A phase 1 study of romidepsin, azacitidine, dexamethasone, and lenalidomide (RAdR) for relapsed/refractory T-cell malignancies

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INTRODUCTION

- Romidepsin, azacitidine and lenalidomide are all active in T-cell malignancies demonstrating single agent objective response rates (ORR) of 20 to 30% (Coiffier 2012; Morschhauser 2013; Dupuis 2022)
- Combinations of these targeted agents improve the rates of complete response (CR) but have significant toxicity due to indefinite administration

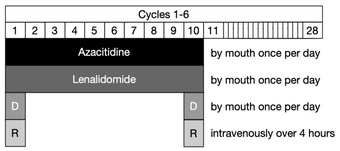
AIMS

We hypothesized that combination multi-targeted therapy, the RAdR regimen, given in fixed duration would be safe and effective

1. Determine the maximum tolerated dose (MTD) of dose escalated lenalidomide with fixed dose romidepsin, azacitidine and dexamethasone
2. Evaluate the overall safety of the RAdR regimen

METHOD

- A phase 1 trial of escalating doses of lenalidomide (5 to 20mg) with fixed doses of romidepsin, azacitidine and dexamethasone
- Patients received a 7-day window of lenalidomide for cytokine correlative research followed by six cycles of romidepsin (12mg/m^2; days 1 and 10), azacitidine (300mg; days 1-10), dexamethasone (40mg; days 1 and 10), and lenalidomide (5-20mg; days 1-10) in 21-day cycles for up to 6 cycles



- The primary endpoint was the MTD of lenalidomide and the primary objective was the overall safety of the regimen. A 3+3 design was used with an additional 9 pts treated at the MTD

RESULTS

		Full cohort (N=26)	Treated at MTD (N=9)
Age			
	Median (range)	61 (28-80)	60 (39-79)
	>65 years	8 (32%)	4 (44%)
Gender			
	Female	8 (31%)	3 (33%)
	Male	18 (69%)	6 (66%)
Race/ethnicity			
	Black	10 (38%)	4 (44%)
	White	8 (31%)	3 (33%)
	Hispanic	4 (15%)	2 (22%)
	Asian	4 (15%)	0
Diagnosis			
	PTCL, NOS	8 (32%)	5 (55%)
	AITL	5 (20%)	0
	ALCL	2 (8%)	2 (22%)
	ENKTL	1 (4%)	0
	ATLL	4 (15%)	0
	MF	6 (23%)	2 (22%)
Stage at diagnosis			
	1-2	3 (12%)	2 (22%)
	3-4	20 (77%)	7 (78%)
	Unknown	3 (12%)	
Time since diagnosis (Months)			
	Median (IQR)	19 (16-27)	27 (19-51)
Prior lines			
	Median (range)	2 (1-8)	2 (1-7)
	>3 lines	8 (31%)	2 (22%)
	Prior allogeneic transplant	2 (8%)	2 (22%)
CNS			
	Positive	3 (12%)	0

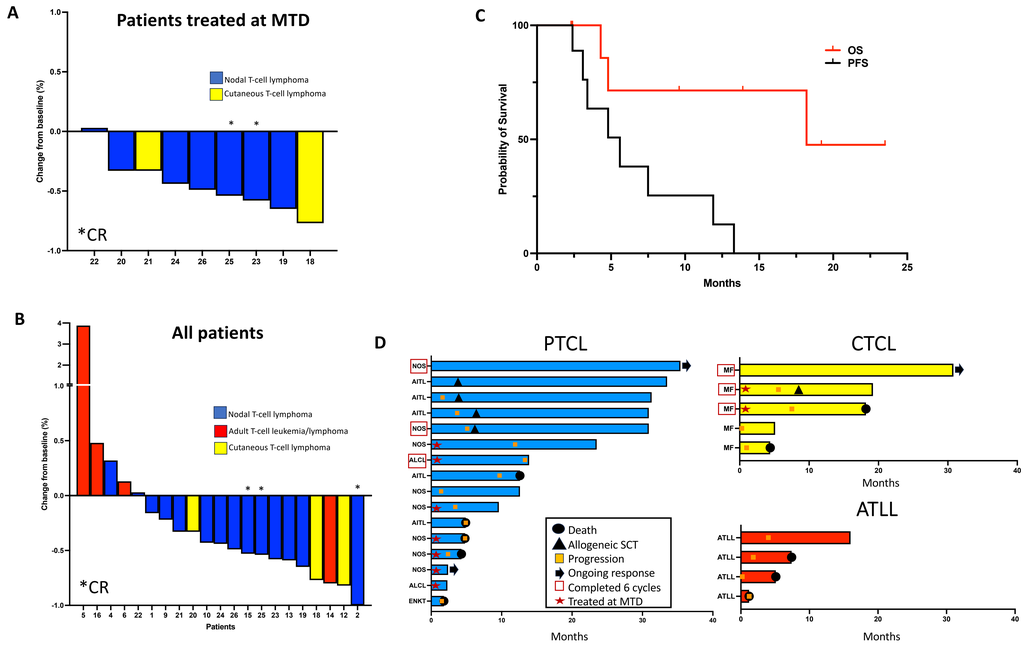
Table. Patient characteristics.

Non-Hematologic AE	Grade 1-2, Total	%	Grade ≥3, Total	%
Abdominal pain	5	**20**	0	
Acute kidney injury	6	**24**	2	**8**
Adrenal insufficiency	1	**4**	2	**8**
Anorexia	8	**32**	2	**8**
Constipation	8	**32**	0	
Diarrhea	12	**48**	0	
Dysgeusia	12	**48**	0	
Limb edema	3	**12**	0	
Fatigue	11	**44**	2	**8**
Fever	6	**24**	0	
Generalized weakness	4	**16**	0	
Hypocalcemia	7	**28**	0	
Hypokalemia	8	**32**	4	**16**
Hyponatremia	4	**16**	0	
Hypomagnesemia	3	**12**	0	
Hypotension	6	**24**	1	**4**
Infection	8	**32**	4	**16**
Liver function (AST)	4	**16**	1	**4**
Liver function (ALT)	5	**20**	1	**4**
Liver function (ALK)	4	**16**	0	
Mucositis	4	**16**	0	
Nausea	15	**60**	0	
Maculopapular rash	6	**24**	0	
Sinus Tachycardia	6	**24**	0	
Vomiting	13	**52**	0	
Weight loss	7	**28**	2	**8**

Table. Adverse events observed in more than two patients. Non-hematologic adverse events are highest grade per patient.

Hematologic AE	Grade 1-2, Total	%	Grade ≥3, Total	%
Anemia	21	**23**	11	**12**
Lymphocytopenia	14	**16**	5	**6**
Neutropenia	14	**16**	20	**22**
Leukopenia	11	**12**	6	**7**
Thrombocytopenia	35	**39**	11	**12**

Table. Adverse events observed in more than two patients. Hematologic adverse events are shown as highest grade per cycle per patient, shown as a percentage of total cycles.



Figures. Best response in evaluable patients treated at the MTD **(A)** and in all patients **(B)**. Progression free survival (PFS) and overall survival (OS) in patients treated at the MTD **(C)**. Swimmers plot in patients with peripheral T-cell lymphoma (PTCL), cutaneous T-cell lymphoma (CTCL) and adult T-cell leukemia/lymphoma (ATLL) **(D).**

- Two DLTs: Gr4 thrombocytopenia (DL1) and Gr3 abdominal pain (DL2)
- Lenalidomide 20mg was the MTD
- Median cycles 4 (range 1-6)

- Reason for stopping therapy: PD (38%), completed 6 cycles (27%), AE (23%)
- ORR 66%, CRR 14% (all patients) and ORR 89%, CR 22% (at MTD)
- Median fu 19 months: median PFS 4 months, 2-year OS 60%

CONCLUSIONS

RAdR is safe and can achieve CR after fixed duration in patients with relapsed refractory T-cell lymphomas

Toxicity is predominantly gastrointestinal and hematologic

Most patients do not achieve durable CR with RAdR alone, but it may be an effective bridging therapy to consolidation

CONTACT & ACKNOWLEDGEMENTS

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