Betalutin®, a novel CD37-targeted radioimmunotherapy for NHL

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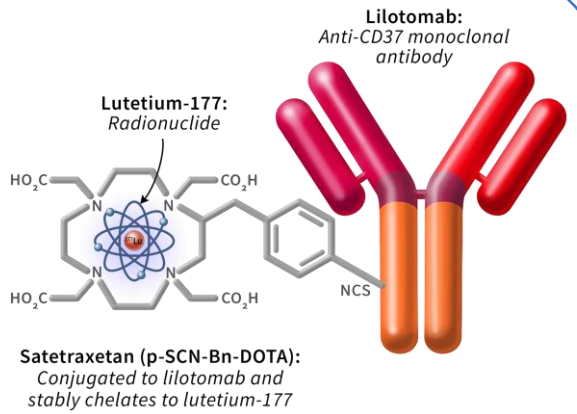
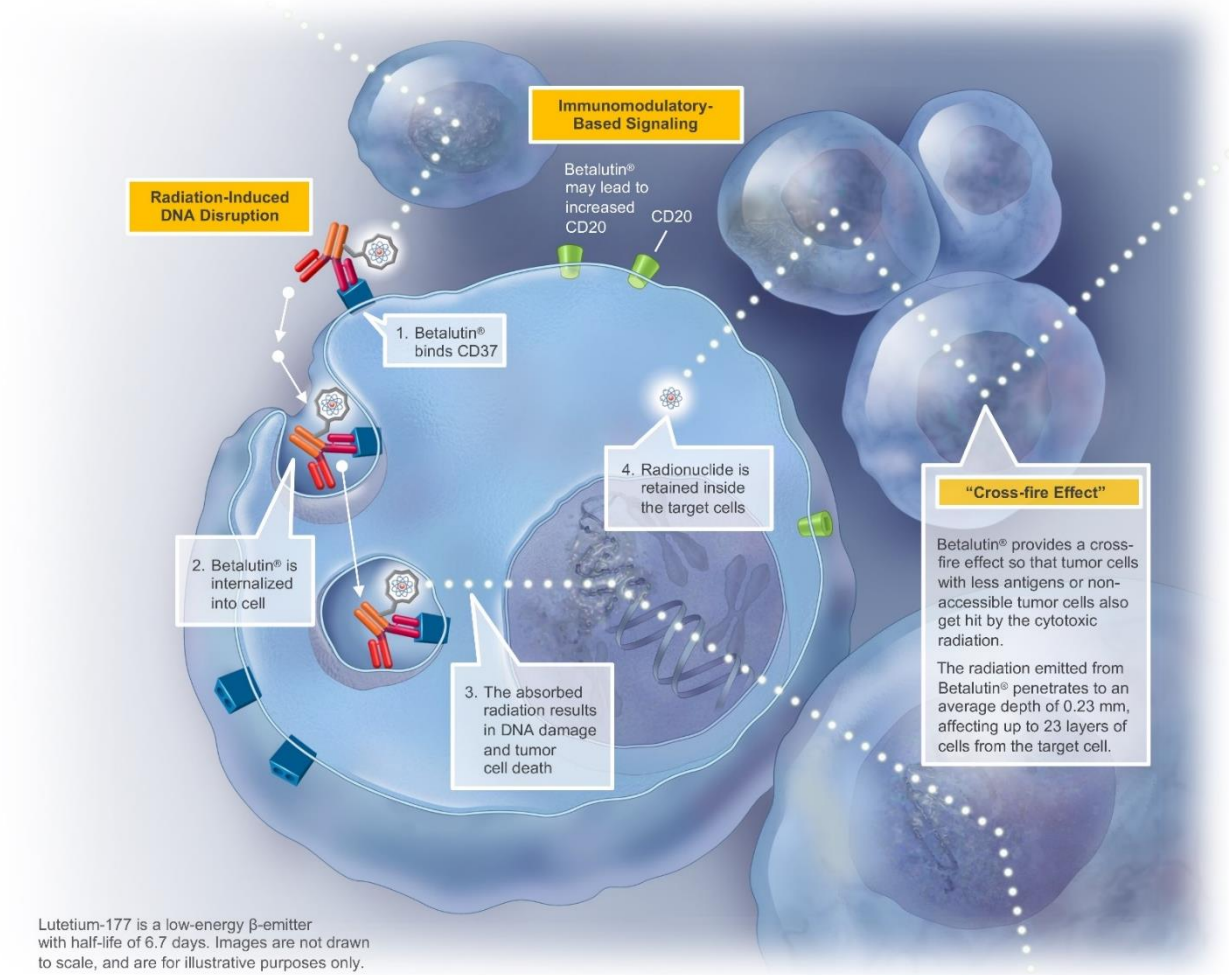
Disclosures of: Arne Kolstad

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Nordic Nanovector	Yes					Yes	
Roche	Yes						
Merck	Yes						

Betalutin®: A novel CD37-targeted radioimmunotherapy (RIT)



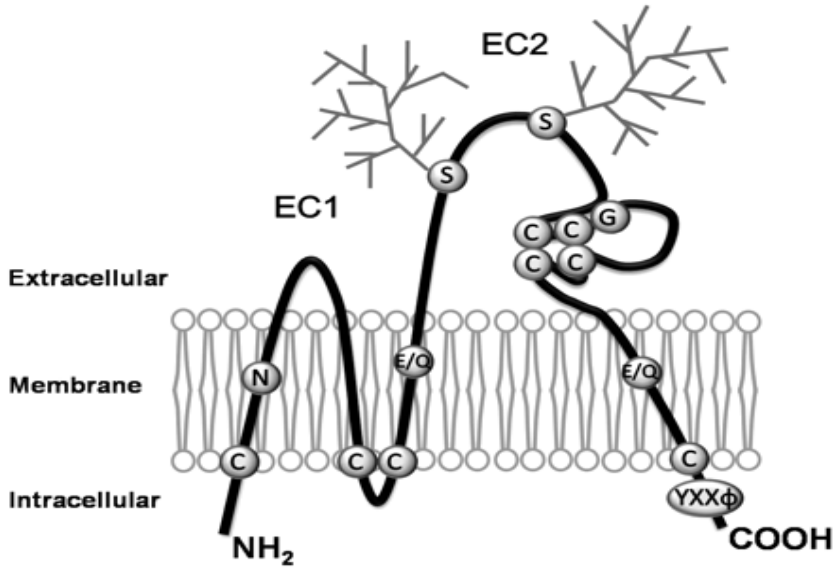


Lutetium-177 is a low-energy β-emitter with half-life of 6.7 days. Images are not drawn to scale, and are for illustrative purposes only.

Novel target antigen: CD37

- Expression overlaps that of CD20
- Highly expressed across the different subtypes of B-cell NHL

Diagnosis	No. of samples	CD37 positive (%)
Diffuse large B cell lymphoma (DLBCL)	25	100
DLBCL transformed from low-grade	19	100
Follicular lymphoma	92	100
Mantle cell lymphoma	28	100
Small lymphocytic lymphoma	37	97.3



Smeland *et al.* Scand J Immunol, 1985; Dahle *et al.* Anticancer Res. 2013

Novel radionuclide: Lutetium-177

Feature	^{177}Lu	^{131}I (Bexxar)	^{90}Y (Zevalin)
Retained inside the cells after internalization?	Yes	No	Yes
Uptake of free radionuclide in body?	No	Thyroid	No
Can be imaged	Yes, low energy γ-photons	Yes, but high γ-energy	No
Need for shielding and isolation of patients?	No	Yes	No
Centralized production feasible?	Yes, t 1/2 6.7 days	Yes, t 1/2 8 days	No, t 1/2 too short (2.7 d)

(*Mariniello et al., EJNMMI, 2016)

Introduction

- Betalutin® has been in clinical development (EU and US) for almost 6 years and approximately 80 patients (the majority with FL) have been treated in trials with iNHL and R/R DLBCL.

- Orphan drug designation (FL) granted in both the US and EU (2014)

- Fast track designation granted by FDA for R/R FL after ≥2 prior therapies (June 2018)

LYMRIT-37-01 phase 1/2 trial in patients with iNHL

- Started at Norwegian Radium Hospital in 2012, 23 centres have participated in this study
- Phase 1/2a dose-escalation study
- 74 patients were enrolled
- Key eligibility criteria:
  - Relapsed/refractory follicular grade I-IIIA, marginal zone, small lymphocytic, lymphoplasmacytic and mantle cell
  - Age ≥ 18 years
  - <25% tumor cells in bone marrow biopsy
  - Measurable disease
- Betalutin® is produced at the Institute for Energy Technology (IFE) in Norway

Centres from 9 countries across Europe participated

Norway
Oslo – Dr Kolstad
Trondheim - Dr. Fagerli
Bergen – Prof Tore Gjertsen

Spain
Madrid - Dr Provencio Pulla
Salamanca - Dr Garcia-Sancho

Sweden
Umeå - Dr. Erlansson
Linkøping - Dr. Lagerløf
Borås - Dr. Andersson

UK
Manchester - Prof. Illidge
Poole - Dr. Bayne
Glasgow - Dr. O'Rourke
Bristol - Dr. Beasley

Austria
Innsbruck - Dr. Willenbacher
Linz - Dr. Welterman
Vienna - Prof. Raderer

Croatia
Zagreb – Dr Aurer

Czech Republic
Ostrava - Prof. Hajek
Olomouc - Prof. Papajik

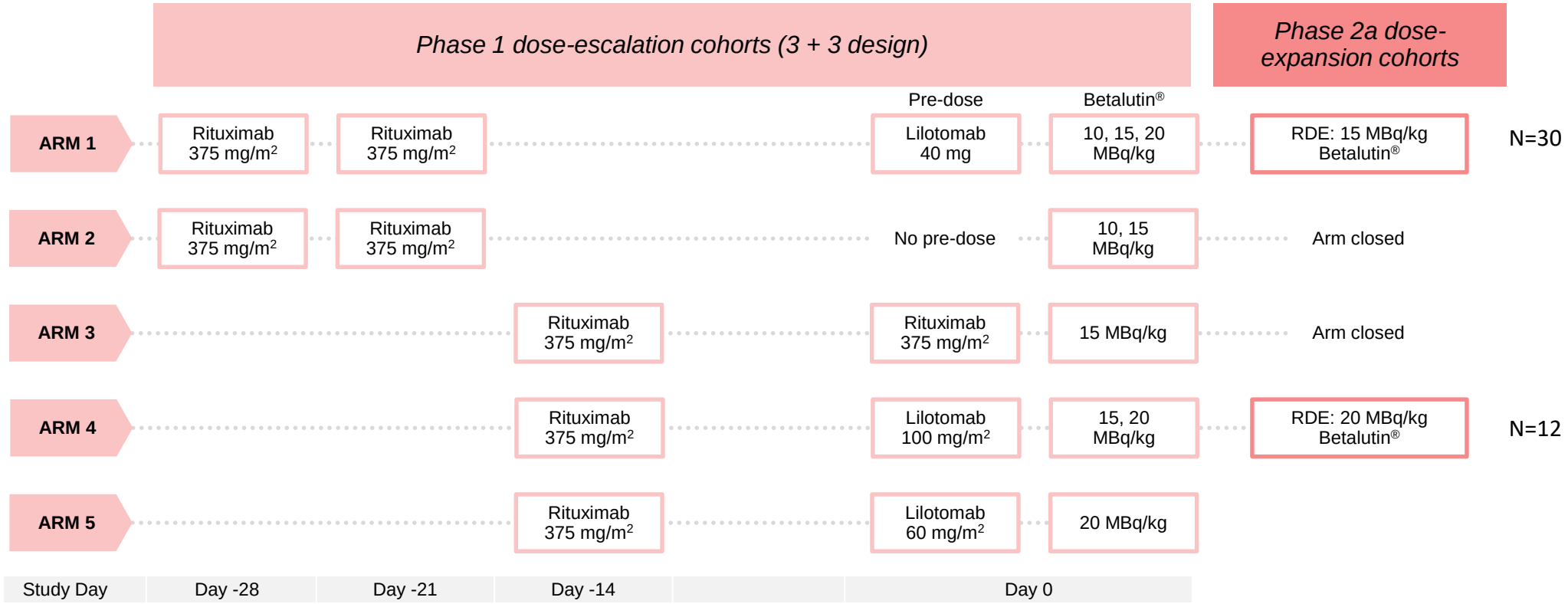
Italy
Firenze - Prof. Bosi
Bologna - Prof. Zinzani

Poland
Kraków - Prof. Jurczak
Warsaw - Prof. Jedrzejczak
Warsaw – Dr Walewski

LYMRIT-37-01: Phase 1/2 trial in relapsed iNHL

Phase 1: Dose-escalation cohorts to determine the MTD/RDE of Betalutin® with different cold antibody (RTX, lilotomab) pre-doses

Phase 2a: Dose expansion cohorts for confirmatory safety and preliminary efficacy



1. Kolstad A, et al. Poster presented at ASH 2017. Abstract 2769.

Patient demographics

	All Patients (n=64)	FL (n=49)	Other (n=15)
Median age, years (range) ≥65, n (%)	69 (40-88) 44 (69%)	69 (40-80) 33 (67%)	68 (57-88) 12 (80%)
Male Female	35 (55%) 29 (45%)	27 (55%) 22 (45%)	8 (53%) 7 (47%)
≥2 prior regimens	44 (69%)	34 (69%)	10 (67%)
≥2 prior rituximab regimens	36 (56%)	28 (57%)	8 (53%)
Prior alkylating agent	52 (81%)	38 (78%)	14 (93%)
Bulky disease >5 cm, n (%)	25 (39%)	22 (45%)	3 (20%)

Kolstad A, et al. Poster presented at ASH 2017. Abstract 2769.

Activity of single-agent Betalutin®

Response rates by subgroup and treatment arm

	ORR (CR + PR)	CR
All patients (n=62)	60%	24%
All FL patients (n=47)	64%	23%
Arm 1 (40/15) (n=25)	68%	28%
Arm 4 (100/20) (n=8)	50%	25%
FL with ≥2 prior therapies (3L FL) (n=32)	66%	25%

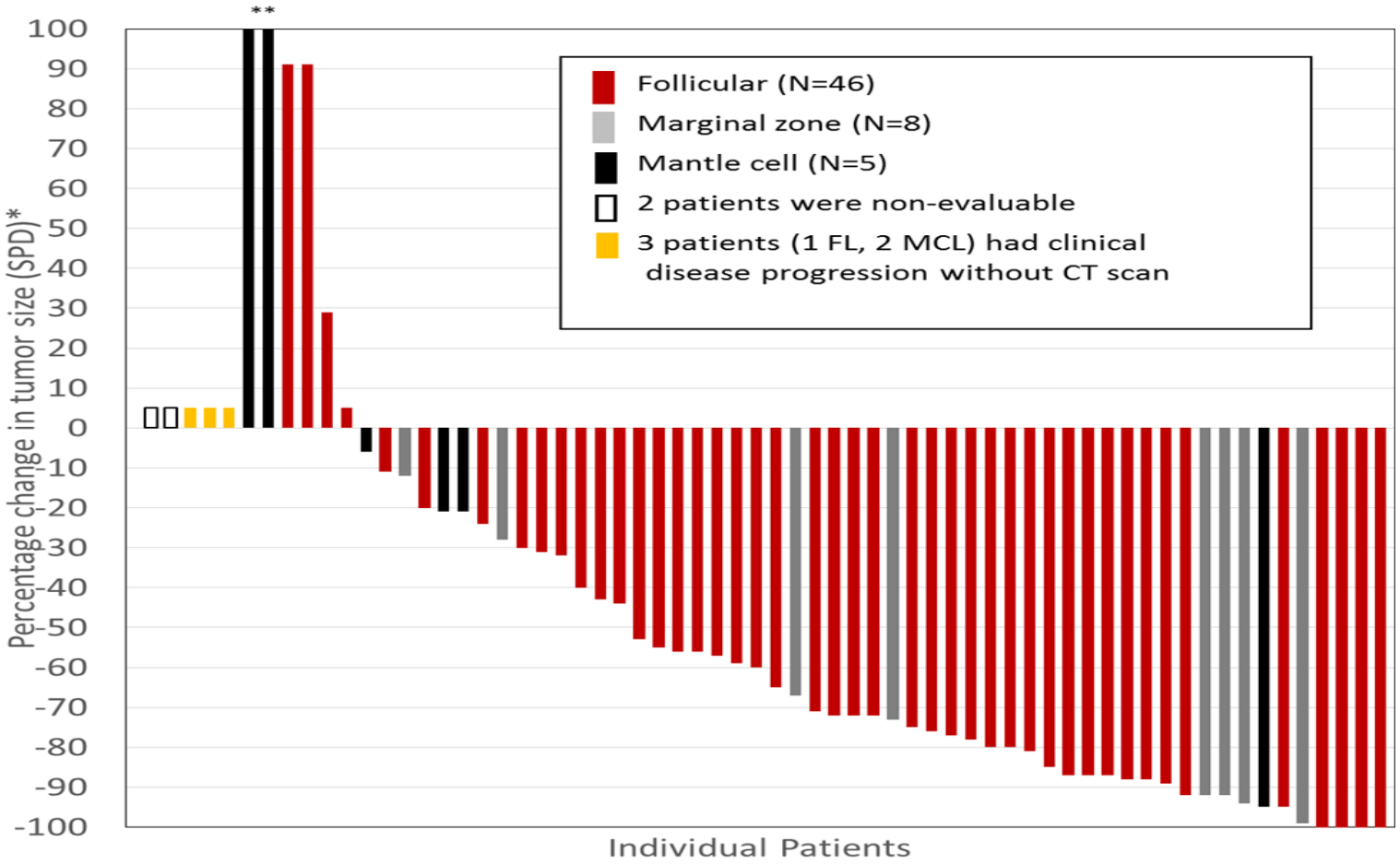
Median duration of response

	Median DoR
All iNHL patients (n=37)	13.3m
iNHL **CR** patients (n=15)	20.5m
All FL patients with 40/15 (n=17)	13.3m
FL **CR** patients with 40/15 (n=7)	22.9m

Kolstad A, et al. Poster presented at ASH 2017. Abstract 2769.

The majority of evaluable patients had a decrease in tumour size

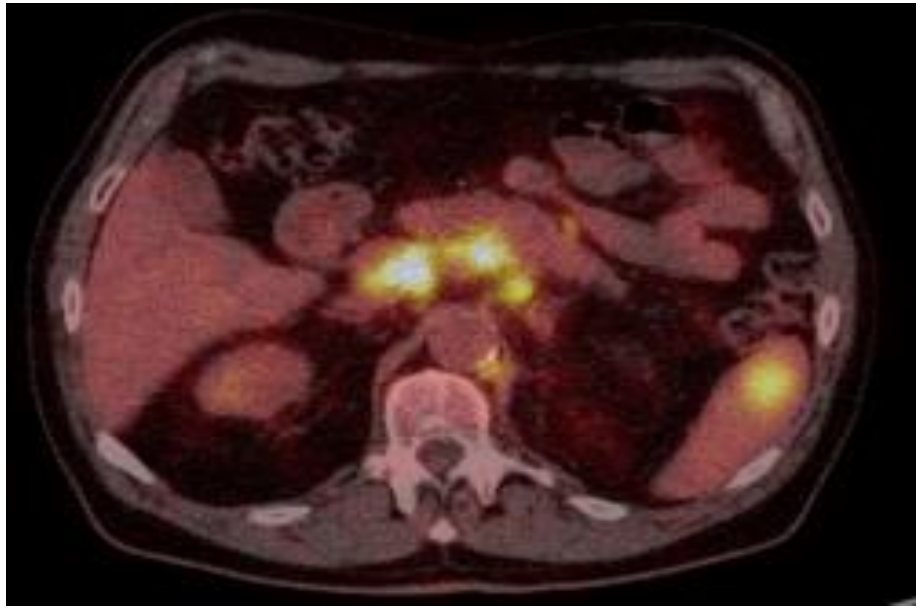
Best percentage change in tumour size from baseline by subtype (n=59)



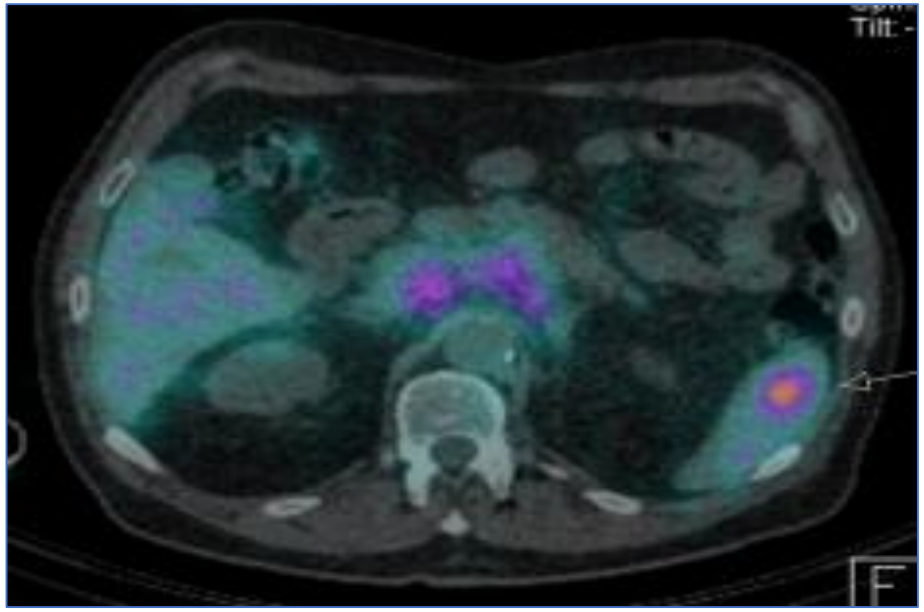
*SPD = sum of the products of the diameters.
**Change in size of target lesion is beyond the scale for this figure (n=2).

1. Kolstad A, et al. Poster presented at ASH 2017. Abstract 2769.

Imaging results: FDG PET/CT and SPECT/CT scans show tumour targeting of Betalutin®



Baseline FDG PET/CT scan showing tumour locations



Day 4 SPECT/CT scan showing radioactivity uptake in tumours

Kolstad A et al. ICML 2017, abstract 282

Grade 3/4 Adverse Events and SAEs in ≥ 2 patients (n=64)

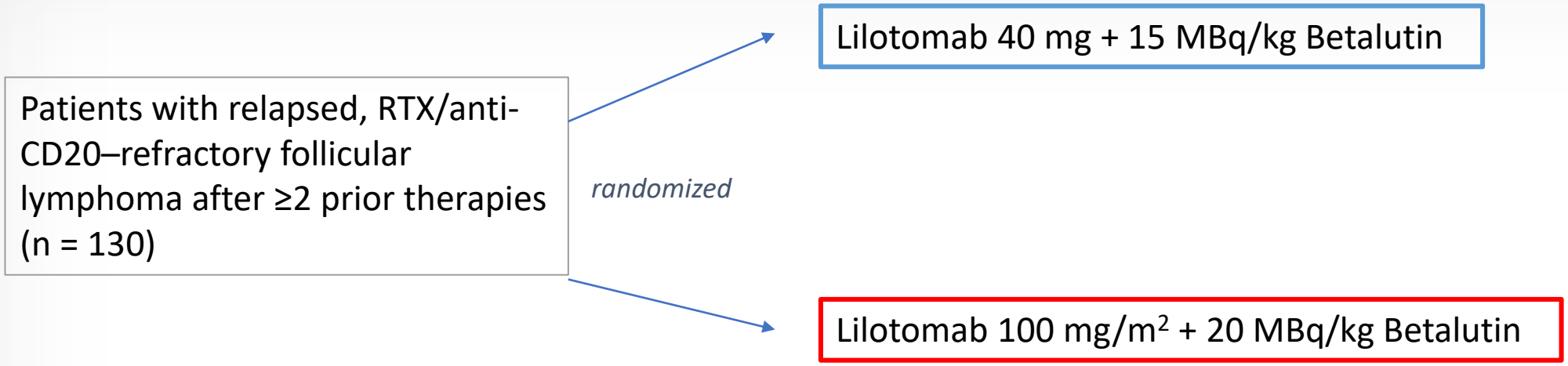
Adverse Event	n (%)[2]
Neutropenia[1]	35 (55%)
Thrombocytopenia[1]	32 (50%)
Leukopenia[1]	32 (50%)
Lymphopenia[1]	22 (34%)
Infections	5 (8%)
Serious Adverse Event (SAE)	
Thrombocytopenia	2 (3%)
Atrial fibrillation	2 (3%)
Sepsis/neutropenic sepsis	2 (3%)

- Overall, Betalutin was very well tolerated
- 18 months after subsequent treatment with bendamustine (24 months after Betalutin®), CMML was reported in 1 patient with prior alkylating agent exposure
- There were no study drug-related deaths in the treatment period

1. Including events reported as 'investigations'. 2. Two patients had not had hematologic recovery at the time of data cut-off.

1. Kolstad A, et al. Poster presented at ASH 2017. Abstract 2769.

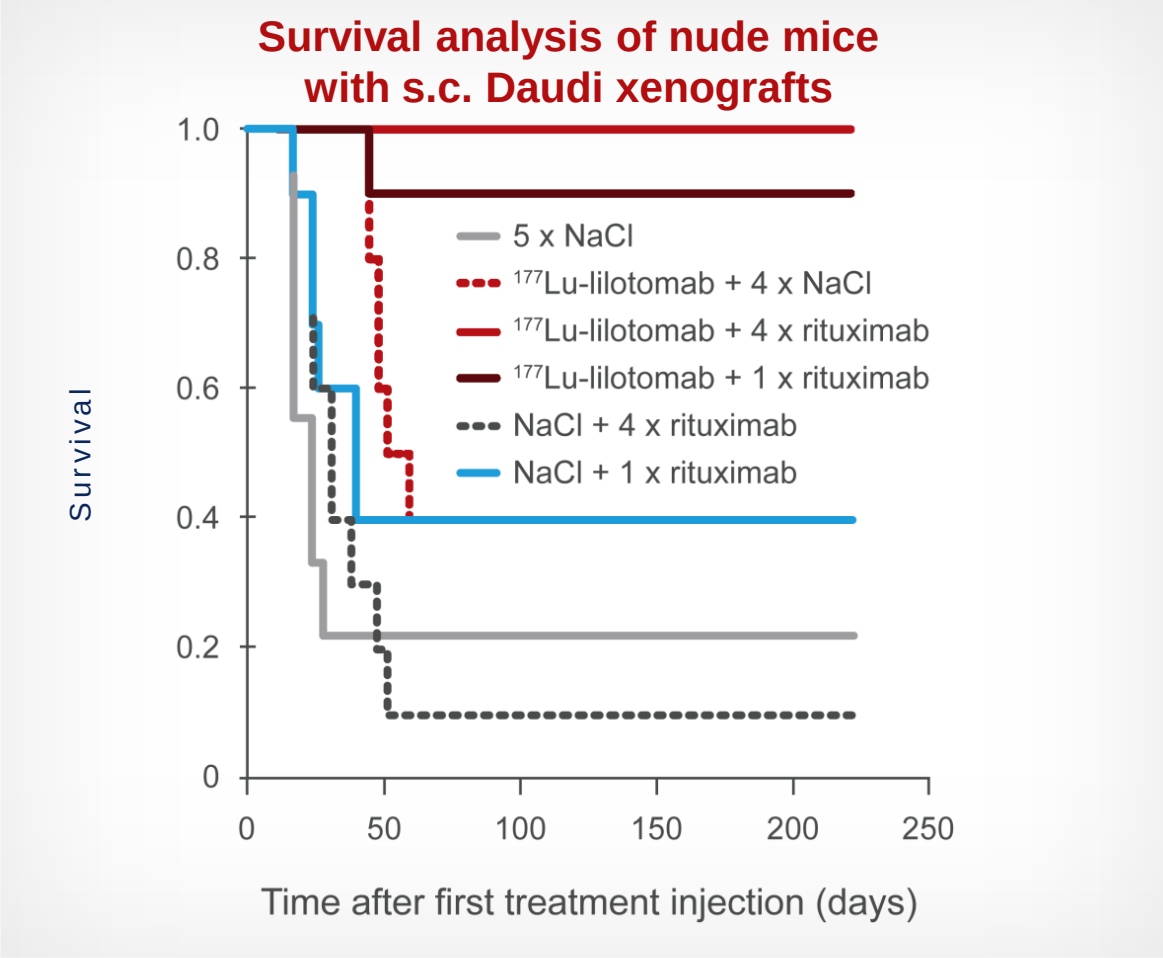
PARADIGME Phase 2b randomized global multi-centre trial: *Now enrolling*



Primary endpoint: ORR

Secondary endpoints: DoR, progression free survival (PFS), overall survival (OS), safety, quality of life

Synergistic effect of Betalutin® in combination with rituximab in a preclinical NHL model

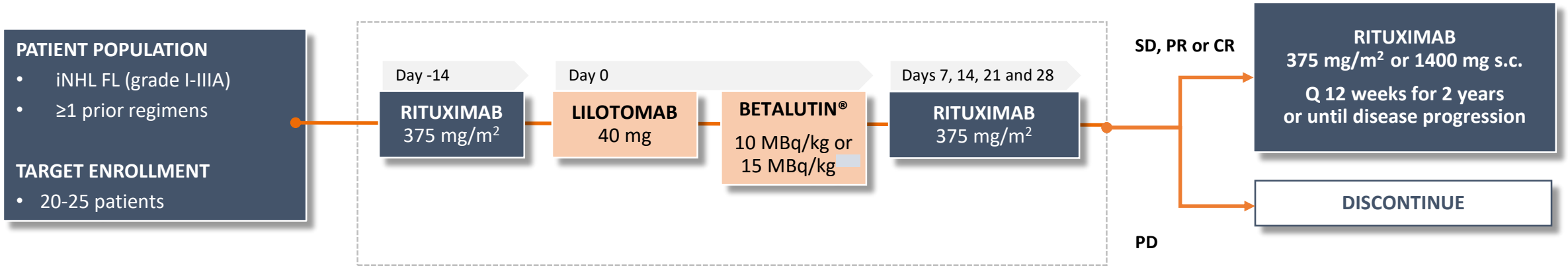


- Betalutin® increased expression of CD20 on NHL cells (Ramos, Rec-1) *in vitro* and uptake of rituximab in NHL tumours *in vivo*[1]
- Synergistic effect of combination of Betalutin® and rituximab on survival of mice with NHL (hazard ratio = 0.024, Cox regression)
- Provides proof of concept for a clinical study
- Pre-clinical data also show that cell lines that are resistant to rituximab can become sensitive after treatment with Betalutin®

[1]Repetto-Llamazares AH et al, Blood 2015; 126(23)
[2]Repetto-Llamazares AH et al. Eur J Haematol. 2018;101:522–531

Archer-1: Betalutin® + rituximab in relapsed/refractory FL

- Design: Phase 1b open-label, single-arm dose escalation study in second line FL.



- Primary objective: To evaluate the safety and tolerability of Betalutin® in combination with RTX
- Secondary objective: To evaluate the preliminary anti-tumour activity of combination treatment
- Enrolling soon

PR – partial response; SD – stable disease; PD – progressive disease

Summary

- Single-agent Betalutin® has promising clinical activity in recurrent indolent NHL:
  - Overall response rate of 60% (CR 24%) for all evaluable patients
  - Highly active in 3L FL (ORR 66%, CR 25%)

- Primary grade 3/4 toxicities were reversible neutropenia and thrombocytopenia.

- The pivotal PARADIGME phase 2b RCT (n=130) is currently enrolling 3. line, CD20-refractory FL patients