COMBINATION OF EVEROLIMUS WITH R-CHOP AS AN INITIAL THERAPY FOR DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): A PHASE I AND FEASIBILITY STUDY (NCCTG N1085 [ALLIANCE])

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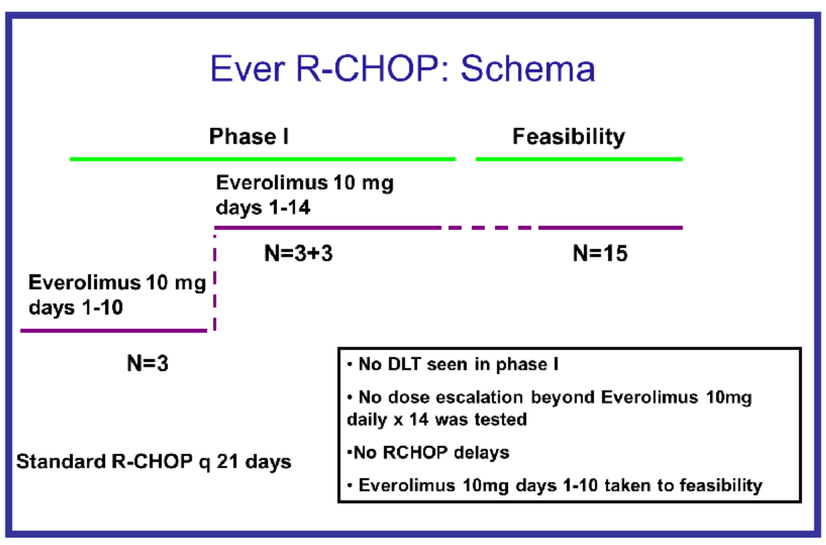
OBJECTIVES

Everolimus was demonstrated to have single agent activity in relapsed DLBCL. However, the safety and efficacy of everolimus in combination with R-CHOP is unknown.
A phase I study was designed to determine if this combination was tolerable and feasible.



METHODS

A phase I study was designed to determine the maximum tolerated dose (MTD) of everolimus on days 1-10 or 1-14 in combination with R-CHOP given every 21 day, with a feasibility cohort to examine response in patients with newly diagnosed cd20+ DLBCL. MTD was defined as the highest safely tolerated dose where at most 1 out of 6 patients experienced DLT. Starting everolimus dose was 10 mg days 1-10 and the planned dose escalation was 10 mg days 1-14. DLT was defined as any grade 3 or higher non-hematologic toxicity or a hematologic toxicity within the first cycle resulting in a delay of the next cycle of chemotherapy. The response was evaluated using PET/CT by standard criteria. A fourteen-patient feasibility extension was planned.

PATIENT CHARACTERISTICS

	Total (N=24)
Age	
N	24
Mean (Range)	59.5 (23.0-78.0)
Gender	
F / M	10 (41.7%) / 14 (58.3%)
Extra Nodal Site Involvement	
Yes	12 (50.0%)
Clinical Stage	
II	6 (25.0%)
III	6 (25.0%)
IV	12 (50.0%)
Subtype	
Germinal center B-cell-like subtype (GBC)	8 (57.1%)
Activated B-cell-like subtype (ABC)	6 (42.9%)

TOXICITY

		Grade 3		Grade 4	
	Toxicity	**N**	**%**	**N**	**%**
Hematologic	**Anemia**	4	16.7		
	Febrile neutropenia	5	20.8		
Cardiac disorders	**Sinus tachycardia**	1	4.2		
Infections	**Sepsis**			1	4.2
	Urinary tract infection	1	4.2		
	Bronchial infection	1	4.2		
	Lung infection	1	4.2		
Lab Abnormalities	**Alkaline phosphatase increased**	1	4.2		
	bilirubin increased	1	4.2		
	Neutropenia			18	75.0
	Thrombocytopenia	3	12.5	2	8.3
	Leukopenia	3	12.5	13	54.2
Metabolic Abnormalities	**Hyperglycemia**	1	4.2		
	Hypertriglyceridemia	3	12.5		
Pulmonary	**Hypoxia**	1	4.2	1	4.2
	Pneumonitis	1	4.2		
Vascular disorders	**Hypotension**	1	4.2		
	Thromboembolic event	2	8.3		

RESPONSES

	Dose level	Dose	N	DLTs	Responders
Phase I	1	Everolimus PO Dose 10 mg once daily Days 1-10	3	0/3	3 CR
	2	Everolimus PO 10 mg once daily Days 1-14	6	0/6	6 CR
Feasibility Phase	2	Everolimus PO Dose 10 mg once daily Days 1-14	15	NA	13 CR, 1 PR, 1 NA

CONCLUSIONS

- Everolimus when combined with R-CHOP combination chemotherapy is well tolerated at 10 mg daily on days 1-10 and 1-14 of a 21 day cycle.
- The initial response rates in the phase I portion appear promising.
- A larger trial will be necessary to confirm the benefits of this novel combination.
- Clinical trial information: NCT1334502

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