Appendix X. Additional data for Clarification questions

Contents

Question A1

Table A1-1 displays the results for the analysis of 97 patients agreed on consensus to have aggressive B-cell lymphoma.

Table A1-1 Endpoint summary for the consensus-determined HITT B-cell analysis set

Outcome	Pixantrone		Physician's choice		p value
	n	N	n	N	
Primary outcome (end of treatment)					
CR/Cru	8	50	3	47	0.202
CR	6	50	0	47	0.027
CRu	2	50	3	47	0.671
Primary outcome (end of study)					
CR/Cru	9	50	4	47	0.236
CR	7	50	0	47	0.013
CRu	2	50	4	47	0.426
Secondary outcomes					
ORR (end of treatment)	17	50	8	47	0.066
CR	6	50	0	47	0.027
CRu	2	50	3	47	0.671
Partial response	9	50	5	47	0.391
ORR (end of study)	18	50	8	47	0.041
CR	7	50	0	47	0.013
CRu	2	50	4	47	0.426
Partial response	9	50	4	47	0.236
Proportion of patients achieving a response (CR/Cru/PR) lasting ≥4 months	7	50	4	47	0.526
Mean relative dose intensity (SD)	84.2 (19.04)	50	87.2 (21.81)	45	0.477
	Result (end of study)	**N**	**Result (end of study)**	**N**	**HR (95% CI) (EOS)**
PFS, months		50		47	
Median (range)	5.6 (0.7-24.0)		2.5 (0.0-24.0)		0.51

Mean (SD)	7.7 (7.75)		3.7 (4.10)		(0.33, 0.78)
OS,months		50		47	
Median (range)	8.1 (0.8-24.0)		6.3 (0.1-24.0)		0.72
Mean (SD)	11.3 (8.80)		8.9 (7.91)		(0.45, 1.13)
Time to response, months		18		8	
Median (range)	2.0 (1.6-8.2)		1.9 (1.6-2.8)		0.56
Mean (SD)	2.8 (1.77)		2.0 (0.38)		(0.23, 1.36)
Time to complete response, months		9		4	
Median (range)	2.0 (1.6-8.2)		3.7 (2.3-19.0)		3.15
Mean (SD)	2.8 (2.13)		7.1 (7.92)		(0.82, 12.1)
Duration of response, months		18		8	
Median (range)	5.2 (2.1-22.5)		3.3 (0.0-22.2)		0.64
Mean (SD)	9.0 (7.27)		5.4 (7.19)		(0.26, 1.56)
Abbreviations used in table: CI, confidence interval; CR, complete response; CRu, unconfirmed complete response; EOS, end of study; n, number of patients with outcome; N, number of patients in subgroup; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SD, standard deviation. Means for the time to event analyses are arithmetic means of the durations					

Table A1-2 displays the results for the analysis set of the 42 HITT B-Cell patients who received their 3rd line of therapy during the PIX301 study.

Table A1-2 Endpoint summary for the consensus-determined HITT B-cell patients receiving third-line therapy analysis set

Outcome	Pixantrone		Physician's choice		p value
	n	N	n	N	
Primary outcome (end of treatment)					
CR/Cru	5	22	1	20	0.187
CR	3	22	0	20	0.233
CRu	2	22	1	20	1.000
Primary outcome (end of study)					
CR/Cru	6	22	1	20	0.096
CR	4	22	0	20	0.109
CRu	2	22	1	20	1.000

Secondary outcomes					
ORR (end of treatment)	10	22	2	20	0.017
CR	3	22	0	20	0.233
CRu	2	22	1	20	1.000
Partial response	5	22	1	20	0.187
ORR (end of study)	10	22	2	20	0.017
CR	4	22	0	20	0.109
CRu	2	22	1	20	1.000
Partial response	4	22	1	20	0.346
Proportion of patients achieving a response (CR/Cru/PR) lasting ≥4 months	6	22	1	20	0.096
Mean relative dose intensity (SD)	84.5 (19.43)	22	93.3 (11.21)	20	0.079
	Result (end of study)	**N**	**Result (end of study)**	**N**	**HR (95% CI) (EOS)**
PFS, months		22		20	
Median (range)	5.7 (1.1-24.0)		2.9 (0.3-13.5)		0.43
Mean (SD)	9.3 (8.87)		3.6 (3.01)		(0.22, 0.85)
OS,months		22		20	
Median (range)	7.0 (1.1-24.0)		7.0 (0.8-21.9)		0.58
Mean (SD)	12.1 (9.42)		8.7 (7.10)		(0.29, 1.18)
Time to response, months		10		2	
Median (range)	2.2 (1.7-6.0)		2.2 (1.6-2.8)		0.61
Mean (SD)	2.8 (1.39)		2.2 (0.86)		(0.12, 3.01)
Time to complete response, months		6		1	
Median (range)	2.2 (1.7-8.2)		3.6 (3.6-3.6)		1.89
Mean (SD)	3.3 (2.49)		3.6 (NE)		(0.21, 17.3)
Duration of response, months		10		2	
Median (range)	11.6 (3.8-22.5)		2.4 (0.0-4.8)		0.20
Mean (SD)	12.7 (7.92)		2.4 (3.39)		(0.03, 1.20)

Abbreviations used in table: CI, confidence interval; CR, complete response; CRu, unconfirmed complete response; EOS, end of study; n, number of patients with outcome; N, number of patients in subgroup; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SD, standard deviation.

Means for the time to event analyses are arithmetic means of the durations

Table A1-3 displays the results for the analysis set of the 36 HITT B-Cell patients who received their fourth line of therapy during the PIX301 study. Due to the very small sample size, only descriptive statistics are presented. Since there was only one patient with a response, which was unconfirmed (CRu), time-to-response and duration-of-response analyses were not performed.

Table A1-3 Endpoint summary for the consensus HITT B-cell patients receiving fourth-line therapy analysis set

Outcome	Pixantrone		Physician's choice		p value
	n	N	n	N	
Primary outcome (end of treatment)					
CR/Cru	3	17	1	19	0.326
CR	3	17	0	19	0.095
CRu	0	17	1	19	1.000
Primary outcome (end of study)					
CR/Cru	3	17	1	19	0.326
CR	3	17	0	19	0.095
CRu	0	17	1	19	1.000
Secondary outcomes					
ORR (end of treatment)	7	17	3	19	0.139
CR	3	17	0	19	0.095
CRu	0	17	1	19	1.000
Partial response	4	17	2	19	0.391
ORR (end of study)	7	17	3	19	0.139
CR	3	17	0	19	0.095
CRu	0	17	1	19	1.000
Partial response	4	17	2	19	0.391
Proportion of patients achieving a response (CR/Cru/PR) lasting ≥4 months	1	17	2	19	1.000
Mean relative dose intensity (SD)	82.7 (18.60)	17	83.5 (26.12)	18	0.912

	Result (end of study)	N	Result (end of study)	N	HR (95% CI) (EOS)
PFS, months		17		19	
Median (range)	5.7 (0.7-24.0)		2.0 (0.0-10.3)		0.51
Mean (SD)	7.1 (6.95)		3.3 (2.93)		(0.25, 1.04)
OS, months		17		19	
Median (range)	11.9 (1.1-24.0)		7.0 (0.2-24.0)		0.76
Mean (SD)	12.0 (8.15)		9.9 (8.86)		(0.35, 1.65)
Time to response, months		7		3	
Median (range)	1.8 (1.6-3.4)		1.8 (1.8-1.9)		0.99
Mean (SD)	2.0 (0.62)		1.9 (0.08)		(0.23, 4.26)
Time to complete response, months		3		1	
Median (range)	1.6 (1.6-1.8)		3.7 (3.7-3.7)		NE
Mean (SD)	1.7 (0.08)		3.7 (NE)		
Duration of response, months		7		3	
Median (range)	4.0 (3.0-8.6)		5.7 (1.7-6.0)		1.27
Mean (SD)	4.7 (1.95)		4.5 (2.40)		(0.30, 5.39)

Abbreviations used in table: CI, confidence interval; CR, complete response; CRu, unconfirmed complete response; EOS, end of study; n, number of patients with outcome; N, number of patients in subgroup; NE, Not Evaluable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SD, standard deviation.

Means for the time to event analyses are arithmetic means of the durations

Table A1-4 displays the results for the analysis set of the 78 HITT B-Cell patients who received either their third or fourth line of therapy during the PIX301 study.

Table A1-4 Endpoint summary for the consensus HITT B-cell patients receiving third or fourth line therapy analysis set

Outcome	Pixantrone		Physician's choice		p value
	n	N	n	N	
Primary outcome (end of treatment)					
CR/Cru	8	39	2	39	0.087
CR	6	39	0	39	0.025
CRu	2	39	2	39	1.000
Primary outcome (end of study)					
CR/Cru	9	39	2	39	0.047
CR	7	39	0	39	0.012
CRu	2	39	2	39	1.000
Secondary outcomes					
ORR (end of treatment)	17	39	5	39	0.005
CR	6	39	0	39	0.025
CRu	2	39	2	39	1.000
Partial response	9	39	3	39	0.114
ORR (end of study)	17	39	5	39	0.005
CR	7	39	0	39	0.012
CRu	2	39	2	39	1.000
Partial response	8	39	3	39	0.192
Proportion of patients achieving a response (CR/Cru/PR) lasting ≥4 months	7	39	3	39	0.310
Mean relative dose intensity (SD)	83.7 (18.85)	39	88.6 (20.05)	38	0.268
	Result (end of study)	**N**	**Result (end of study)**	**N**	**HR (95% CI) (EOS)**
PFS, months		39		39	
Median (range)	5.7 (0.7-24.0)		2.8 (0.0-13.5)		0.44
Mean (SD)	8.3 (8.07)		3.4 (2.94)		(0.27, 0.71)
OS,months		39		39	
Median (range)	11.9 (1.1-24.0)		7.0 (0.2-24.0)		0.67

Mean (SD)	12.1 (8.78)		9.3 (7.92)		(0.40, 1.12)
Time to response, months		17		5	
Median (range)	2.0 (1.6-6.0)		1.8 (1.6-2.8)		0.57 (0.20, 1.61)
Mean (SD)	2.5 (1.18)		2.0 (0.48)		
Time to complete response, months		9		2	
Median (range)	2.0 (1.6-8.2)		3.7 (3.6-3.7)		2.36 (0.47, 11.9)
Mean (SD)	2.8 (2.13)		3.7 (0.02)		
Duration of response, months		17		5	
Median (range)	5.5 (3.0-22.5)		4.8 (0.0-6.0)		0.40 (0.13, 1.20)
Mean (SD)	9.4 (7.29)		3.7 (2.65)		
Abbreviations used in table: CI, confidence interval; CR, complete response; CRu, unconfirmed complete response; EOS, end of study; n, number of patients with outcome; N, number of patients in subgroup; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SD, standard deviation. Means for the time to event analyses are arithmetic means of the durations					

Table A1-5 displays the results for the analysis set of the 56 HITT B-Cell patients who had rituximab exposure prior to enrolment in the PIX301 study. This table includes all patients with consensus-agreement of aggressive histology, receiving third or further lines of therapy.

Table A1-5 Endpoint summary for the consensus HITT B-cell patients with prior rituximab analysis set

Outcome	Pixantrone		Physician's choice		p value
	n	N	n	N	
Primary outcome (end of treatment)					
CR/Cru	5	30	2	26	0.431
CR	4	30	0	26	0.115
CRu	1	30	2	26	0.592
Primary outcome (end of study)					
CR/Cru	6	30	3	26	0.481
CR	5	30	0	26	0.055
CRu	1	30	3	26	0.328
Secondary outcomes					

ORR (end of treatment)	9	30	5	26	0.537
CR	4	30	0	26	0.115
CRu	1	30	2	26	0.592
Partial response	4	30	3	26	1.000
ORR (end of study)	9	30	5	26	0.537
CR	5	30	0	26	0.055
CRu	1	30	3	26	0.328
Partial response	3	30	2	26	1.000
Proportion of patients achieving a response (CR/Cru/PR) lasting ≥4 months	4	30	2	26	0.675
Mean relative dose intensity (SD)	79.8 (22.23)	30	85.0 (23.43)	24	0.410
	Result (end of study)	**N**	**Result (end of study)**	**N**	**HR (95% CI) (EOS)**
PFS, months		30		26	
Median (range)	3.5 (0.7-24.0)		2.3 (0.0-24.0)		0.66
Mean (SD)	5.9 (6.20)		3.6 (4.78)		(0.38, 1.14)
OS,months		30		26	
Median (range)	6.0 (0.8-24.0)		4.6 (0.1-24.0)		0.85
Mean (SD)	8.9 (7.90)		7.7 (7.80)		(0.48, 1.50)
Time to response, months		9		5	
Median (range)	1.8 (1.6-6.0)		1.9 (1.8-2.3)		0.88
Mean (SD)	2.3 (1.39)		2.0 (0.18)		(0.28, 2.82)
Time to complete response, months		6		3	
Median (range)	1.8 (1.6-8.2)		3.7 (2.3-19.0)		3.49
Mean (SD)	2.8 (2.64)		8.3 (9.27)		(0.67, 18.3)
Duration of response, months		9		5	
Median (range)	5.5 (3.6-22.5)		1.7 (1.0-22.2)		0.71
Mean (SD)	8.5 (6.20)		6.4 (9.04)		(0.21, 2.40)
Abbreviations used in table: CI, confidence interval; CR, complete response; CRu,					

unconfirmed complete response; EOS, end of study; n, number of patients with outcome; N, number of patients in subgroup; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SD, standard deviation.

Means for the time to event analyses are arithmetic means of the durations

Table A1-6 displays the results for the analysis set of the 41 HITT B-Cell patients who had no rituximab exposure prior to enrolment in the PIX301 study.

Table A1-6 Endpoint summary for the HITT B-cell patients with no prior rituximab analysis set

Outcome	Pixantrone		Physician's choice		p value
	n	N	n	N	
Primary outcome (end of treatment)					
CR/Cru	3	20	1	21	0.343
CR	2	20	0	21	0.232
CRu	1	20	1	21	1.000
Primary outcome (end of study)					
CR/Cru	3	20	1	21	0.343
CR	2	20	0	21	0.232
CRu	1	20	1	21	1.000
Secondary outcomes					
ORR (end of treatment)	8	20	3	21	0.085
CR	2	20	0	21	0.232
CRu	1	20	1	21	1.000
Partial response	5	20	2	21	0.238
ORR (end of study)	9	20	3	21	0.043
CR	2	20	0	21	0.232
CRu	1	20	1	21	1.000
Partial response	6	20	2	21	0.130
Proportion of patients achieving a response (CR/Cru/PR) lasting ≥4 months	3	20	2	21	0.663
Mean relative dose intensity (SD)	90.8 (10.26)	20	89.7 (20.06)	21	0.832
	Result (end of study)	**N**	**Result (end of study)**	**N**	**HR (95% CI)**

					(EOS)
PFS, months		20		21	
Median (range)	6.3 (1.3-24.0)		3.5 (0.3-13.5)		0.35
Mean (SD)	10.4 (9.13)		3.7 (3.17)		(0.17, 0.70)
OS,months		20		21	
Median (range)	16.1 (1.8-24.0)		7.8 (1.2-24.0)		0.52
Mean (SD)	14.8 (9.07)		10.4 (7.98)		(0.24, 1.11)
Time to response, months		9		3	
Median (range)	2.4 (1.7-8.2)		1.8 (1.6-2.8)		0.34
Mean (SD)	3.2 (2.07)		2.1 (0.65)		(0.08, 1.45)
Time to complete response, months		3		1	
Median (range)	2.4 (2.0-3.6)		3.6 (3.6-3.6)		NE
Mean (SD)	2.7 (0.83)		3.6 (NE)		
Duration of response, months		9		3	
Median (range)	3.9 (2.1-21.2)		4.8 (0.0-6.0)		0.52
Mean (SD)	9.5 (8.56)		3.6 (3.18)		(0.12, 2.21)

Abbreviations used in table: CI, confidence interval; CR, complete response; CRu, unconfirmed complete response; EOS, end of study; n, number of patients with outcome; N, number of patients in subgroup; NE, Not Evaluable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SD, standard deviation.

Means for the time to event analyses are arithmetic means of the durations

Table A1-7 displays the results for the analysis set of the 38 HITT B-Cell patients who received their 3rd or 4th line of therapy as part of PIX301 and had prior exposure to rituximab therapy. This set of patients most closely reflects the approved population. Due to the small number of patients with CR/Cru in either group (≤10 patients), the hazard ratios for the three responder analyses were not evaluable.

Among this subgroup, 10 (50%) of patients receiving pixantrone received between 4 and 6 cycles of therapy compared with 5 (28%) of patients receiving physician's choice of chemotherapy. Please see additional statistical tables in Appendix Z on the accompanying CD for more details.

Table A1-7 Endpoint summary for the HITT B-cell patients receiving third or fourth-line therapy with prior rituximab analysis set

Outcome	Pixantrone		Physician's choice		p value
	n	N	n	N	
Primary outcome (end of treatment)					
CR/Cru	5	20	1	18	0.184
CR	4	20	0	18	0.107
CRu	1	20	1	18	1.000
Primary outcome (end of study)					
CR/Cru	6	20	1	18	0.093
CR	5	20	0	18	0.048
CRu	1	20	1	18	1.000
Secondary outcomes					
ORR (end of treatment)	9	20	2	18	0.033
CR	4	20	0	18	0.107
CRu	1	20	1	18	1.000
Partial response	4	20	1	18	0.344
ORR (end of study)	9	20	2	18	0.033
CR	5	20	0	18	0.048
CRu	1	20	1	18	1.000
Partial response	3	20	1	18	0.606
Proportion of patients achieving a response (CR/Cru/PR) lasting ≥4 months	4	20	1	18	0.344
Mean relative dose intensity (SD)	77.5 (22.98)	20	87.4 (20.58)	17	0.182
	Result (end of study)	**N**	**Result (end of study)**	**N**	**HR (95% CI) (EOS)**
PFS, months		20		18	
Median (range)	5.4 (0.7-24.0)		2.8 (0.0-10.3)		0.52
Mean (SD)	6.4 (6.19)		3.2 (2.71)		(0.26, 1.04)
OS,months		20		18	
Median (range)	7.5 (1.1-24.0)		5.4 (0.2-22.5)		0.76

Mean (SD)	9.9 (8.15)		7.9 (7.85)		(0.38, 1.55)
Time to response, months		9		2	
Median (range)	1.8 (1.6-6.0)		1.9 (1.8-1.9)		NE
Mean (SD)	2.3 (1.39)		1.9 (0.09)		
Time to complete response, months		6		1	
Median (range)	1.8 (1.6-8.2)		3.7 (3.7-3.7)		NE
Mean (SD)	2.8 (2.64)		3.7 (NE)		
Duration of response, months		9		2	
Median (range)	5.5 (3.6-22.5)		3.7 (1.7-5.7)		NE
Mean (SD)	8.5 (6.20)		3.7 (2.81)		
Abbreviations used in table: CR, complete response; CRu, unconfirmed complete response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SD, standard deviation; NE, Not Evaluable. Means for the time to event analyses are arithmetic means of the durations.					

Table A1-8 displays the results for the analysis set of the 40 HITT B-cell patients who received their 3rd or 4th line of therapy in PIX301 and had no prior rituximab therapy. Due to the small number of patients with response in either group (≤10 patients),
the hazard ratios for the three responder analyses were not evaluable.
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Table A1-8 Endpoint summary for the HITT B-cell patients receiving third or fourth-line therapy and no prior rituximab analysis set

Outcome	Pixantrone		Physician's choice		p value
	n	N	n	N	
Primary outcome (end of treatment)					
CR/Cru	3	19	1	21	0.331
CR	2	19	0	21	0.219
CRu	1	19	1	21	1.000
Primary outcome (end of study)					
CR/Cru	3	19	1	21	0.331
CR	2	19	0	21	0.219
CRu	1	19	1	21	1.000
Secondary outcomes					
ORR (end of treatment)	8	19	3	21	0.078

CR	2	19	0	21	0.219
CRu	1	19	1	21	1.000
Partial response	5	19	2	21	0.226
ORR (end of study)	8	19	3	21	0.078
CR	2	19	0	21	0.219
CRu	1	19	1	21	1.000
Partial response	5	19	2	21	0.226
Proportion of patients achieving a response (CR/Cru/PR) lasting ≥4 months	3	19	2	21	0.654
Mean relative dose intensity (SD)	90.2 (10.24)	19	89.7 (20.06)	21	0.919
	Result (end of study)	**N**	**Result (end of study)**	**N**	**HR (95% CI) (EOS)**
PFS, months		19		21	
Median (range)	6.1 (1.3-24.0)		3.5 (0.3-13.5)		0.36
Mean (SD)	10.4 (9.38)		3.7 (3.17)		(0.18, 0.73)
OS,months		19		21	
Median (range)	14.5 (1.8-24.0)		7.8 (1.2-24.0)		0.56
Mean (SD)	14.3 (9.05)		10.4 (7.98)		(0.26, 1.20)
Time to response, months		8		3	
Median (range)	2.2 (1.7-4.2)		1.8 (1.6-2.8)		NE
Mean (SD)	2.6 (0.96)		2.1 (0.65)		
Time to complete response, months		3		1	
Median (range)	2.4 (2.0-3.6)		3.6 (3.6-3.6)		NE
Mean (SD)	2.7 (0.83)		3.6 (NE)		
Duration of response, months		8		3	
Median (range)	5.5 (3.0-21.2)		4.8 (0.0-6.0)		NE
Mean (SD)	10.4 (8.67)		3.6 (3.18)		

Abbreviations used in table: CR, complete response; CRu, unconfirmed complete response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SD, standard deviation; NE, Not Evaluable.

Means for the time to event analyses are arithmetic means of the durations.

Question A3

Table A3-1. PIX301 patient baseline demographic characteristics (consensus-determined HITT B-cell analysis set, all lines of therapy)

	Pixantrone (N=50)	**Comparator** (N=47)	**p-value**
Age at Randomisation (years)			
Mean (SD)	59.6 (12.4)	55.3 (13.4)	0.104
Median (range)	60.0 (28-80)	58.0 (26-77)	
Age Category at Randomisation (years), n (%)			0.056
18 to <30	2 (4.0%)	2 (4.3%)	1.000
30 to <40	2 (4.0%)	8 (17.0%)	0.047
40 to <50	8 (16.0%)	2 (4.3%)	0.093
50 to <60	11 (22.0%)	12 (25.5%)	0.812
60 to <70	14 (28.0%)	18 (38.3%)	0.388
70 to <80	12 (24.0%)	5 (10.6%)	0.111
≥80	1 (2.0%)	0	1.000
Sex, n (%)			0.310
Male	31 (62.0%)	24 (51.1%)	
Female	19 (38.0%)	23 (48.9%)	
Race, n (%)			0.471
Caucasian	35 (70.0%)	27 (57.4%)	0.213
Black	0	0	
Asian	6 (12.0%)	11 (23.4%)	0.184
Hispanic	4 (8.0%)	3 (6.4%)	1.000
Native American	0	1 (2.1%)	0.485
Other	5 (10.0%)	5 (10.6%)	1.000
Baseline ECOG Performance Status, n (%)			0.931
0	17 (34.0%)	14 (29.8%)	0.670
1	21 (42.0%)	21 (44.7%)	0.839
2	12 (24.0%)	11 (23.4%)	1.000
3	0	1 (2.1%)	0.485

Geographic Region, n (%)			0.514
North America	3 (6.0%)	4 (8.5%)	0.709
Western Europe	16 (32.0%)	10 (21.3%)	0.259
Rest of World	31 (62.0%)	33 (70.2%)	0.520
Weight (kg)			
Mean (SD)	70.9 (16.8)	66.8 (15.7)	0.213
Median (range)	70.0 (45-117)	65.0 (37-105)	

Abbreviations used in table: ECOG, Eastern Cooperative Oncology Group; kg, kilogram; n, number of patients with characteristic; N, number of patients in subgroup; SD, standard deviation

Fisher exact test was used to compare proportions between the group and a two-sided student's t-test was used in the comparison of means between treatment groups.

Table A3-2. PIX301 patient baseline history (consensus-determined HITT B-cell analysis set, all lines of therapy)

	Pixantrone (N=50)	**Comparator** (N=47)	**p-value**
Overall			0.559
Diffuse large B-cell lymphoma	42 (84.0%)	40 (85.1%)	1.000
Transformed indolent lymphoma	7 (14.0%)	4 (8.5%)	0.526
Follicular lymphoma grade III	0	2 (4.3%)	0.232
Peripheral T-cell lymphoma NOC	1 (2.0%)	1 (2.1%)	1.000
Anaplastic large cell lymphoma/null cell/primary systemic	0	0	

Abbreviations used in table: N, number of patients in subgroup; NOC, not otherwise classified; SD, standard deviation

Fisher exact test was used to compare proportions between the group

Table A3-3. PIX301 patient baseline disease characteristics (consensus-determined HITT B-cell analysis set, all lines of therapy)

	Pixantrone (N=50)	**Comparator** (N=47)	**p-value**
Duration of NHL (months)			
Mean (SD)	43.1 (36.2)	40.8 (41.6)	0.779
Median (range)	32.0 (7-160)	30.9 (0-223)	
Ann Arbor Stage of NHL, n (%)			1.000
I/II	13 (26.0%)	12 (25.5%)	
III/IV	37 (74.0%)	35 (74.5%)	
International Prognostic Index, n (%)			0.817
0, 1	12 (24.0%)	13 (27.7%)	
≥2	38 (76.0%)	34 (72.3%)	
Number of Extranodal Sites, n (%)			1.000
0	25 (50.0%)	24 (51.1%)	1.000
≥1	24 (48.0%)	22 (46.8%)	1.000
Missing	1 (2.0%)	1 (2.1%)	1.000
Time from Last Chemotherapy to Randomisation (months)			
Mean (SD)	12.6 (15.0)	10.2 (7.11)	0.307
Median (range)	8.5 (1-86)	8.0 (1-30)	

Abbreviations used in table: n, number of patients with outcome; N, number of patients in subgroup; SD, standard deviation

Fisher exact test was used to compare proportions between the groups, and a two-sided student's t test was used in the comparison of means between treatment groups. As these are post-hoc explanatory subset analyses, p-values are for reference purposes only.

Table A3-4. PIX301 Prior NHL treatment (consensus-determined HITT B-Cell Analysis Set, all lines of therapy)

	Pixantrone (N=50)	**Comparator** (N=47)	**p-value**
Chemotherapy regimens			
Mean (SD)	3.0 (1.4)	2.9 (1.2)	0.754
Median (range)	3.0 (2-9)	3.0 (2-8)	
Number of chemotherapy regimens			1.000
2	22 (44.0%)	20 (42.6%)	1.000
3-5	25 (50.0%)	24 (51.1%)	1.000
≥6	3 (6.0%)	3 (6.4%)	1.000
Category of prior chemotherapy			
Biologics (anti-CD20 mAB)	30 (60.0%)	26 (55.3%)	1.000
Anthracyclines/anthracenediones	50 (100.0%)	47 (100.0%)	NA
Other topoisomerase inhibitors (a)	38 (76.0%)	37 (78.7%)	0.811
Platinum-based agents	27 (54.0%)	25 (53.2%)	1.000
Antimetabolites	33 (66.0%)	30 (63.8%)	0.835
Alkylating agents	50 (100.0%)	47 (100.0%)	NA
Spindle poison/mitotic inhibitors (SPs/MIs)	50 (100.0%)	46 (97.9%)	0.485
Corticosteroids	47 (94.0%)	43 (91.5%)	0.709
Other (b)	15 (30.0%)	18 (38.3%)	0.401
Disease response category			0.242
Refractory	32 (64.0%)	26 (55.3%)	0.414
Relapsed	16 (32.0%)	21 (44.7%)	0.217
Missing	2 (4.0%)	0	0.495
Patients who had radiotherapy, n (%)			
	25 (50.0%)	24 (51.1%)	1.000
Patients who received SCT, n (%)			
	7 (14.0%)	8 (17.0%)	0.782
Anthracycline dose equivalent (mg/m^2)			
Mean (SD)	286.0 (95.9)	324.5 (102.7)	0.060
Median (range)	290.5 (78-472)	312.7 (75-516)	

(a) Other topoisomerase inhibitors were etoposide and teniposide

(b) “Other” includes targeted therapies, non-classified anticancer therapies and supportive therapies

Abbreviations used in table: n, number of patients with prior therapy; N, number of patients in subgroup; NA, not applicable; SCT, stem cell therapy; SD, standard deviation

Fisher exact test was used to compare proportions between the groups, and a two-sided student’s t test was used in the comparison of means between treatment groups.

Question A8

Table A8-1 summarises the subgroup analyses for CR/CRu rate to the end of treatment for the HITT B-Cell analysis set.

Table A8-1 Subgroup analysis of CR/CRu rate to the end of t5reatment for the consensus-determined HITT B-cell analysis set

Subgroup	CR/CRu Rate to EOT				
	Pixantrone		Physician’s choice		% difference (95% CI)
	n	N	n	N	
Prior stem cell transplant					
Yes	0 (0.0%)	7	1 (12.5%)	8	-12.5% (-35.4%, 10.4%)
No	8 (18.6%)	43	2 (5.1%)	39	13.5% (-0.1%, 27.0%)
Prior rituximab					
Yes	5 (16.7%)	30	2 (7.7%)	26	9.0% (-7.8%, 25.8%)
No	3 (15.0%)	20	1 (4.8%)	21	10.2% (-7.9%, 28.3%)
Patient location					
North America	0 (0.0%)	3	0 (0.0%)	4	0.0% (0.0%, 0.0%)
Western Europe	1 (6.3%)	16	0 (0.0%)	10	6.3% (-5.6%, 18.1%)
Rest of the World	7 (22.6%)	31	3 (9.1%)	33	13.5% (-4.2%, 31.2%)
Age					
≥65	4 (22.2%)	18	0 (0.0%)	13	22.2% (3.0%, 41.4%)
<65	4 (12.5%)	32	3 (8.8%)	34	3.7% (-11.2%, 18.6%)
Gender					
Male	4 (12.9%)	31	2 (8.3%)	24	4.6% (-11.6%, 20.7%)
Female	4 (21.1%)	19	1 (4.3%)	23	16.7% (-3.4%, 36.8%)

Abbreviations used in table: CI, confidence interval; EOT, end of treatment; n, number of patients with characteristic; N, number of patients in subgroup

Table A8-2 summarises the subgroup analyses for CR/CRu rate to the end of study for the HITT B-Cell analysis set.

Table A8-2 Subgroup analysis of CR/CRu rate to the end of study for the consensus-determined HITT B-cell analysis set

Subgroup	CR/CRu Rate through EOS				
	Pixantrone		Physician's choice		% difference (95% CI)
	n	N	n	N	
Prior stem cell transplant					
Yes	0 (0.0%)	7	2 (25.0%)	8	-25.0% (-55.0%, 5.0%)
No	9 (20.9%)	43	2 (5.1%)	39	15.8% (1.8%, 29.8%)
Prior rituximab					
Yes	6 (20.0%)	30	3 (11.5%)	26	8.5% (-10.4%, 27.3%)
No	3 (15.0%)	20	1 (4.8%)	21	10.2% (-7.9%, 28.3%)
Patient location					
North America	0 (0.0%)	3	0 (0.0%)	4	0.0% (0.0%, 0.0%)
Western Europe	1 (6.3%)	16	1 (10.0%)	10	-3.8% (-25.8%, 18.3%)
Rest of the World	8 (25.8%)	31	3 (9.1%)	33	16.7% (-1.5%, 35.0%)
Age					
≥65	4 (22.2%)	18	0 (0.0%)	13	22.2% (3.0%, 41.4%)
<65	5 (15.6%)	32	4 (11.8%)	34	3.9% (-12.7%, 20.5%)
Gender					
Male	4 (12.9%)	31	2 (8.3%)	24	4.6% (-11.6%, 20.7%)
Female	5 (26.3%)	19	2 (8.7%)	23	17.6% (-5.3%, 40.5%)

Abbreviations used in table: CI, confidence interval; EOS, end of study; n, number of patients with characteristic; N, number of patients in subgroup

Table A8-3 summarises the subgroup analyses for overall response rate to the end of treatment for the HITT B-Cell analysis set.

Table A8-3 Subgroup analysis of overall response rate to the end of treatment for the consensus-determined HITT B-cell analysis set

Subgroup	Overall Response Rate through EOT				
	Pixantrone		Physician's choice		% difference (95% CI)
	n	N	n	N	
Prior stem cell transplant					
Yes	0 (0.0%)	7	3 (37.5%)	8	-37.5% (-71.0%, -4.0%)
No	17(39.5%)	43	5 (12.8%)	39	26.7% (8.7%, 44.7%)
Prior rituximab					
Yes	9 (30.0%)	30	5 (19.2%)	26	10.8% (-11.6%, 33.1%)
No	8 (40.0%)	20	3 (14.3%)	21	25.7% (-0.5%, 51.9%)
Patient location					
North America	1 (33.3%)	3	0 (0.0%)	4	33.3% (-20.0%, 86.7%)
Western Europe	2 (12.5%)	16	3 (30.0%)	10	-17.5% (-50.2%, 15.2%)
Rest of the World	14 (45.2%)	31	5 (15.2%)	33	30.0% (8.6%, 51.4%)
Age					
≥65	8 (44.4%)	18	1 (7.7%)	13	36.8% (9.6%, 63.9%)
<65	9 (28.1%)	32	7 (20.6%)	34	7.5% (-13.1%, 28.2%)
Gender					
Male	7 (22.6%)	31	4 (16.7%)	24	5.9% (-15.0%, 26.9%)
Female	10 (52.6%)	19	4 (17.4%)	23	35.2% (8.0%, 62.5%)
Abbreviations used in table: CI, confidence interval; EOT, end of treatment; n, number of patients with characteristic; N, number of patients in subgroup					

Table A8-4 summarises the subgroup analyses for overall response rate to the end of study for the HITT B-Cell analysis set.

Table A8-4 Subgroup analysis of overall response rate to the end of study for the HITT B-cell analysis set

Subgroup	Overall Response Rate through EOS				
	Pixantrone		Physician's choice		% difference (95% CI)
	n	N	n	N	
Prior stem cell transplant					
Yes	0 (0.0%)	7	3 (37.5%)	8	-37.5% (-71.0%, -4.0%)
No	18 (41.9%)	43	5 (12.8%)	39	29.0% (10.9%, 47.1%)
Prior rituximab					
Yes	9 (30.0%)	30	5 (19.2%)	26	10.8% (-11.6%, 33.1%)
No	9 (45.0%)	20	3 (14.3%)	21	30.7% (4.3%, 57.2%)
Patient location					
North America	1 (33.3%)	3	0 (0.0%)	4	33.3% (-20.0%, 86.7%)
Western Europe	2 (12.5%)	16	3 (30.0%)	10	-17.5% (-50.2%, 15.2%)
Rest of the World	15 (48.4%)	31	5 (15.2%)	33	33.2% (11.8%, 54.7%)
Age					
≥65	8 (44.4%)	18	1 (7.7%)	13	36.8% (9.6%, 63.9%)
<65	10 (31.3%)	32	7 (20.6%)	34	10.7% (-10.4%, 31.7%)
Gender					
Male	8 (25.8%)	31	4 (16.7%)	24	9.1% (-12.3%, 30.6%)
Female	10 (52.6%)	19	4 (17.4%)	23	35.2% (8.0%, 62.5%)

Abbreviations used in table: CI, confidence interval; EOS, end of study; n, number of patients with characteristic; N, number of patients in subgroup

Table A8-5 summarises the subgroup analyses for progression-free survival for the consensus-determined HITT B-Cell analysis set.

Table A8-5 Subgroup analysis of progression-free survival for the HITT B-cell analysis set

Subgroup	Progression-Free Survival	
	Pixantrone N=50	**Physician's choice** N=47
	Hazard Ratio (95% CI)	
Prior stem cell transplant		
Yes	1.03 (0.34, 3.09)	
No	0.43 (0.27, 0.69)	
Prior rituximab		
Yes	0.66 (0.38, 1.14)	
No	0.35 (0.17, 0.70)	
Patient location		
North America	0.00 (0.00, NE)	
Western Europe	1.23 (0.54, 2.81)	
Rest of the World	0.35 (0.20, 0.61)	
Age (years)		
≥65	0.50 (0.23, 1.08)	
<65	0.52 (0.30, 0.87)	
Gender		
Male	0.53 (0.29, 0.96)	
Female	0.48 (0.25, 0.93)	
Abbreviations used in table: CI, confidence interval; N, number of patients in subgroup; NE, not evaluable		

Table A8-6 summarises the subgroup analyses for overall survival for the consensus-determined HITT B-Cell analysis set.

Table A8-6 Subgroup analysis of overall survival for the HITT B-cell analysis set

Subgroup	Overall Survival	
	Pixantrone N=50	**Physician's choice** N=47
	Hazard Ratio (95% CI)	
Prior stem cell transplant		
Yes	0.86 (0.29, 2.60)	

No	0.66 (0.40, 1.09)
Prior rituximab	
Yes	0.85 (0.48, 1.50)
No	0.52 (0.24, 1.11)
Patient location	
North America	0.00 (0.00, NE)
Western Europe	1.73 (0.70, 4.32)
Rest of the World	0.47 (0.26, 0.85)
Age (years)	
≥65	0.82 (0.37, 1.79)
<65	0.63 (0.36, 1.12)
Gender	
Male	1.01 (0.56, 1.84)
Female	0.45 (0.22, 0.94)
Abbreviations used in table: CI, confidence interval; N, number of patients in subgroup; NE, not evaluable	

Question B1

The analyses are updates of the ones presented in appendix B and C and section 7.9.3 of the original submission documents for the other patient populations.

Table B1-1 displays the data that populated the Kaplan-Meier curves for overall survival and progression-free survival in consensus-determined aggressive B-cell lymphoma.

Table B1-1. Kaplan-Meier data for consensus-determined aggressive B-cell subpopulation

	Pixantrone			Physician's choice		
Cycle	**Progression-free Survival**	**Overall Survival**	**Treatment Discontinuation**	**Progression-free Survival**	**Overall Survival**	**Treatment Discontinuation**
0	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
1	1.0000	1.0000	1.0000	0.9783	0.9787	0.8222
2	1.0000	1.0000	0.9000	0.9130	0.9570	0.8222
3	1.0000	1.0000	0.8000	0.9130	0.9570	0.8222
4	0.9796	0.9800	0.8000	0.8478	0.9352	0.7556
5	0.9166	0.9200	0.8000	0.8043	0.8917	0.6444
6	0.8947	0.9200	0.8000	0.8043	0.8482	0.6000
7	0.8947	0.9000	0.7600	0.7602	0.8265	0.5556

8	0.8729	0.8800	0.6800	0.6932	0.8265	0.5333
9	0.8074	0.8200	0.6000	0.5750	0.8265	0.4444
10	0.7201	0.8000	0.5600	0.5510	0.8047	0.3778
11	0.6765	0.8000	0.5600	0.5510	0.8047	0.3778
12	0.6765	0.8000	0.5400	0.5510	0.8047	0.3556
13	0.6765	0.7795	0.5400	0.5020	0.7395	0.2667
14	0.6547	0.7590	0.4800	0.4769	0.6960	0.2667
15	0.6329	0.7385	0.4200	0.4518	0.6960	0.2444
16	0.6329	0.7179	0.4000	0.3765	0.6960	0.1556
17	0.6329	0.6974	0.3800	0.3765	0.6742	0.1333
18	0.6110	0.6974	0.3600	0.3243	0.6307	0.1333
19	0.6110	0.6974	0.3600	0.2973	0.6307	0.1333
20	0.6110	0.6974	0.3400	0.2703	0.5872	0.0889
21	0.6110	0.6974	0.3400	0.2703	0.5872	0.0889
22	0.6110	0.6769	0.3400	0.2433	0.5872	
23	0.5884	0.6564	0.1800	0.2433	0.5872	
24	0.5884	0.6564	0.0800	0.2433	0.5655	
25	0.5205	0.6359	0.0800	0.2433	0.5437	
26	0.4752	0.5949	0.0600	0.2433	0.5437	
27	0.4515	0.5949	0.0200	0.2433	0.5002	
28	0.4515	0.5744	0.0200	0.1892	0.4785	
29	0.4040	0.5744	0.0200	0.1892	0.4785	
30	0.4040	0.5538	0.0200	0.1892	0.4785	
31	0.4040	0.5333	0.0200	0.1577	0.4350	
32	0.4040	0.5333	0.0200	0.1577	0.4350	
33	0.4040	0.5128	0.0200	0.1577	0.4350	
34	0.4040	0.5128		0.0946	0.3915	
35	0.4040	0.5128		0.0946	0.3915	
36	0.4040	0.4923		0.0946	0.3697	
37	0.4040	0.4923		0.0946	0.3480	
38	0.4040	0.4923		0.0946	0.3262	
39	0.3770	0.4923		0.0946	0.3262	
40	0.3770	0.4923		0.0946	0.3262	
41	0.3770	0.4923		0.0946	0.3045	
42	0.3770	0.4923		0.0946	0.3045	

43	0.3770	0.4923		0.0946	0.3045	
44	0.3770	0.4923		0.0946	0.3045	
45	0.3480	0.4718		0.0631	0.2827	
46	0.3480	0.4718		0.0631	0.2827	
47	0.3164	0.4718		0.0631	0.2827	
48	0.3164	0.4513		0.0631	0.2827	
49	0.3164	0.4513		0.0631	0.2827	
50	0.3164	0.4513		0.0631	0.2827	
51	0.3164	0.4513		0.0631	0.2827	
52	0.3164	0.4103		0.0631	0.2827	
53	0.2848	0.4103		0.0631	0.2827	
54	0.2848	0.4103		0.0631	0.2827	
55	0.2848	0.4103		0.0631	0.2827	
56	0.2848	0.4103		0.0631	0.2827	
57	0.2848	0.4103		0.0631	0.2827	
58	0.2848	0.4103		0.0631	0.2827	
59	0.2848	0.4103		0.0315	0.2827	
60	0.2848	0.4103				
61	0.2848	0.3897				
62	0.2848	0.3897				
63	0.2848	0.3897				
64	0.2848	0.3692				
65	0.2848	0.3692				
66	0.2848	0.3692				
67	0.2848	0.3487				
68	0.2848	0.3487				
69	0.2848	0.3282				
70	0.2848	0.3282				
71	0.2848	0.3077				
72	0.2848	0.3077				
73	0.2848	0.3077				
74	0.2848	0.3077				
75	0.2848	0.3077				
76	0.2848	0.3077				
77	0.2848	0.2872				

78	0.2848	0.2872				
79	0.2848	0.2872				
80	0.2848	0.2872				
81	0.2848	0.2872				
82	0.2848	0.2872				
83	0.2848	0.2872				
84	0.2531	0.2872				
85	0.2531	0.2872				
86	0.2531	0.2872				
87	0.2531	0.2872				
88	0.2531	0.2872				
89	0.2531	0.2872				
90	0.2531	0.2872				
91	0.2531	0.2872				
92	0.2531	0.2872				
93	0.2531	0.2667				
94	0.2531	0.2667				
95	0.2531	0.2667				
96	0.2531	0.2667				
97	0.2531	0.2667				
98	0.2531	0.2667				
99	0.2531	0.2667				
100	0.2531	0.2667				
101	0.2109	0.2667				
102						
103						
104						

Table B1-2 displays the data for parametric fittings relating to overall survival in consensus-determined aggressive B-cell lymphoma with pixantrone and physician's choice of chemotherapy.

Table B1-2. Parametric fittings of the consensus-determined aggressive B-cell population - overall survival

	Parameter 1	SE	Parameter 2	SE	Parameter 3	SE.	AIC	BIC
	Intercept		Scale		Shape			
Pixantrone								
Weibull	4.2240	0.1852	1.1103	0.1570	0.9006	0.1274	159.224	163.048
Log-normal	3.6956	0.2030	1.3556	0.1702			153.759	157.583
Log-logistic	3.6784	0.2069	0.8187	0.1127			155.496	159.320
Generalized Gamma	3.0724	0.4871	1.3266	0.2019	-1.0372	0.7295	153.787	159.523
Physician's choice								
Weibull	3.8302	0.1745	1.0808	0.1424	0.9252	0.1219	153.684	157.385
Log-normal	3.2795	0.2036	1.3540	0.1586			153.130	156.831
Log-logistic	3.3074	0.1952	0.7650	0.1026			152.231	155.931
Generalized Gamma	3.5223	0.3222	1.2462	0.1978	0.4202	0.4652	154.304	159.854

Abbreviations used in the table: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; SE, standard error

Figure B1-1 displays the parametric fittings of data for the consensus-determined aggressive B-cell lymphoma subgroup for overall survival with pixantrone, plotted for the duration of the PIX301 trial.

Figure B1-1 Parametric fittings of consensus-determined aggressive B-cell population – overall survival with pixantrone, duration of trial

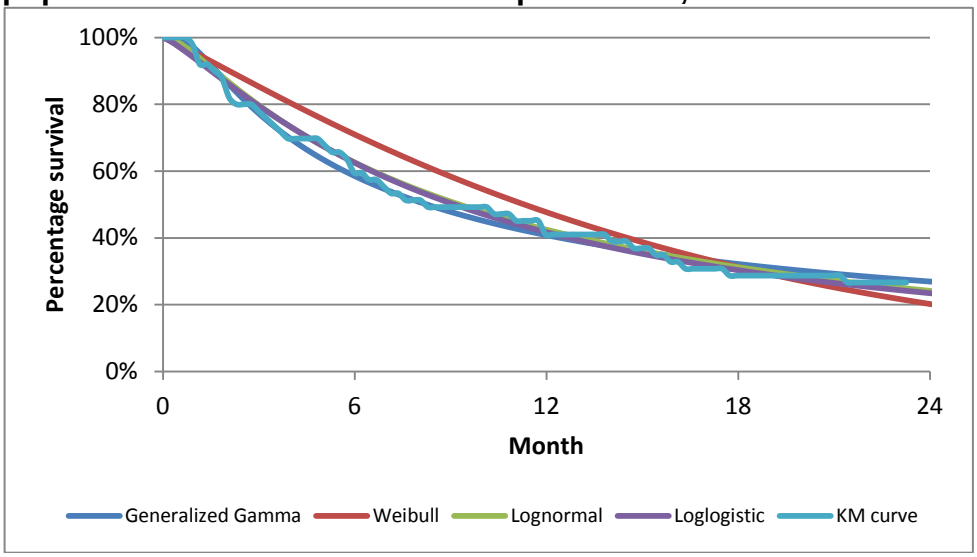


Figure B1-2 displays the parametric fittings of data for the consensus-determined aggressive B-cell lymphoma subgroup for overall survival with pixantrone, plotted with a long-term projection to 6 years.

Figure B2-2 Parametric Fittings of consensus-determined aggressive B-cell population – overall survival with pixantrone, long term projection.

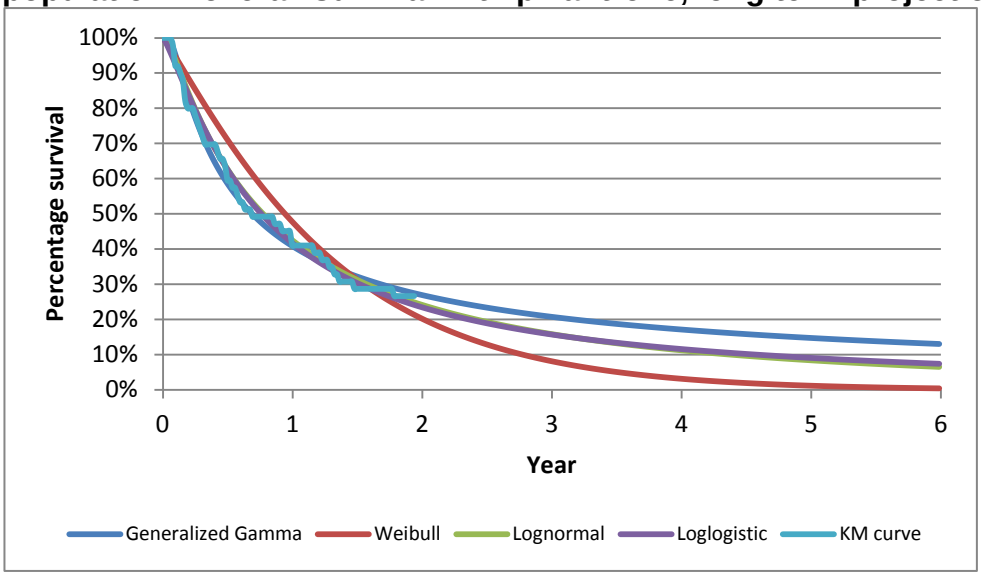


Figure B1-3 displays the parametric fittings of data for the consensus-determined aggressive B-cell lymphoma subgroup for overall survival in the physician's choice group, plotted for the duration of the PIX301 trial.

Figure B1-3 Parametric Fittings of consensus-determined aggressive B-cell population – overall survival with physician's choice, duration of trial

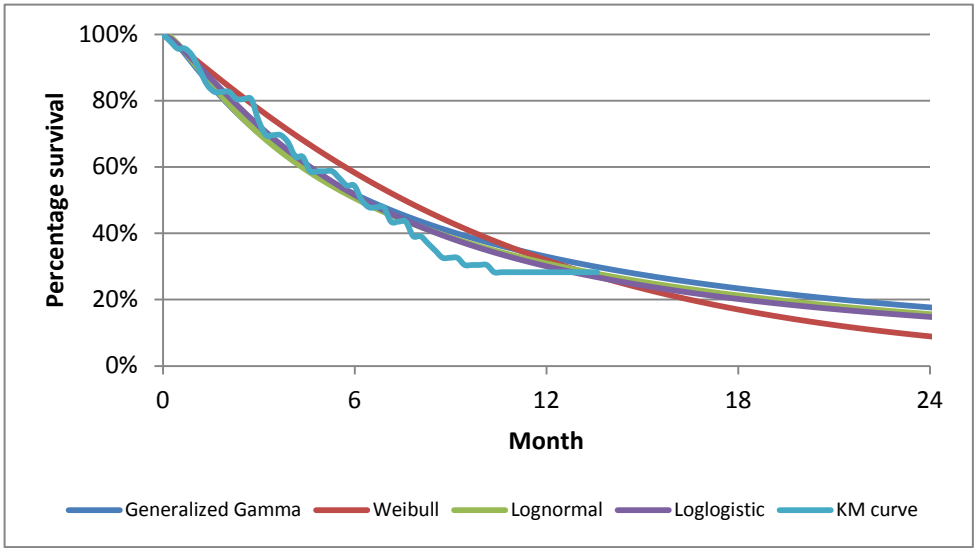


Figure B1-4 displays the parametric fittings of data for the consensus-determined aggressive B-cell lymphoma subgroup for overall survival in the physician's choice group, plotted with a long-term projection of 6 years.

Figure B1-4 Parametric Fittings of consensus-determined aggressive B-cell population – overall survival with physician's choice, long-term projection

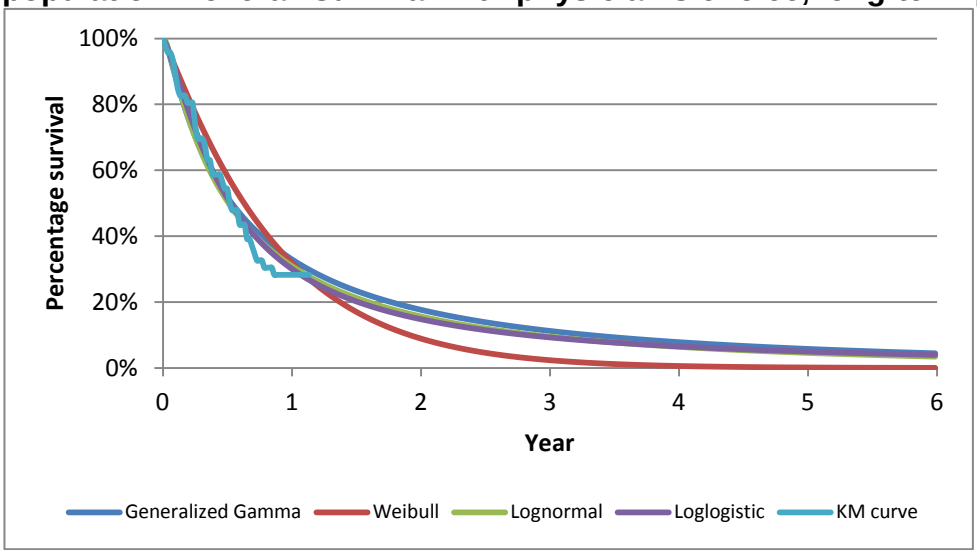


Figure B1-5 displays the resulting Kaplan-Meier curve for overall survival for patients with consensus-determined aggressive B-cell lymphoma. In this figure, pixantrone is represented by “BBR 2778” and physician’s choice by “Chemotherapeutic agent”.

Figure B1-5 Kaplan-Meier curve for Overall Survival in consensus-determined aggressive B-cell population

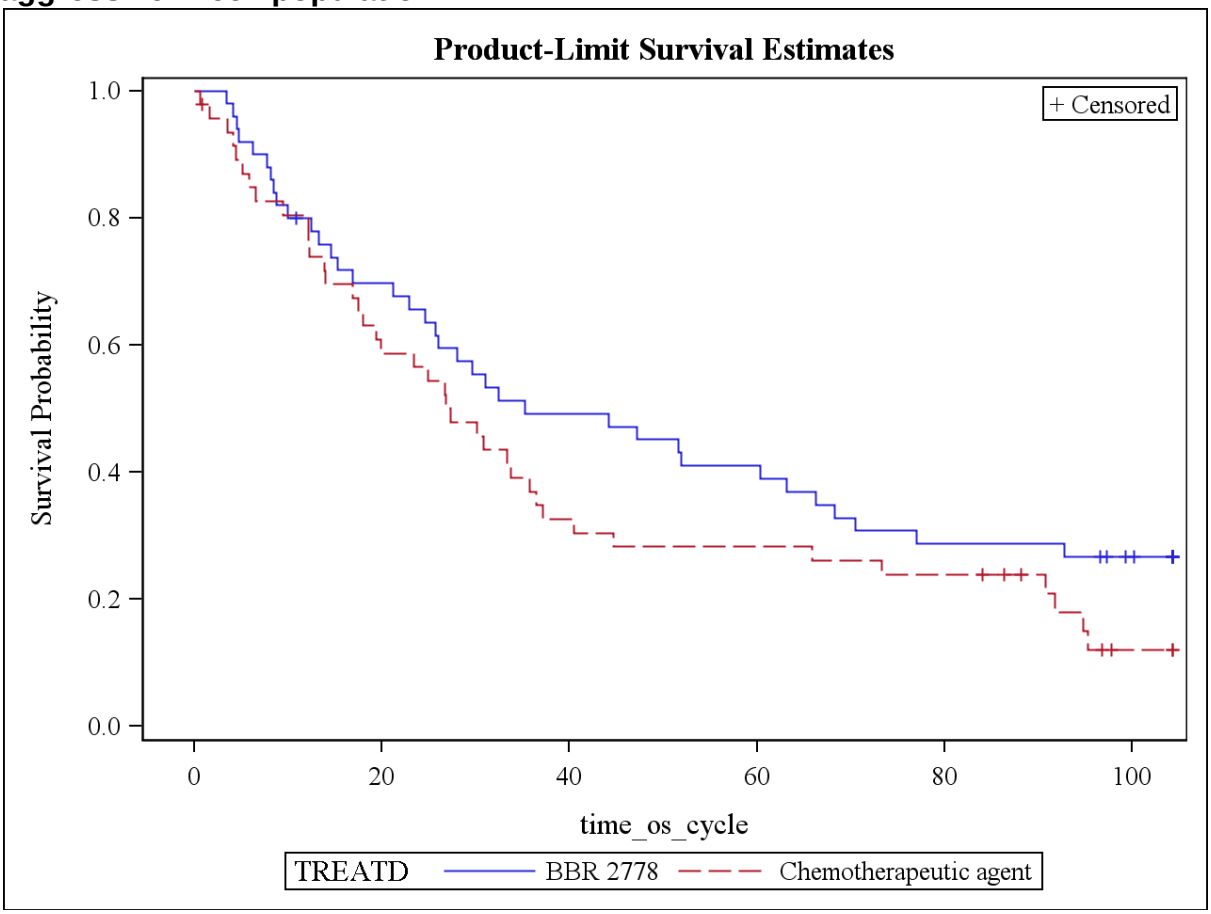


Figure B1-6 displays the negative log of estimated survivor functions for overall survival in the consensus-determined aggressive B-cell population. In this figure, pixantrone is represented by “BBR 2778” and physician’s choice by “Chemotherapeutic agent”.

Figure B1-6 Overall Survival for consensus-determined aggressive B-cell population - negative log of estimated survivor functions

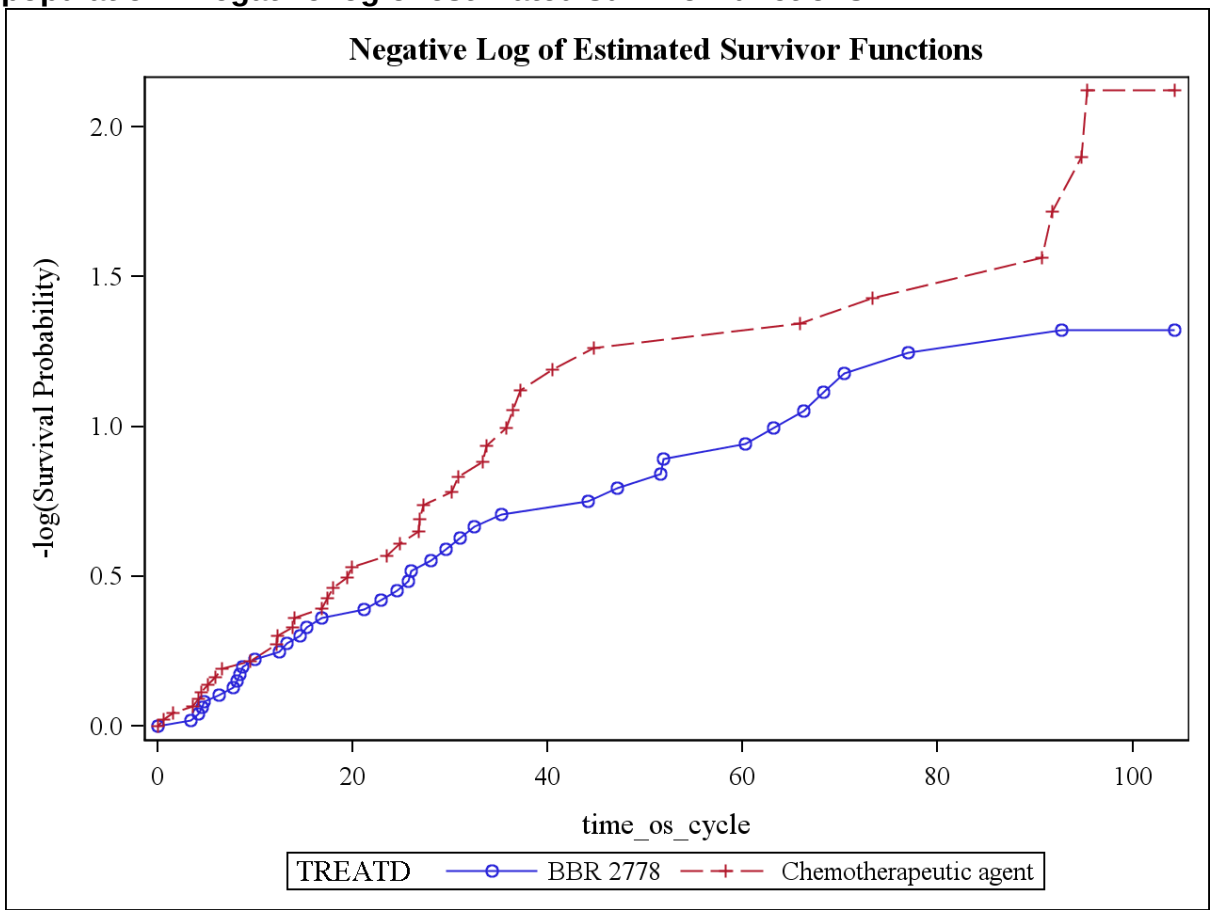


Figure B1-7 displays the Epanechnikov Kernel-smoothed hazard functions for overall survival in the consensus-determined aggressive B-cell population. In this figure, pixantrone is represented by “BBR 2778” and physician’s choice by “Chemotherapeutic agent”.

Figure B1-7 Overall survival for consensus-determined aggressive B-cell population – Epanechnikov Kernel-smoothed hazard functions

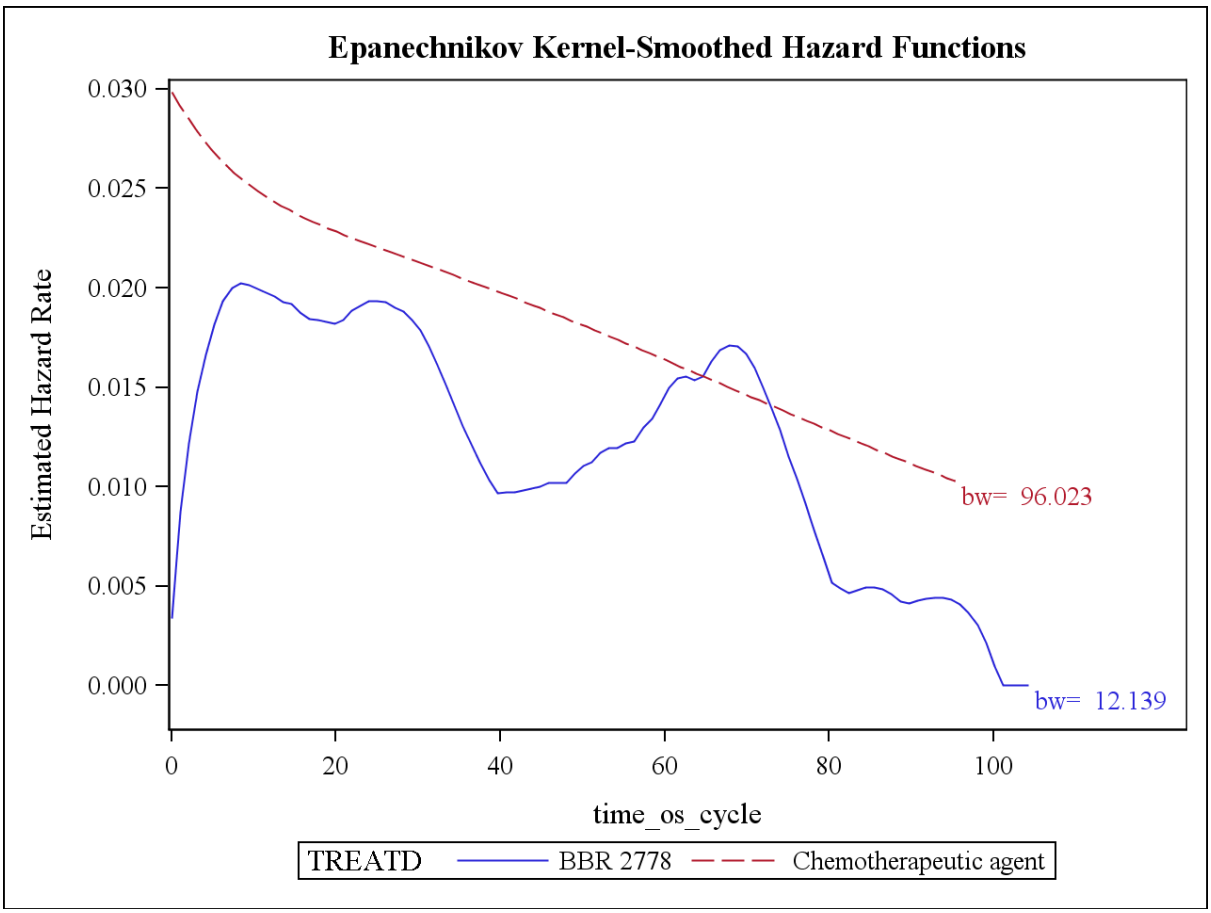


Table B1-3 displays the data for parametric fittings relating to progression-free survival in consensus-determined aggressive B-cell lymphoma. Progression-free survival is defined as absence of death or progressive disease.

Table B1-3 Parametric fittings of consensus=determined aggressive B-cell population – progression-free survival

	Parameter 1	SE	Parameter 2	SE	Parameter 3	SE	AIC	BIC
	Intercept		Scale		Shape			
Pixantrone								
Weibull	3.9290	0.1936	1.1115	0.1530	0.8997	0.1238	146.040	149.864
Log-normal	3.3789	0.1962	1.2591	0.1619			137.673	141.497
Log-logistic	3.3241	0.2018	0.7599	0.1075			139.514	143.338
Generalized Gamma	2.4431	0.3785	1.0101	0.2146	-1.7474	0.7649	133.779	139.515
Physician's choice								
Weibull	2.9617	0.1582	0.9688	0.1147	1.0323	0.1222	136.349	140.049
Log-normal	2.4645	0.1699	1.1179	0.1281			134.511	138.211
Log-logistic	2.5043	0.1594	0.6163	0.0829			133.009	136.710
Generalized Gamma	2.6539	0.2473	1.0538	0.1373	0.3745	0.3734	135.555	141.105

Abbreviations used in the table: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; SE, standard error

Figure B1-8 displays the parametric fittings of data for the consensus-determined aggressive B-cell lymphoma subgroup for progression-free survival with pixantrone, plotted for the duration of the PIX301 trial.

Figure B1-8 Parametric Fittings of consensus-determined aggressive B-cell population – progression-free survival with pixantrone for duration of trial.

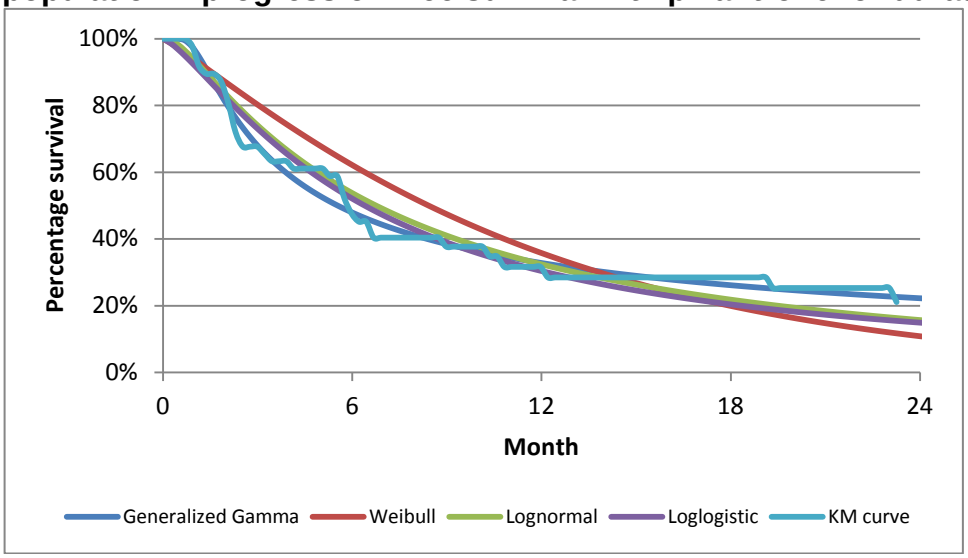


Figure B1-9 displays the parametric fittings of data for the consensus-determined aggressive B-cell lymphoma subgroup for progression-free survival with pixantrone, plotted with a long-term projection to 6 years.

Figure B1-9 Parametric fittings of consensus-determined aggressive B-cell population – progression-free survival with pixantrone with long-term projection

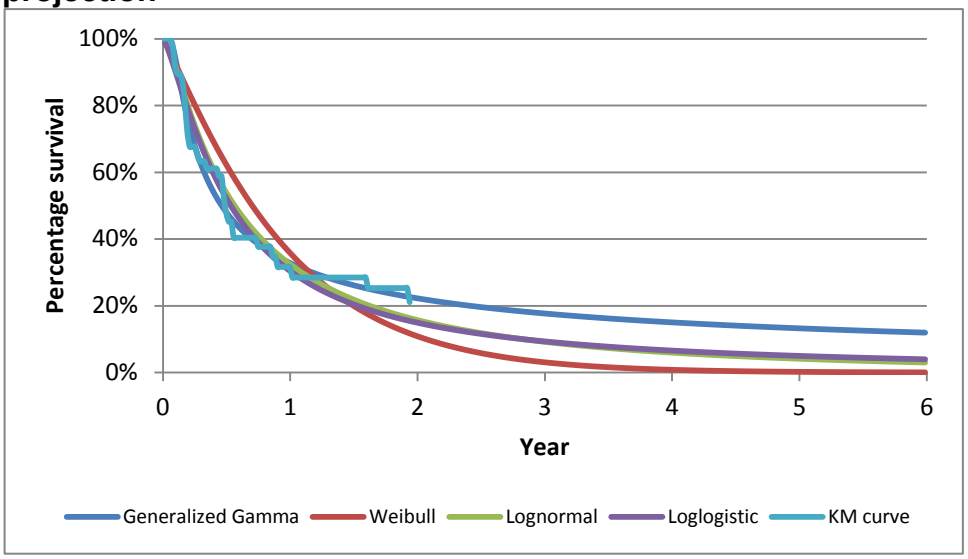


Figure B1-10 displays the parametric fittings of data for the consensus-determined aggressive B-cell lymphoma subgroup for progression-free survival in the physician's choice group, plotted for the duration of the PIX301 trial. Progression-free is defined as absence of death or disease progression.

Figure B1-10 Parametric fittings of consensus-determined aggressive B-cell population – progression-free survival with physician's choice for duration of trial

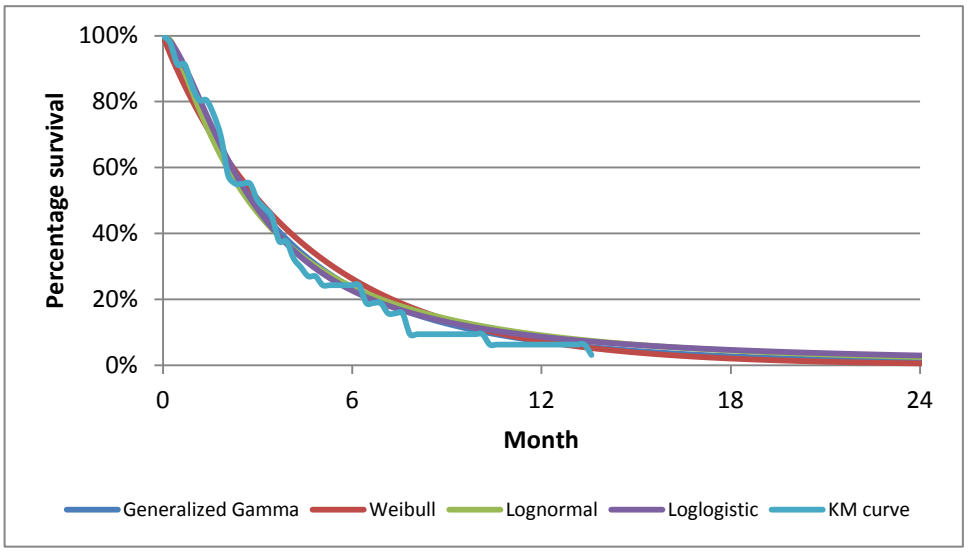


Figure B1-11 displays the parametric fittings of data for the consensus-determined aggressive B-cell lymphoma subgroup for progression-free survival in the physician's choice group, plotted with a long-term projection of 6 years

Figure B1-11 Parametric fittings of consensus-determined aggressive B-cell population – progression-free survival with physician's choice with long-term projection

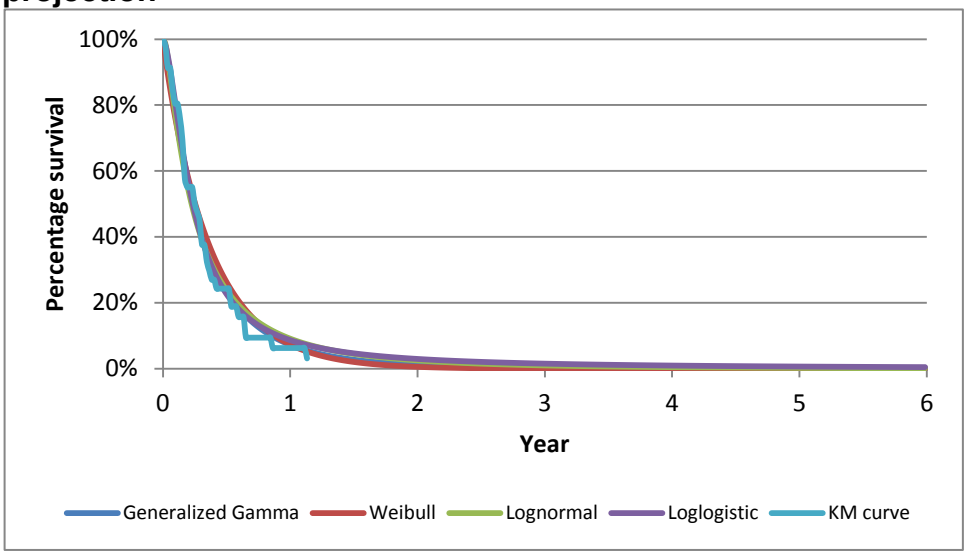


Figure B1-12 displays the resulting Kaplan-Meier curve for progression-free survival for patients with consensus-determined aggressive B-cell lymphoma. In this figure, pxantrone is represented by “BBR 2778” and physician’s choice by “Chemotherapeutic agent”.

Figure B1-12 Kaplan-Meier curve for Ppogression-free survival in consensus-determined aggressive B-cell population

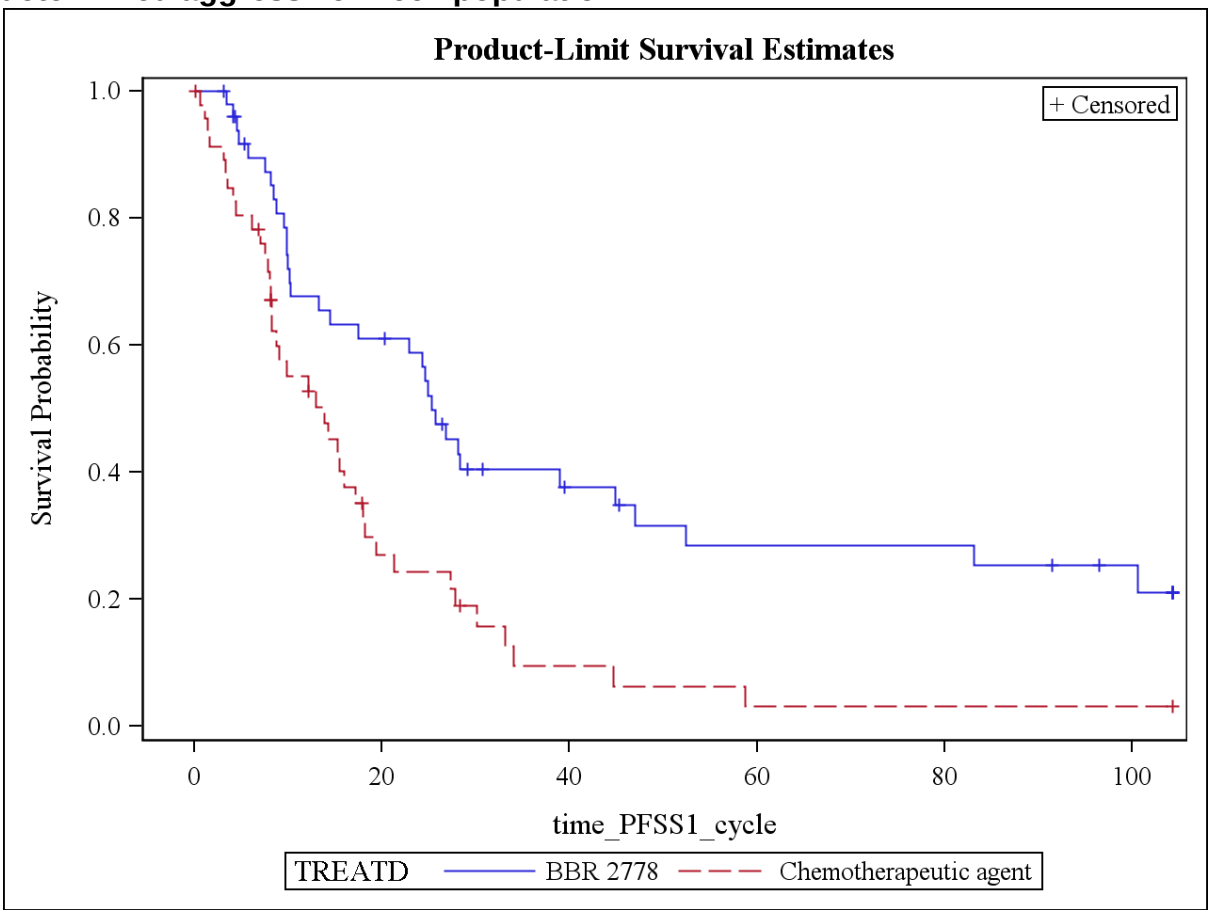


Figure B1-13 displays the negative log of estimated survivor functions for progression-free survival in the consensus-determined aggressive B-cell population. In this figure, pixantrone is represented by “BBR 2778” and physician’s choice by “Chemotherapeutic agent”.

Figure B1-13 Progression-free survival in consensus-determined aggressive B-cell population - negative log of estimated survivor functions

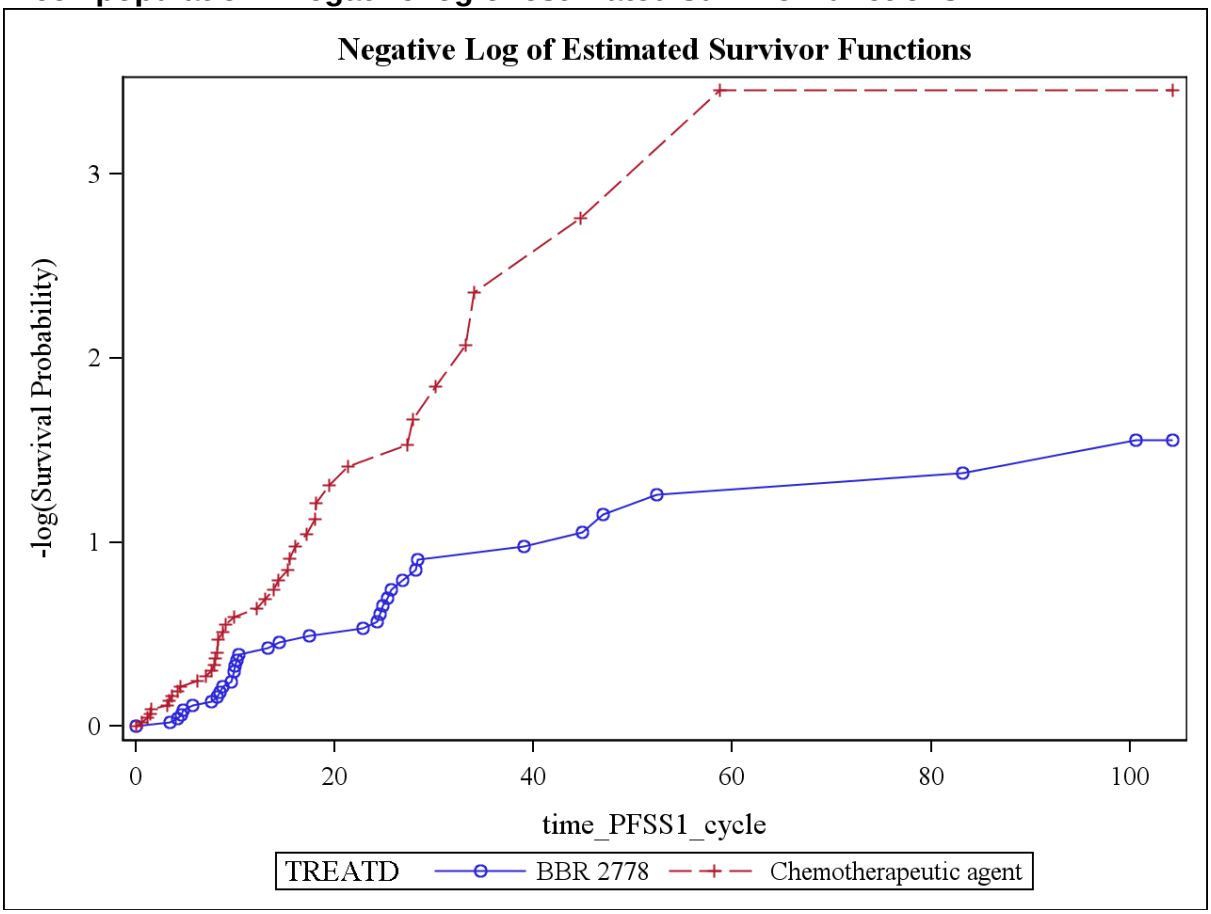
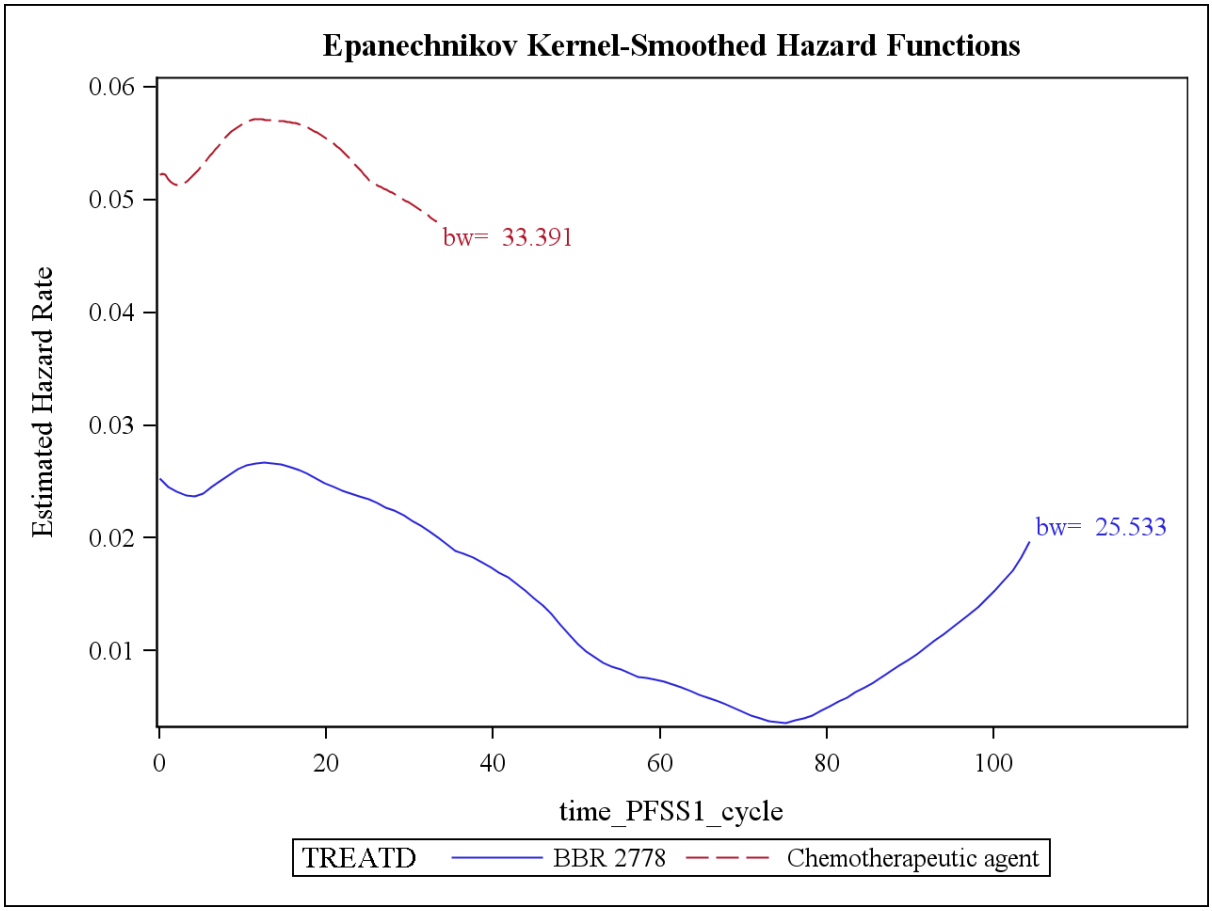


Figure B1-14 displays the Epanechnikov Kernel-smoothed hazard functions for progression-free survival in the consensus-determined aggressive B-cell population. In this figure, pixantrone is represented by “BBR 2778” and physician’s choice by “Chemotherapeutic agent”.

Figure B1-14 Progression-Free Survival in consensus-determined aggressive B-cell population – Epanechnikov Kernel-smoothed hazard functions



Question B10

Table B10-1 Drug costs – chemotherapy agents (Table 13 in Appendix F of the original submission)

Medication	Concentration	Tablet or Vial Size	Price	Source
Bleomycin	15,000 units	15,000 units	£15.56	BNF 64 (Dec 2012)
Cyclophosphamide	500 mg	500 mg	£5.66	BNF 64 (Dec 2012)
	1000 mg	1000 mg	£10.66	BNF 64 (Dec 2012)
Cytarabine	20 mg/mL	5 mL	£3.90	BNF 64 (Dec 2012)
	20 mg/mL	25 mL	£19.50	BNF 64 (Dec 2012)
	100 mg/mL	10 mL	£39.00	BNF 64 (Dec 2012)
	100 mg/mL	20 mL	£ 77.50	BNF 64 (Dec 2012)
Cisplatin	1 mg/mL	10 mL	£5.85	BNF 64 (Dec 2012)

	1 mg/mL	100 mL	£50.22	BNF 64 (Dec 2012)
	50 mg	50 mg	£17.00	BNF 64 (Dec 2012)
Dexamethasone	0.50 mg	0.50 mg	£38.00	BNF 64 (Dec 2012)
	2 mg	2 mg	£6.77	BNF 64 (Dec 2012)
	2 mg/mL	150 mL	£42.30	BNF 64 (Dec 2012)
Doxorubicin	10 mg	10 mg	£18.72	BNF 64 (Dec 2012)
	50 mg	50 mg	£96.86	BNF 64 (Dec 2012)
	2 mg/ml	100 mL	£275.00	BNF 64 (Dec 2012)
Epirubicin	2 mg/mL	5 mL	£19.04	BNF 64 (Dec 2012)
	2 mg/mL	50 mL	£95.54	BNF 64 (Dec 2012)
	2 mg/mL	100 mL	£306.20	BNF 64 (Dec 2012)
	50 mg	50 mg	£91.54	BNF 64 (Dec 2012)
Etoposide IV	20 mg/mL	5 mL	£12.15	BNF 64 (Dec 2012)
	20 mg/mL	10 mL	£29.00	BNF 64 (Dec 2012)
	20 mg/mL	25 mL	£60.75	BNF 64 (Dec 2012)
Etoposide oral	50 mg	20-cap	£99.82	BNF 64 (Dec 2012)
	100 mg	10 cap	£87.23	BNF 64 (Dec 2012)
Gemcitabine	200 mg	200 mg	£32.00	BNF 64 (Dec 2012)
	1000 mg	1000 mg	£162.00	BNF 64 (Dec 2012)
	1500 mg	1500 mg	£213.93	BNF 64 (Dec 2012)
	2000 mg	2000 mg	£324.00	BNF 64 (Dec 2012)
Ifosfamide	1000 mg	1000 mg	£43.53	BNF 64 (Dec 2012)
	2000 mg	2000 mg	£88.62	BNF 64 (Dec 2012)
Mesna	100 mg/mL	4 mL	£3.95	BNF 64 (Dec 2012)
	100 mg/mL	10 mL	£9.77	BNF 64 (Dec 2012)
Methotrexate	2.5 mg/mL	2 mL	£1.68	BNF 64 (Dec 2012)
	25 mg/mL	2 mL	£3.00	BNF 64 (Dec 2012)
	25 mg/mL	20 mL	£30.00	BNF 64 (Dec 2012)
	100 mg/mL	10 mL	£78.33	BNF 64 (Dec 2012)
	100 mg/mL	50 mL	£380.07	BNF 64 (Dec 2012)
Mitoxantrone	2 mg/mL	10 mL	£100.00	BNF 64 (Dec 2012)
	2 mg/mL	13 mL	£152.33	BNF 64 (Dec 2012)
	2 mg/mL	15 mL	£203.04	BNF 64 (Dec 2012)
Oxaliplatin	50 mg	50 mg	£150.00	BNF 64 (Dec 2012)
	100 mg	100 mg	£299.50	BNF 64 (Dec 2012)
	5 mg/mL	40 mL	£622.38	BNF 64 (Dec 2012)
Prednisolone	1 mg	1 mg	£1.18	BNF 64 (Dec 2012)
	5 mg	5 mg	£1.21	BNF 64 (Dec 2012)

	25 mg	25 mg	£30.00	BNF 64 (Dec 2012)
	2.50 mg	2.50 mg	£30.79	BNF 64 (Dec 2012)
	5.00 mg	5.00 mg	£31.04	BNF 64 (Dec 2012)
	5.00 mg	5.00 mg	£9.65	BNF 64 (Dec 2012)
	25 mg/mL	1 mL	£5.73	BNF 64 (Dec 2012)
Pixantrone	29mg	29mg	£343.80	CTI
Rituximab	10 mg/mL	10 mL	£174.63	BNF 64 (Dec 2012)
	10 mg/mL	50 mL	£873.15	BNF 64 (Dec 2012)
Vincristine	1 mg/mL	1 mL	£13.47	BNF 64 (Dec 2012)
	1 mg/mL	2 mL	£26.66	BNF 64 (Dec 2012)
	1 mg/mL	5 mL	£44.16	BNF 64 (Dec 2012)
Vinorelbine	10 mg/mL	1 mL	£29.00	BNF 64 (Dec 2012)
	10 mg/mL	5 mL	£139.00	BNF 64 (Dec 2012)

Question C3

Table C3-1: PIX301 baseline demographic characteristics (ITT population, table 14 in original submission)

	Pixantrone (N=70)	**Comparator** (N=70)	**p-value**
Age at Randomisation (years)			
Mean (SD)	58.2 (13.5)	56.2 (12.9)	0.382
Median (range)	60.0 (18-80)	58.0 (26-82)	
Age Category at Randomisation, n (%)			0.230
18 to <30	5 (7.1%)	2 (2.9%)	0.441
30 to <40	2 (2.9%)	9 (12.9%)	0.055
40 to <50	9 (12.9%)	7 (10.0%)	0.791
50 to <60	18 (25.7%)	21 (30.0%)	0.706
60 to <70	20 (28.6%)	21 (30.0%)	1.000
70 to <80	15 (21.4%)	9 (12.9%)	0.262
≥80	1 (1.4%)	1 (1.4%)	1.000
Sex, n (%)			0.385
Male	46 (65.7%)	40 (57.1%)	
Female	24 (34.3%)	30 (42.9%)	
Race, n (%)			0.957
Caucasian	46 (65.7%)	44 (62.9%)	0.860
Black	0	0	NE
Asian	10 (14.3%)	13 (18.6%)	0.649
Hispanic	7 (10.0%)	6 (8.6%)	1.000
Native American	1 (1.4%)	1 (1.4%)	1.000
Other	6 (8.6%)	6 (8.6%)	1.000
Baseline ECOG Performance Status, n (%)			0.881
0	26 (37.1%)	23 (32.9%)	0.723
1	30 (42.9%)	32 (45.7%)	0.865
2	14 (20.0%)	14 (20%)	1.000
3	0	1 (1.4%)	1.000
Geographic Region, n (%)			1.000
North America	4 (5.7%)	4 (5.7%)	1.000
Western Europe	19 (27.1%)	19 (27.1%)	1.000
Rest of World	47 (67.1%)	47 (67.1%)	1.000

Weight (kg)			
Mean (SD)	70.9 (15.8)	68.7 (15.3)	0.394
Median (range)	70.0 (45-117)	67.5 (37-115)	

Abbreviations used in this table: ECOG, Eastern Cooperative oncology Group; kg, kilogram; n, number of patients with characteristic; N, number of patients in subgroup; SD,standard deviation, NE,not evaluable

Fisher exact test was used to compare proportions between the group and a two-sided student's t-test was used in the comparison of means between treatment groups.

Table C3-2: PIX301 baseline disease characteristics (table 16 in original submission)

	Pixantrone (n=70)	Comparator (n=70)	p-value
Duration of NHL (months)			
Mean (SD)	43.6 (35.6)	46.6 (51.7)	0.693
Median (range)	32.0 (7-160)	31.6 (0-333)	
Ann Arbor Stage of NHL, n (%)			0.426
I/II	19 (27.1%)	14 (20.0%)	
III/IV	51 (72.9%)	56 (80.0%)	
International Prognostic Index, n (%)			0.569
0, 1	21 (30.0%)	17 (24.3%)	0.569
≥2	49 (70%)	52 (74.3%)	0.706
Missing	0	1 (1.4%)	1.000
Number of Extranodal Sites, n (%)			1.000
0	35 (50%)	35 (50%)	1.000
≥1	34 (48.6%)	33 (47.1%)	1.000
Missing	1 (1.4%)	2 (2.9%)	1.000
Time from Last Chemotherapy to Randomisation (months)			
Mean (SD)	13.6 (15.7)	13.2 (23.5)	0.886
Median (range)	9.0 (1-86)	8.0 (1-190)	

Abbreviations used in this table: SD, Standard deviation

Fisher exact test was used to compare proportions between the groups, and a two-sided student's t test was used in the comparison of means between treatment groups. P-values are for reference purposes only.

Table C3-3: Prior NHL treatment (table 17 in original submission)

	Pixantrone (n=70)	**Comparator** (n=70)	**p-value**
Chemotherapy regimens			
Mean (SD)	2.9 (1.3)	3.1 (1.2)	0.535
Median (range)	3.0 (2-9)	3.0 (2-8)	
Number of chemotherapy regimens			0.396
2	32 (45.7%)	24 (34.3%)	0.227
3-5	35 (50%)	42 (60%)	0.308
≥6	3 (4.3%)	4 (5.7%)	1.000
Category of prior chemotherapy			
Biologics (anti-CD20 mAB)	38 (54.3%)	39 (55.7%)	1.000
Anthracyclines/anthracenediones	70 (100.0%)	70 (100.0%)	NE
Other topoisomerase inhibitors (a)	53 (75.7%)	55 (78.6%)	0.841
Platinum-based agents	36 (51.4%)	35 (50.0%)	1.000
Antimetabolites	42 (60.0%)	44 (62.9%)	0.862
Alkylating agents	70 (100.0%)	70 (100.0%)	NE
Spindle poison/mitotic inhibitors (SP/MIs))	70 (100.0%)	69 (98.6%)	1.000
Corticosteroids	66 (94.3%)	65 (92.9%)	1.000
Other (b)	21 (30.0%)	30 (42.9%)	0.160
Disease response category			0.544
Refractory	40 (57.1%)	40 (57.1%)	1.000
Relapsed	28 (40.0%)	30 (42.9%)	0.864
Missing	2 (2.9%)	0	0.496
Patients who had radiotherapy, n (%)			
	34 (48.6%)	30 (42.9%)	0.611
Received SCT, n (%)			
	11 (15.7%)	10 (14.3%)	1.000
Anthracycline dose equivalent (mg/m^2) (b)			
Mean (SD)	284.8 (98.1)	321.9 (119.0)	0.046
Median (range)	292.9 (51-472)	315.5 (15-681)	

(a) Other topoisomerase inhibitors were etoposide and teniposide

(b) Other includes targeted therapies, non-classified anticancer therapies and supportive therapies

Abbreviations used in this table: SCT, stem cell transplant; SD, Standard deviation, NE,Not evaluable

Fisher exact test was used to compare proportions between the groups, and a two-sided student's t test was used in the comparison of means between treatment groups.