LYMRIT-37-01: A phase I/II study of ^{177}Lu-lilotomab satetraxetan antibody-radionuclide conjugate (ARC) for the treatment of relapsed non-Hodgkin's lymphoma (NHL): Analysis with 6 month follow-up

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BACKGROUND

- ^{177}Lu-satetraxetan-lilotomab (Betalutin®) is a novel beta-emitting anti-CD37 antibody-radionuclide conjugate (ARC) in a ready-to-use formulation for single-dose administration.
- Betalutin® has a Fast Track designation for follicular lymphoma (FL) patients who have received ≥2 prior therapies (US), and a Promising Innovative Medicine (PIM) designation in the UK for advanced relapsed/refractory FL.
- CD37 is a tetraspanin membrane protein that is highly expressed (>90%) on B cells, including B-cell NHL.
- This phase 1/2, open-label, multicenter study was conducted to assess the safety, PK and activity of Betalutin® in patients with relapsed iNHL.

STUDY DESIGN

Key Eligibility Criteria

- Histologically confirmed relapsed B-cell indolent NHL
- <25% bone marrow involvement
- Platelet count >150 x 10^9/L
- ANC ≥ 1.5 x 10^9/L
- No previous hematopoietic stem cell transplantation or RIT

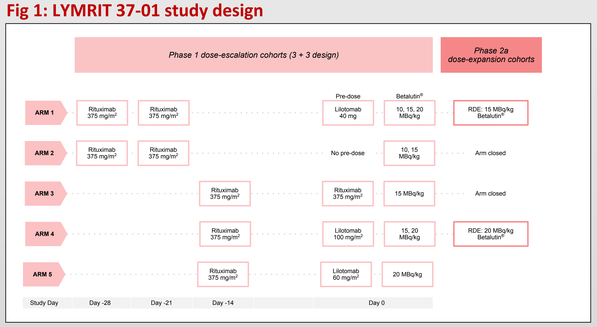
Study Schema

The study was conducted in two parts: Four dose-escalation cohorts to determine the optimal cold antibody (lilotomab or rituximab, RTX) pre-dosing and Betalutin® regimen (phase 1), and dose expansion cohorts to confirm safety and evaluate efficacy (phase 2a). Three additional patients were enrolled in a separate arm (Arm 5) for additional PK data (60 mg/m^2 lilotomab + 20 MBq/kg Betalutin®).

The recommended dose for expansion (RDE) of Betalutin® in Arm 1 was 15 MBq/kg and 20 MBq/kg in Arm 4. Patients were subsequently enrolled into 2 phase 2 expansion cohorts (Fig 1).

All patients received pre-treatment with rituximab (RTX) (375 mg/m^2) to deplete peripheral B cells and improve biodistribution of Betalutin®.

Fig 1: LYMRIT 37-01 study design



Assessments

- Dose-limiting toxicities (DLTs) were assessed during the first 12 weeks.
- Incidence and severity of adverse events (AEs) according to CTCAE v4.
- Response assessments: conducted at 3, 6 (FDG PET-CT), 9, 12, 18, 24, 36 and 48 months (CT) per the International Working Group (IWG) criteria for NHL (Cheson BD et al. *J Clin Oncol* 2007; 25: 579-586 & Cheson BD et al. *J Clin Oncol* 1999; 17: 1244-1253).

RESULTS

Data on 74 patients (data cut-off: 2 Nov 18) are reported in this analysis; the median follow-up time for all patients is 18.4 months (3.2-61.6 m).

Phase 1 (n=32)				Phase 2a (n=42)
Arm	Pre-dose	Betalutin® (MBq/kg)	N	N
1	40 mg lilotomab	10	3	
	40 mg lilotomab	**15**	**6**	**30**
	40 mg lilotomab	20	3	
2	None	10*	2	
	None	15	2	
3	RTX 375 mg/m^2	15	3	
4	100 mg/m^2 lilotomab	15	3	
	100 mg/m^2 lilotomab	**20**	**7**	**12**
5	60 mg/m^2 lilotomab	20	3	

*Includes first patient enrolled in study.

Table 1: Baseline characteristics

	All Patients (n=74)	FL* (n=57)	Other** (n=17)
Median age, years (range)	68 (38-87)	69 (40-80)	68 (57-88)
≥65, n (%)	51 (69%)	36 (63%)	12 (70%)
Male	41 (55%)	32 (56%)	9 (53%)
Female	33 (45%)	25 (44%)	8 (47%)
Ann Arbor stage at diagnosis***			
I/II	5 (12%)	5 (17%)	0 (0%)
III/IV	27 (64%)	18 (62%)	9 (69%)
Unknown	10 (24%)	6 (21%)	4 (31%)
Prior regimens, median (range)	3 (1-9)	3 (1-9)	3 (1-7)
≥2 prior regimens	48 (65%)	37 (65%)	11 (65%)
Prior alkylating agent	60 (81%)	44 (77%)	16 (94%)
Rituximab refractory	33 (44%)	30 (53%)	3 (18%)
Bulky disease ≥7 cm, n (%)	20 (27%)	15 (26%)	5 (29%)

*Follicular grades: I (n=16), II (n=32), IIIa (n=9).
**Mantle cell lymphoma (MCL; n=7), marginal zone lymphoma (MZL; n=9), small lymphocytic lymphoma (SLL; n=1).
***Information collected for phase 2 patients only (N=42).

SAFETY

- Overall, Betalutin® was well-tolerated. The most common grade 3/4 TEAEs were reversible neutropenia and thrombocytopenia (Table 2). G4 neutropenia/thrombocytopenia occurred in 19%/17% & 16%/10% of Arm 1 (40/15) and Arm 4 (100/20) pts respectively.
- SAEs occurred in 14 patients (19%). SAEs in ≥2 pts. were atrial fibrillation, thrombocytopenia, NHL progression and sepsis (all n=2).
- 5 patients received platelets (1 epistaxis, 1 hematuria; both G3), 3 for low platelet count; 1 RBC transfusion for anemia. 3 pts. received G-CSF.
- 18 m after subsequent treatment with bendamustine (24 m post- Betalutin®), MDS/AML was reported in 1 patient with prior alkylating agent exposure.
- There were no study drug-related deaths in the treatment period.

Table 2: Grade 3/4 TEAEs in ≥2 patients

Adverse Event	G3 n (%)	G4 n (%)
Neutropenia	26 (35%)	14 (19%)
Thrombocytopenia	21 (25%)	15 (20%)
Leukopenia	30 (40%)	4 (5%)
Lymphopenia	23 (31%)	2 (3%)
Infections	1 (1%)	2 (3%)
Urinary tract infection		
Sepsis/neutropenic sepsis	1 (1%)	
Pneumonia		
Bleeding	1 (1%)	
Epistaxis	1 (1%)	
Hematuria		
Hyperglycemia	2 (3%)	--
Lymphoma progression	4 (5%)	1 (1%)

EFFICACY

- Overall, objective responses (ORR = CR + PR) were observed in 45/74 (61%) of patients; 28% (n=21) obtained a CR.
- 90% of evaluable patients had a decrease in tumor size (Figure 3).
- For all patients with FL the ORR was 65% (CR 28%). The ORR for FL patients receiving the Arm 1 Betalutin® RDE of 15 MBq/kg was 64% (CR 32%). The ORR for FL patients receiving the Arm 4 Betalutin® RDE of 20 MBq/kg was 69% (CR 25%) (Table 3).
- For FL patients with ≥2 prior therapies (n=37), the ORR was 70% (CR 32%).
- 44% of patients were refractory to RTX: the ORR was 62% for RTX-refractory FL patients with 2 or more prior therapies (CR 19%).
- The median duration of response (DoR) for all patients (n=45) was 9.0 months; 25 pts (34%) remained free of disease progression for ≥12 m. For all patients with a CR (n=21), the median duration of response was 20.7 months (Figure 4).

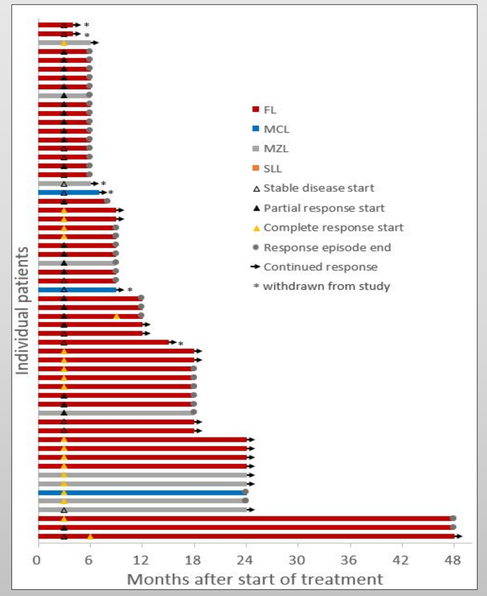
Table 3: Response rates: all patients

Subtype	ORR n (%)	CR n (%)	PR n (%)	SD n (%)	PD n (%)
FL (n=57)	37 (65%)	16 (28%)	21 (37%)	10 (18%)	10 (18%)
MZL (n=9)	7 (78%)	4 (44%)	3 (33%)	2 (22%)	--
MCL (n=7)	1 (14%)	1 (14%)	--	2 (28%)	4 (57%)
SLL (n=1)	--	--	--	--	1
Total	61%	28%	32%	19%	20%

Table 4: Response rates: FL patients

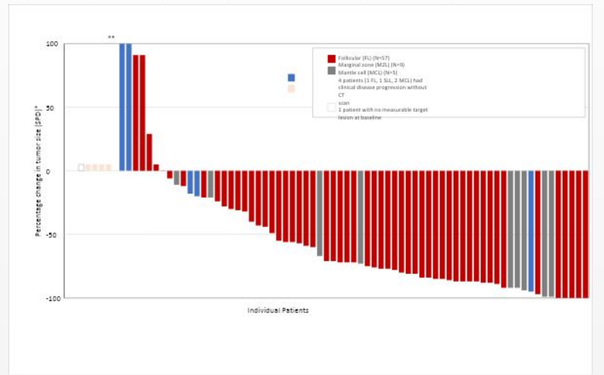
	ORR (CR + PR)	CR
All FL patients (n=57)	65%	28%
Arm 1 (40/15) (n=25)	64%	32%
Arm 4 (100/20) (n=16)	69%	25%
FL with ≥2 prior therapies (n=37)	70%	32%
RTX refractory FL, ≥2 prior therapies (n=21)	62%	19%

Fig 2: Response duration for all patients by NHL subtype*



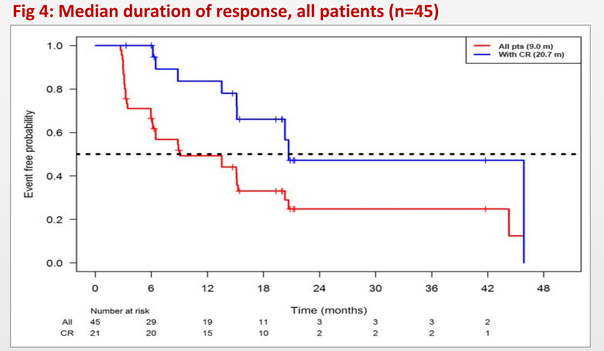
*includes CR, PR and SD responses

Fig 3: Best percentage change in tumor size by NHL subtype



*SPD = sum of the products of the diameters.
**Change in size of target lesion is beyond the scale for this figure (n=2).

Fig 4: Median duration of response, all patients (n=45)



CONCLUSIONS

- Single-agent Betalutin® was effective and well-tolerated in this elderly heavily pre-treated population of patients with recurrent iNHL:
  - Overall response rate of 61% (CR 28%)
  - Highly active in FL patients with ≥2 prior therapies (ORR 70% CR 32%), and RTX-refractory FL (ORR 62% CR 19%)
  - Durable responses, especially for patients with a CR (20.7 months for all patients)
- Main grade 3/4 toxicities are reversible neutropenia and thrombocytopenia; low incidence of infections (5.4%).
- With its promising clinical profile, ready-to-use formulation and one-time administration, Betalutin® has the potential to be a novel, safe and effective therapy for recurrent B-cell lymphoma.
- The 2 RDEs are now being compared in a randomized phase 2b cohort ("PARADIGME") in relapsed, anti CD20-refractory FL patients who have received ≥2 prior therapies.