Final results of a phase I trial of evorpacept (ALX 148), lenalidomide, rituximab for patients with B-cell non-Hodgkin lymphoma

Tony Z. Zhuang[1], Lei Feng[2], Andrey Tyshevich[3], Darya Shavronskaya[3], Julia Alesse[3], Noel English[3], Lizzie Sheehan[3], Nikita Syzrantsev[3], Alexander Nesmelov[3], Dai Chihara[1], Jason Westin[1], Sairah Ahmed[1], Luis Fayad[1], Jared Henderson[1], Kylie Dent[1], Elizabeth McChesney[1], Sattva S. Neelapu[1], Christopher R. Flowers[1], Paolo Strati[1]

[1]Department of Lymphoma and Myeloma, [2]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston TX; [3]BostonGene Corporation, Waltham, MA

Introduction. Increase in pro-tumoral SIRPα+ macrophages has been described as a mechanism of resistance to lenalidomide and rituximab (R^2) inpatients (pts) with relapsed or refractory (RR) B-cell non-Hodgkin lymphoma (B-NHL). Evorpacept (ALX148) is a novel high-affinity CD47 blocker that abrogates the 'do-not-eat-me signal' provided to SIRPα+ macrophages. We hypothesized that the combination of evorpacept and R^2 will be safe and effective for pts with RR B-NHL.

Methods. This single arm phase I study (NCT05025800) was conducted between 11/2021 and 9/2023 (data cut-off 01/2025). Adult pts with RR B-NHL who had received at least 2 prior lines of systemic therapy (1 line in case of indolent B-NHL [iNHL]) were included. Evorpacept was administered intravenously (IV), in a 28-day cycle, until progression (or for 12 cycles in case of CR), at two dose levels (DL): 30 mg/Kg on day (D) 1 and D15 (DL1), or 60 mg/Kg on day 1 (DL2); rituximab 375 mg/m2 IV was given weekly during cycle 1, and on D1 during cycles 2-6; lenalidomide 20 mg was given orally on D1-21 during cycles 1-6. Dose limiting toxicity (DLT) was evaluated according to CTCAE v5 during cycle 1 and a Bayesian Optimal Interval design was used, with a target DLT rate of 0.3. Response was assessed according to Lugano 2014. Single-cell RNA sequencing was performed on tumor biopsies collected before treatment and during cycle 1.

Results. Twenty pts were included in the study. Median age was 61 (27-85) years, 10 (50%) were male, and 7 (35%) were non-white; 15 (75%) had follicular lymphoma, 3 (15%) marginal zone lymphoma, 1 (5%) mantle cell lymphoma, and 1 (5%) Richter Syndrome; all had previously received an anti-CD20 monoclonal antibody, 13 (72%) chemoimmunotherapy, and 16 (80%) had progressed within 24 months. Three pts were treated at DL1, 17 at DL2, and no DLT was observed. The most common grade 3-4 adverse events included: neutropenia (60%), infections (30%), and ALT increase (15%). Sixteen (80%) pts achieved CR and best overall response rate was 90%.

After a median follow-up of 28 months (95% CI, 18-28 months), 2-year PFS rate was 69% and 2-year OS rate was 84%. Serial tumor tissue samples were successfully sequenced in 16 patients. During treatment, a significant decrease in B cells, and a significant increase in T cells and macrophages was observed. In macrophages, pathways associated with cytokines, innate immune system, TLR signaling, endocytosis, phagocytosis, extracellular matrix interactions, and antigen presentation were upregulated.

Conclusions. The combination of evorpacept and R^2 has a safe toxicity profile, promising anti-tumoral activity (historical CR rate 30%), and induces favorable biological effects on multiple components of the tumoral immune microenvironment. A phase 2 study investigating its efficacy in pts with previously untreated and high tumor burden iNHL has completed enrollment.

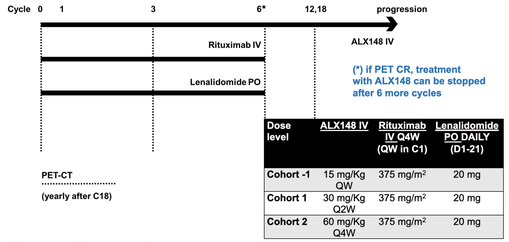
Background

- Increase in pro-tumoral SIRPα+ macrophages has been described as a mechanism of resistance to lenalidomide and rituximab (R^2) inpatients (pts) with relapsed or refractory (RR) B-cell non-Hodgkin lymphoma (B-NHL).
- Evorpacept (ALX148) is a novel high-affinity CD47 blocker that abrogates the 'do-not-eat-me signal' provided to SIRPα+ macrophages.
- We hypothesized that the combination of evorpacept and R2 will be safe and effective for pts with RR B-NHL.

Methods

- This single arm phase I study (NCT05025800) was conducted between 11/2021 and 9/2023 (data cut-off 01/2025).
- Adult pts with RR B-NHL who had received at least 2 prior lines of systemic therapy (1 line in case of indolent B-NHL [iNHL]) were included.
- Evorpacept was administered intravenously (IV), in a 28-day cycle, until progression (or for 12 cycles in case of CR), at two dose levels (DL): 30 mg/Kg on day (D) 1 and D15 (DL1), or 60 mg/Kg on day 1 (DL2); rituximab 375 mg/m2 IV was given weekly during cycle 1, and on D1 during cycles 2-6; lenalidomide 20 mg was given orally on D1-21 during cycles 1-6.
- Dose limiting toxicity (DLT) was evaluated according to CTCAE v5 during cycle 1 and a Bayesian Optimal Interval design was used, with a target DLT rate of 0.3.
- Response was assessed according to Lugano 2014.
- Single-cell RNA sequencing was performed on tumor biopsies collected before treatment and during cycle 1.

Treatment schema



Dose level	ALX148 IV	Rituximab IV Q4W (QW in C1)	Lenalidomide PO DAILY (D1-21)
Cohort -1	15 mg/Kg QW	375 mg/m^2	20 mg
Cohort 1	30 mg/Kg Q2W	375 mg/m^2	20 mg
Cohort 2	60 mg/Kg Q4W	375 mg/m^2	20 mg

Baseline characteristics

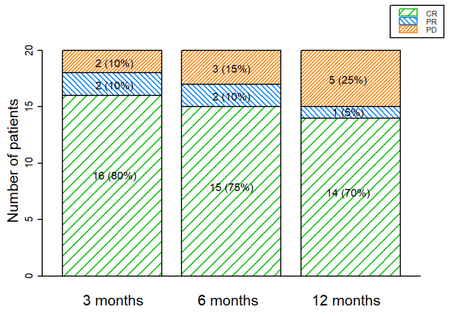
Patients (N=20)	Number (%); Median [Range]
Age	61 [27-85]
Caucasian	13 (65)
Male	10 (50)
Hemoglobin (g/dL)	12.8 [9.2-15.2]
β2-microglobulin (mg/L)	2.3 [0.8-6.2]
Lactate dehydrogenase (U/L)	222 [129-338]
Follicular lymphoma (FL)	15 (75)
Marginal zone lymphoma	3 (15)
Mantle cell lymphoma	1 (5)
Richter syndrome	1 (5)
FL Grade 3A	3/15 (20)
Bone marrow, involved	4 (20)
B-symptoms, present	3 (15)
Ann Arbor Stage III-IV	18 (90)
Involved nodal areas (n)	3 [1-5]
Largest lymph node (cm)	2.9 [1.5-5.6]
Extra-nodal disease, present	11 (55)
SUV_{max}	15.8 [3.9-53.7]
FLIPI score, low	3/18 (17)
Intermediate	6/18 (33)
high	9/18 (50)
FLIPI-2 score, low	4/18 (22)
Intermediate	10/18 (56)
high	4/18 (22)
PRIMA PI, low	13 (72)
Intermediate	4 (22)
high	1 (6)
Previous systemic therapies (n)	1 [1-3]
Previous anti-CD20 antibody	20 (100)
Previous chemotherapy	13 (72)
Previous POD24	16 (80)

Treatment-emergent adverse events

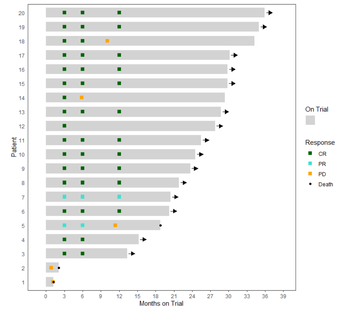
Patients (N=20)	Grade 1-2	Grade 3-4
Neutropenia	6 (30)	11 (55)
Other infections	5 (23)	6 (30)
ALT increased	12 (60)	3 (15)
Skin rash	8 (40)	2 (10)
Anemia	12 (60)	2 (10)
AST increase	12 (60)	2 (10)
ALP increased	4 (20)	1 (5)
Infusion-related reaction	6 (30)	1 (5)
Myocarditis	0 (0)	1 (5)
Fatigue	13 (65)	0 (0)
Thrombocytopenia	10 (50)	0 (0)
Creatinine increase	10 (50)	0 (0)
Musculo-skeletal pain	9 (45)	0 (0)
Constipation	7 (35)	0 (0)
Nausea	5 (25)	0 (0)
COVID infection	5 (25)	0 (0)
Hyponatremia	4 (20)	0 (0)
Diarrhea	4 (20)	0 (0)
Dizziness	4 (20)	0 (0)
Bilirubin increase	4 (20)	0 (0)
Peripheral neuropathy	3 (15)	0 (0)
Headache	3 (15)	0 (0)
Hypercalcemia	3 (15)	0 (0)
Xerostomia	2 (10)	0 (0)
Mucositis	2 (10)	0 (0)

Three patients received DL1; 17 patients DL2, no DLT observed

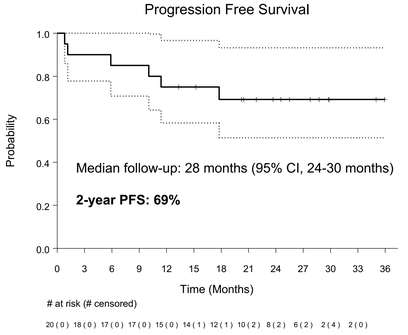
Response to therapy

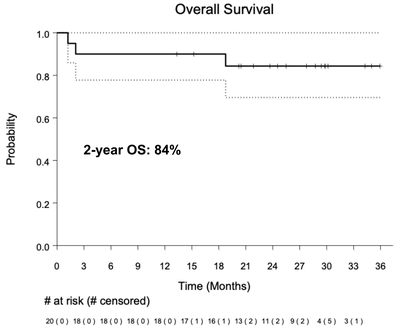


Duration of response

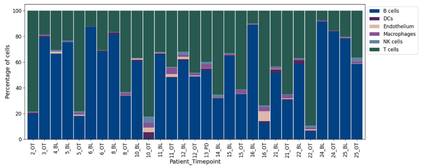


Progression-free and overall survival

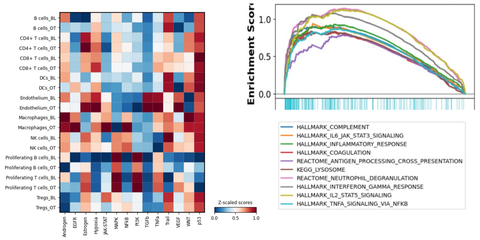




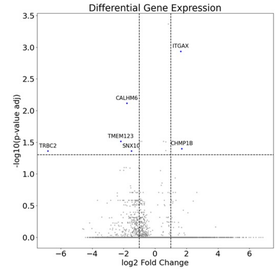
The combination induces significant changes in B cells, T cells and macrophages



The combination increases the antitumoral properties of macrophages



Baseline macrophage phenotype can predict response to therapy



Conclusions

- The combination of evorpacept and R^2 has a safe toxicity profile, promising anti-tumoral activity (historical CR rate 30%), and induces favorable biological effects on multiple components of the tumoral immune microenvironment.
- A phase 2 study investigating its efficacy in pts with previously untreated and high tumor burden iNHL has completed enrollment.

Contacts

Tony Zhuang, MD: tzzhuang@mdanderson.org
Paolo Strati, MD: pstrati@mdanderson.org