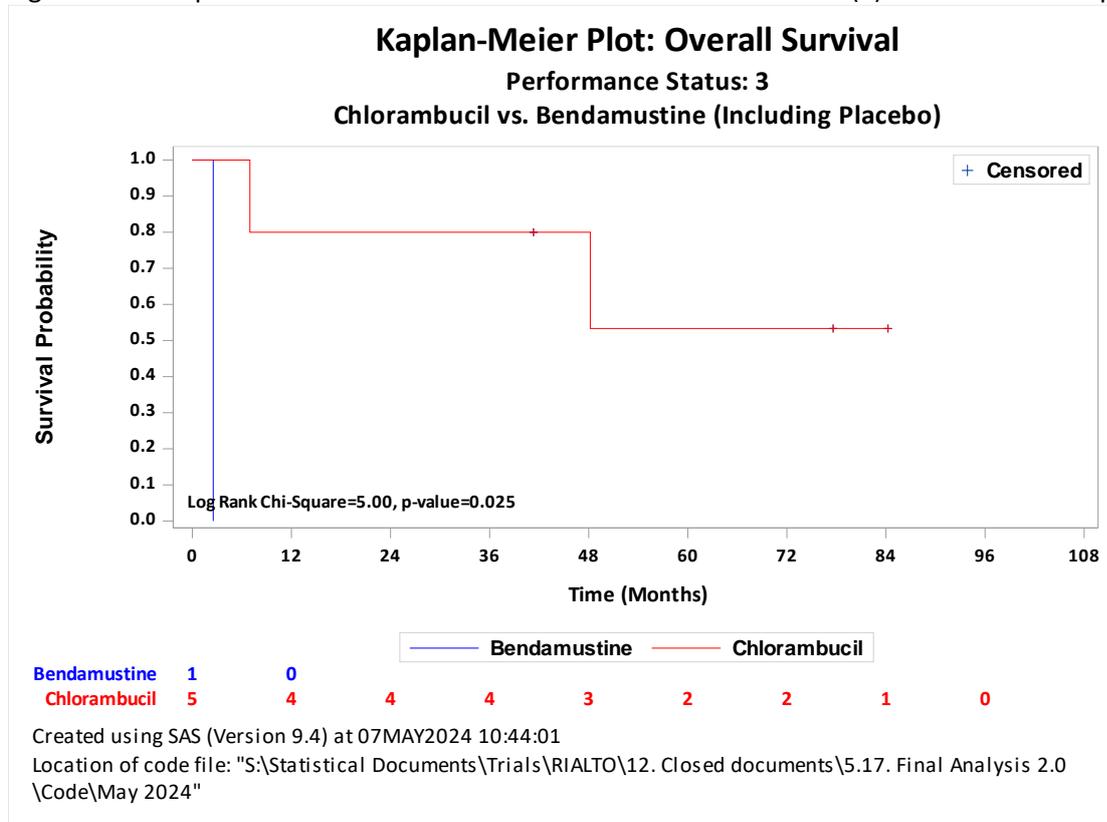


Figure 16-25 Kaplan Meier Plot: Overall Survival – Performance Status (3) – Treatment Comparison



16.2.1.3 VES-13

Figure 16-26 Kaplan Meier Plot: Overall Survival – VES-13 (<3 vs. ≥3)

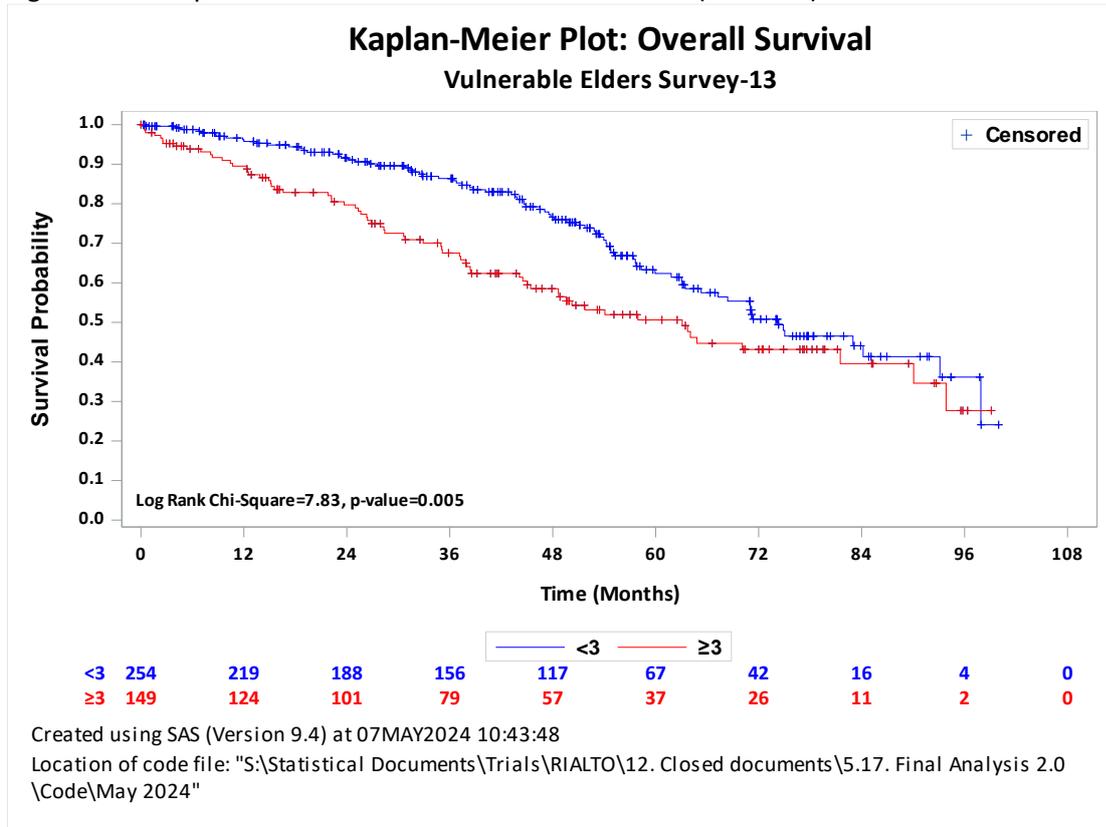


Figure 16-27 Kaplan Meier Plot: Overall Survival – VES-13 (<3) – Treatment Comparison

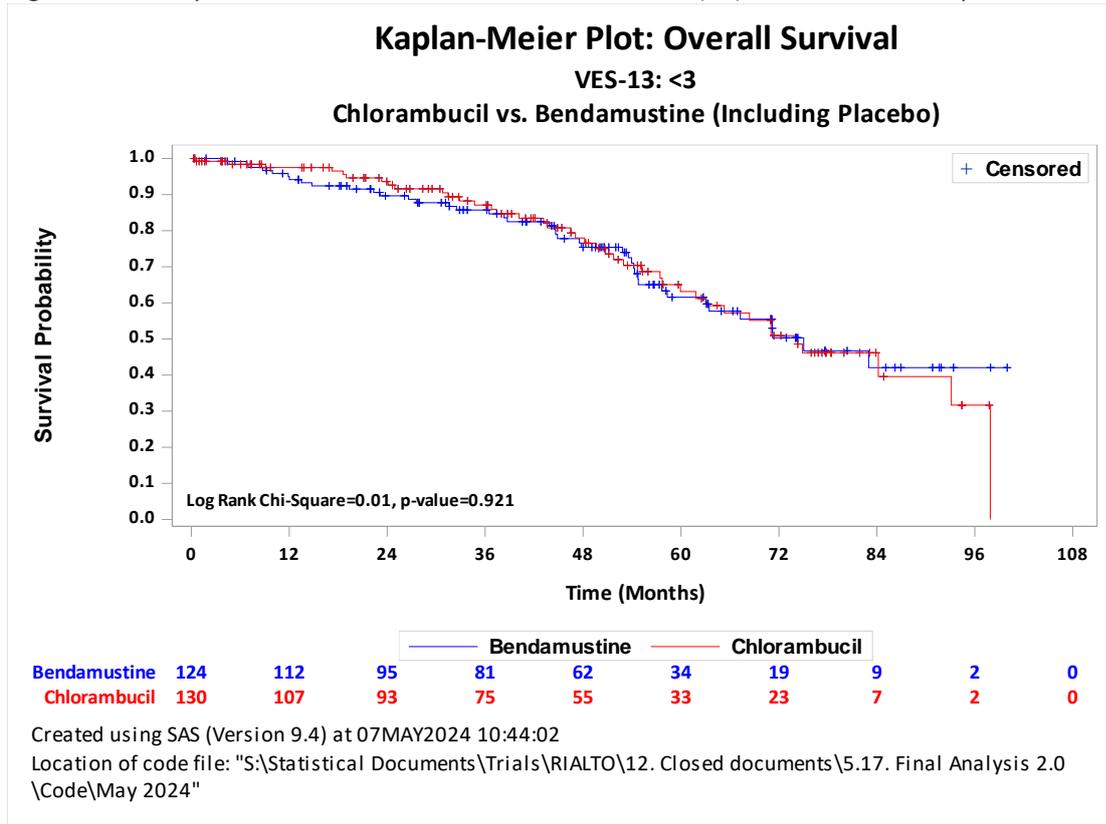
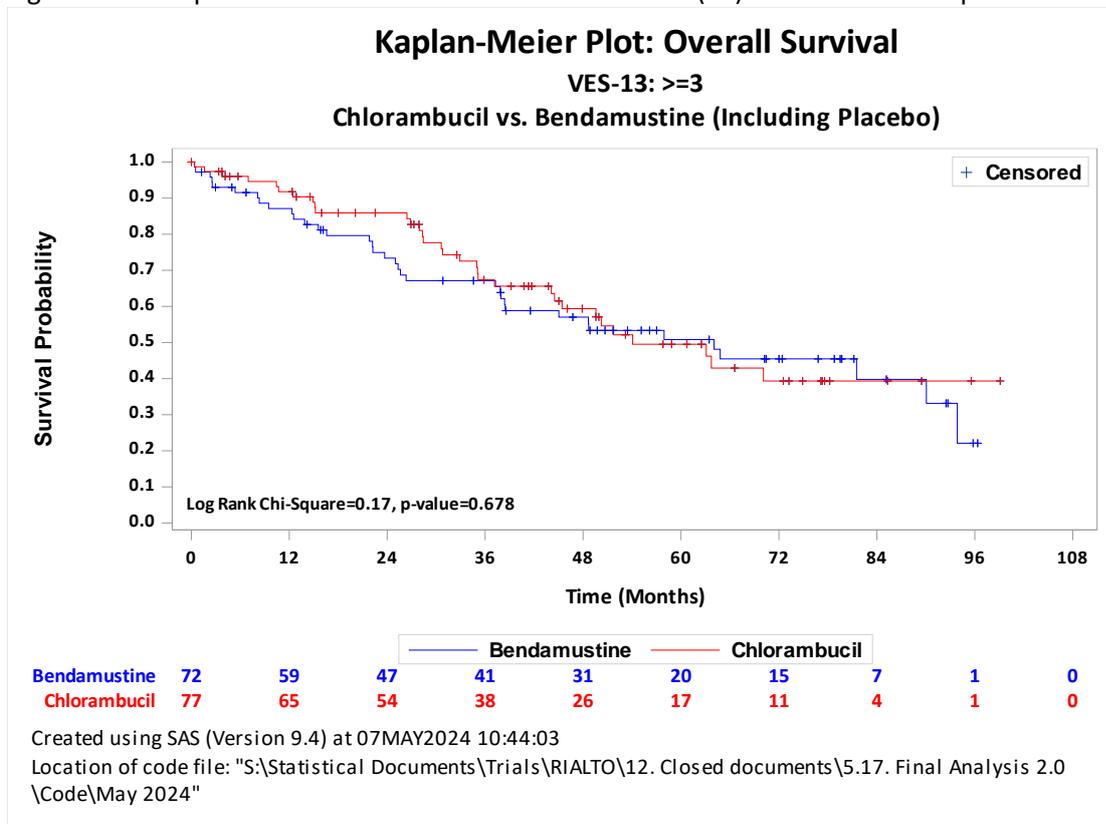


Figure 16-28 Kaplan Meier Plot: Overall Survival – VES-13 (≥3) – Treatment Comparison



16.2.1.4 GFI

Figure 16-29 Kaplan Meier Plot: Overall Survival – GFI (<4 vs. ≥4)

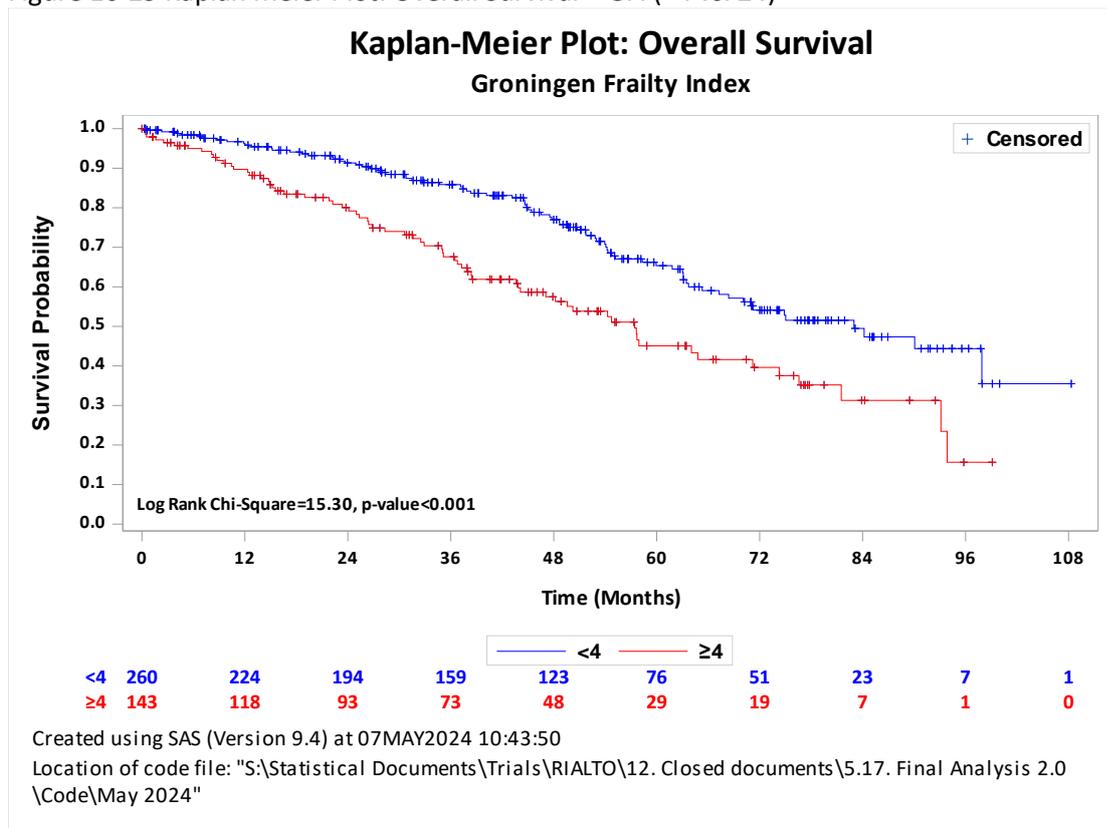


Figure 16-30 Kaplan Meier Plot: Overall Survival – GFI (<4) – Treatment Comparison

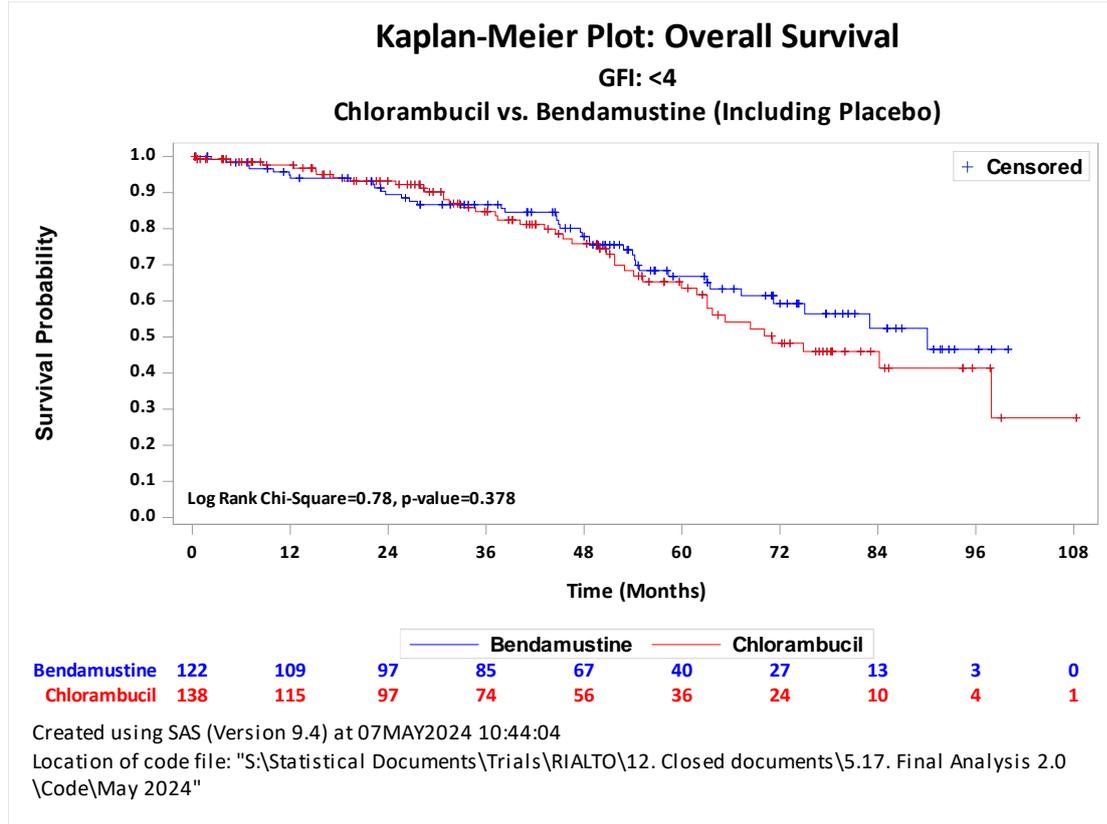
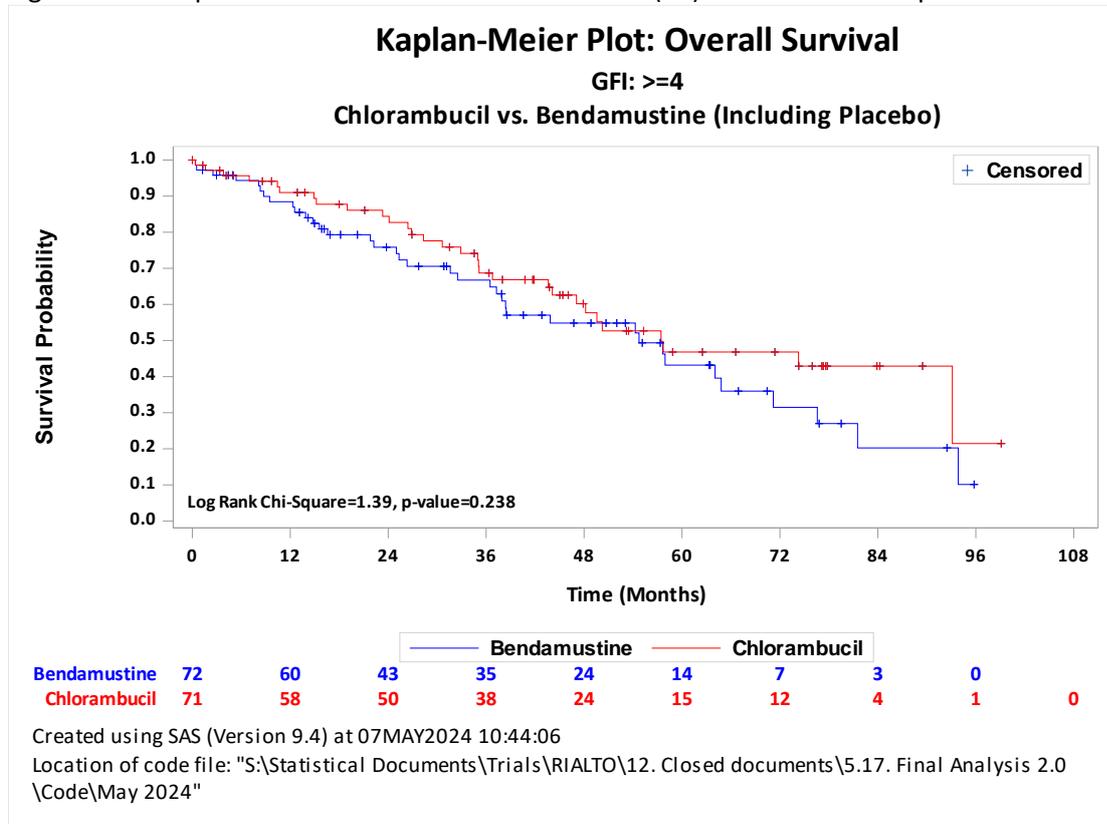


Figure 16-31 Kaplan Meier Plot: Overall Survival – GFI (≥4) – Treatment Comparison



16.2.1.5 Timed Up and Go

Figure 16-32 Kaplan Meier Plot: Overall Survival – Timed Up and Go (<10 vs. ≥10)

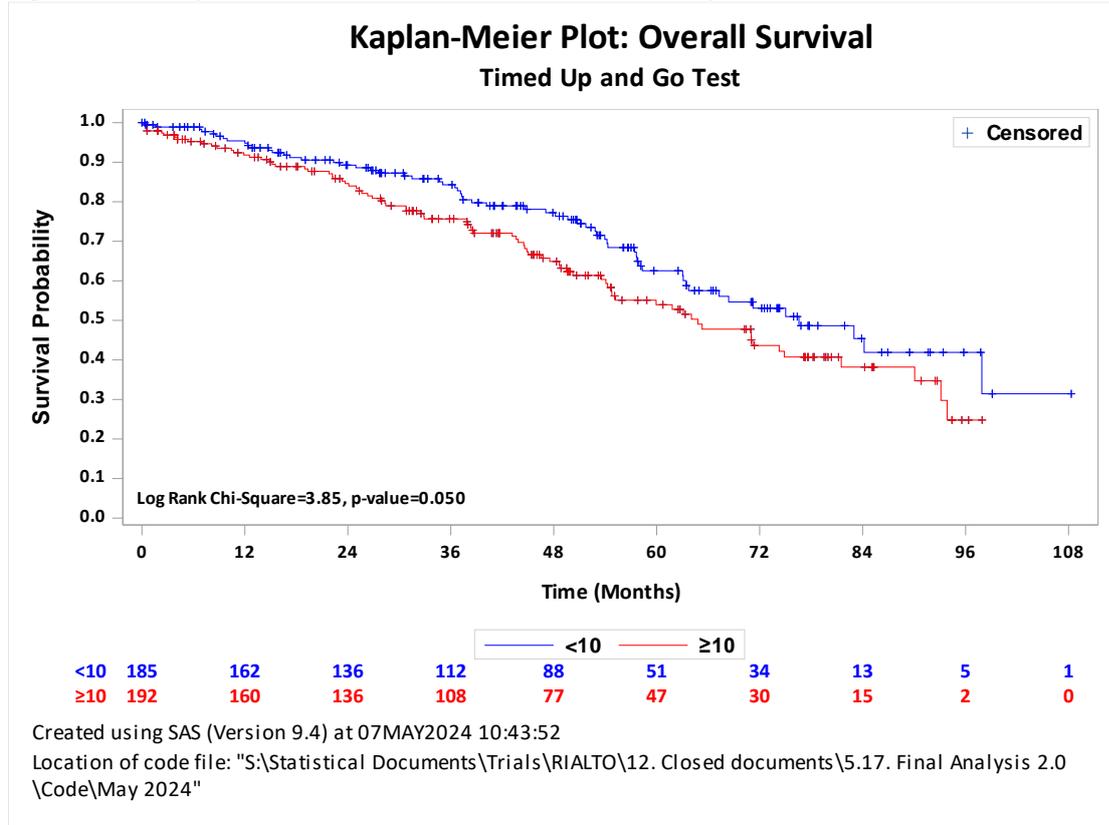


Figure 16-33 Kaplan Meier Plot: Overall Survival – Timed Up and Go (<10) – Treatment Comparison

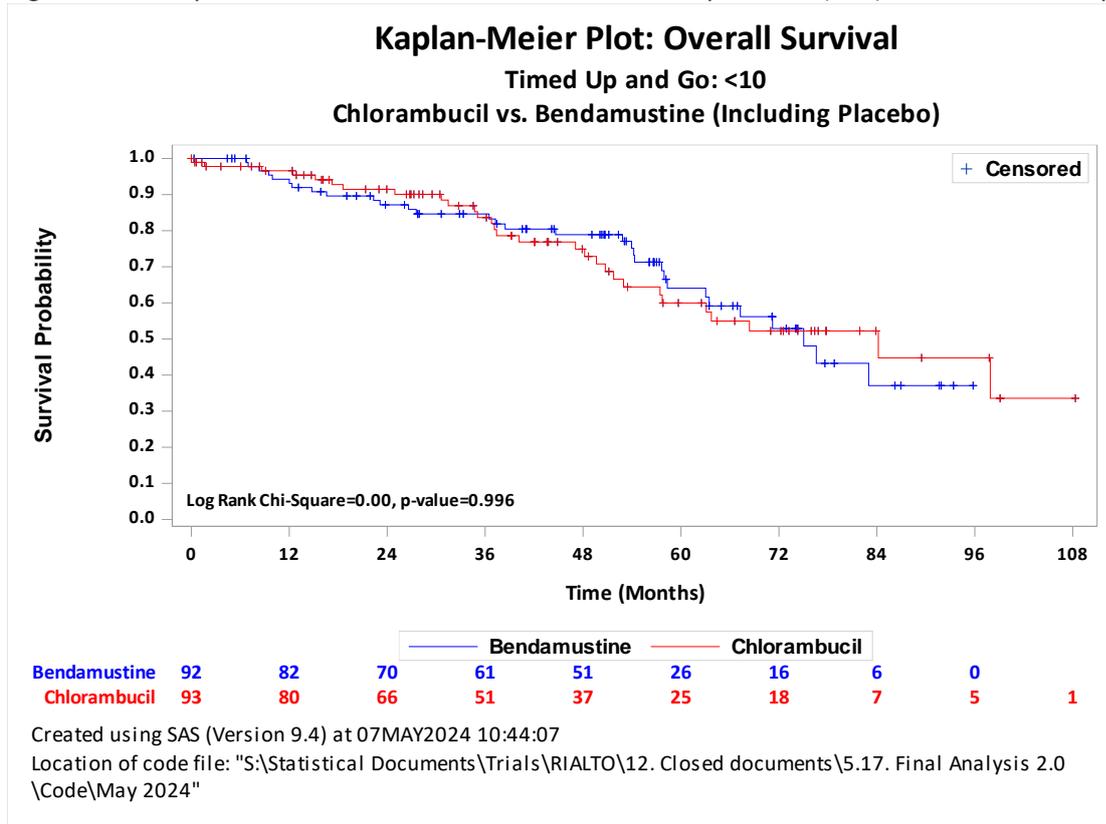
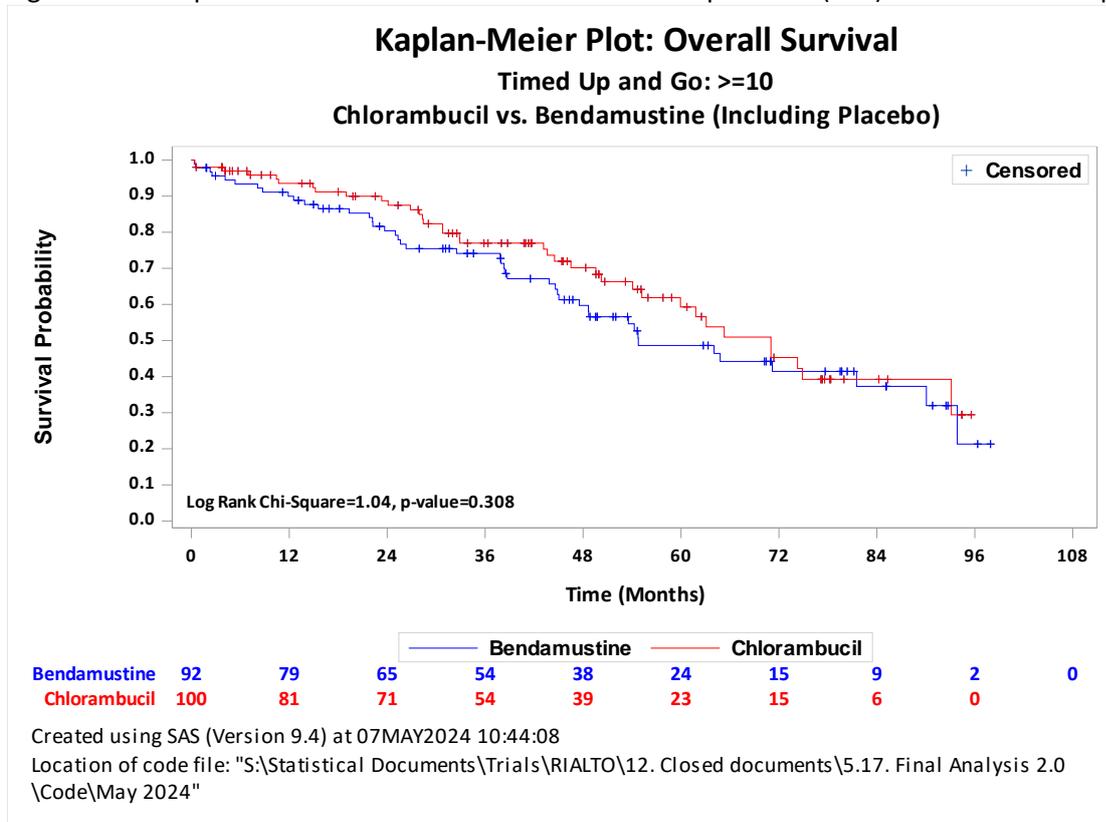


Figure 16-34 Kaplan Meier Plot: Overall Survival – Timed Up and Go (≥10) – Treatment Comparison



16.3 Time to Treatment Failure

Table 16-1 Frailty and Comorbidity – Time to Treatment Failure – Treatment Comparison

Frailty/Comorbidity	Comparison	Hazard Ratio (95% CI)*
Cumulative Illness Rating Score	≤6 vs. >6	0.92 (1.20;0.71)
Performance Status	0 vs. 1	0.76 (0.59;0.97)
	0 vs. 2	0.62 (0.44;0.88)
	0 vs. 3	0.63 (0.26;1.54)
	1 vs. 2	0.81 (0.58;1.14)
	1 vs. 3	0.82 (0.34;2.01)
	2 vs. 3	1.01 (0.40;2.56)
Vulnerable Elders Survey-13	<3 vs. ≥3	0.96 (0.76;1.22)
Groningen Frailty Index	<4 vs. ≥4	0.74 (0.58;0.94)
Timed Up and Go Test	<10 vs. ≥10	0.83 (0.65;1.06)

*Cox PH model

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Table 16-2 Frailty and Comorbidity – Time to Treatment Failure – Subgroup Comparison

Frailty/Comorbidity	Subgroup	Comparison	Hazard Ratio (95% CI)*
Cumulative Illness Rating Score	≤6	Bendamustine vs. Chlorambucil	0.66 (0.51;0.85)
	>6	Bendamustine vs. Chlorambucil	0.77 (0.49;1.23)
Performance Status	0	Bendamustine vs. Chlorambucil	0.55 (0.37;0.80)
	1	Bendamustine vs. Chlorambucil	0.77 (0.56;1.07)
	2	Bendamustine vs. Chlorambucil	0.70 (0.39;1.28)
	3	Bendamustine vs. Chlorambucil	NA (NA;NA)
VES-13	<3	Bendamustine vs. Chlorambucil	0.63 (0.47;0.84)
	≥3	Bendamustine vs. Chlorambucil	0.86 (0.59;1.27)
GFI	<4	Bendamustine vs. Chlorambucil	0.53 (0.39;0.72)
	≥4	Bendamustine vs. Chlorambucil	1.06 (0.72;1.55)
Timed Up and Go	<10	Bendamustine vs. Chlorambucil	0.63 (0.44;0.90)
	≥10	Bendamustine vs. Chlorambucil	0.73 (0.53;1.02)

*Cox PH model

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16.3.1 Kaplan Meier Plots – Time to Treatment Failure

16.3.1.1 Cumulative Illness Rating Score

Figure 16-35 Kaplan Meier Plot: Time to Treatment Failure – Cumulative Illness Rating Score (≤ 6 vs. >6)

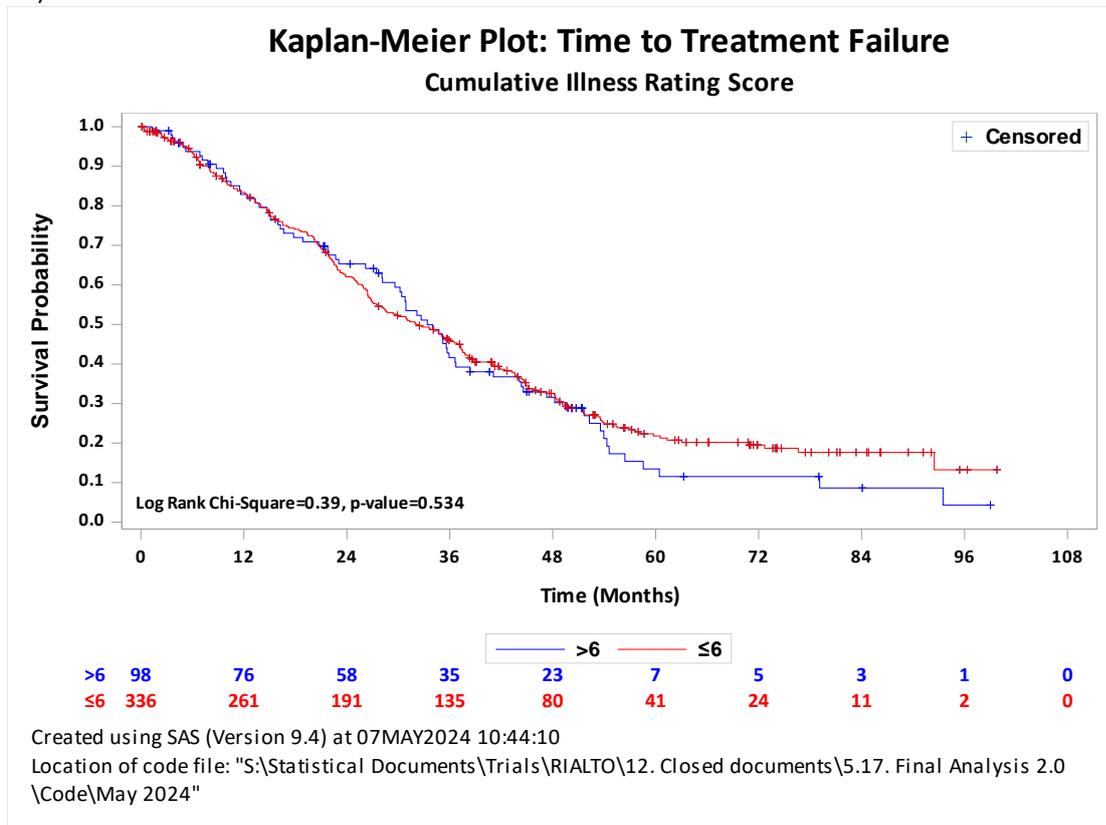


Figure 16-36 Kaplan Meier Plot: Time to Treatment Failure – Cumulative Illness Rating Score (≤ 6) – Treatment Comparison

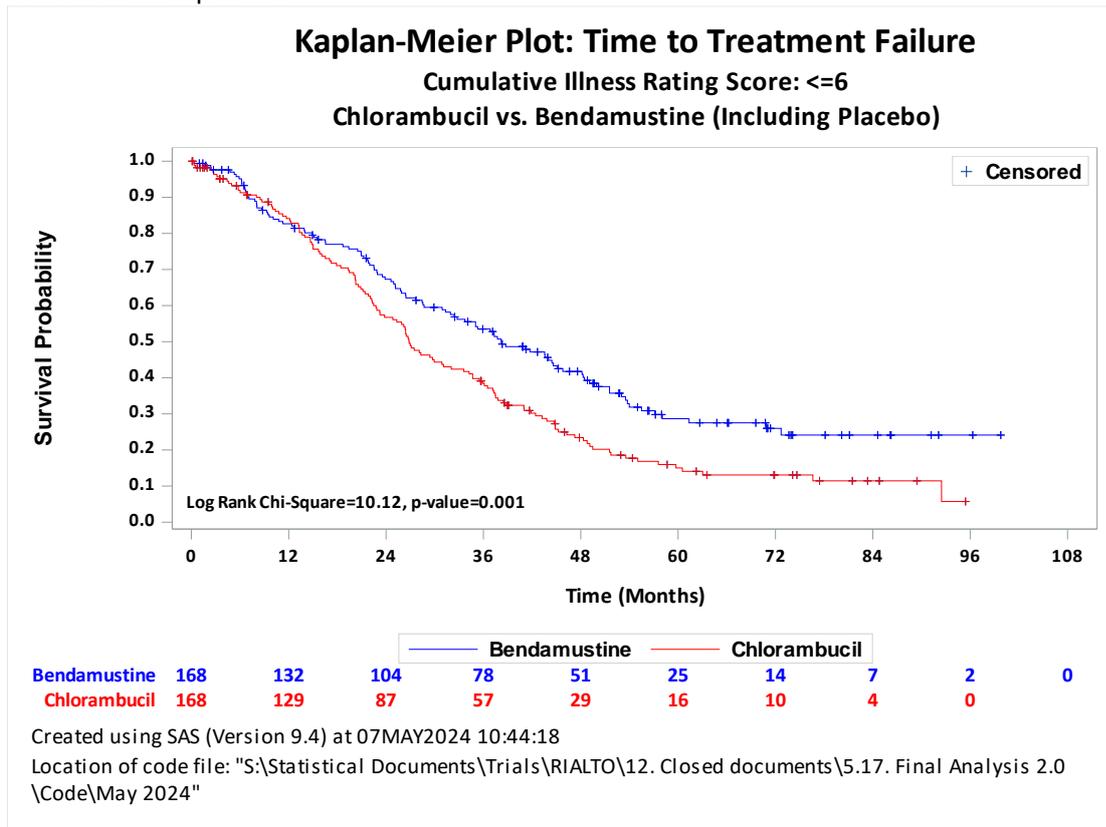
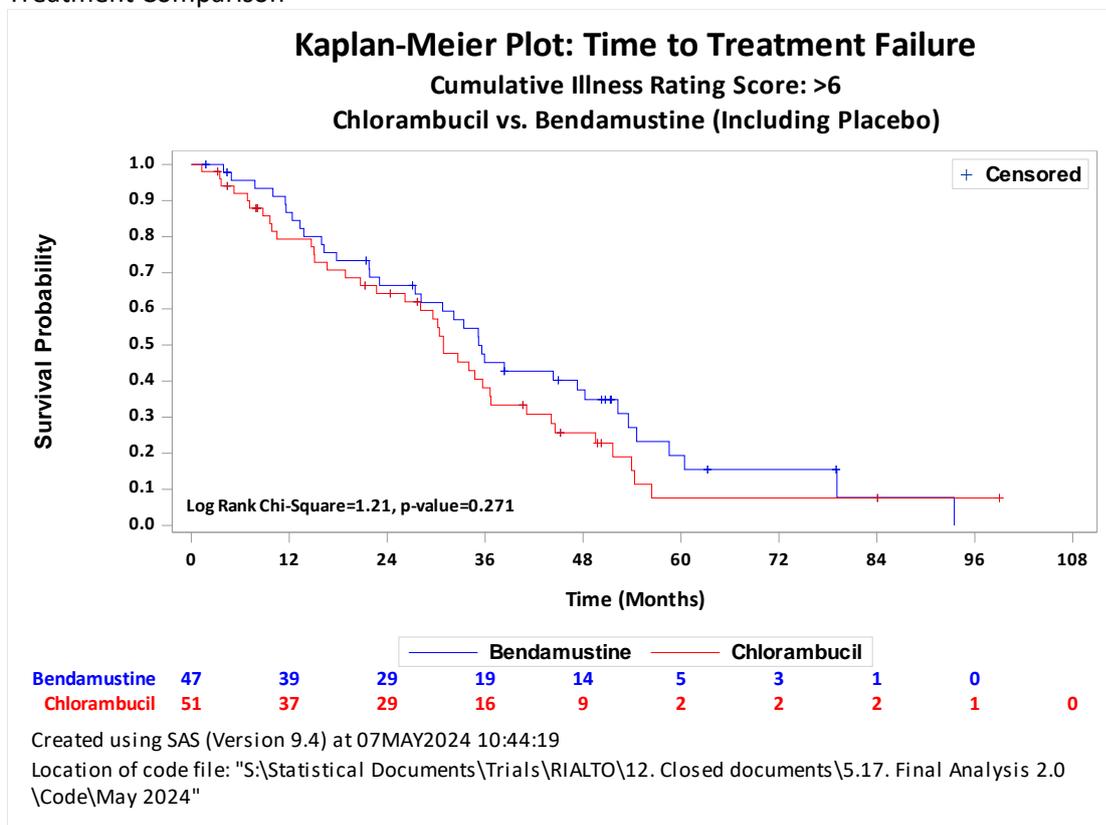


Figure 16-37 Kaplan Meier Plot: Time to Treatment Failure – Cumulative Illness Rating Score (>6) – Treatment Comparison



16.3.1.2 Performance Status

Figure 16-38 Kaplan Meier Plot: Time to Treatment Failure – Performance Status (0 vs. 1 vs. 2 vs. 3)

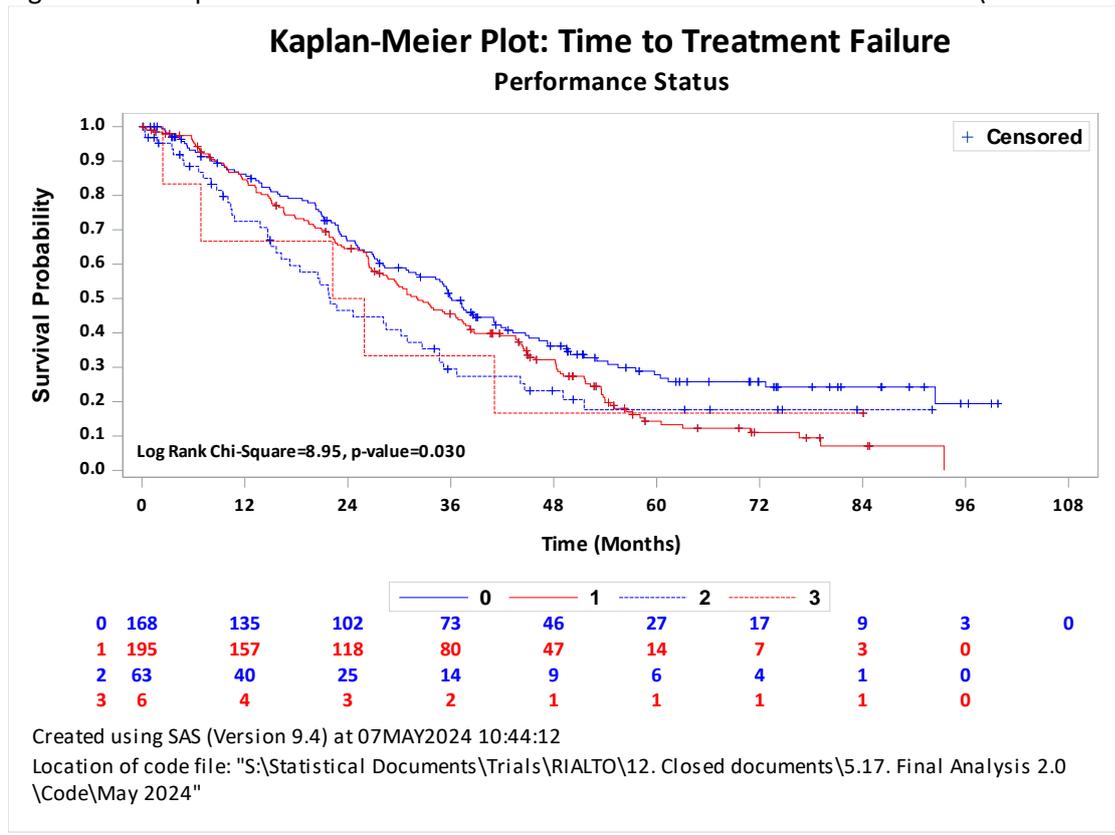


Figure 16-39 Kaplan Meier Plot: Time to Treatment Failure – Performance Status (0) – Treatment Comparison

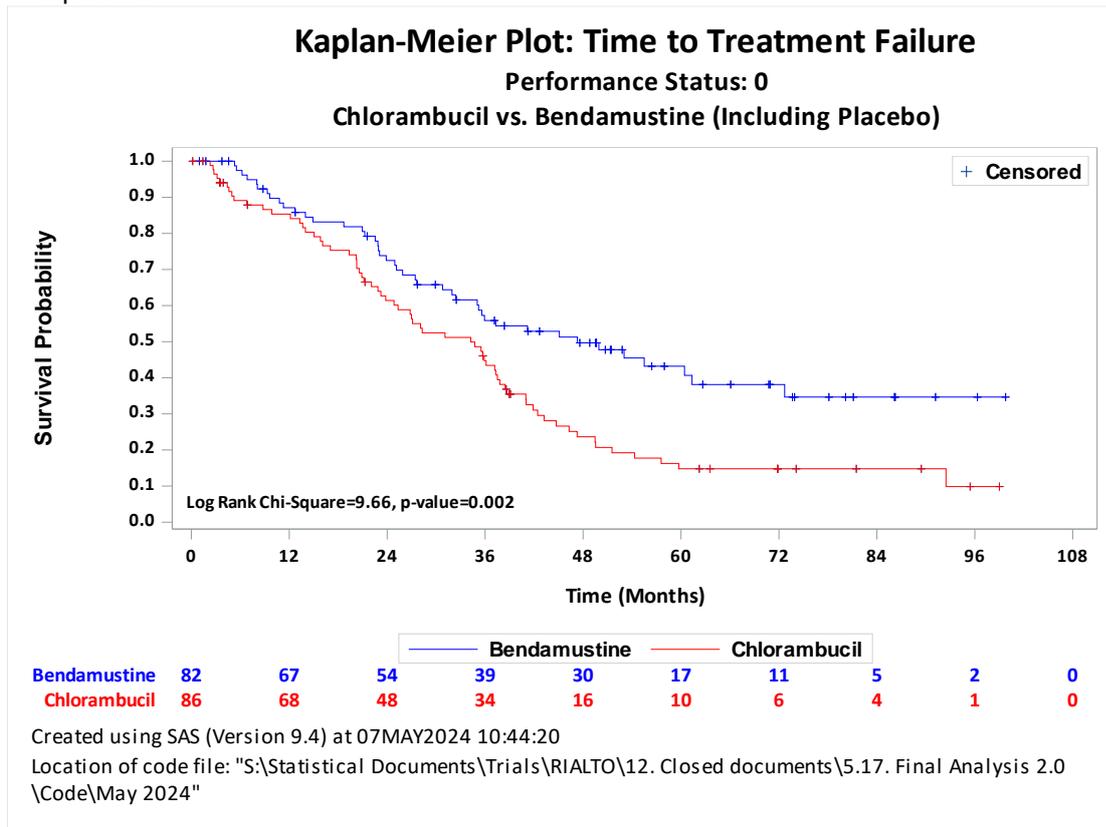


Figure 16-40 Kaplan Meier Plot: Time to Treatment Failure – Performance Status (1) – Treatment Comparison

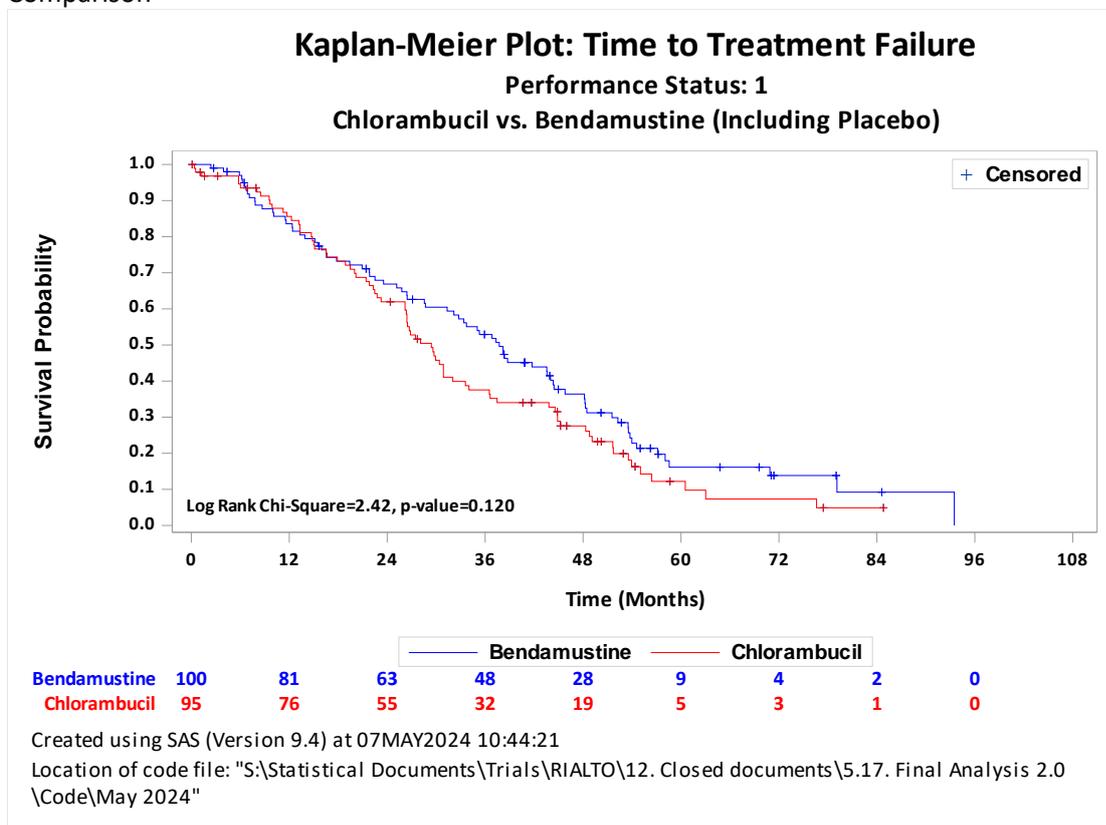


Figure 16-41 Kaplan Meier Plot: Time to Treatment Failure – Performance Status (2) – Treatment Comparison

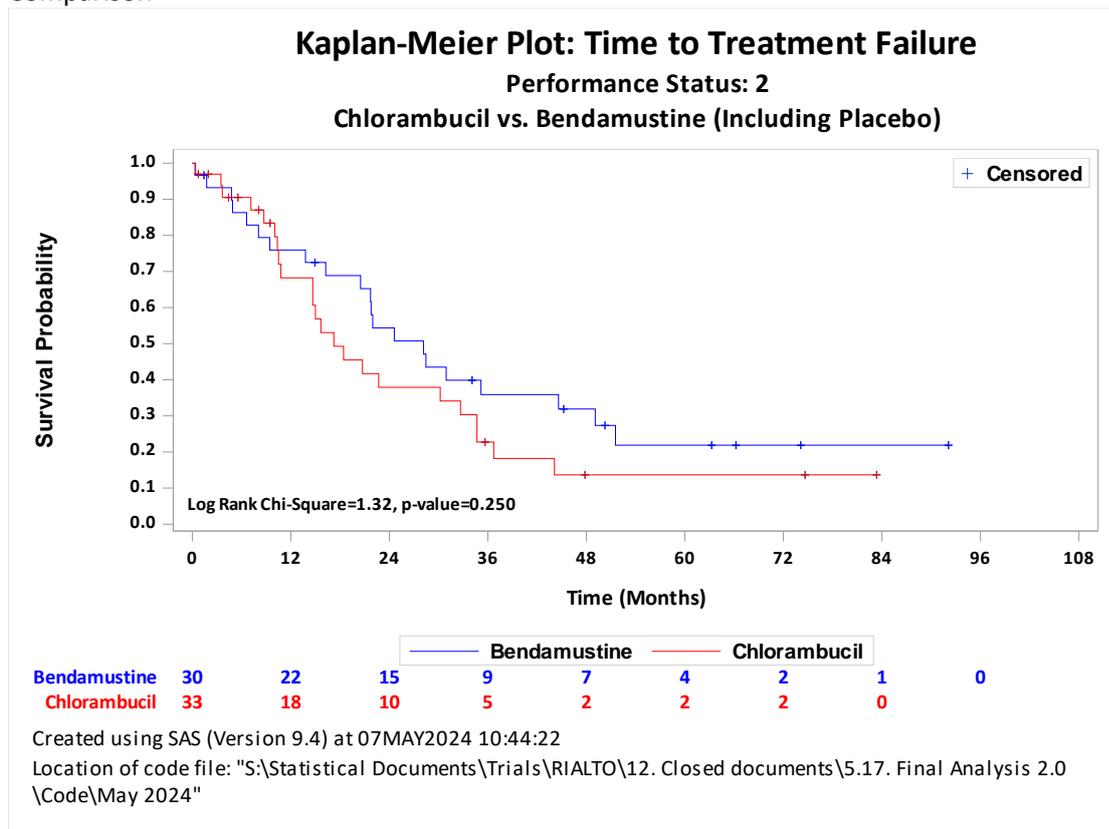


Figure 16-42 Kaplan Meier Plot: Time to Treatment Failure – Performance Status (3) – Treatment Comparison

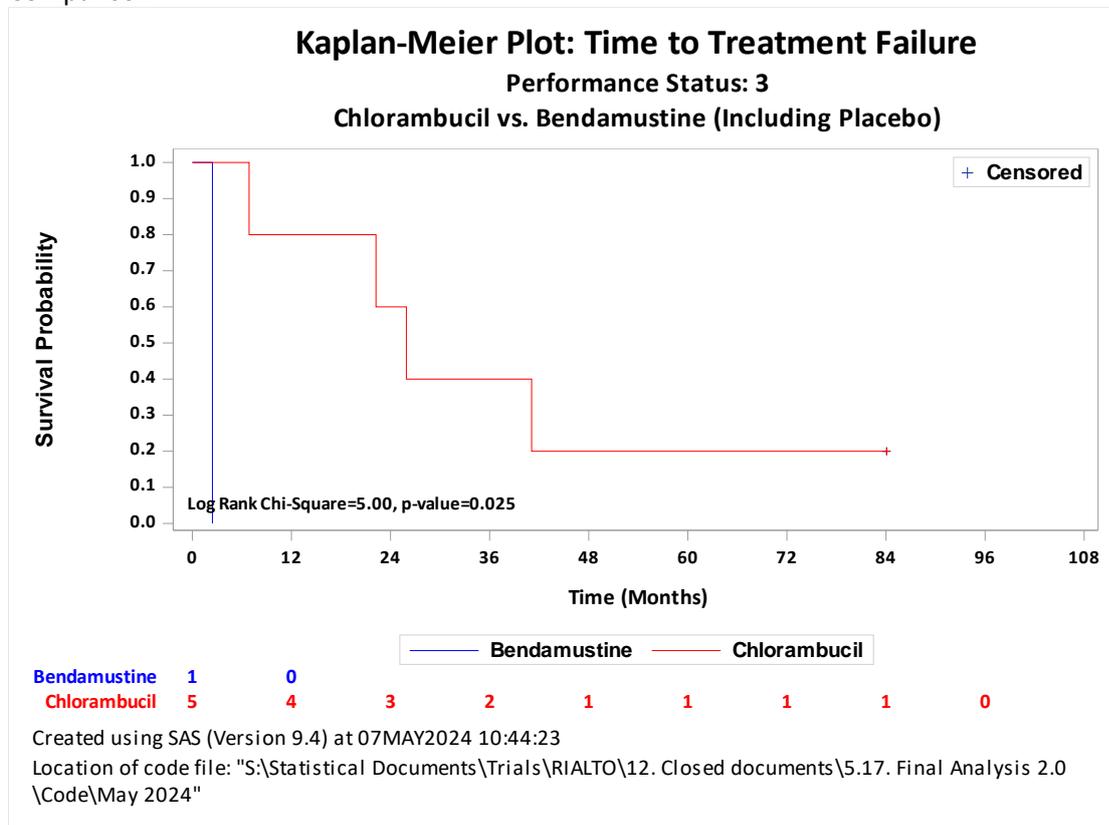


Figure 16-44 Kaplan Meier Plot: Time to Treatment Failure – VES-13 (<3) – Treatment Comparison

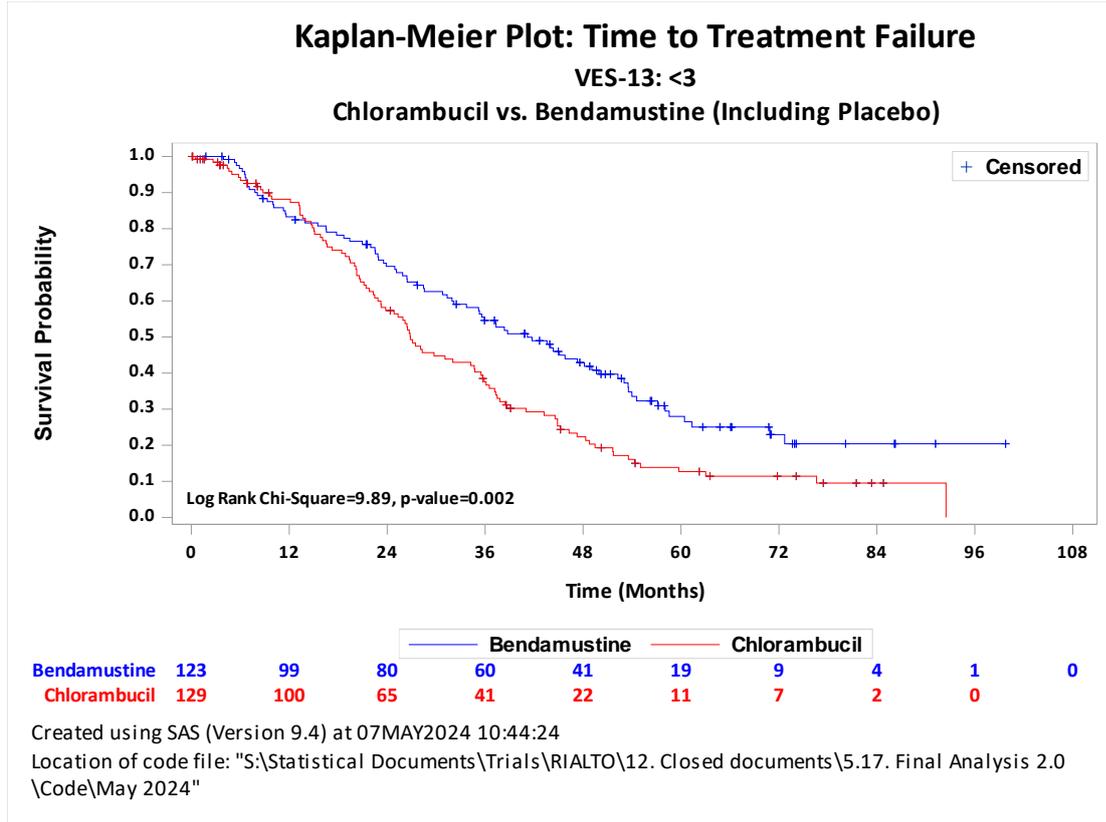
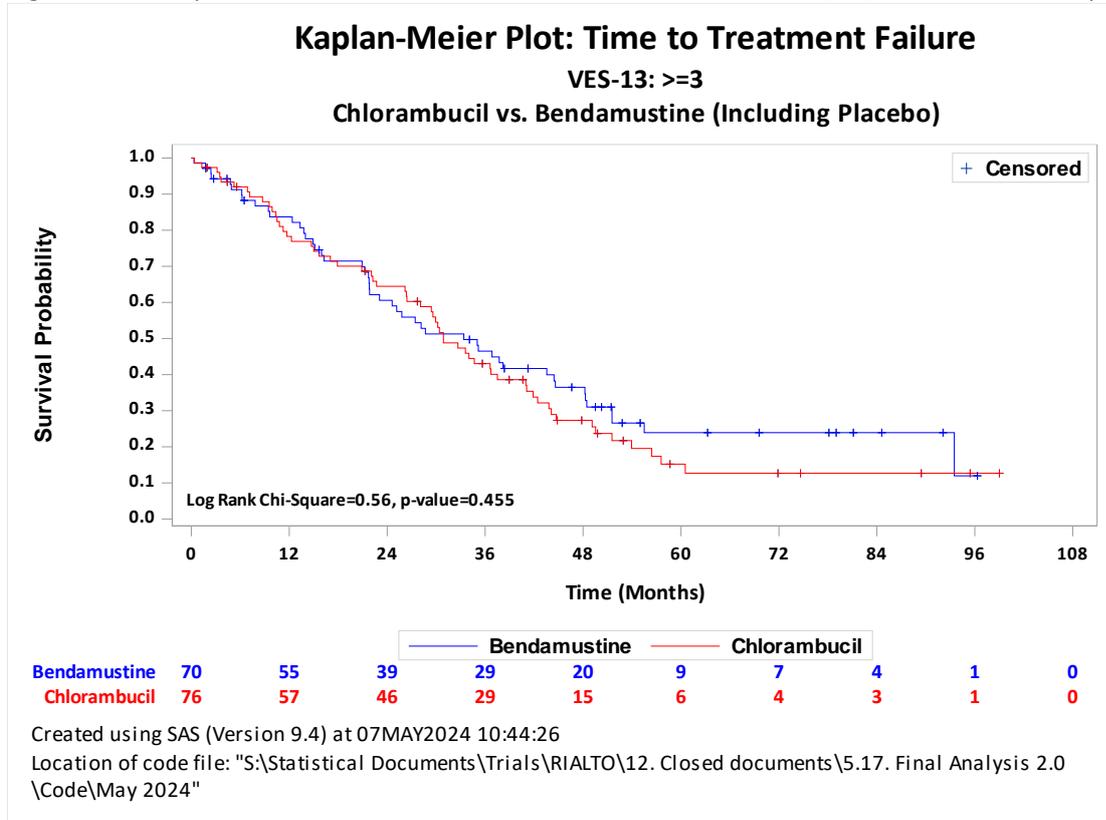


Figure 16-45 Kaplan Meier Plot: Time to Treatment Failure – VES-13 (≥3) – Treatment Comparison



16.3.1.4 GFI

Figure 16-46 Kaplan Meier Plot: Time to Treatment Failure – GFI (<4 vs. ≥4)

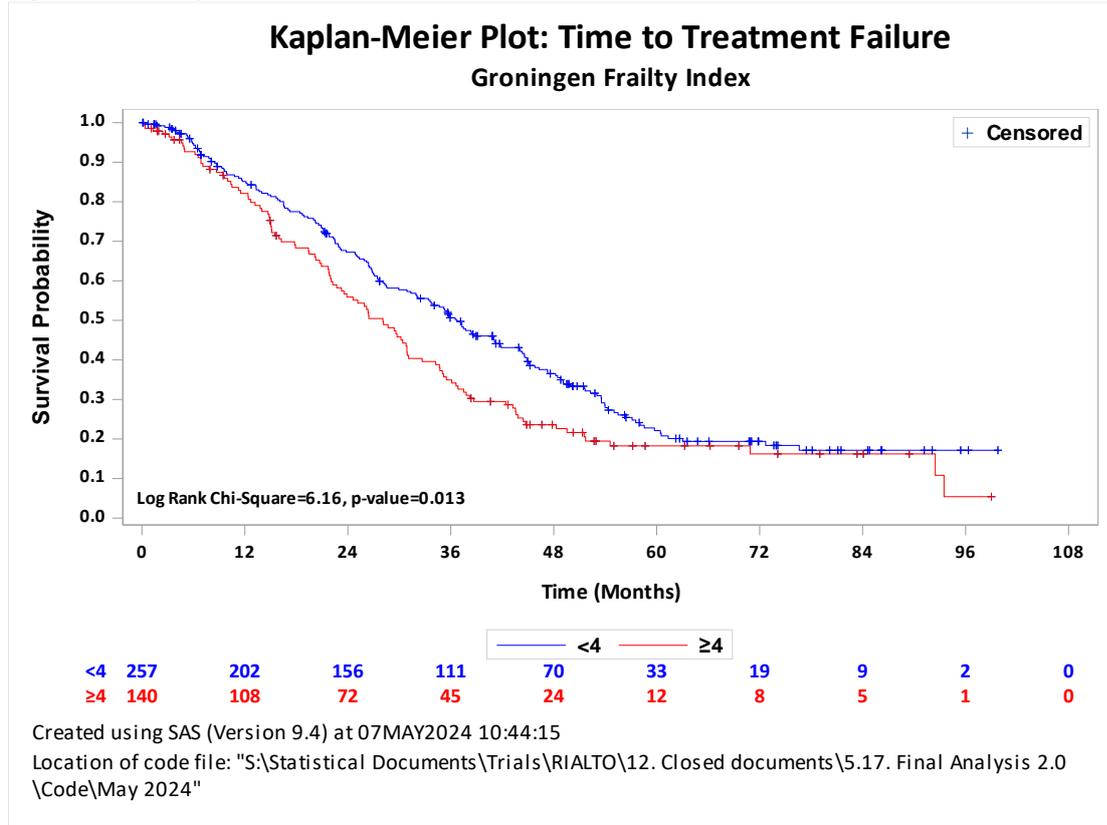


Figure 16-47 Kaplan Meier Plot: Time to Treatment Failure – GFI (<4) – Treatment Comparison

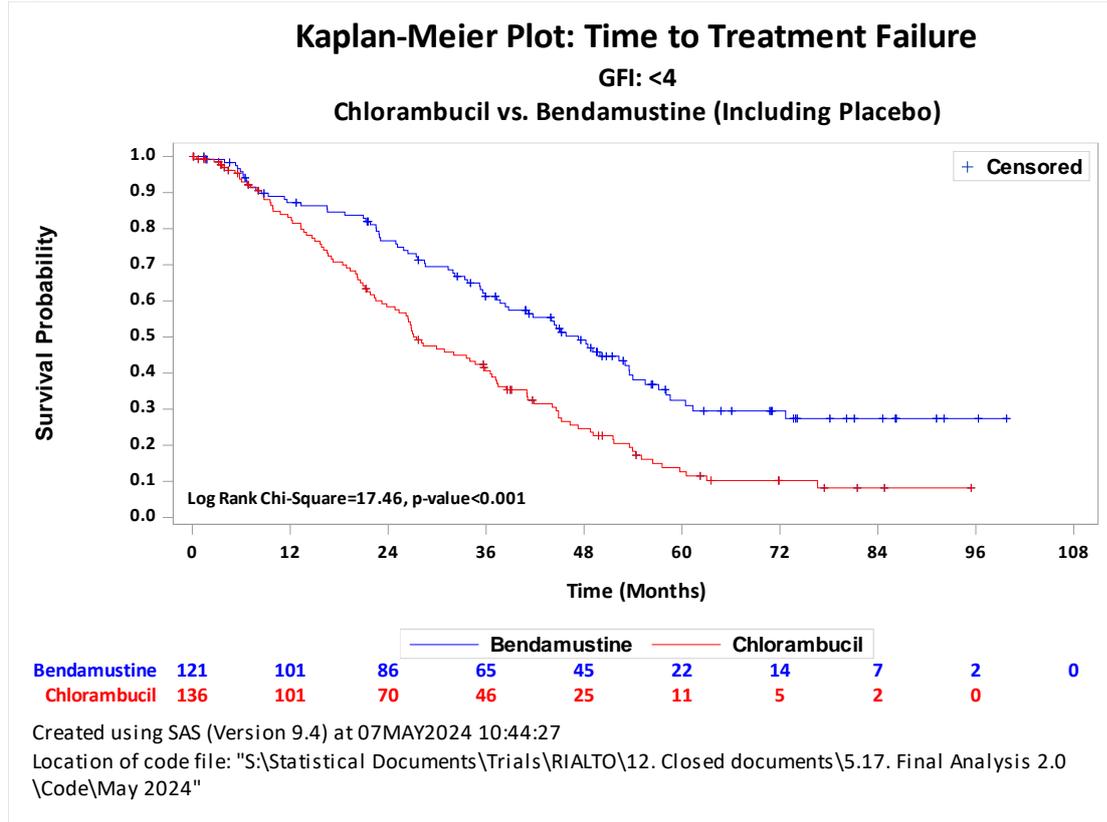
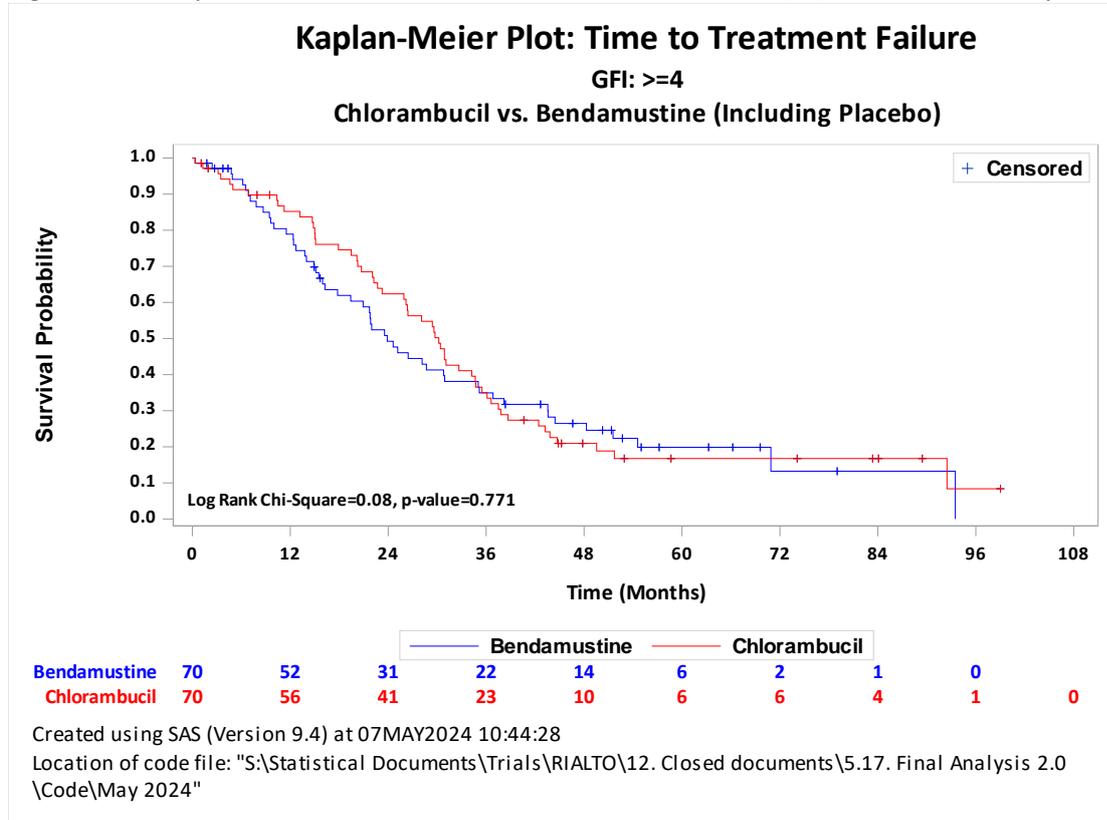


Figure 16-48 Kaplan Meier Plot: Time to Treatment Failure – GFI (≥4) – Treatment Comparison



16.3.1.5 Timed Up and Go

Figure 16-49 Kaplan Meier Plot: Time to Treatment Failure – Timed Up and Go (<10 vs. ≥10)

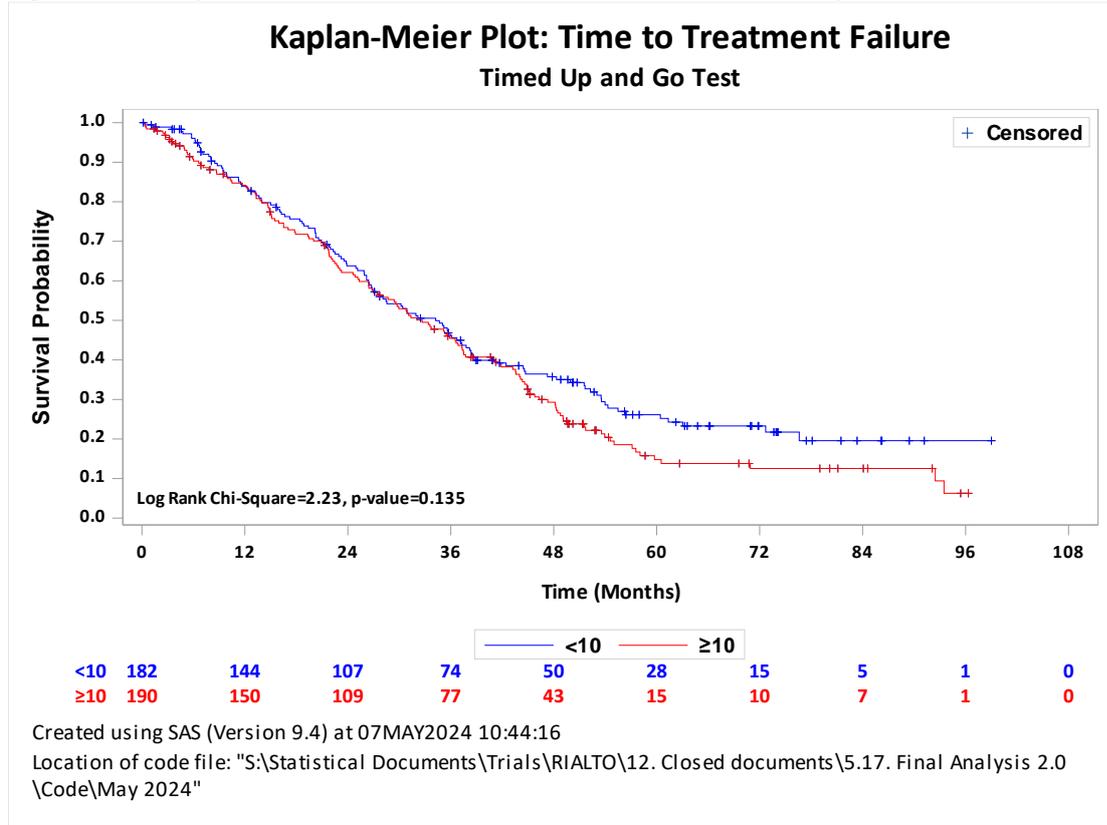


Figure 16-50 Kaplan Meier Plot: Time to Treatment Failure – Timed Up and Go (<10) – Treatment Comparison

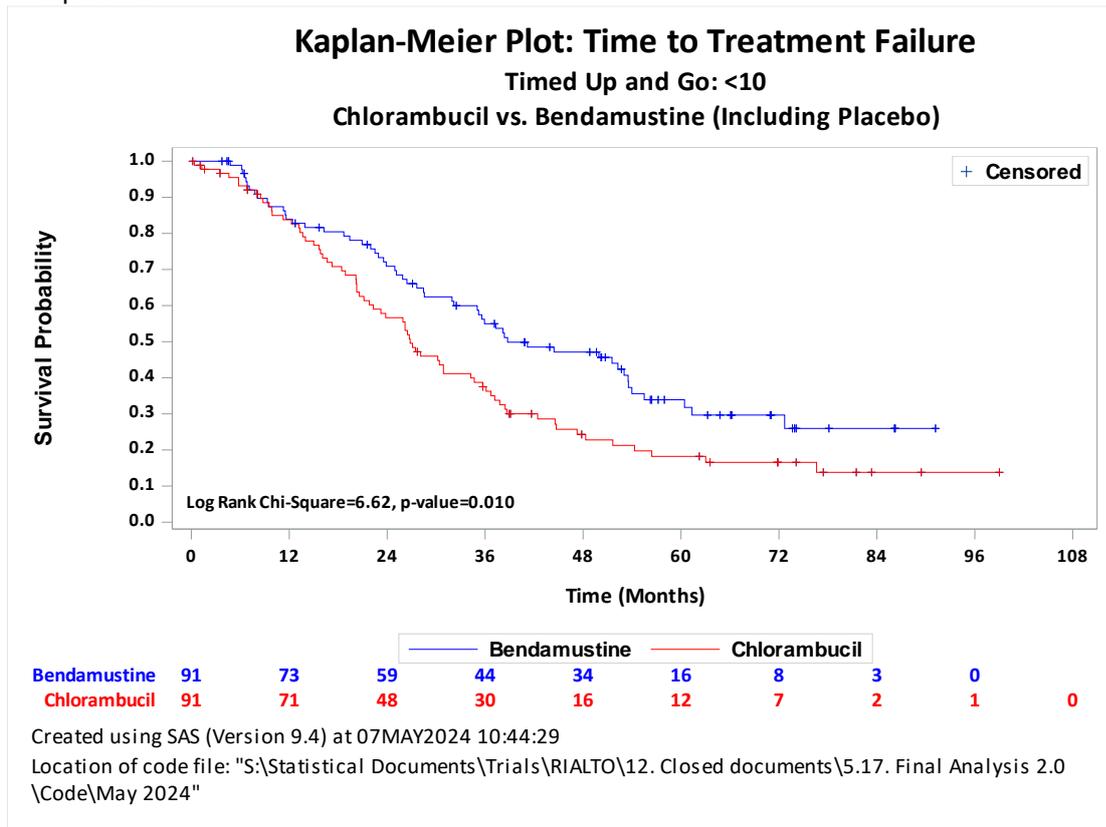
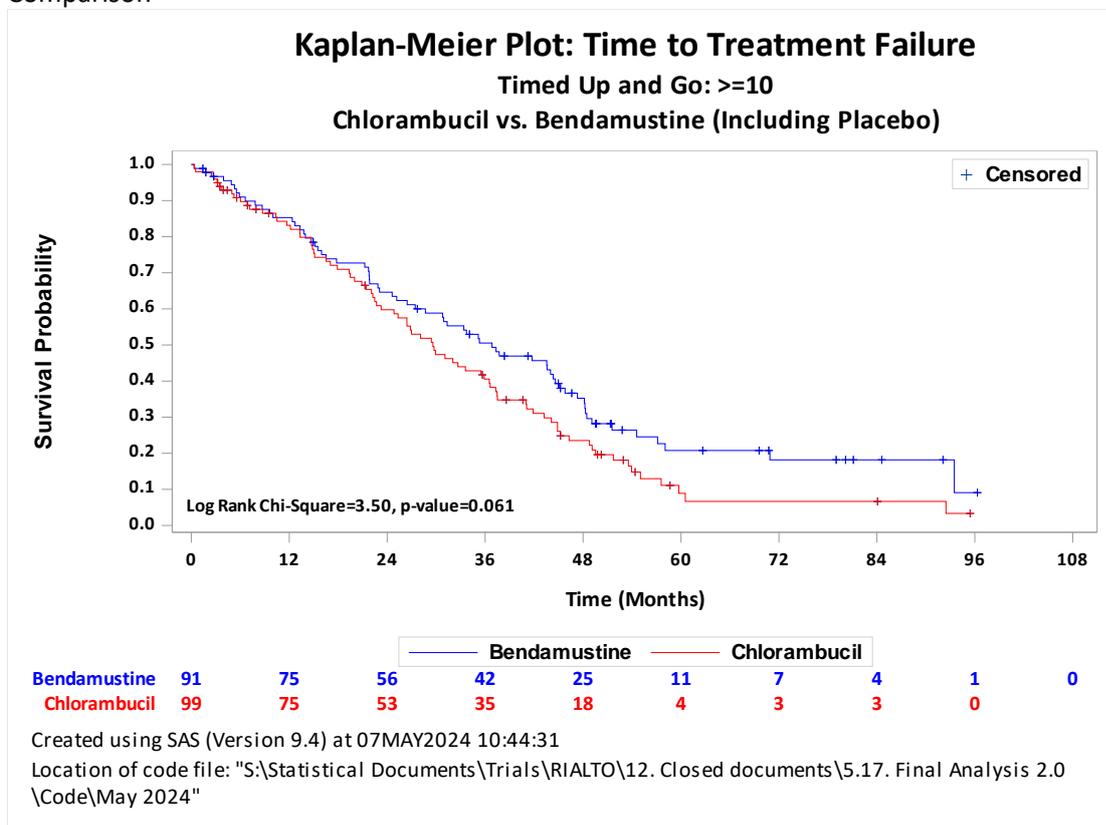


Figure 16-51 Kaplan Meier Plot: Time to Treatment Failure – Timed Up and Go (≥10) – Treatment Comparison



16.4 Response/MRD

Table 17-6 Response/MRD by CIRS (≤ 6 vs. >6)

Response/MRD	≤ 6	>6	Total
Response			
Response, no. patients	344	101	445
Complete remission	1 (0%)	1 (1%)	2 (0%)
Partial remission	170 (49%)	42 (42%)	212 (48%)
Stable disease	43 (13%)	16 (16%)	59 (13%)
Progressive disease	10 (3%)	1 (1%)	11 (2%)
Missing	120 (35%)	41 (41%)	161 (36%)
MRD			
MRD, no. patients	344	101	445
MRD+ve	118 (34%)	25 (25%)	143 (32%)
MRD-ve	17 (5%)	7 (7%)	24 (5%)
Missing	209 (61%)	69 (68%)	278 (62%)

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Table 17-7 Response/MRD by Performance Status (0 vs. 1 vs. 2 vs. 3)

Response/MRD	0	1	2	3	Total
Response					
Response, no. patients	173	199	65	6	443
Complete remission	0 (0%)	2 (1%)	0 (0%)	0 (0%)	2 (0%)
Partial remission	89 (51%)	98 (49%)	22 (34%)	3 (50%)	212 (48%)
Stable disease	26 (15%)	25 (13%)	8 (12%)	0 (0%)	59 (13%)
Progressive disease	5 (3%)	4 (2%)	2 (3%)	0 (0%)	11 (2%)
Missing	53 (31%)	70 (35%)	33 (51%)	3 (50%)	159 (36%)
MRD					
MRD, no. patients	173	199	65	6	443
MRD+ve	67 (39%)	64 (32%)	9 (14%)	2 (33%)	142 (32%)
MRD-ve	10 (6%)	9 (5%)	5 (8%)	0 (0%)	24 (5%)
Missing	96 (55%)	126 (63%)	51 (78%)	4 (67%)	277 (63%)

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Table 17-8 Response/MRD by VES-13 (<3 vs. ≥3)

Response/MRD	<3	≥3	Total
Response			
Response, no. patients	254	149	403
Complete remission	2 (1%)	0 (0%)	2 (0%)
Partial remission	123 (48%)	72 (48%)	195 (48%)
Stable disease	41 (16%)	18 (12%)	59 (15%)
Progressive disease	7 (3%)	2 (1%)	9 (2%)
Missing	81 (32%)	57 (38%)	138 (34%)
MRD			
MRD, no. patients	254	149	403
MRD+ve	95 (37%)	41 (28%)	136 (34%)
MRD-ve	13 (5%)	10 (7%)	23 (6%)
Missing	146 (57%)	98 (66%)	244 (61%)

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Table 17-9 Response/MRD by GFI (<4 vs. ≥4)

Response/MRD	<4	≥4	Total
Response			
Response, no. patients	260	143	403
Complete remission	2 (1%)	0 (0%)	2 (0%)
Partial remission	127 (49%)	68 (48%)	195 (48%)
Stable disease	36 (14%)	20 (14%)	56 (14%)
Progressive disease	8 (3%)	1 (1%)	9 (2%)
Missing	87 (33%)	54 (38%)	141 (35%)
MRD			
MRD, no. patients	260	143	403
MRD+ve	93 (36%)	43 (30%)	136 (34%)
MRD-ve	16 (6%)	7 (5%)	23 (6%)
Missing	151 (58%)	93 (65%)	244 (61%)

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Table 17-10 Response/MRD by Timed Up and Go (<10 vs. ≥10)

Response/MRD	<10	≥10	Total
Response			
Response, no. patients	185	192	377
Complete remission	1 (1%)	1 (1%)	2 (1%)
Partial remission	92 (50%)	90 (47%)	182 (48%)
Stable disease	26 (14%)	27 (14%)	53 (14%)
Progressive disease	4 (2%)	3 (2%)	7 (2%)
Missing	62 (34%)	71 (37%)	133 (35%)
MRD			
MRD, no. patients	185	192	377
MRD+ve	62 (34%)	68 (35%)	130 (34%)
MRD-ve	11 (6%)	12 (6%)	23 (6%)
Missing	112 (61%)	112 (58%)	224 (59%)

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Table 17-11 Response/MRD by all Frailty and Comorbidity Assessments – Treatment Comparison

Frailty/Comorbidity	Subgroup	Response/MRD	Bendamustine	Chlorambucil	Total	
Cumulative Illness Rating Score	<=6	Response				
		Response, no. patients	172	172	344	
		Complete remission	1 (1%)	0 (0%)	1 (0%)	
		Partial remission	87 (51%)	83 (48%)	170 (49%)	
		Stable disease	18 (10%)	25 (15%)	43 (13%)	
		Progressive disease	7 (4%)	3 (2%)	10 (3%)	
		Missing	59 (34%)	61 (35%)	120 (35%)	
		MRD				
		MRD, no. patients	172	172	344	
		MRD+ve	49 (28%)	69 (40%)	118 (34%)	
		MRD-ve	14 (8%)	3 (2%)	17 (5%)	
		Missing	109 (63%)	100 (58%)	209 (61%)	
		>6	Response			
			Response, no. patients	50	51	101
	Complete remission		0 (0%)	1 (2%)	1 (1%)	
	Partial remission		24 (48%)	18 (35%)	42 (42%)	
	Stable disease		5 (10%)	11 (22%)	16 (16%)	
	Progressive disease		1 (2%)	0 (0%)	1 (1%)	
	Missing		20 (40%)	21 (41%)	41 (41%)	
	MRD					
	MRD, no. patients		50	51	101	
	MRD+ve		10 (20%)	15 (29%)	25 (25%)	
MRD-ve	6 (12%)		1 (2%)	7 (7%)		
Missing	34 (68%)		35 (69%)	69 (68%)		
Performance Status	0	Response				
		Response, no. patients	85	88	173	
		Partial remission	47 (55%)	42 (48%)	89 (51%)	
		Stable disease	10 (12%)	16 (18%)	26 (15%)	
		Progressive disease	3 (4%)	2 (2%)	5 (3%)	
		Missing	25 (29%)	28 (32%)	53 (31%)	
		MRD				
		MRD, no. patients	85	88	173	
		MRD+ve	30 (35%)	37 (42%)	67 (39%)	
		MRD-ve	7 (8%)	3 (3%)	10 (6%)	
		Missing	48 (56%)	48 (55%)	96 (55%)	

Frailty/Comorbidity	Subgroup	Response/MRD	Bendamustine	Chlorambucil	Total	
	1	Response				
		Response, no. patients	102	97	199	
		Complete remission	1 (1%)	1 (1%)	2 (1%)	
		Partial remission	53 (52%)	45 (46%)	98 (49%)	
		Stable disease	11 (11%)	14 (14%)	25 (13%)	
		Progressive disease	3 (3%)	1 (1%)	4 (2%)	
		Missing	34 (33%)	36 (37%)	70 (35%)	
		MRD				
		MRD, no. patients	102	97	199	
		MRD+ve	22 (22%)	42 (43%)	64 (32%)	
		MRD-ve	8 (8%)	1 (1%)	9 (5%)	
		Missing	72 (71%)	54 (56%)	126 (63%)	
	2	Response				
		Response, no. patients	32	33	65	
		Partial remission	11 (34%)	11 (33%)	22 (34%)	
		Stable disease	2 (6%)	6 (18%)	8 (12%)	
		Progressive disease	2 (6%)	0 (0%)	2 (3%)	
		Missing	17 (53%)	16 (48%)	33 (51%)	
		MRD				
		MRD, no. patients	32	33	65	
		MRD+ve	6 (19%)	3 (9%)	9 (14%)	
		MRD-ve	5 (16%)	0 (0%)	5 (8%)	
		Missing	21 (66%)	30 (91%)	51 (78%)	
		3	Response			
	Response, no. patients		1	5	6	
	Partial remission		0 (0%)	3 (60%)	3 (50%)	
	Missing		1 (100%)	2 (40%)	3 (50%)	
	MRD					
	MRD, no. patients		1	5	6	
	MRD+ve		0 (0%)	2 (40%)	2 (33%)	
	Missing	1 (100%)	3 (60%)	4 (67%)		
	VES-13	<3	Response			
			Response, no. patients	124	130	254
Complete remission			1 (1%)	1 (1%)	2 (1%)	
Partial remission			65 (52%)	58 (45%)	123 (48%)	
Stable disease			16 (13%)	25 (19%)	41 (16%)	

Frailty/Comorbidity	Subgroup	Response/MRD	Bendamustine	Chlorambucil	Total
GFI		Progressive disease	5 (4%)	2 (2%)	7 (3%)
		Missing	37 (30%)	44 (34%)	81 (32%)
		MRD			
		MRD, no. patients	124	130	254
		MRD+ve	41 (33%)	54 (42%)	95 (37%)
		MRD-ve	9 (7%)	4 (3%)	13 (5%)
		Missing	74 (60%)	72 (55%)	146 (57%)
	≥3	Response			
		Response, no. patients	72	77	149
		Partial remission	35 (49%)	37 (48%)	72 (48%)
		Stable disease	7 (10%)	11 (14%)	18 (12%)
		Progressive disease	1 (1%)	1 (1%)	2 (1%)
		Missing	29 (40%)	28 (36%)	57 (38%)
		MRD			
		MRD, no. patients	72	77	149
		MRD+ve	14 (19%)	27 (35%)	41 (28%)
		MRD-ve	10 (14%)	0 (0%)	10 (7%)
		Missing	48 (67%)	50 (65%)	98 (66%)
	<4	Response			
		Response, no. patients	122	138	260
		Complete remission	1 (1%)	1 (1%)	2 (1%)
		Partial remission	67 (55%)	60 (43%)	127 (49%)
		Stable disease	12 (10%)	24 (17%)	36 (14%)
		Progressive disease	5 (4%)	3 (2%)	8 (3%)
		Missing	37 (30%)	50 (36%)	87 (33%)
		MRD			
MRD, no. patients		122	138	260	
MRD+ve		38 (31%)	55 (40%)	93 (36%)	
MRD-ve		12 (10%)	4 (3%)	16 (6%)	
Missing		72 (59%)	79 (57%)	151 (58%)	
≥4		Response			
		Response, no. patients	72	71	143
	Partial remission	31 (43%)	37 (52%)	68 (48%)	
	Stable disease	10 (14%)	10 (14%)	20 (14%)	
	Progressive disease	1 (1%)	0 (0%)	1 (1%)	
	Missing	30 (42%)	24 (34%)	54 (38%)	

Frailty/Comorbidity	Subgroup	Response/MRD	Bendamustine	Chlorambucil	Total	
Timed Up and Go		MRD				
		MRD, no. patients	72	71	143	
		MRD+ve	16 (22%)	27 (38%)	43 (30%)	
		MRD-ve	7 (10%)	0 (0%)	7 (5%)	
		Missing	49 (68%)	44 (62%)	93 (65%)	
	<10	Response				
		Response, no. patients	92	93	185	
		Complete remission	0 (0%)	1 (1%)	1 (1%)	
		Partial remission	45 (49%)	47 (51%)	92 (50%)	
		Stable disease	13 (14%)	13 (14%)	26 (14%)	
		Progressive disease	3 (3%)	1 (1%)	4 (2%)	
		Missing	31 (34%)	31 (33%)	62 (34%)	
		MRD				
		MRD, no. patients	92	93	185	
		MRD+ve	25 (27%)	37 (40%)	62 (34%)	
		MRD-ve	7 (8%)	4 (4%)	11 (6%)	
		Missing	60 (65%)	52 (56%)	112 (61%)	
		≥10	Response			
			Response, no. patients	92	100	192
			Complete remission	1 (1%)	0 (0%)	1 (1%)
			Partial remission	49 (53%)	41 (41%)	90 (47%)
Stable disease	9 (10%)		18 (18%)	27 (14%)		
Progressive disease	2 (2%)		1 (1%)	3 (2%)		
Missing	31 (34%)		40 (40%)	71 (37%)		
MRD						
MRD, no. patients	92		100	192		
MRD+ve	29 (32%)		39 (39%)	68 (35%)		
MRD-ve	12 (13%)		0 (0%)	12 (6%)		
Missing	51 (55%)	61 (61%)	112 (58%)			

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Table 17-12 Adverse Events by all Frailty and Comorbidity Assessments – Treatment Comparison

Frailty/Comorbidity	Subgroup	AE Severity	Bendamustine	Chlorambucil	Total
Cumulative Illness Rating Score	<=6	1	894 (54%)	780 (52%)	1674 (53%)
		2	563 (34%)	510 (34%)	1073 (34%)
		3	167 (10%)	173 (12%)	340 (11%)
		4	36 (2%)	22 (1%)	58 (2%)
		Missing	8 (0%)	15 (1%)	23 (1%)
	>6	1	268 (57%)	325 (56%)	593 (56%)
		2	131 (28%)	194 (33%)	325 (31%)
		3	53 (11%)	49 (8%)	102 (10%)
		4	7 (1%)	10 (2%)	17 (2%)
		5	0 (0%)	1 (0%)	1 (0%)
		Missing	9 (2%)	4 (1%)	13 (1%)
Performance Status	0	1	478 (58%)	442 (58%)	920 (58%)
		2	262 (32%)	237 (31%)	499 (31%)
		3	69 (8%)	66 (9%)	135 (8%)
		4	17 (2%)	9 (1%)	26 (2%)
		Missing	4 (0%)	6 (1%)	10 (1%)
	1	1	529 (52%)	394 (49%)	923 (51%)
		2	339 (33%)	302 (37%)	641 (35%)
		3	113 (11%)	92 (11%)	205 (11%)
		4	21 (2%)	15 (2%)	36 (2%)
		5	0 (0%)	1 (0%)	1 (0%)
		Missing	10 (1%)	8 (1%)	18 (1%)
	2	1	155 (53%)	217 (52%)	372 (53%)
		2	93 (32%)	136 (33%)	229 (32%)
		3	38 (13%)	50 (12%)	88 (12%)
		4	5 (2%)	7 (2%)	12 (2%)
		Missing	3 (1%)	4 (1%)	7 (1%)
	3	1	0 (0%)	52 (54%)	52 (54%)
		2	0 (0%)	29 (30%)	29 (30%)
		3	0 (0%)	14 (14%)	14 (14%)
		4	0 (0%)	1 (1%)	1 (1%)
		Missing	0 (0%)	1 (1%)	1 (1%)
VES-13	<3	1	758 (59%)	603 (53%)	1361 (56%)
		2	370 (29%)	376 (33%)	746 (31%)
		3	120 (9%)	124 (11%)	244 (10%)

Frailty/Comorbidity	Subgroup	AE Severity	Bendamustine	Chlorambucil	Total	
		4	32 (2%)	19 (2%)	51 (2%)	
		Missing	14 (1%)	7 (1%)	21 (1%)	
	>=3	1	336 (48%)	438 (54%)	774 (51%)	
		2	272 (39%)	278 (34%)	550 (36%)	
		3	86 (12%)	78 (10%)	164 (11%)	
		4	7 (1%)	9 (1%)	16 (1%)	
		5	0 (0%)	1 (0%)	1 (0%)	
		Missing	3 (0%)	9 (1%)	12 (1%)	
GFI	<4	1	716 (56%)	575 (50%)	1291 (53%)	
		2	399 (31%)	414 (36%)	813 (33%)	
		3	135 (10%)	134 (12%)	269 (11%)	
		4	33 (3%)	16 (1%)	49 (2%)	
		5	0 (0%)	1 (0%)	1 (0%)	
		Missing	3 (0%)	4 (0%)	7 (0%)	
	>=4	1	350 (51%)	447 (58%)	797 (54%)	
		2	244 (35%)	234 (30%)	478 (33%)	
		3	75 (11%)	67 (9%)	142 (10%)	
		4	9 (1%)	11 (1%)	20 (1%)	
		Missing	14 (2%)	13 (2%)	27 (2%)	
	Timed Up and Go	<10	1	503 (57%)	389 (56%)	892 (56%)
			2	251 (29%)	225 (32%)	476 (30%)
3			91 (10%)	69 (10%)	160 (10%)	
4			25 (3%)	7 (1%)	32 (2%)	
Missing			10 (1%)	9 (1%)	19 (1%)	
>=10		1	540 (51%)	581 (52%)	1121 (52%)	
		2	384 (36%)	378 (34%)	762 (35%)	
		3	115 (11%)	128 (12%)	243 (11%)	
		4	14 (1%)	19 (2%)	33 (2%)	
		5	0 (0%)	1 (0%)	1 (0%)	
		Missing	6 (1%)	6 (1%)	12 (1%)	

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Table 17-13 Serious Adverse Events by all Frailty and Comorbidity Assessments – Treatment Comparison

Frailty/Comorbidity	Subgroup	SAE Severity	Bendamustine	Chlorambucil	Total
Cumulative Illness Rating Score	<=6	1	48 (21%)	29 (18%)	77 (20%)
		2	69 (30%)	41 (26%)	110 (28%)
		3	73 (31%)	60 (38%)	133 (34%)
		4	14 (6%)	15 (9%)	29 (7%)
		5	5 (2%)	2 (1%)	7 (2%)
		Missing	24 (10%)	12 (8%)	36 (9%)
	>6	1	10 (14%)	12 (16%)	22 (15%)
		2	19 (26%)	28 (36%)	47 (31%)
		3	22 (30%)	25 (32%)	47 (31%)
		4	4 (5%)	5 (6%)	9 (6%)
		5	4 (5%)	1 (1%)	5 (3%)
		Missing	14 (19%)	6 (8%)	20 (13%)
Performance Status	0	1	10 (14%)	13 (19%)	23 (16%)
		2	27 (37%)	18 (27%)	45 (32%)
		3	23 (32%)	23 (34%)	46 (33%)
		4	5 (7%)	5 (7%)	10 (7%)
		5	1 (1%)	1 (1%)	2 (1%)
		Missing	7 (10%)	7 (10%)	14 (10%)
	1	1	39 (23%)	17 (17%)	56 (21%)
		2	35 (21%)	33 (32%)	68 (25%)
		3	52 (31%)	37 (36%)	89 (33%)
		4	11 (7%)	8 (8%)	19 (7%)
		5	5 (3%)	1 (1%)	6 (2%)
		Missing	24 (14%)	7 (7%)	31 (12%)
	2	1	9 (15%)	9 (16%)	18 (15%)
		2	25 (41%)	15 (26%)	40 (34%)
		3	16 (26%)	22 (38%)	38 (32%)
		4	2 (3%)	7 (12%)	9 (8%)
		5	2 (3%)	1 (2%)	3 (3%)
		Missing	7 (11%)	4 (7%)	11 (9%)
	3	1	0 (0%)	2 (25%)	2 (17%)
		2	1 (25%)	3 (38%)	4 (33%)
		3	2 (50%)	3 (38%)	5 (42%)
		5	1 (25%)	0 (0%)	1 (8%)

Frailty/Comorbidity	Subgroup	SAE Severity	Bendamustine	Chlorambucil	Total
VES-13	<3	1	30 (19%)	17 (15%)	47 (17%)
		2	41 (26%)	33 (28%)	74 (27%)
		3	43 (27%)	37 (32%)	80 (29%)
		4	10 (6%)	16 (14%)	26 (10%)
		5	4 (3%)	3 (3%)	7 (3%)
		Missing	29 (18%)	10 (9%)	39 (14%)
	>=3	1	23 (19%)	21 (20%)	44 (20%)
		2	37 (31%)	31 (30%)	68 (30%)
		3	39 (33%)	41 (39%)	80 (36%)
		4	8 (7%)	4 (4%)	12 (5%)
		5	5 (4%)	0 (0%)	5 (2%)
		Missing	6 (5%)	8 (8%)	14 (6%)
GFI	<4	1	27 (19%)	23 (18%)	50 (18%)
		2	33 (23%)	37 (29%)	70 (26%)
		3	51 (35%)	41 (33%)	92 (34%)
		4	13 (9%)	13 (10%)	26 (10%)
		5	5 (3%)	3 (2%)	8 (3%)
		Missing	16 (11%)	9 (7%)	25 (9%)
	>=4	1	28 (21%)	14 (14%)	42 (18%)
		2	44 (32%)	28 (29%)	72 (31%)
		3	36 (26%)	41 (42%)	77 (33%)
		4	5 (4%)	6 (6%)	11 (5%)
		5	4 (3%)	0 (0%)	4 (2%)
		Missing	19 (14%)	9 (9%)	28 (12%)
Timed Up and Go	<10	1	28 (21%)	13 (13%)	41 (18%)
		2	45 (34%)	32 (33%)	77 (33%)
		3	29 (22%)	30 (31%)	59 (26%)
		4	7 (5%)	9 (9%)	16 (7%)
		5	4 (3%)	1 (1%)	5 (2%)
		Missing	21 (16%)	12 (12%)	33 (14%)
	>=10	1	26 (19%)	23 (19%)	49 (19%)
		2	35 (26%)	31 (26%)	66 (26%)
		3	48 (35%)	49 (42%)	97 (38%)
		4	10 (7%)	10 (8%)	20 (8%)
		5	5 (4%)	0 (0%)	5 (2%)
		Missing	12 (9%)	5 (4%)	17 (7%)

Frailty/Comorbidity	Subgroup	SAE Severity	Bendamustine	Chlorambucil	Total
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16.5 Frailty and Comorbidity Summary

Higher frailty scores were associated with shorter OS using all five assessments (CIRS, Performance Status, VES-13, GFI, TUAG) and with shorter PFS and TTF in the Performance Status and VES-13 assessments only. Compared to Chlorambucil, Bendamustine produced deeper responses irrespective of frailty, but its PFS and TTF advantage was confined to less frail patients defined by all five scoring systems. Overall, the more complex frailty assessments had no clear advantage over Performance Status.

17 Secondary Outcome – Predictive Value of Biomarkers

17.1 Primary Analysis – Bendamustine vs. Chlorambucil (Including Placebo)

Figure 18-1 Kaplan Meier Plot: Progression Free Survival – IGHV Status

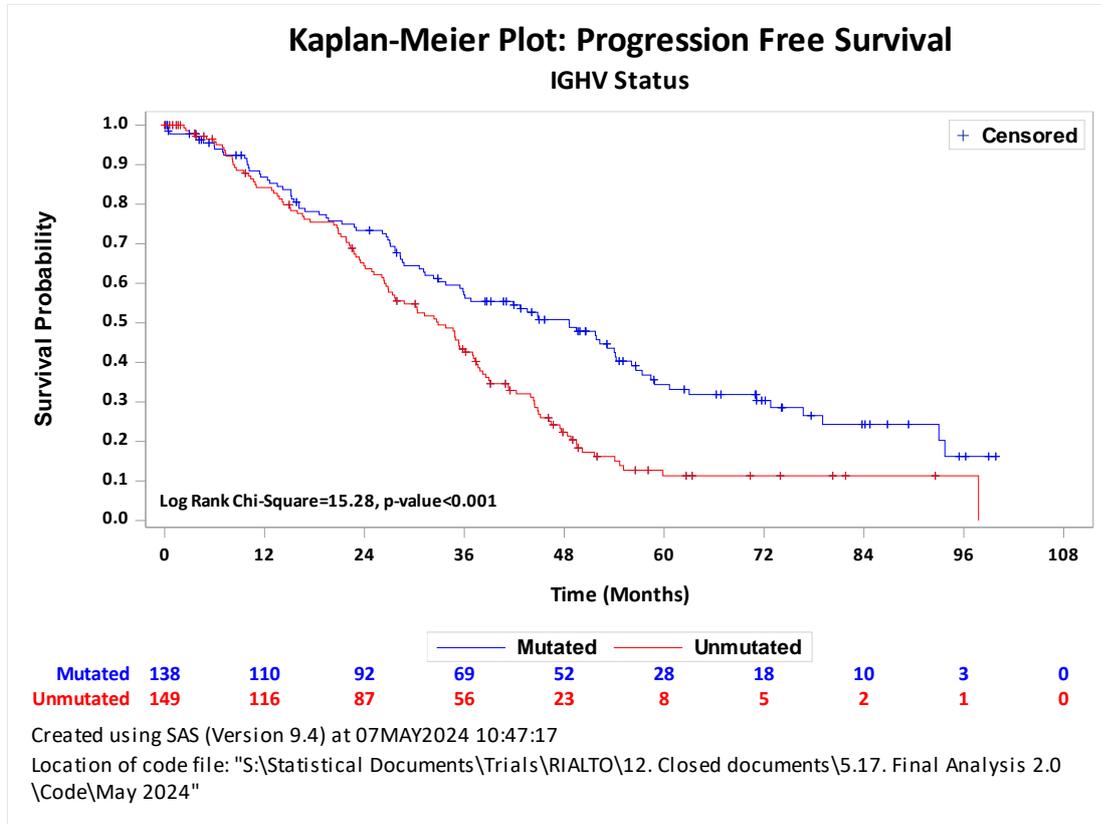


Figure 18-2 Kaplan Meier Plot: Progression Free Survival – IGHV (Mutated) – Treatment Comparison

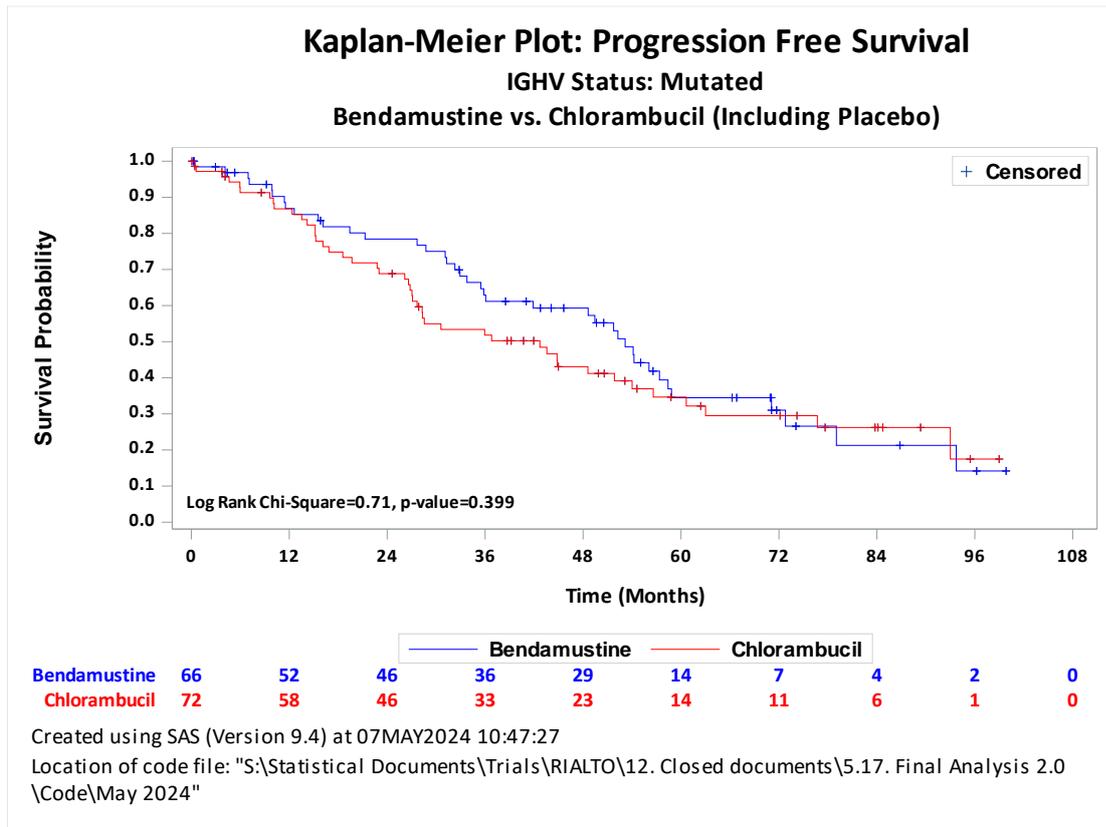


Figure 18-3 Kaplan Meier Plot: Progression Free Survival – IGHV (Unmutated) – Treatment Comparison

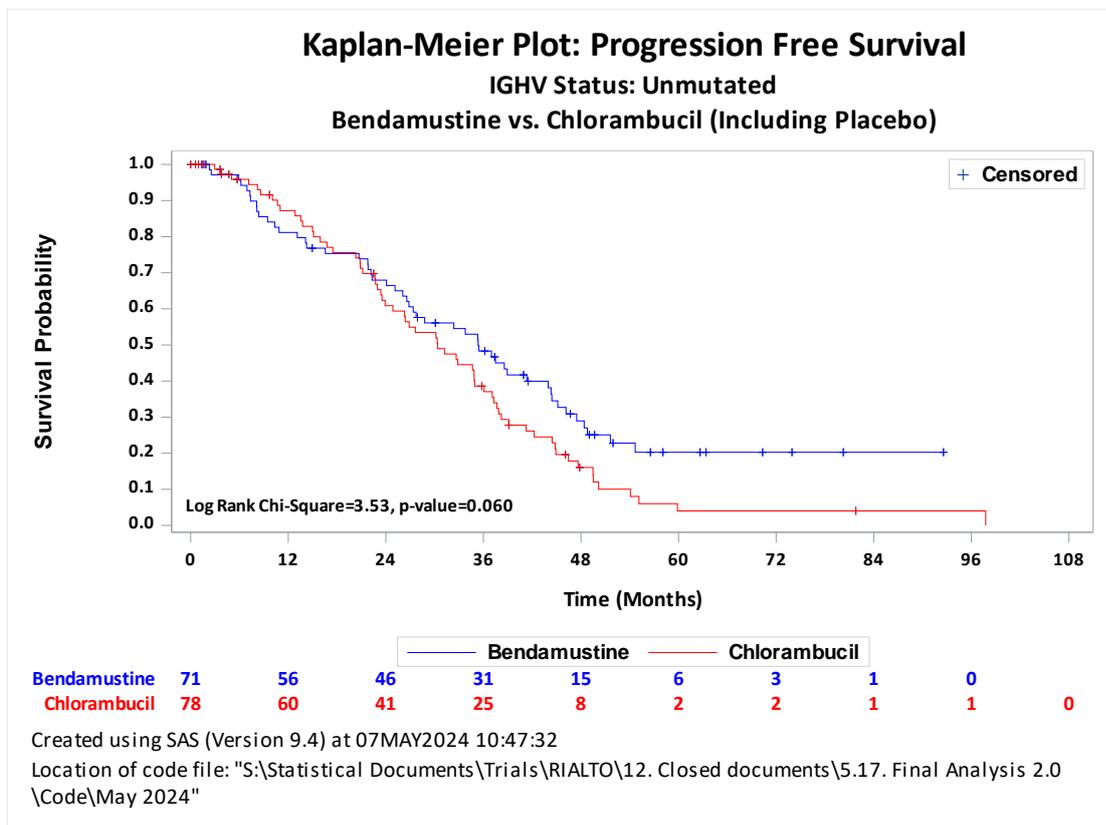


Figure 18-4 Kaplan Meier Plot: Progression Free Survival – FISH Status

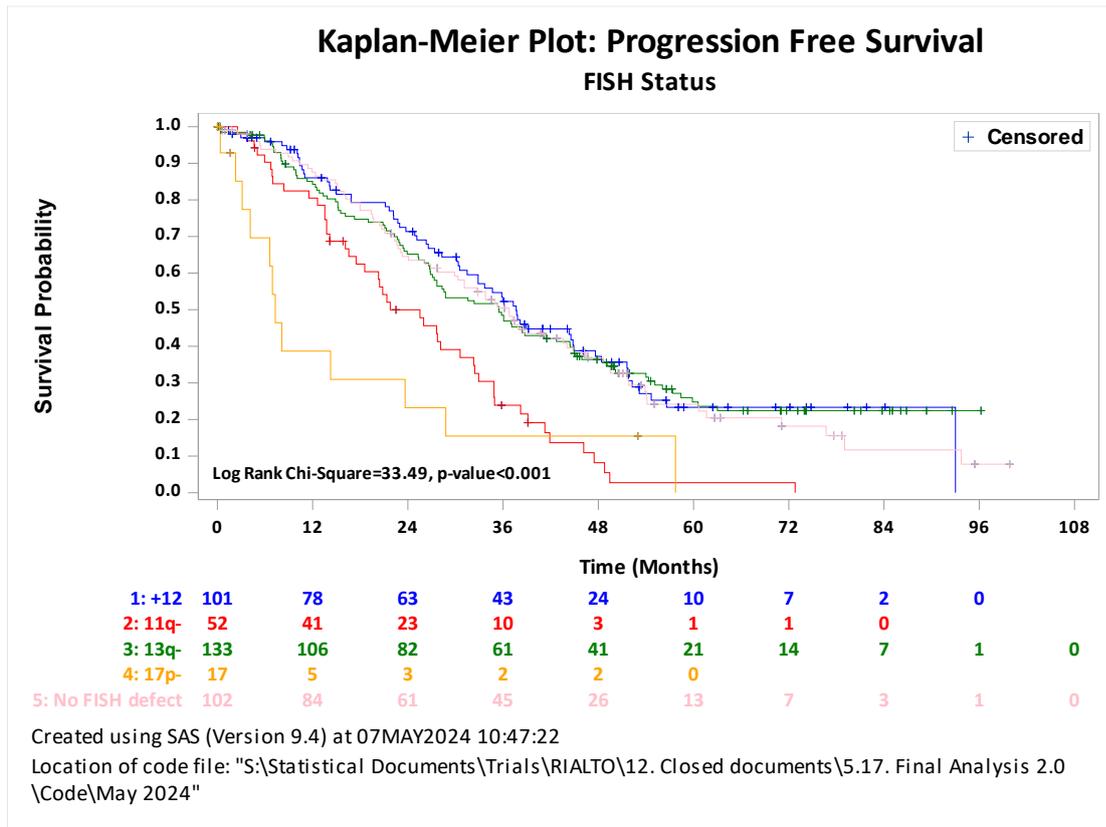


Figure 18-5 Kaplan Meier Plot: Progression Free Survival – FISH (17p-) – Treatment Comparison

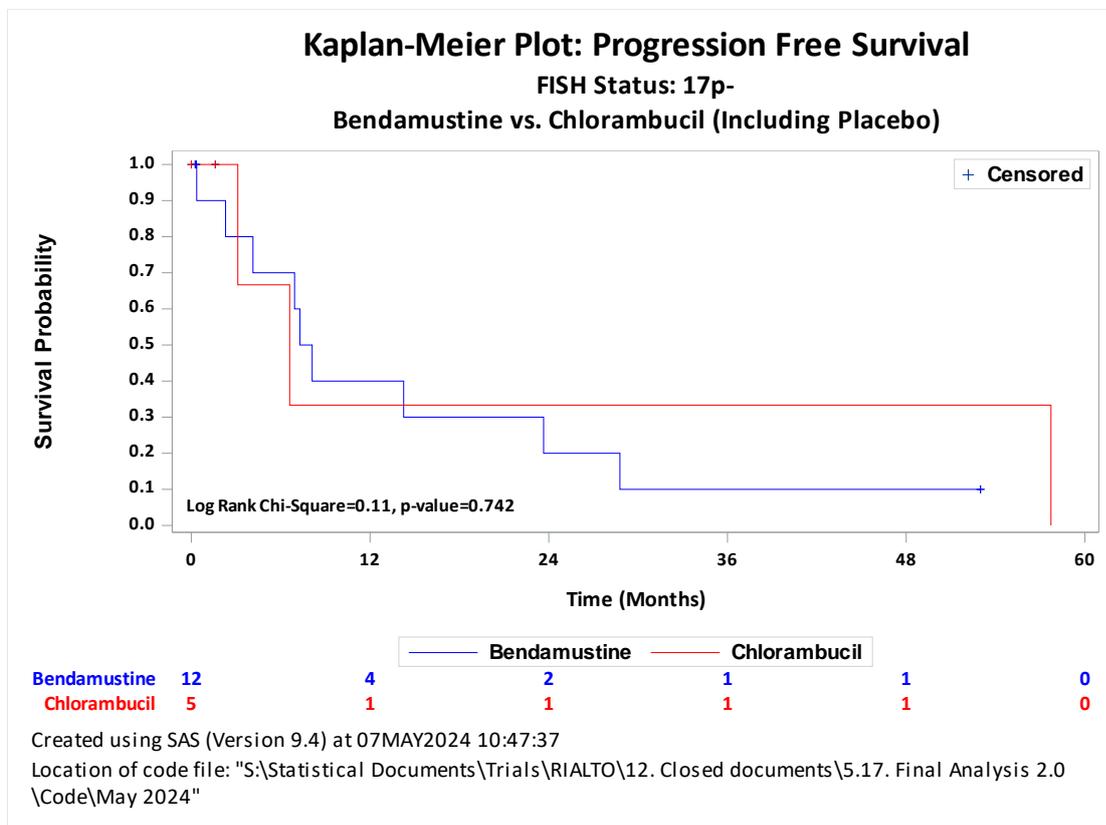


Figure 18-6 Kaplan Meier Plot: Progression Free Survival – FISH (11q-) – Treatment Comparison

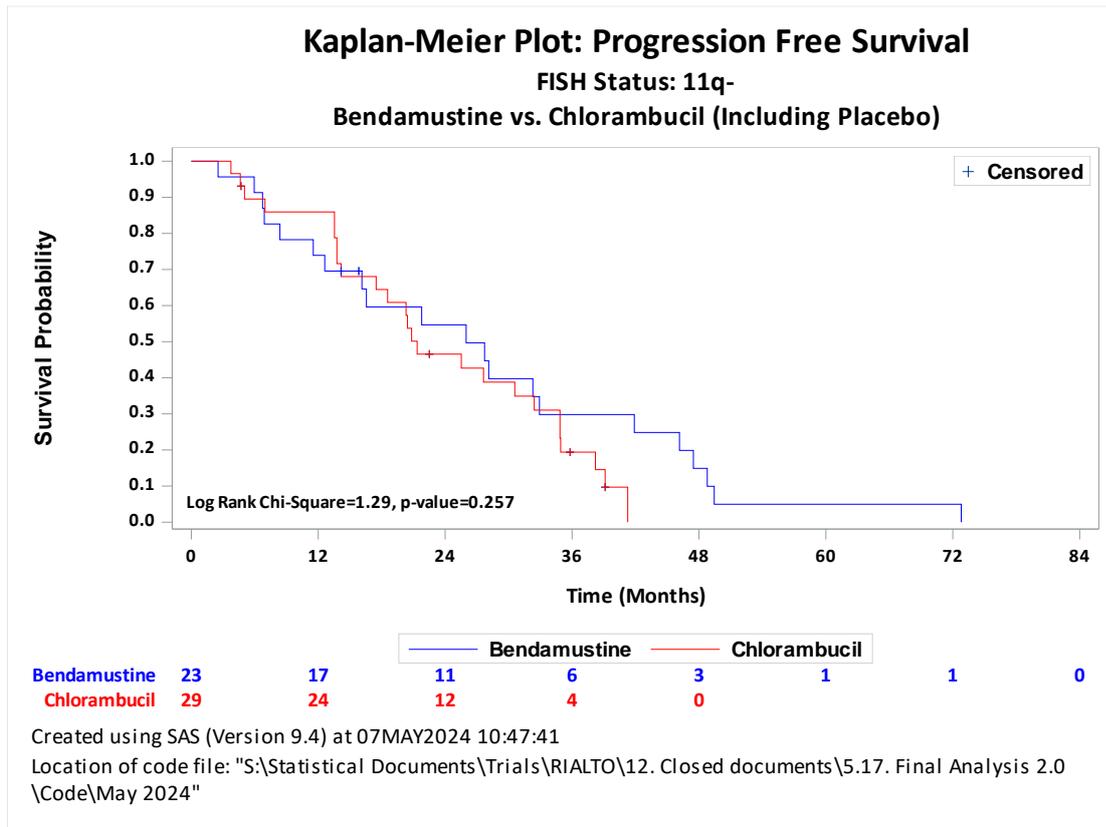


Figure 18-7 Kaplan Meier Plot: Progression Free Survival – FISH (+12) – Treatment Comparison

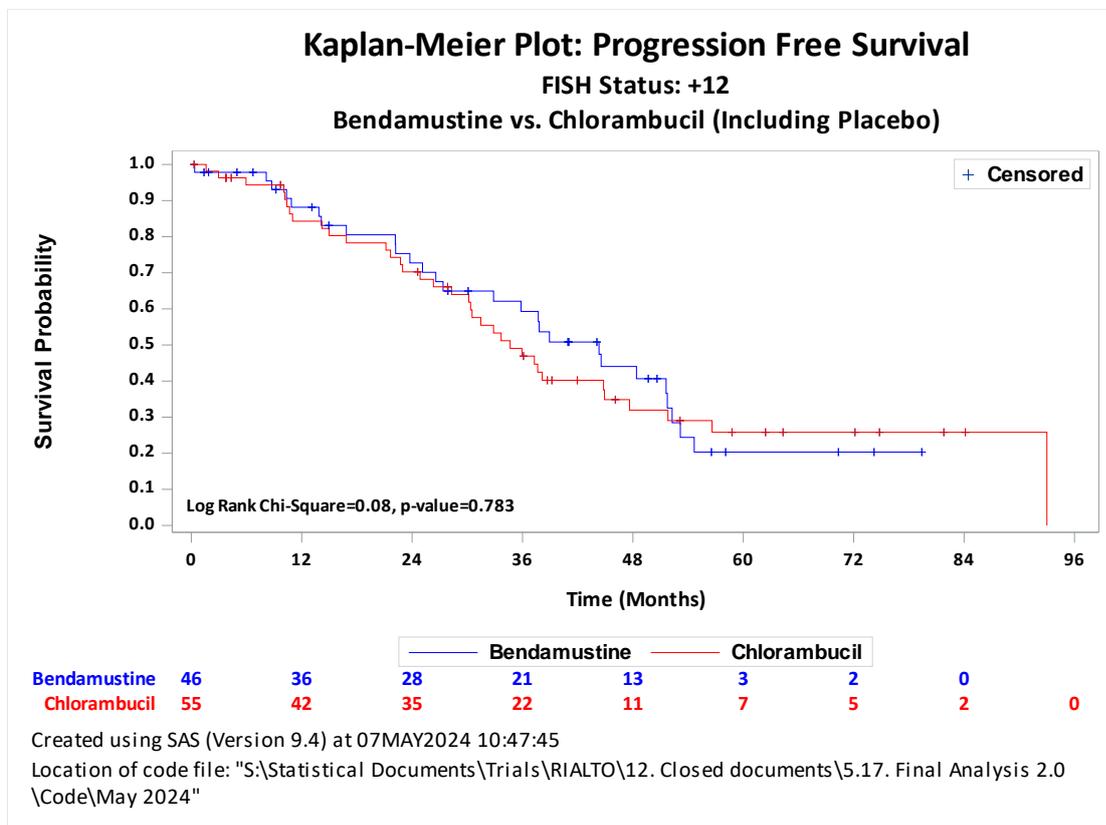


Figure 18-8 Kaplan Meier Plot: Progression Free Survival – FISH (13q-) – Treatment Comparison

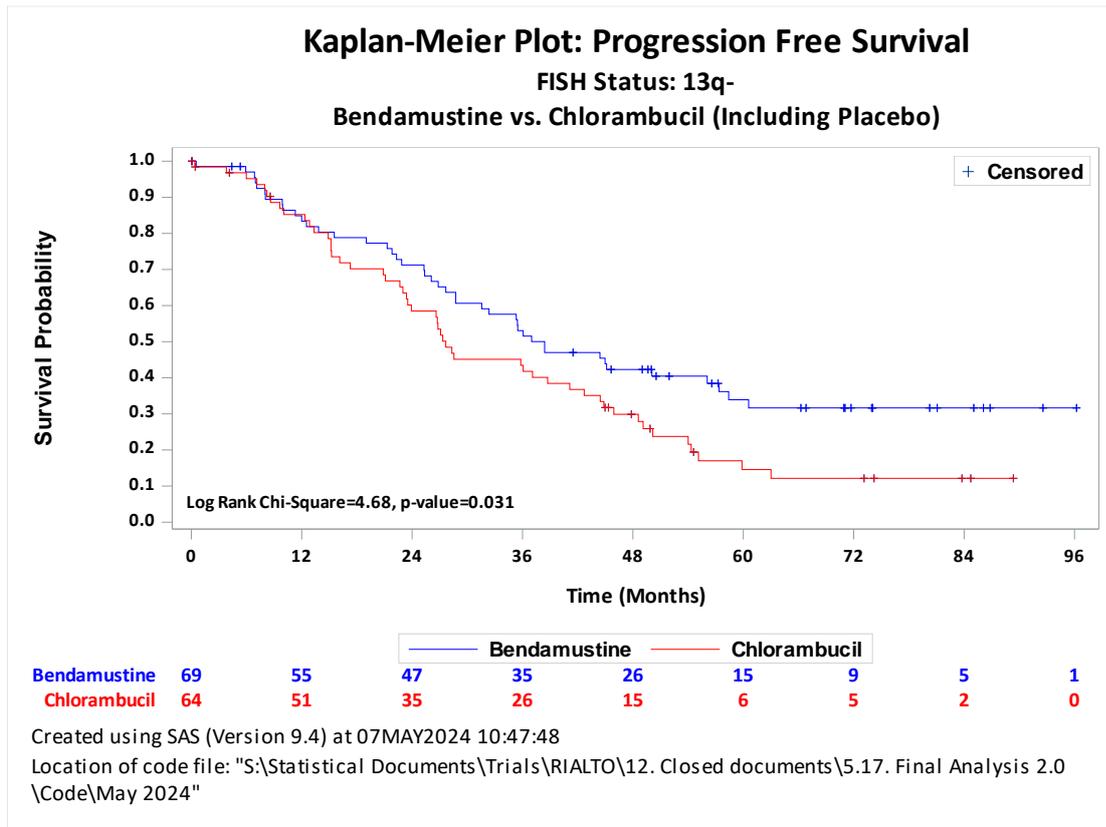


Figure 18-9 Kaplan Meier Plot: Progression Free Survival – FISH (No FISH Defect) – Treatment Comparison

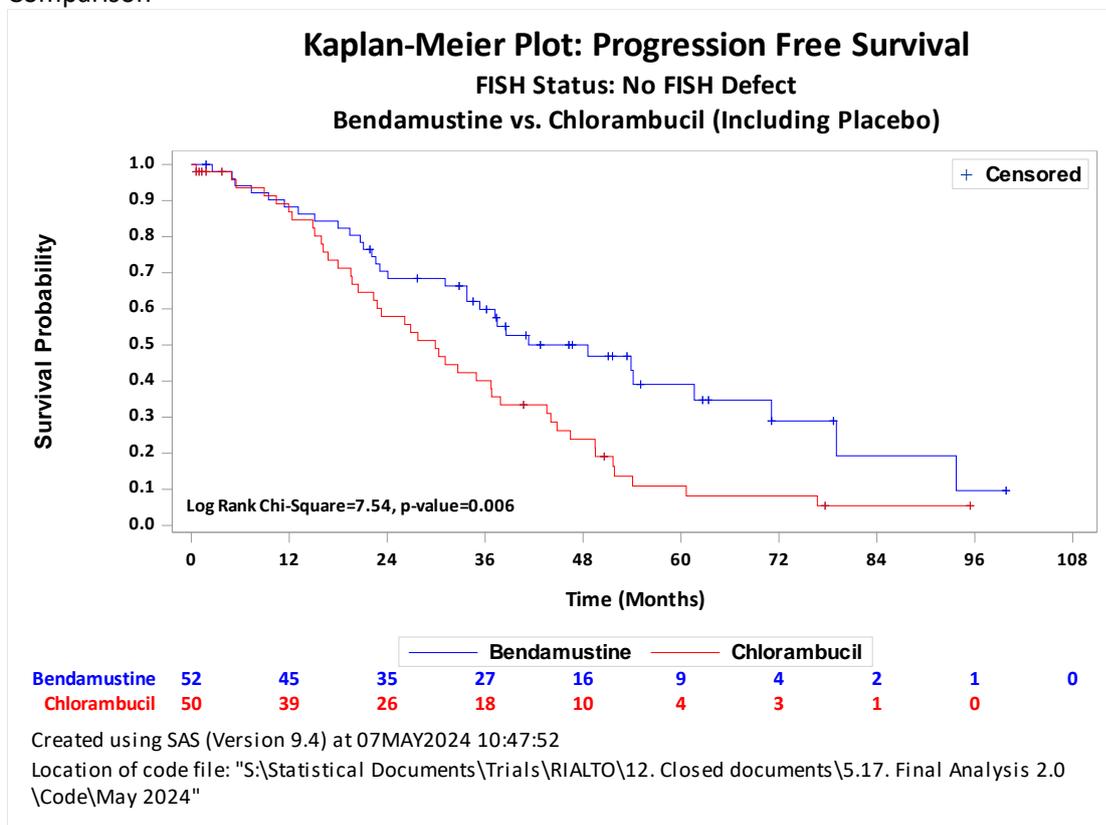


Figure 18-10 Kaplan Meier Plot: Overall Survival – IGHV Status

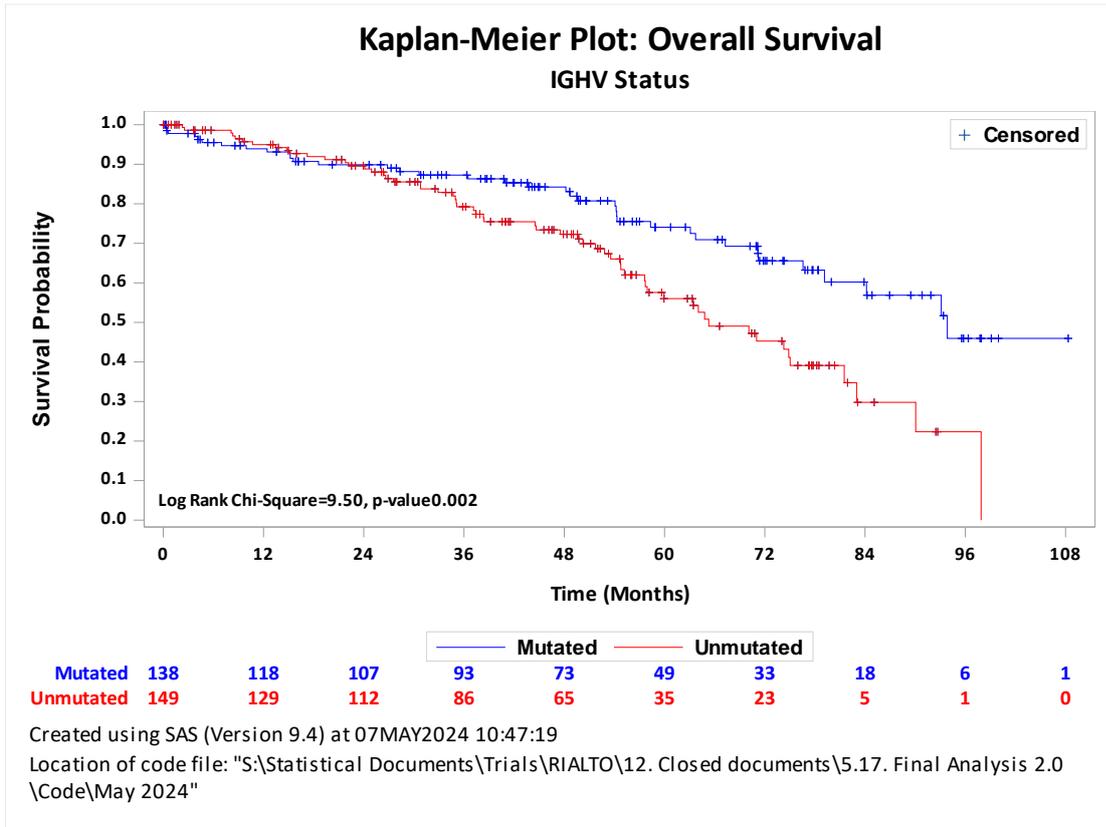


Figure 18-11 Kaplan Meier Plot: Overall Survival – IGHV (Mutated) – Treatment Comparison

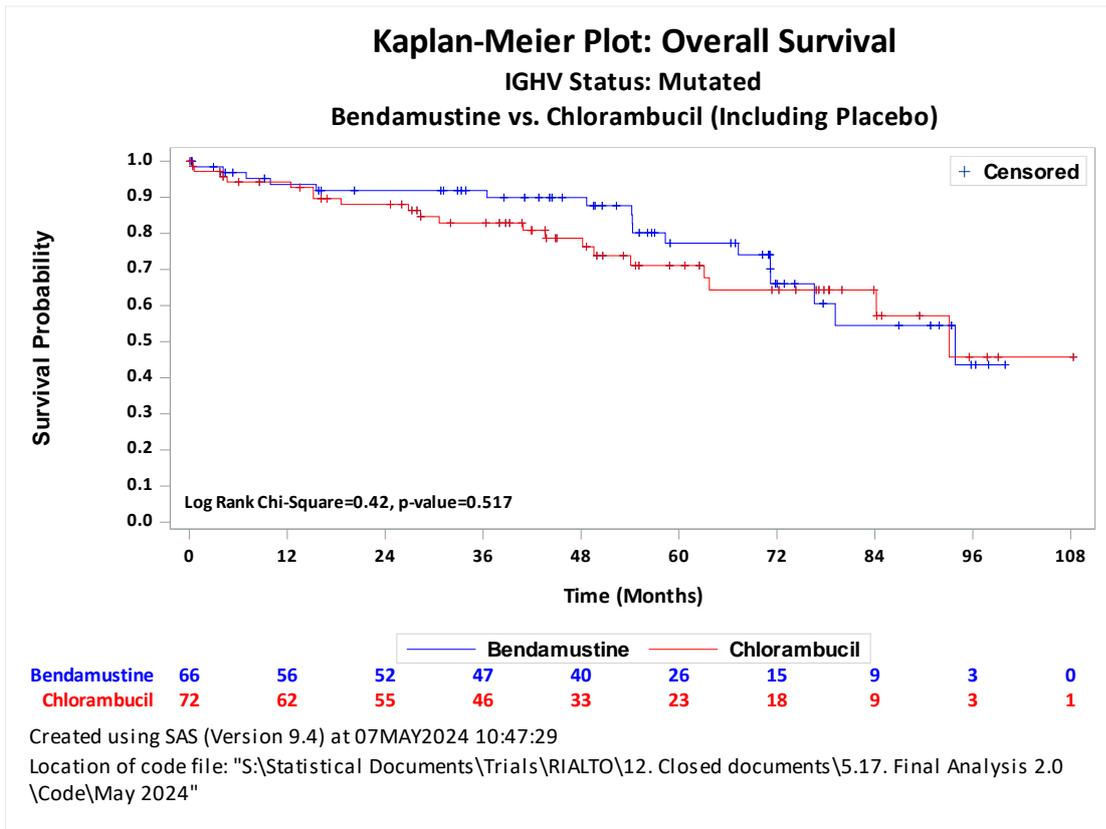


Figure 18-12 Kaplan Meier Plot: Overall Survival – IGHV (Unmutated) – Treatment Comparison

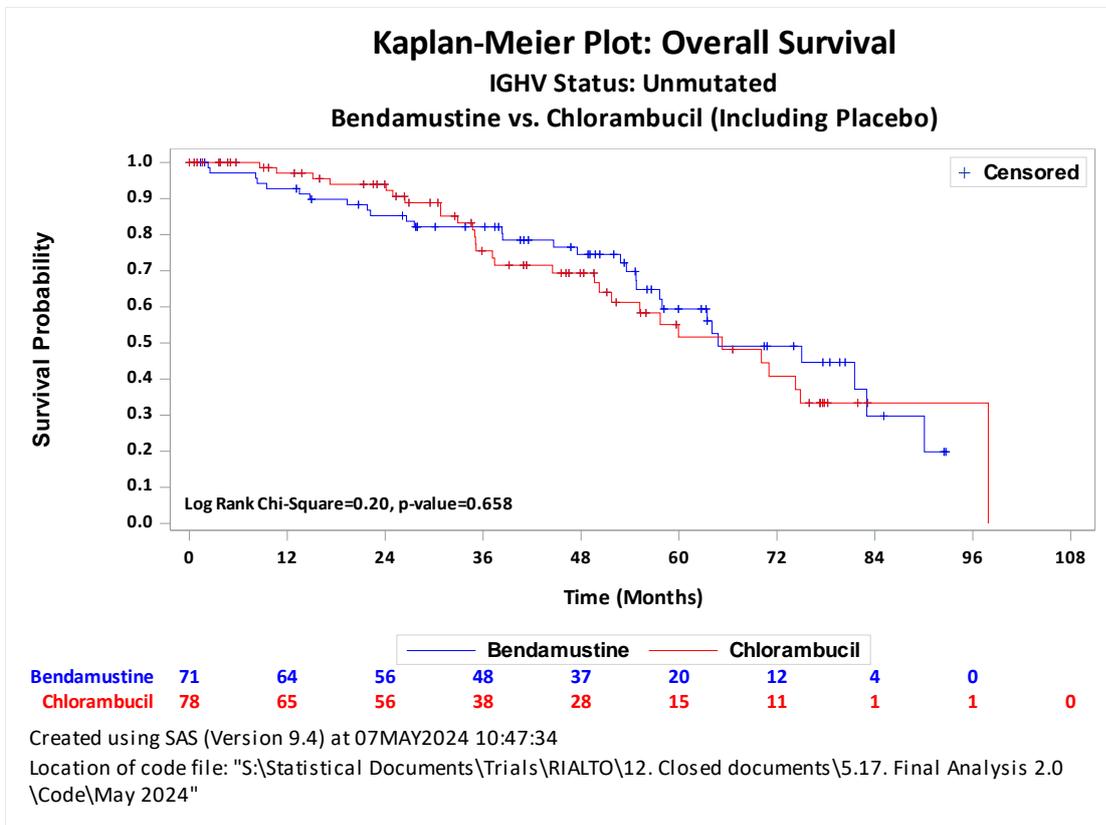


Figure 18-13 Kaplan Meier Plot: Overall Survival – FISH Status

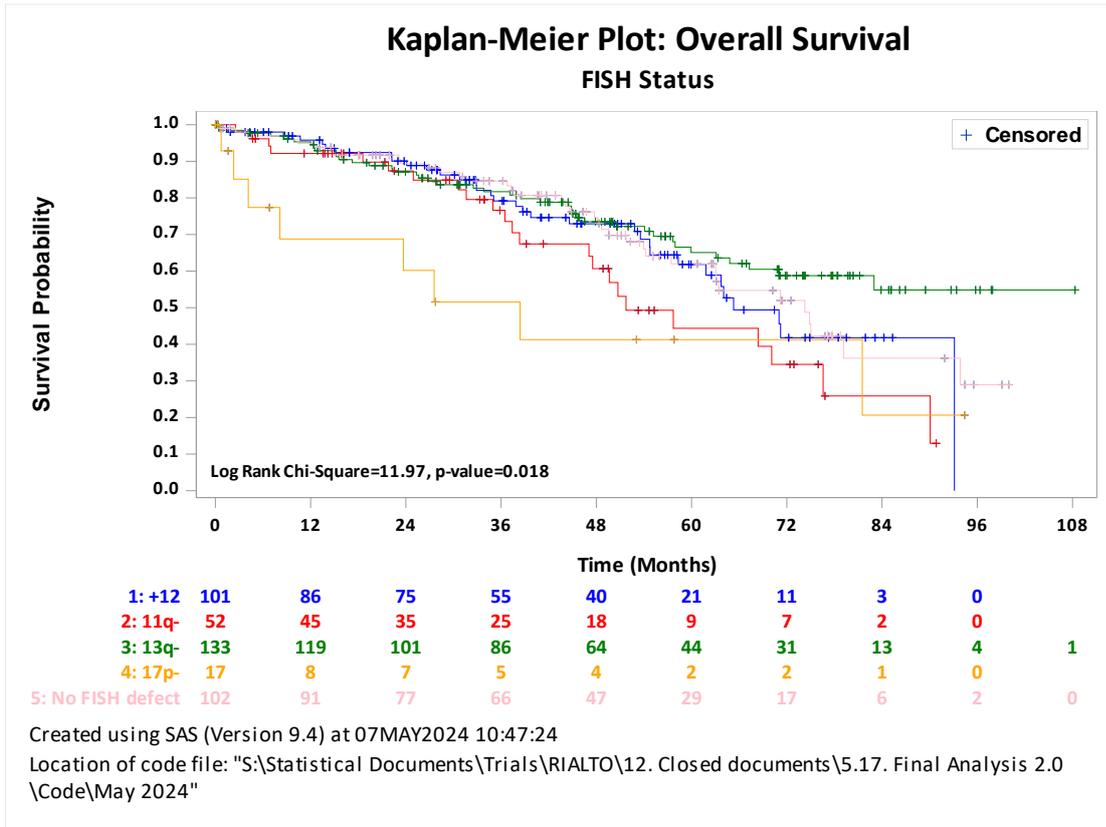


Figure 18-14 Kaplan Meier Plot: Overall Survival – FISH (17p-) – Treatment Comparison

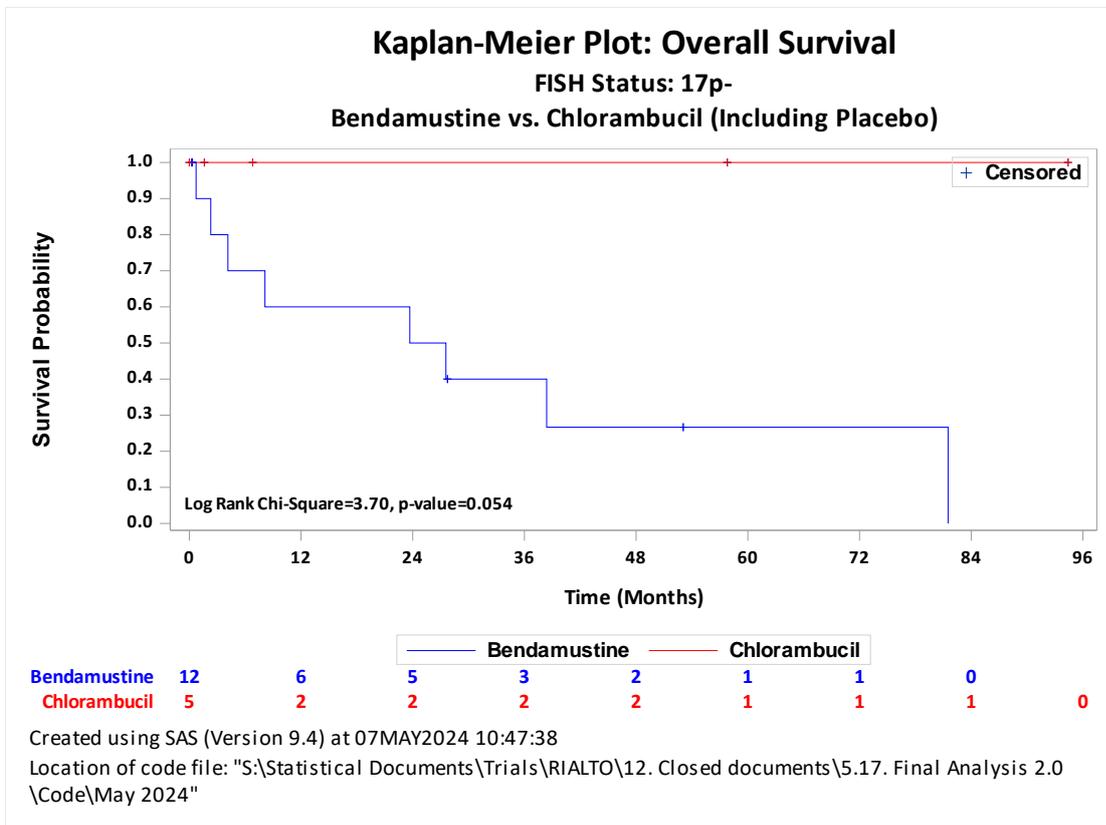


Figure 18-15 Kaplan Meier Plot: Overall Survival – FISH (11q-) – Treatment Comparison

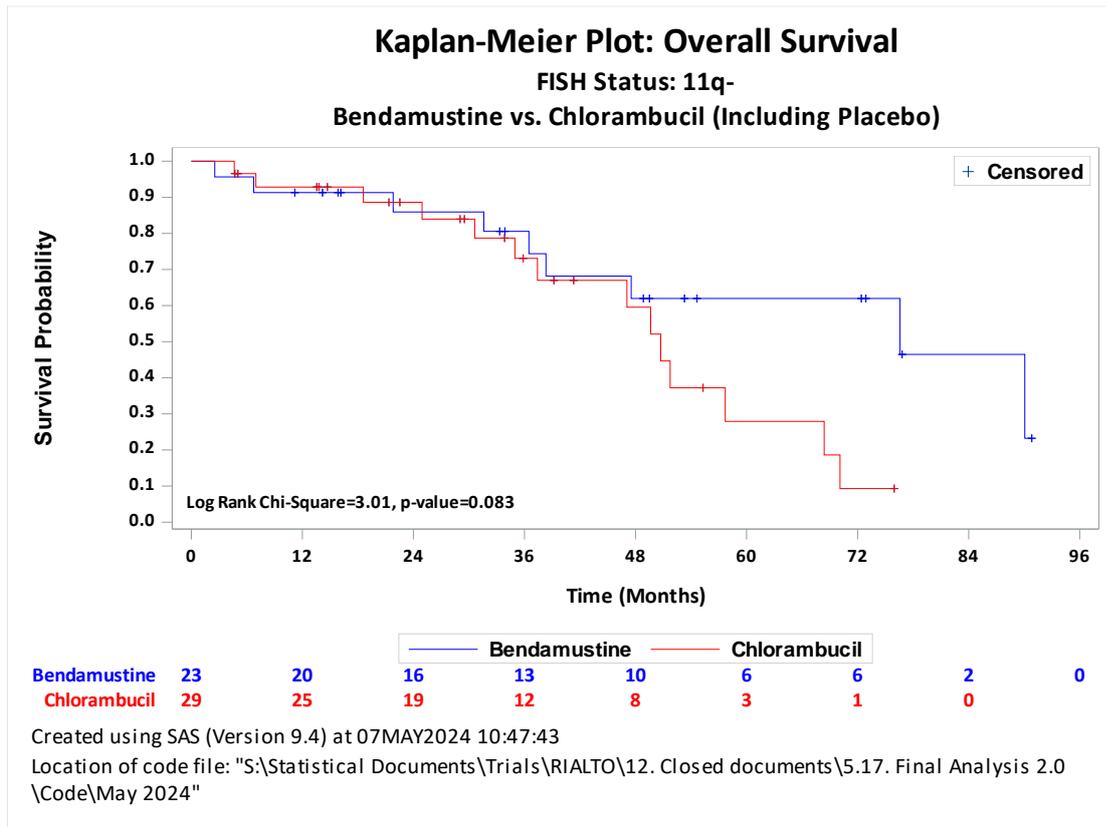


Figure 18-16 Kaplan Meier Plot: Overall Survival – FISH (+12) – Treatment Comparison

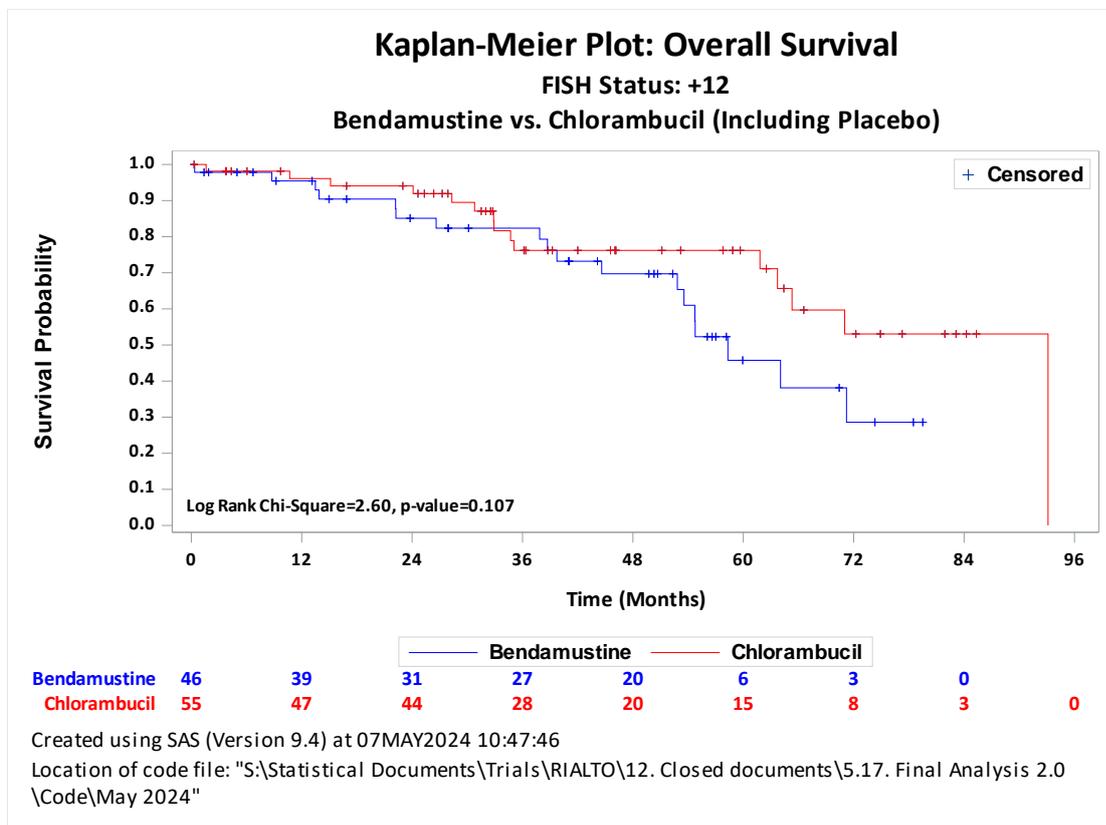


Figure 18-17 Kaplan Meier Plot: Overall Survival – FISH (13q-) – Treatment Comparison

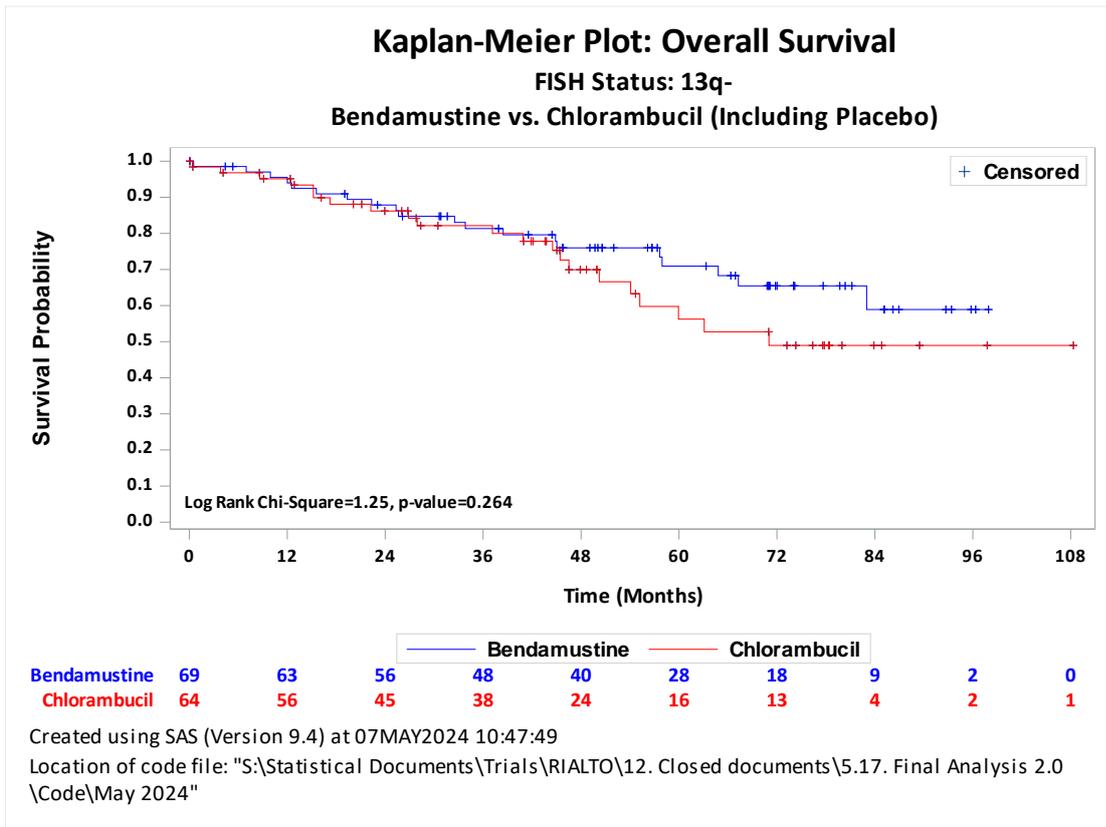


Figure 18-18 Kaplan Meier Plot: Overall Survival – FISH (No FISH Defect) – Treatment Comparison

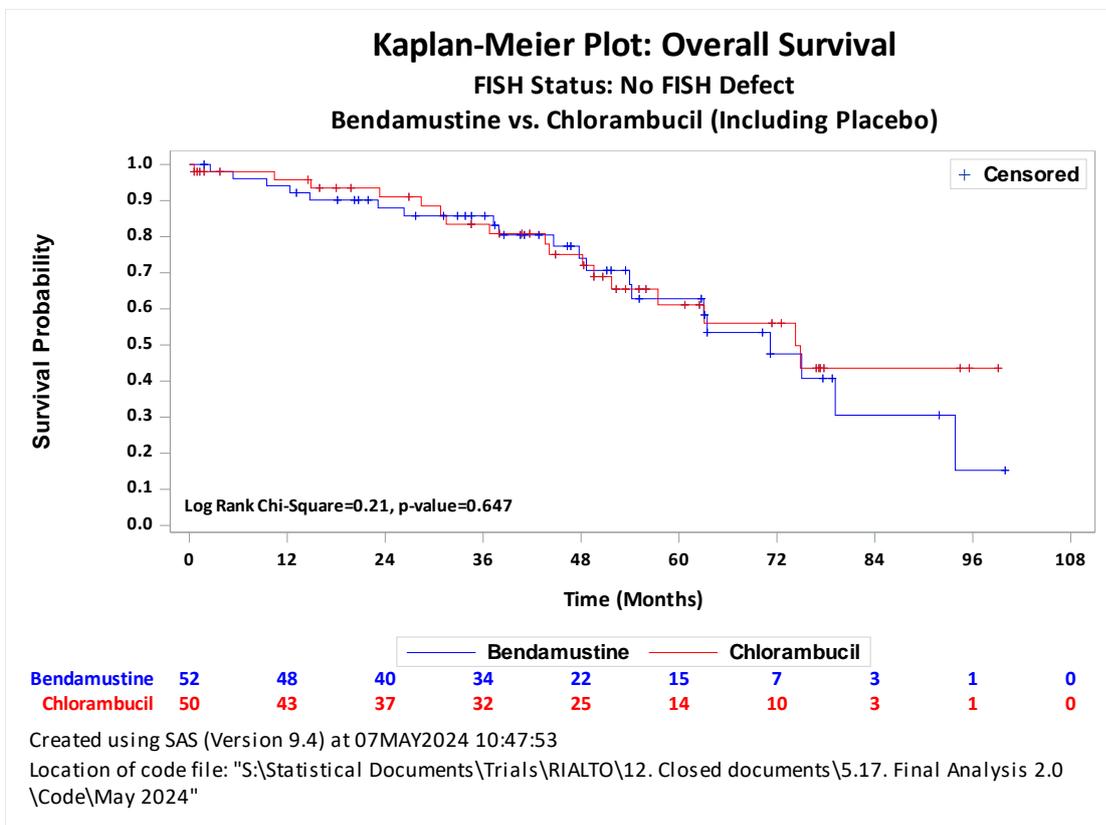


Figure 18-19 Kaplan Meier Plot: Time to Treatment Failure – IGHV Status

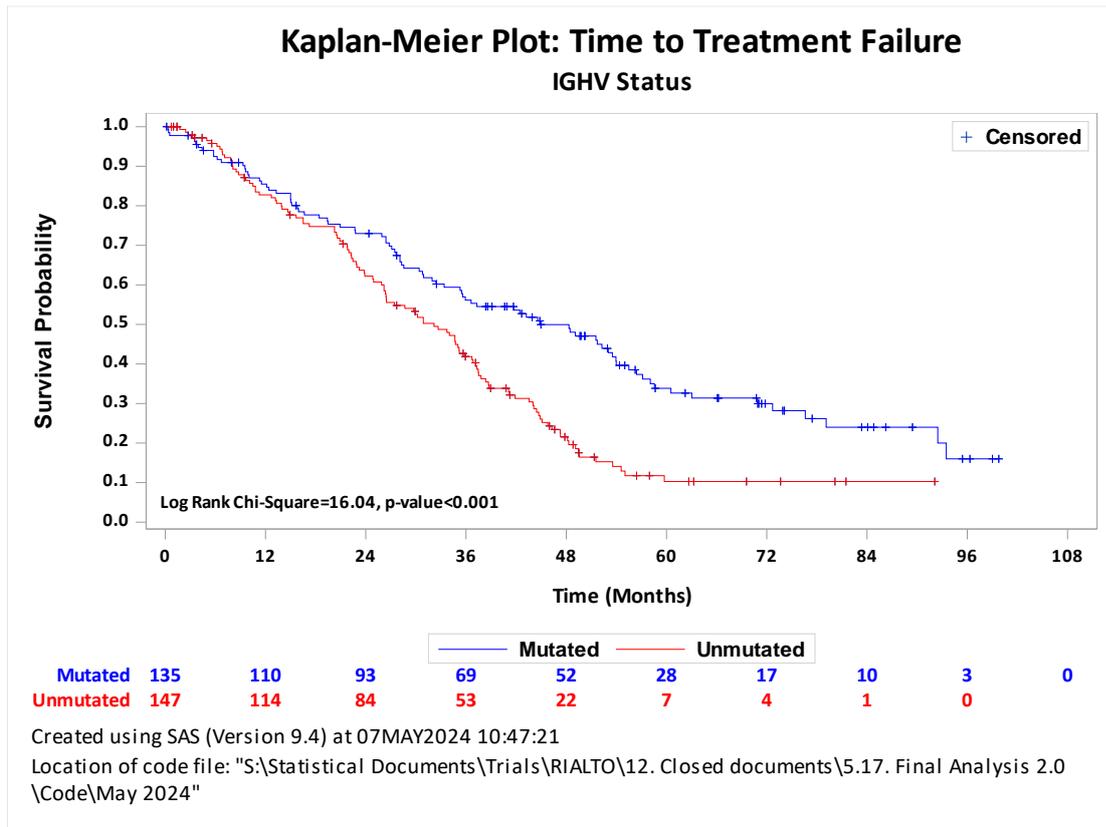


Figure 18-20 Kaplan Meier Plot: Time to Treatment Failure – IGHV (Mutated) – Treatment Comparison

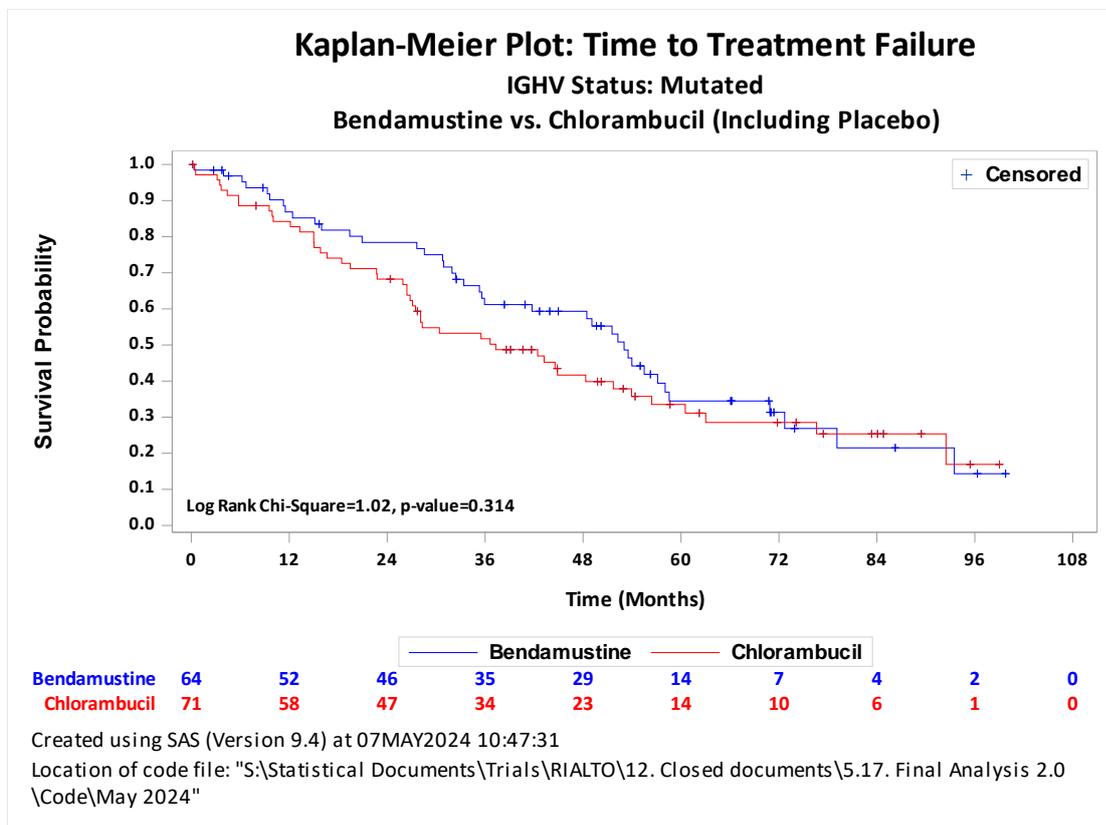


Figure 18-21 Kaplan Meier Plot: Time to Treatment Failure – IGHV (Unmutated) – Treatment Comparison

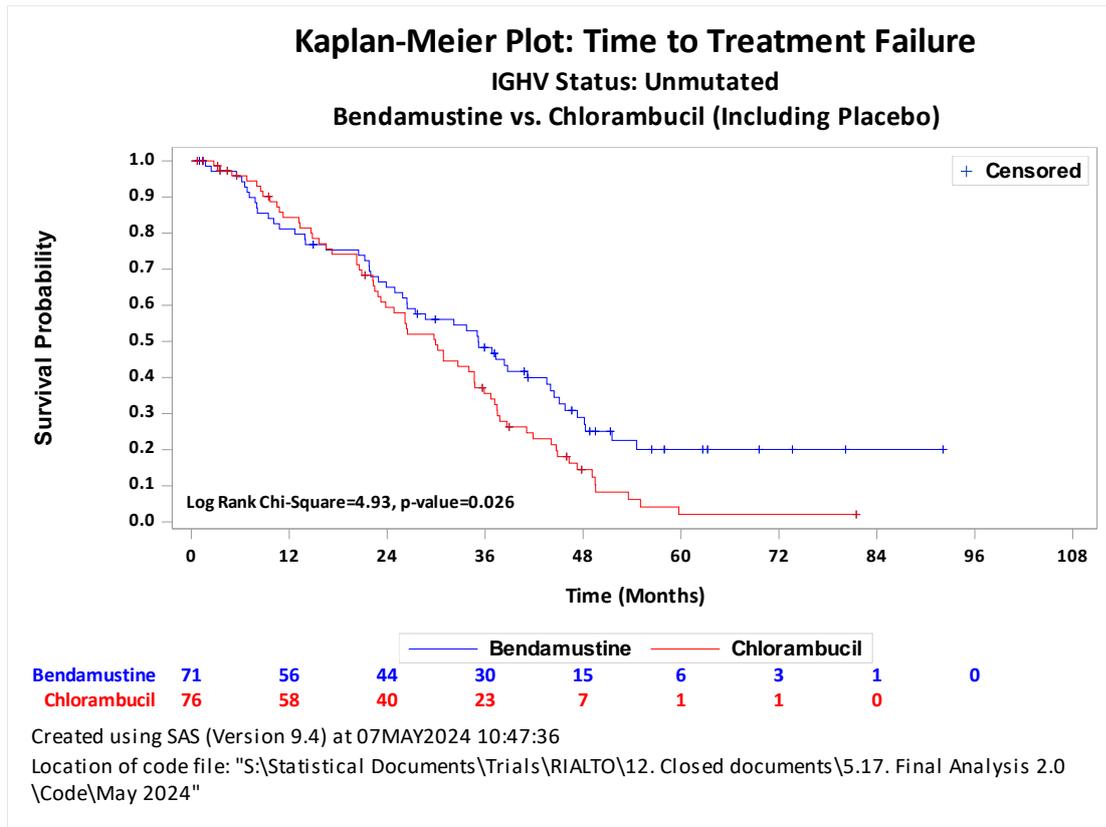


Figure 18-22 Kaplan Meier Plot: Time to Treatment Failure – FISH Status

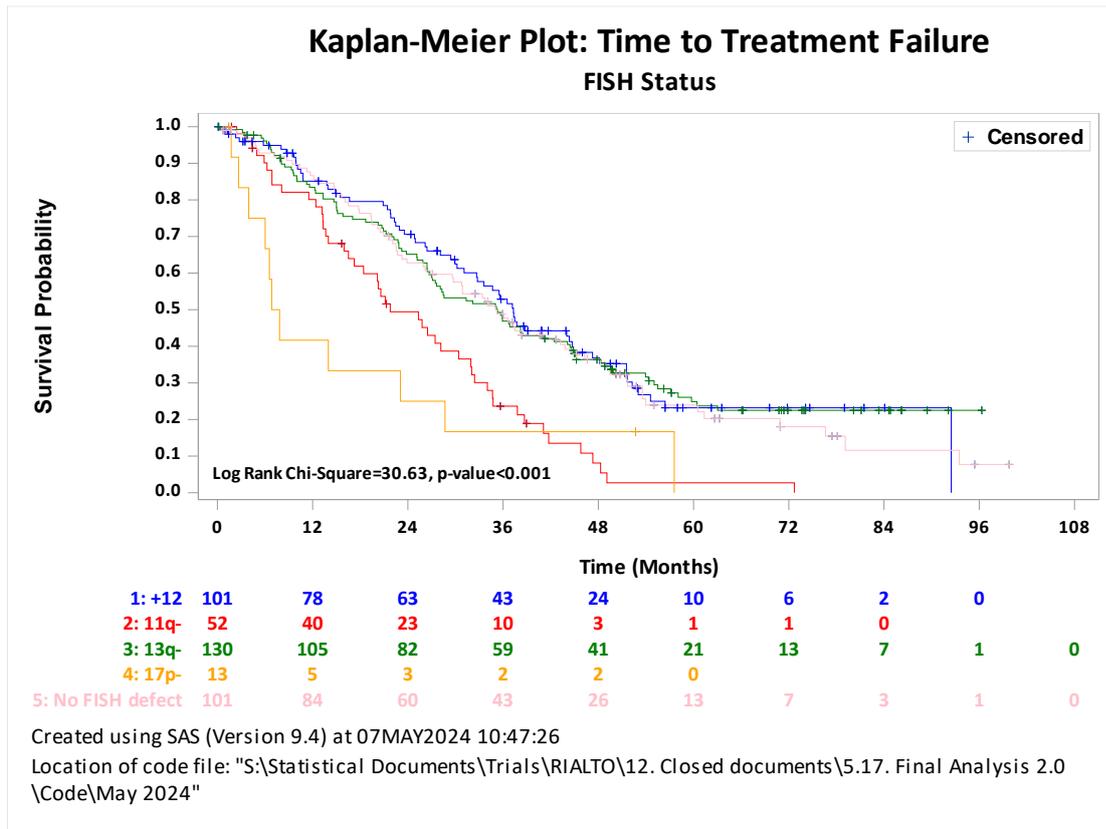


Figure 18-23 Kaplan Meier Plot: Time to Treatment Failure – FISH (17p-) – Treatment Comparison

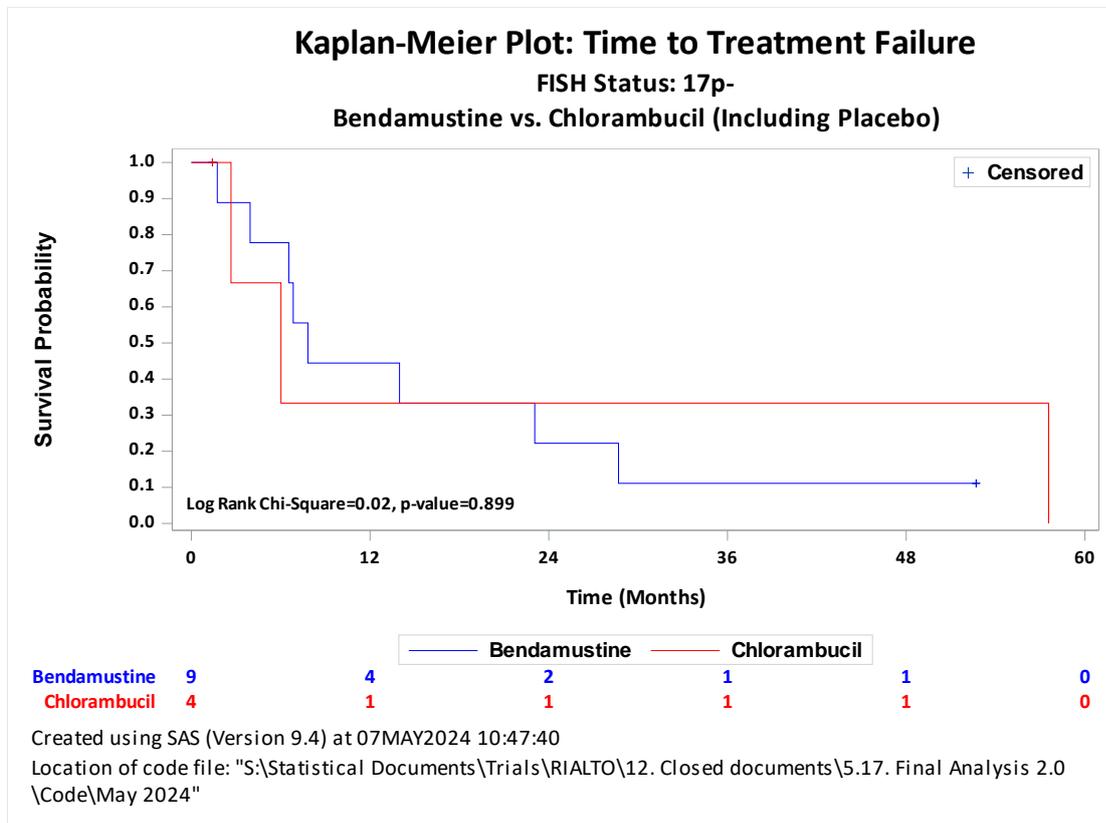


Figure 18-24 Kaplan Meier Plot: Time to Treatment Failure – FISH (11q-) – Treatment Comparison

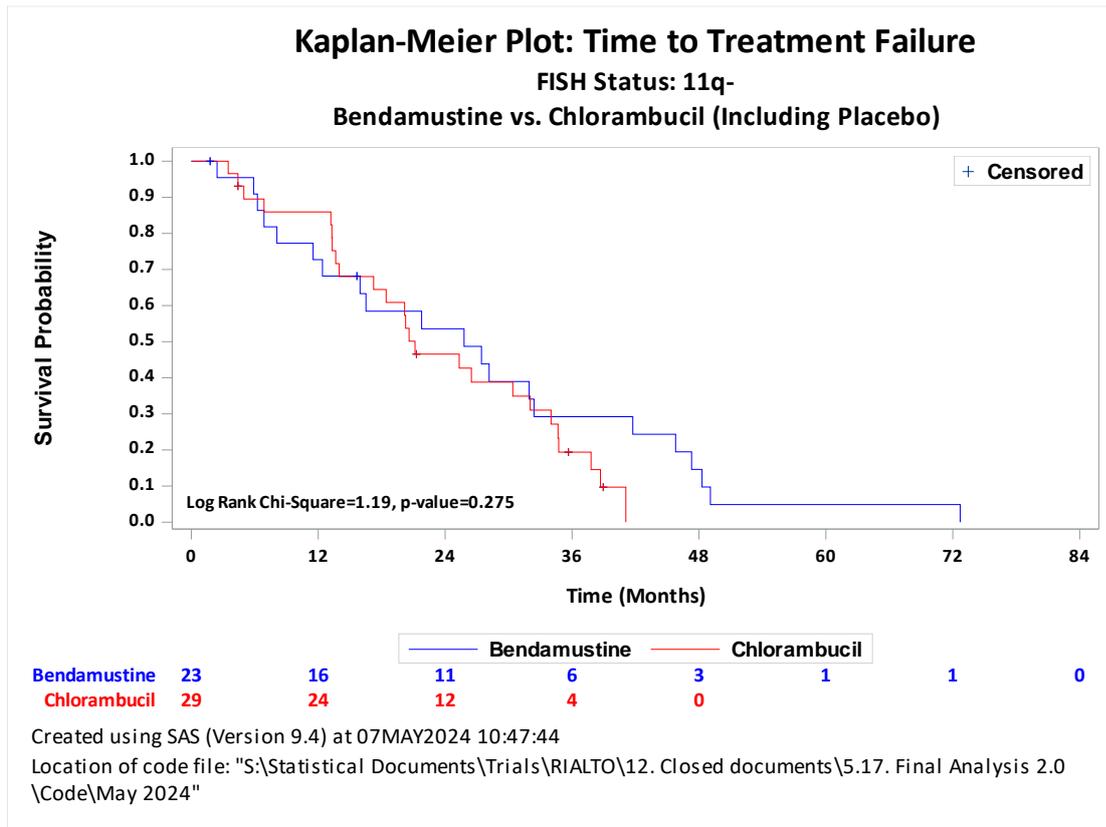


Figure 18-25 Kaplan Meier Plot: Time to Treatment Failure – FISH (+12) – Treatment Comparison

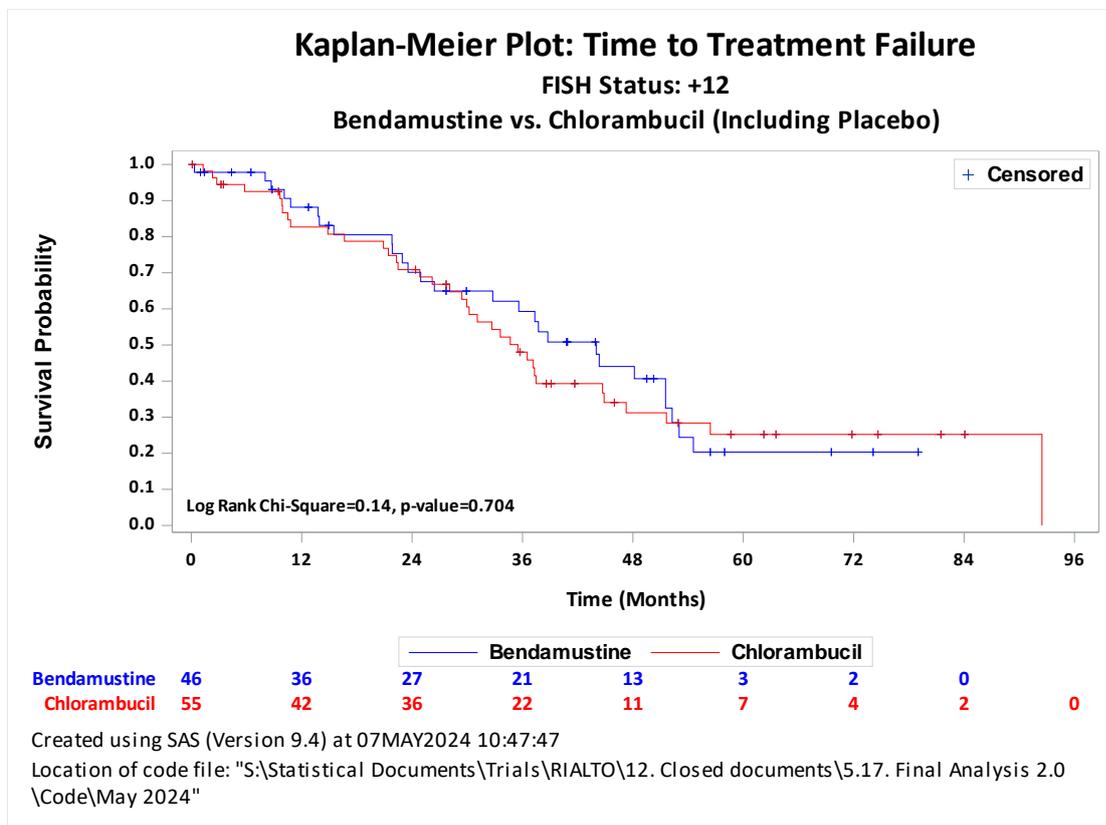


Figure 18-26 Kaplan Meier Plot: Time to Treatment Failure – FISH (13q-) – Treatment Comparison

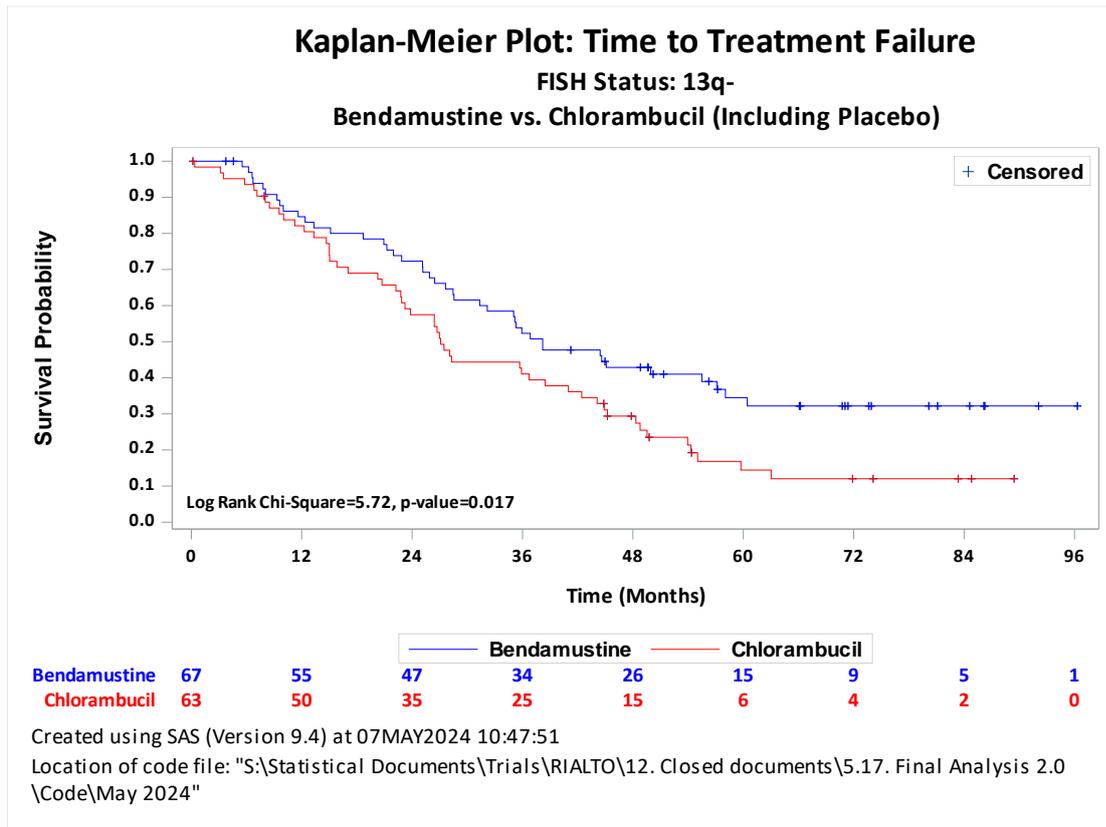


Figure 18-27 Kaplan Meier Plot: Time to Treatment Failure – FISH (No FISH Defect) – Treatment Comparison

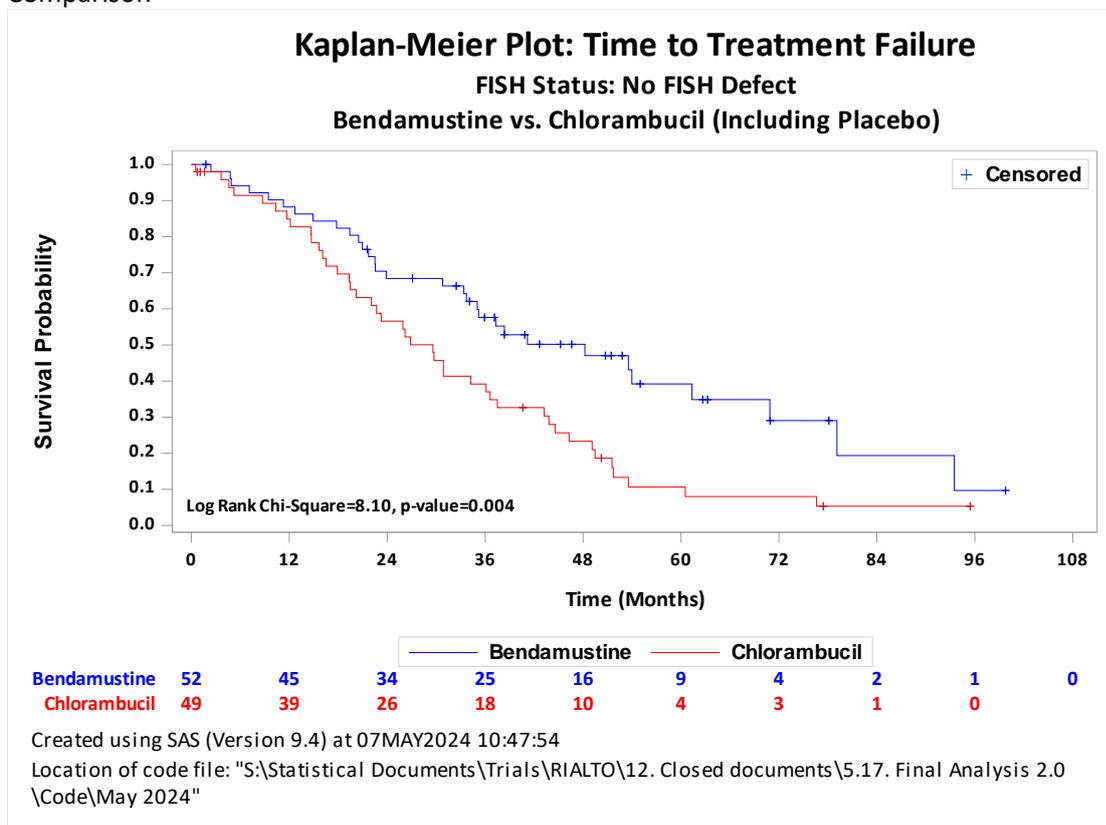


Table 18-1 Response/MRD by Biomarkers – Treatment Comparison

IGHV/FISH Status	Subgroup	Response/MRD	Bendamustine	Chlorambucil	Total
IGHV Status	Mutated	Response			
		Response, no. patients	66	72	138
		Complete remission	1 (2%)	1 (1%)	2 (1%)
		Partial remission	39 (59%)	36 (50%)	75 (54%)
		Stable disease	7 (11%)	10 (14%)	17 (12%)
		Progressive disease	1 (2%)	2 (3%)	3 (2%)
		Missing	18 (27%)	23 (32%)	41 (30%)
		MRD			
		MRD, no. patients	66	72	138
		MRD+ve	21 (32%)	32 (44%)	53 (38%)
		MRD-ve	4 (6%)	1 (1%)	5 (4%)
		Missing	41 (62%)	39 (54%)	80 (58%)
	Unmutated	Response			
		Response, no. patients	71	78	149
		Partial remission	37 (52%)	32 (41%)	69 (46%)
		Stable disease	9 (13%)	15 (19%)	24 (16%)
		Progressive disease	3 (4%)	0 (0%)	3 (2%)
		Missing	22 (31%)	31 (40%)	53 (36%)
		MRD			
		MRD, no. patients	71	78	149
		MRD+ve	22 (31%)	23 (29%)	45 (30%)
		MRD-ve	8 (11%)	1 (1%)	9 (6%)
Missing		41 (58%)	54 (69%)	95 (64%)	
FISH Status		17p-	Response		
	Response, no. patients		12	5	17
	Partial remission		2 (17%)	1 (20%)	3 (18%)
	Stable disease		1 (8%)	0 (0%)	1 (6%)
	Progressive disease		2 (17%)	1 (20%)	3 (18%)
	Missing		7 (58%)	3 (60%)	10 (59%)
	MRD				
	MRD, no. patients		12	5	17
	MRD+ve		4 (33%)	1 (20%)	5 (29%)
	Missing	8 (67%)	4 (80%)	12 (71%)	
	11q-	Response			

IGHV/FISH Status	Subgroup	Response/MRD	Bendamustine	Chlorambucil	Total
		Response, no. patients	23	29	52
		Partial remission	10 (43%)	12 (41%)	22 (42%)
		Stable disease	5 (22%)	7 (24%)	12 (23%)
		Progressive disease	1 (4%)	1 (3%)	2 (4%)
		Missing	7 (30%)	9 (31%)	16 (31%)
		MRD			
		MRD, no. patients	23	29	52
		MRD+ve	9 (39%)	14 (48%)	23 (44%)
		MRD-ve	2 (9%)	0 (0%)	2 (4%)
		Missing	12 (52%)	15 (52%)	27 (52%)
	+12	Response			
		Response, no. patients	46	55	101
		Partial remission	24 (52%)	22 (40%)	46 (46%)
		Stable disease	2 (4%)	10 (18%)	12 (12%)
		Progressive disease	1 (2%)	1 (2%)	2 (2%)
		Missing	19 (41%)	22 (40%)	41 (41%)
		MRD			
		MRD, no. patients	46	55	101
		MRD+ve	9 (20%)	21 (38%)	30 (30%)
		MRD-ve	5 (11%)	4 (7%)	9 (9%)
	Missing	32 (70%)	30 (55%)	62 (61%)	
	13q-	Response			
		Response, no. patients	69	64	133
		Complete remission	1 (1%)	0 (0%)	1 (1%)
		Partial remission	41 (59%)	37 (58%)	78 (59%)
		Stable disease	7 (10%)	8 (13%)	15 (11%)
		Progressive disease	4 (6%)	0 (0%)	4 (3%)
		Missing	16 (23%)	19 (30%)	35 (26%)
		MRD			
		MRD, no. patients	69	64	133
		MRD+ve	22 (32%)	24 (38%)	46 (35%)
	MRD-ve	4 (6%)	0 (0%)	4 (3%)	
	Missing	43 (62%)	40 (63%)	83 (62%)	
No FISH defect	Response				
	Response, no. patients	52	50	102	
	Complete remission	0 (0%)	1 (2%)	1 (1%)	

IGHV/FISH Status	Subgroup	Response/MRD	Bendamustine	Chlorambucil	Total
		Partial remission	27 (52%)	21 (42%)	48 (47%)
		Stable disease	8 (15%)	10 (20%)	18 (18%)
		Missing	17 (33%)	18 (36%)	35 (34%)
		MRD			
		MRD, no. patients	52	50	102
		MRD+ve	14 (27%)	19 (38%)	33 (32%)
		MRD-ve	5 (10%)	0 (0%)	5 (5%)
		Missing	33 (63%)	31 (62%)	64 (63%)

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Table 18-2 Response/MRD by IGHV Status (Mutated vs. Unmutated)

Response/MRD	Mutated	Unmutated	Total
Response			
Response, no. patients	138	149	287
Complete remission	2 (1%)	0 (0%)	2 (1%)
Partial remission	75 (54%)	69 (46%)	144 (50%)
Stable disease	17 (12%)	24 (16%)	41 (14%)
Progressive disease	3 (2%)	3 (2%)	6 (2%)
Missing	41 (30%)	53 (36%)	94 (33%)
MRD			
MRD, no. patients	138	149	287
MRD+ve	53 (38%)	45 (30%)	98 (34%)
MRD-ve	5 (4%)	9 (6%)	14 (5%)
Missing	80 (58%)	95 (64%)	175 (61%)

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Table 18-3 Response/MRD by FISH Status (17p- vs. 11q- vs. +12 vs. 13q- vs. no FISH defect)

Response/MRD	17p-	11q-	+12	13q-	No FISH Defect	Total
Response						
Response, no. patients	17	52	101	133	102	405
Complete remission	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)	2 (0%)
Partial remission	3 (18%)	22 (42%)	46 (46%)	78 (59%)	48 (47%)	197 (49%)
Stable disease	1 (6%)	12 (23%)	12 (12%)	15 (11%)	18 (18%)	58 (14%)
Progressive disease	3 (18%)	2 (4%)	2 (2%)	4 (3%)	0 (0%)	11 (3%)
Missing	10 (59%)	16 (31%)	41 (41%)	35 (26%)	35 (34%)	137 (34%)
MRD						
MRD, no. patients	17	52	101	133	102	405
MRD+ve	5 (29%)	23 (44%)	30 (30%)	46 (35%)	33 (32%)	137 (34%)
MRD-ve	0 (0%)	2 (4%)	9 (9%)	4 (3%)	5 (5%)	20 (5%)
Missing	12 (71%)	27 (52%)	62 (61%)	83 (62%)	64 (63%)	248 (61%)

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Table 18-4 Adverse Events by Biomarkers – Treatment Comparison

Biomarker	Subgroup	AE Severity	Bendamustine	Chlorambucil	Total
IGHV	Mutated	1	367 (56%)	433 (53%)	800 (55%)
		2	205 (31%)	261 (32%)	466 (32%)
		3	65 (10%)	96 (12%)	161 (11%)
		4	14 (2%)	13 (2%)	27 (2%)
		5	0 (0%)	1 (0%)	1 (0%)
		Missing	1 (0%)	11 (1%)	12 (1%)
	Unmutated	1	377 (55%)	350 (54%)	727 (54%)
		2	245 (35%)	225 (35%)	470 (35%)
		3	54 (8%)	64 (10%)	118 (9%)
		4	8 (1%)	8 (1%)	16 (1%)
		Missing	7 (1%)	3 (0%)	10 (1%)
	FISH	17p-	1	68 (55%)	3 (30%)
2			43 (35%)	5 (50%)	48 (36%)
3			12 (10%)	2 (20%)	14 (11%)
11q-		1	76 (52%)	99 (51%)	175 (51%)
		2	52 (35%)	66 (34%)	118 (35%)
		3	18 (12%)	22 (11%)	40 (12%)
		4	1 (1%)	5 (3%)	6 (2%)
		Missing	0 (0%)	1 (1%)	1 (0%)
+12		1	242 (54%)	323 (60%)	565 (57%)
		2	159 (35%)	154 (29%)	313 (32%)
		3	41 (9%)	46 (9%)	87 (9%)
		4	4 (1%)	7 (1%)	11 (1%)
		Missing	5 (1%)	4 (1%)	9 (1%)
13q-		1	491 (62%)	285 (48%)	776 (56%)
		2	215 (27%)	228 (38%)	443 (32%)
		3	70 (9%)	71 (12%)	141 (10%)
		4	13 (2%)	11 (2%)	24 (2%)
		5	0 (0%)	1 (0%)	1 (0%)
		Missing	7 (1%)	4 (1%)	11 (1%)
No FISH defect		1	213 (46%)	275 (54%)	488 (50%)
		2	167 (36%)	179 (35%)	346 (35%)
		3	62 (13%)	50 (10%)	112 (11%)
		4	20 (4%)	4 (1%)	24 (2%)
		Missing	5 (1%)	3 (1%)	8 (1%)

Biomarker	Subgroup	AE Severity	Bendamustine	Chlorambucil	Total
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Table 18-5 Serious Adverse Events by Biomarkers – Treatment Comparison

Biomarker	Subgroup	SAE Severity	Bendamustine	Chlorambucil	Total
IGHV	Mutated	1	18 (16%)	14 (13%)	32 (15%)
		2	42 (37%)	39 (37%)	81 (37%)
		3	34 (30%)	39 (37%)	73 (33%)
		4	5 (4%)	5 (5%)	10 (5%)
		5	3 (3%)	2 (2%)	5 (2%)
		Missing	12 (11%)	6 (6%)	18 (8%)
	Unmutated	1	19 (21%)	9 (14%)	28 (18%)
		2	21 (23%)	17 (27%)	38 (25%)
		3	29 (32%)	23 (36%)	52 (34%)
		4	5 (5%)	9 (14%)	14 (9%)
		5	3 (3%)	1 (2%)	4 (3%)
		Missing	14 (15%)	5 (8%)	19 (12%)
FISH	17p-	1	3 (18%)	0 (0%)	3 (18%)
		2	2 (12%)	0 (0%)	2 (12%)
		3	6 (35%)	0 (0%)	6 (35%)
		4	1 (6%)	0 (0%)	1 (6%)
		5	2 (12%)	0 (0%)	2 (12%)
		Missing	3 (18%)	0 (0%)	3 (18%)
	11q-	1	3 (11%)	7 (21%)	10 (16%)
		2	5 (18%)	9 (27%)	14 (23%)
		3	14 (50%)	8 (24%)	22 (36%)
		4	1 (4%)	2 (6%)	3 (5%)
		5	1 (4%)	2 (6%)	3 (5%)
		Missing	4 (14%)	5 (15%)	9 (15%)
	+12	1	12 (18%)	9 (18%)	21 (18%)
		2	21 (32%)	17 (33%)	38 (33%)
		3	16 (25%)	17 (33%)	33 (28%)
		4	2 (3%)	6 (12%)	8 (7%)
		5	1 (2%)	1 (2%)	2 (2%)
		Missing	13 (20%)	1 (2%)	14 (12%)
	13q-	1	19 (18%)	8 (11%)	27 (15%)
		2	37 (35%)	25 (36%)	62 (35%)
		3	27 (26%)	28 (40%)	55 (31%)
		4	8 (8%)	4 (6%)	12 (7%)
		5	4 (4%)	0 (0%)	4 (2%)

Biomarker	Subgroup	SAE Severity	Bendamustine	Chlorambucil	Total
		Missing	10 (10%)	5 (7%)	15 (9%)
	No FISH defect	1	13 (20%)	13 (22%)	26 (21%)
		2	21 (32%)	12 (20%)	33 (26%)
		3	20 (31%)	26 (43%)	46 (37%)
		4	3 (5%)	5 (8%)	8 (6%)
		5	1 (2%)	0 (0%)	1 (1%)
		Missing	7 (11%)	4 (7%)	11 (9%)

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17.2 Secondary Outcome – Predictive Value of Biomarkers Summary

Unmutated IGHV and adverse FISH status were both associated with shorter PFS, OS and TTF. The PFS/TTF advantage of Bendamustine over Chlorambucil was confined to the groups with 13q- or no FISH defects and was not seen in the other FISH groups. Bendamustine appeared to confer an early PFS/TTF advantage in the group with mutated IGHV and a late PFS/TTF advantage in the group with unmated IGHV. However, these differences failed to reach statistical significance.

18 Additional Analyses

18.1 Primary Analysis – Bendamustine vs. Chlorambucil (Including Placebo)

Table 19-1 Time to Second Line Treatment (From Initiation of Study Treatment)

Treatment Arm	No. patients	No. events (%)	Median events in months (95% CI)	12-month events rate (95% CI)	Hazard Ratio (95% CI)*	p-value**
Bendamustine	79	79 (100%)	27.93 (23.52;35.59)	80% (71%;89%)	0.72 (0.53;0.98)	0.034
Chlorambucil	108	108 (100%)	26.32 (21.45;29.87)	75% (67%;83%)	NA	NA
Total	187	187 (100%)	26.68 (24.01;29.87)	77% (71%;83%)	NA	NA

*Stratified Cox PH model

**Stratified log rank test

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Figure 19-1 Kaplan Meier Plot: Time to Second Line Treatment (From Initiation of Study Treatment)

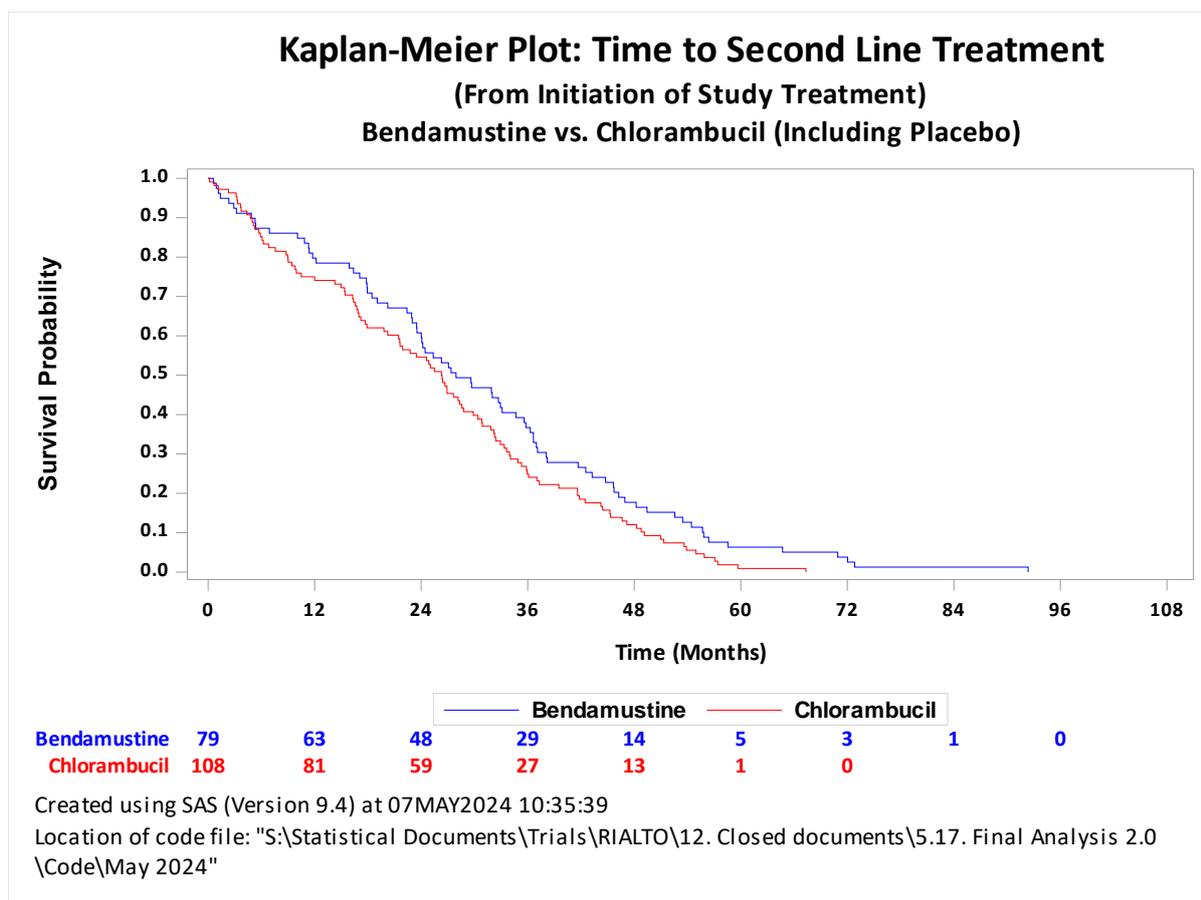


Table 19-2 Time to Third Line Treatment (From Randomisation)

Treatment Arm	No. patients	No. events (%)	Median events in months (95% CI)	12-month events rate (95% CI)	Hazard Ratio (95% CI)*	p-value**
Bendamustine	222	21 (9%)	NA (92.76;NA)	98% (95%;100%)	0.49 (0.28;0.84)	0.009
Chlorambucil	223	37 (17%)	NA (NA;NA)	97% (94%;99%)	NA	NA
Total	445	58 (13%)	NA (NA;NA)	97% (95%;99%)	NA	NA

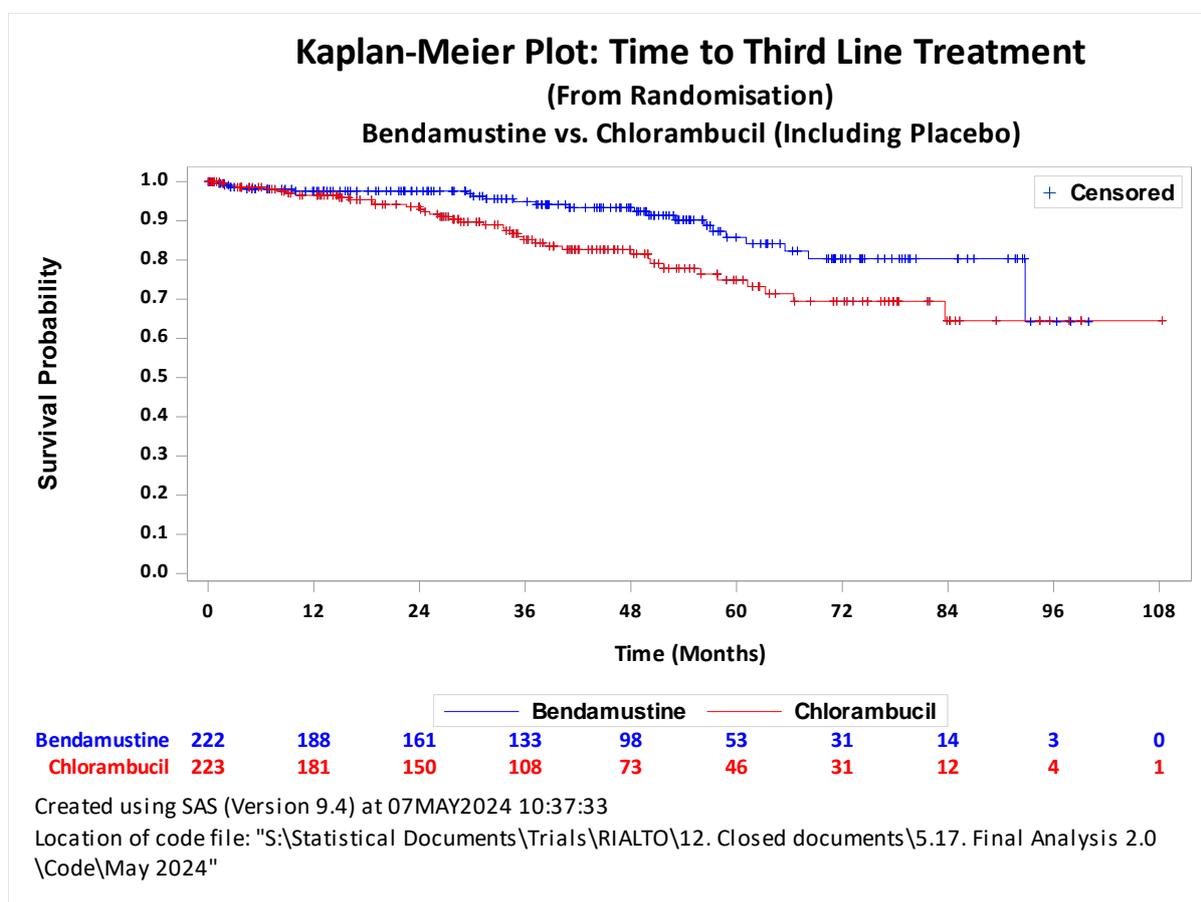
*Stratified Cox PH model

**Stratified log rank test

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Figure 19-2 Kaplan Meier Plot: Time to Third Line Treatment (From Randomisation)



18.2 Additional Analysis Summary

Time to second line treatment from initiation of study treatment is improved on Bendamustine compared to Chlorambucil [HR=0.72 (0.53;0.98); p=0.034]. Time to third line treatment from randomisation is also improved on Bendamustine compared to Chlorambucil [HR=0.49 (0.28;0.84;p=0.009)].

19 Final Statistical Analysis Report Lay Summary

The profile of patients enrolled on the trial was as expected and similar across the different treatment groups.

For the main comparison of bendamustine vs chlorambucil, treatment was given as planned in most patients, with very few dropping out of treatment or follow-up. Progression-free survival (the proportion of patients alive and in remission; PFS) was longer for bendamustine compared to chlorambucil (~38 vs ~30 months on average). The same was true of time to treatment failure (defined as death, progression or not responding; TTF) (~38 vs ~28 months). In contrast, there was no difference in overall survival (OS) between the two treatment arms. The number of patients who went into remission was similar in the two treatment arms, but more patients in the bendamustine arm achieved levels of disease below 1 CLL cell in 10,000 normal cells. Among patients who responded to treatment, those in the bendamustine arm stayed in remission for longer compared to patients in the chlorambucil arm (~44 vs ~30 months on average). Time from first to second- and third line treatment was longer in the bendamustine arm compared to the chlorambucil arm.

More serious adverse events (SAEs) were reported in the bendamustine arm compared to the chlorambucil arm (307 vs 234). This was largely due to a greater number of lung infections (39 vs 20) and skin cancers (47 vs 24) in the bendamustine arm.

The quality-of-life questionnaire QLQ-30 showed that patients in the chlorambucil arm experienced lower emotional functioning and more fatigue, insomnia and appetite loss compared to those in the bendamustine arm. The CLL-specific QLQ-CLL16 questionnaire showed that dry mouth, bruising and skin problems were also more pronounced in the chlorambucil arm. No differences between the two treatment arms were seen with the EuroQoL visual analogue scale (EQ-VAS) assessment.

Higher frailty scores were associated with shorter OS irrespective of which of five different scoring systems were used (Cumulative Illness Rating Scale (CIRS), Performance Status (PS), Vulnerable Elders Survey-13 (VES-13), Groningen Frailty Index (GFI), timed up-and-go test). However, shorter PFS and TTF was only seen in patients defined as frail by PS or VES-13 scores. The PFS and TTF advantage of bendamustine over chlorambucil was confined to less frail patients as defined by all five scoring systems. More complex frailty assessments had no advantage over PS in predicting worse outcomes.

Adverse genetic alterations were associated with shorter PFS, OS and TTF. The PFS/TTF advantage of bendamustine over chlorambucil was more pronounced in patients with a 13q deletion or no FISH defects compared to those with trisomy 12, 11q deletion or 17p deletion.

In the exploratory analysis of idelalisib versus placebo, there was no consistent difference in PFS, TTF or OS between the two arms. More SAEs were reported in more patients in the idelalisib arm compared to the placebo arm (141 vs 99). This was largely due to an excess of pyrexia (18 vs 1, respectively) and infection (53 vs 18) including neutropenic sepsis/ febrile neutropenia (19 vs 2). In contrast, fewer SAEs relating to neoplasms were reported in the idelalisib arm compared to the placebo arm (17 vs 44). This was largely due to a lower frequency of skin cancers in the idelalisib arm (7 vs 30). Reports of immune-mediated toxicity typically associated with idelalisib (dermatitis, hepatitis, colitis, pneumonitis) were infrequent and similar in the idelalisib and placebo arms.