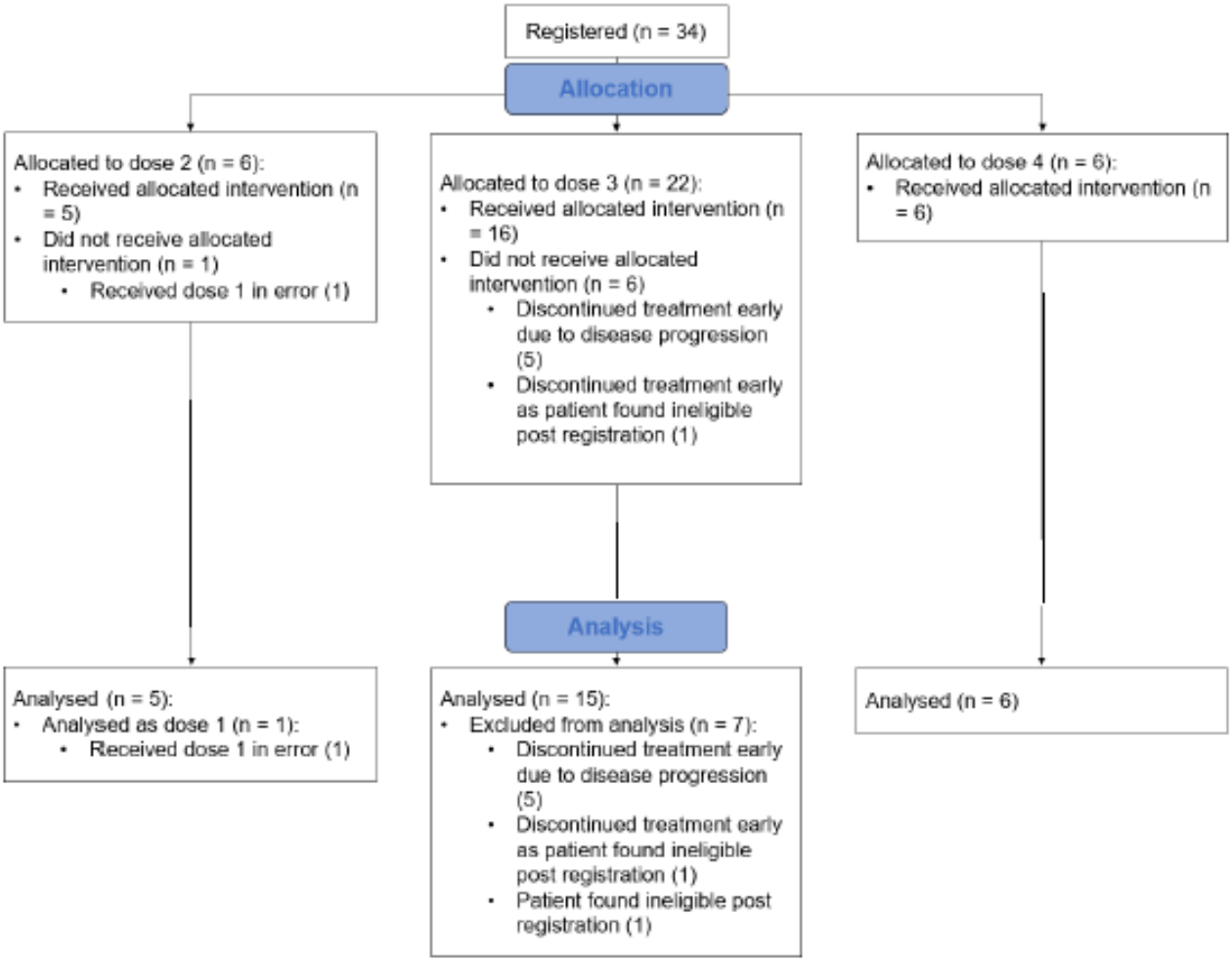
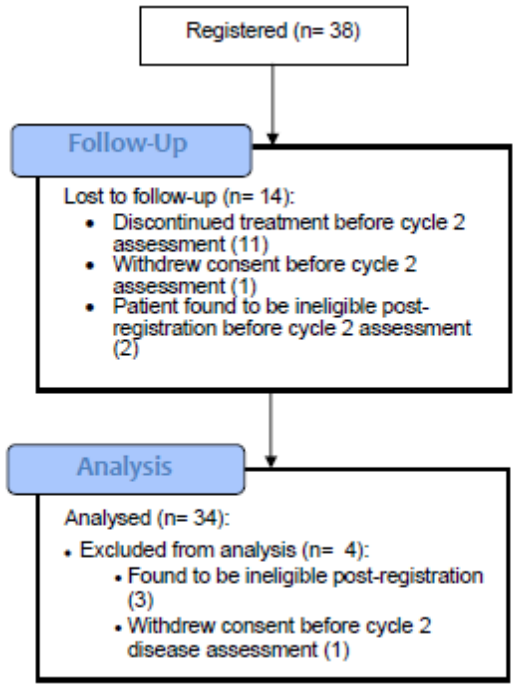
Participant Flow

Phase I Primary Outcome Consort Diagram



Phase II Primary Outcome Consort Diagram



Baseline Characteristics

Summary	Dose 2 (N = 6)	Dose 3 (N = 38)	Dose 4 (N = 6)	Overall
Age (Years)				
N	6	38	6	50
Min	51	22	64	22
Q25	54	53	66	54
Median	65	61	69	63
Q75	72	65	71	69
Max	76	86	72	86
Sex (% (N))				
Female	67% (4)	26% (10)	17% (1)	30% (15)
Male	33% (2)	74% (28)	83% (5)	70% (35)
Ethnicity (% (N))				
White British	100% (6)	76% (29)	100% (6)	82% (41)
Asian Chinese	-	3% (1)	-	2% (1)
Black Caribbean	-	3% (1)	-	2% (1)
Not Known	-	3% (1)	-	2% (1)
Other	-	13% (5)	-	10% (5)
White Irish	-	3% (1)	-	2% (1)
British Origin (% (N))				
Yes	100% (6)	76% (29)	100% (6)	82% (41)
No	-	21% (8)	-	16% (8)
Not Known	-	3% (1)	-	2% (1)

Summary	Dose 2 (N = 6)	Dose 3 (N = 38)	Dose 4 (N = 6)	Overall
Histology (% (N))				
Angioimmunoblastic T-cell lymphoma	50% (3)	39% (15)	33% (2)	40% (20)
Peripheral T-cell lymphoma not otherwise specified	50% (3)	47% (18)	67% (4)	50% (25)
Anaplastic large cell lymphoma	-	5% (2)	-	4% (2)
Enteropathy associated T-cell lymphoma	-	3% (1)	-	2% (1)
Extranodal NK/T-cell lymphoma	-	3% (1)	-	2% (1)
Transformed mycosis fungoides	-	3% (1)	-	2% (1)
Time from First Diagnosis to Registration (Years)				
N	6	37	6	49
Min	1	0.1	0.4	0.1
Q25	1.4	0.7	0.5	0.8
Median	2.1	1	1	1.1
Q75	2.6	1.6	1.4	1.8
Max	19.2	5.8	3.8	19.2
Disease Status at Registration (% (N))				
Refractory Lymphoma	50% (3)	58% (22)	33% (2)	54% (27)
Relapsed Lymphoma	50% (3)	42% (16)	67% (4)	46% (23)
Time from Histological Confirmation of Relapsed/Refractory Disease to Registration (Weeks)				
N	6	30	6	42
Min	1.3	0	1	0
Q25	1.6	1.6	2.1	1.4
Median	2.7	3	5.4	3
Q75	12.5	6.6	5.9	6.9
Max	20.3	39.7	9	39.7
Relapsed/Refractory Disease Confirmed at MDT (% (N))				
Not Applicable	100% (6)	82% (31)	100% (6)	86% (43)
No	-	5% (2)	-	4% (2)
Yes	-	13% (5)	-	10% (5)

Primary Outcome Measures

Phase I Primary Outcome MTD

Table 24: CRM Results.

Dose	Number of patients	Number of DLTs*	Prior Prob(DLT)	Posterior Prob(DLT)	90% Credible Interval
1	1	1	0.05	0.089	(0.029, 0.192)
2	5	0	0.10	0.156	(0.065, 0.282)
3	15	2	0.15	0.216	(0.106, 0.352)
4	6	3	0.25	0.327	(0.194, 0.466)
5	0	0	0.35	0.429	(0.288, 0.561)
6	0	0	0.50	0.571	(0.44, 0.683)

* Number of patients experiencing DLTs

Table shows the results of the CRM model. The trial target rate of DLT is 0.25 (25%). Dose level 3 had posterior probability estimate of 0.216 (90% Credible Interval: 0.106, 0.352) which was the closest to this target rate of 0.25. **The modified Continual Reassessment Method (CRM) model recommended dose level 3 as the MTD.**

Phase 2 Primary Outcome - Best Response in First 8 Cycles

Responders	Total	Response Rate	Lower 95% confidence interval bound	Upper 95% confidence interval bound
11	**34**	**0.32**	**0.19**	**0.49**

As more patients were recruited than the required sample size, the threshold for a successful phase 2 outcome should be adjusted. A sample size of 28 patients were expected and if at least 12 were to achieve at least a partial response our outcome would be successful, with type 1 error rate of 0.1 and a type 2 error rate of 0.17. As there are 34 patients, for success at least 14 would need to have at least a partial response, with type 1 error rate of 0.11 and a type 2 error rate of 0.11. As there were 11 responses, the phase 2 success criteria have not been met.

Summary of Best Response Within First 8 Cycles.

Characteristic	N = 34
Best Response Within First 8 Cycles	
Complete Response	5 (22%)
Partial Response	6 (26%)
Relapsed Disease/Progressive Disease	6 (26%)
Stable Disease	6 (26%)
Did not reach cycle 2 disease assessment	11

Secondary Outcomes

Phase 1 Secondary Outcome - Best Response in First 8 Cycles

Summary of Best Response Within First 8 Cycles.

Characteristic	2, N = 5	3, N = 34	4, N = 6
Best Response Within First 8 Cycles			
Complete Response	1 (25%)	5 (22%)	0 (0%)
Partial Response	1 (25%)	6 (26%)	3 (75%)
Relapsed Disease/Progressive Disease	2 (50%)	6 (26%)	0 (0%)
Stable Disease	0 (0%)	6 (26%)	1 (25%)
Did not reach cycle 2 disease assessment	1	11	2

Phase 2 Secondary Outcome - Best Response After 8 Cycles

Summary of Best Response Across All 8 Cycles.

Characteristic	N = 34
Best Response Across All Cycles	
Complete Response	5 (22%)
Partial Response	6 (26%)
Relapsed Disease/Progressive Disease	6 (26%)
Stable Disease	6 (26%)
Did not reach cycle 2 disease assessment	11

Summary of Best Response After First 8 Cycles.

Characteristic	N = 6
Best Response After First 8 Cycles	
Complete Response	3 (50%)
Partial Response	1 (17%)
Relapsed Disease/Progressive Disease	2 (33%)

Overall survival

(defined as the time from date of registration to the date of death from any cause)

Secondary outcome measure	
Overall survival at 6 months	62% (95% CI: 48-81%)
Overall survival at 12 months	41% (95% CI: 28-62%)
Overall survival at 24 months	23% (95% CI: 13-43%)
Overall survival at 36 months	17% (95% CI: 8-40%)

Progression free survival

(defined as time from date of registration to date of progression or death from any cause)

Secondary outcome measure	
Progression-free survival at 6 months	29% (95% CI: 17-48%)
Progression-free survival at 12 months	17% (95% CI: 8-36%)

Adverse Events

Percentage of patients experiencing treatment related grade 3 and 4 events

Event	Grade 3	Grade 4	Grade 3 or 4
Platelet count decreased	29	14	37
Neutrophil count decreased	24	10	33
Anemia	18	0	20
Hyponatremia	2	2	8
Fatigue	2	0	6
Fever	4	0	6
Hypotension	6	0	6
Sepsis	2	4	6
Acute kidney injury	2	0	4
Diarrhea	2	0	4
Influenza A	2	0	4
Lung infection	4	0	4
Lymphocyte count decreased	2	0	4
Nausea	4	0	4
Vomiting	4	0	4
Pneumonia	0	2	4
Colonic hemorrhage	2	0	2
Dehydration	2	0	2
Central venous catheter infection	2	0	2
Hypokalemia	2	0	2
Hypophosphatemia	2	0	2
Infusion related reaction	2	0	2
Microangiopathic haemolytic anaemia	2	0	2
Non-cardiac chest pain	2	0	2
NSTEMI (SAE)	2	0	2
Post chemo emesis (SAE)	2	0	2
Pulmonary embolis	2	0	2
Upper respiratory infection	2	0	2
White blood cell decreased	2	0	2
Dyspnea	0	2	2
Febrile neutropenia	0	2	2
Influenza	0	2	2

Serious Adverse Events

56 SAEs were reported during the trial, occurring in 31 patients. 938 AEs were reported during the trial, occurring in 49 patients. There were 39 deaths.

Details of SAEs

Summary	N (%)
Categorisation	
Non fatal/life-threatening SUSAR	2 (4%)
SAR	35 (62%)
Unrelated SAE	19 (34%)
Carfilzomib Relatedness	
Unrelated	12 (21%)
Unlikely to be related	11 (20%)
Possibly related	22 (39%)
Probably related	10 (18%)
Definitely related	1 (2%)
Romidepsin Relatedness	
Unrelated	10 (18%)
Unlikely to be related	12 (21%)
Possibly related	26 (46%)
Probably related	7 (13%)
Definitely related	1 (2%)
Outcome	
Death	2 (4%)
Resolved - no sequelae	37 (66%)
Resolved - with sequelae	8 (14%)
Unresolved	9 (16%)
Grade	
1	8 (14%)
2	9 (16%)
3	29 (52%)
4	10 (18%)

List of all SAEs that occurred during the trial

SAE Ref.	Category	SAE Start Date	Outcome	Carfilzomib Relatedness	Romidepsin Relatedness	Grade	Event(s)	Admit
1	SAR	2015-09-15	Resolved - no sequelae	Probably related	Unrelated	2 3 3	Fever Infusion related reaction Hypotension	*
2	SAR	2015-10-03	Resolved - no sequelae	Unrelated	Unrelated	2 3	Fever Hypotension	*
3	SAR	2015-10-20	Resolved - with sequelae	Unlikely to be related	Unlikely to be related	3 4	Hypotension Fever	*
4	SAR	2015-11-26	Resolved - with sequelae	Possibly related	Possibly related	2 3	Fever Hypotension	*
5	SAR	2015-10-08	Resolved - no sequelae	Possibly related	Possibly related	2 2 3 3 4	Atrial fibrillation Diarrhea Colonic hemorrhage Bronchial infection Platelet count decreased	*
6	Unrelated SAE	2015-11-25	Resolved - no sequelae	Unlikely to be related	Unlikely to be related	1 3	Fever Catheter related infection	*
7	Unrelated SAE	2015-12-09	Resolved - no sequelae	Unlikely to be related	Unlikely to be related	1 3	Fever Infection - central venous catheter	*
8	Non fatal/life-threatening SUSAR	2016-03-24	Resolved - no sequelae	Possibly related	Possibly related	1 1 4	Electrolyte imbalance (potassium and calcium low) Acute kidney injury Influenza A	*
9	SAR	2016-08-31	Unresolved	Possibly related	Possibly related	3	Pulmonary Embolism	*
10	Unrelated SAE	2018-03-18	Resolved - no sequelae	Unrelated	Unrelated	1	Fever 39oC	*
11	SAR	2018-12-19	Resolved - no sequelae	Unrelated	Probably related	3	Sepsis	*
12	Unrelated SAE	2020-01-15	Resolved - with sequelae	Unrelated	Unrelated	3	Squamous Cell Carcinoma	*

Table 41: SAE Line Listing. *(continued)*

SAE Ref.	Category	SAE Start Date	Outcome	Relatedness: Carfilzomib Relatedness	Relatedness: Romidepsin	Grade	Event(s)	Admit
13	SAR	2016-11-15	Resolved - no sequelae	Possibly related	Possibly related	1	Fever	*
						2	Methaemoglobinemia	
						2	Hypoxia	
14	SAR	2017-05-22	Resolved - no sequelae	Possibly related	Possibly related	1	Fever	*
15	SAR	2017-03-15	Resolved - no sequelae	Probably related	Probably related	3	Vomiting	*
16	Unrelated SAE	2017-07-20	Resolved - no sequelae	Unrelated	Unrelated	1	Fever	*
						2	Cough	
17	SAR	2018-02-23	Resolved - no sequelae	Unlikely to be related	Possibly related	1	Cough	
						2	Fatigue	
						3	Lung infection	*
18	SAR	2017-06-07	Resolved - with sequelae	Possibly related	Possibly related	4	Dyspnea	*
19	SAR	2017-07-26	Resolved - no sequelae	Possibly related	Probably related	1	Acute kidney injury	
						3	Hypotension	*
20	Unrelated SAE	2017-08-23	Resolved - no sequelae	Unrelated	Unrelated	1	Diarrhea	
						2	QTC prolonged	
						3	Hypokalemia	*
21	SAR	2017-09-05	Resolved - no sequelae	Possibly related	Possibly related	2	Diarrhea	
						3	Fatigue	*
						3	Fever	
22	SAR	2017-09-22	Resolved - no sequelae	Probably related	Probably related	2	Enterocolitis infectious	
						3	Nausea	
						4	Sepsis	*
23	Unrelated SAE	2018-02-17	Resolved - no sequelae	Unrelated	Unrelated	2	Nausea	
						3	Non-cardiac chest pain	*
						3	Abdominal pain NOS	
24	Unrelated SAE	2018-03-01	Resolved - with sequelae	Unlikely to be related	Unlikely to be related	1	Fever	*
						2	Diarrhea	
						2	Vomiting	
25	SAR	2018-03-15	Resolved - no sequelae	Unrelated	Probably related	1	Fever	*
26	SAR	2017-12-11	Resolved - no sequelae	Possibly related	Possibly related	2	Dehydration	*

Table 41: SAE Line Listing. *(continued)*

SAE Ref.	Category	SAE Start Date	Outcome	Carfilzomib Relatedness	Romidepsin Relatedness	Grade	Event(s)	Admit
27	Non fatal/life-threatening SUSAR	2017-12-15	Resolved - with sequelae	Possibly related	Possibly related	1	Cardiac Troponin I increased	*
28	SAR	2018-01-04	Resolved - no sequelae	Possibly related	Possibly related	3	Vomiting	*
29	SAR	2018-02-02	Resolved - no sequelae	Unrelated	Possibly related	3	Hypotension	*
30	SAR	2018-03-09	Resolved - no sequelae	Probably related	Probably related	4 4	Thrombocytopenia Pneumonia	*
31	SAR	2018-05-16	Resolved - no sequelae	Probably related	Unlikely to be related	2 2	Fever Neutropenia	*
32	SAR	2018-05-19	Resolved - no sequelae	Possibly related	Possibly related	1	Fever	*
33	Unrelated SAE	2018-06-29	Resolved - no sequelae	Unlikely to be related	Unlikely to be related	1 2	Sinus tachycardia Fever	*
34	Unrelated SAE	2018-07-01	Resolved - no sequelae	Unrelated	Unrelated	1 2 3 3	Sinus tachycardia Fever PICC line infection Neutrophil count decreased	*
35	Unrelated SAE	2018-10-08	Resolved - no sequelae	Unrelated	Unrelated	2	Fever	*
36	Unrelated SAE	2018-08-17	Resolved - no sequelae	Unlikely to be related	Unlikely to be related	1	Fever	*
37	SAR	2018-09-10	Unresolved	Possibly related	Possibly related	1	Fever	*
38	SAR	2019-02-24	Unresolved	Possibly related	Possibly related	3	Lung infection	*
39	Unrelated SAE	2019-12-16	Resolved - no sequelae	Unlikely to be related	Unlikely to be related	1 2	Cough Flu like symptoms	*
40	Unrelated SAE	2018-12-14	Unresolved	Unrelated	Unrelated	2	Chills	*
41	SAR	2019-02-11	Unresolved	Possibly related	Possibly related	2 3	Pain Lung infection	*
42	Unrelated SAE	2018-12-21	Resolved - no sequelae	Unrelated	Unrelated	3	PICC line infection	*
43	Unrelated SAE	2019-01-04	Resolved - no sequelae	Unrelated	Unrelated	3	Fever	*

Table 41: SAE Line Listing. *(continued)*

SAE Ref.	Category	SAE Start Date	Outcome	Carfilzomib Relatedness	Romidepsin Relatedness	Grade	Event(s)	Admit
44	SAR	2019-02-22	Unresolved	Possibly related	Possibly related	3 3 3 3	Anemia Lung infection Neutrophil count decreased decreased	*
45	Unrelated SAE	2019-02-20	Unresolved	Unlikely to be related	Unlikely to be related	3	Thrombocytopenia	*
46	SAR	2019-05-08	Resolved - with sequelae	Probably related	Possibly related	3	Micro Angiopathic Haemolytic Anaemia	*
47	SAR	2020-02-22	Resolved - no sequelae	Possibly related	Possibly related	3	Abdominal pain	*
48	SAR	2019-07-02	Resolved - no sequelae	Possibly related	Possibly related	1 1 3 3	Chills Fever Sepsis Bronchial infection	*
49	SAR	2019-07-08	Resolved - with sequelae	Unlikely to be related	Unlikely to be related	2 3	Pain Abdominal pain	*
50	SAR	2019-07-21	Resolved - no sequelae	Possibly related	Possibly related	1	Fever	*
51	SAR	2019-08-21	Unresolved	Probably related	Probably related	4 4	Febrile neutropenia Respiratory failure	*
52	SAR	2019-09-03	Resolved - no sequelae	Probably related	Probably related	3	Supraventricular tachycardia	*
53	SAR	2019-08-21	Unresolved	Possibly related	Possibly related	1 2 3	Fever Platelet count decreased Anemia	*
54	SAR	2019-08-23	Death	Possibly related	Possibly related	4 4	Hypotension Hypovolemia	*
55	Unrelated SAE	2019-10-13	Resolved - no sequelae	Unlikely to be related	Unlikely to be related	1 1 2 4	Vomiting Fever Nausea Sepsis	*

Table 41: SAE Line Listing. *(continued)*

SAE Ref.	Category	SAE Start Date	Outcome	Carfilzomib Relatedness	Romidepsin Relatedness	Grade	Event(s)	Admit
						3	Adult respiratory	

	56	Unrelated SAE	2019-11-		
17		Death	Unrelated	Unrelated	

	distress syndrome	
3	Dyspnea	
4	Lung infection	*