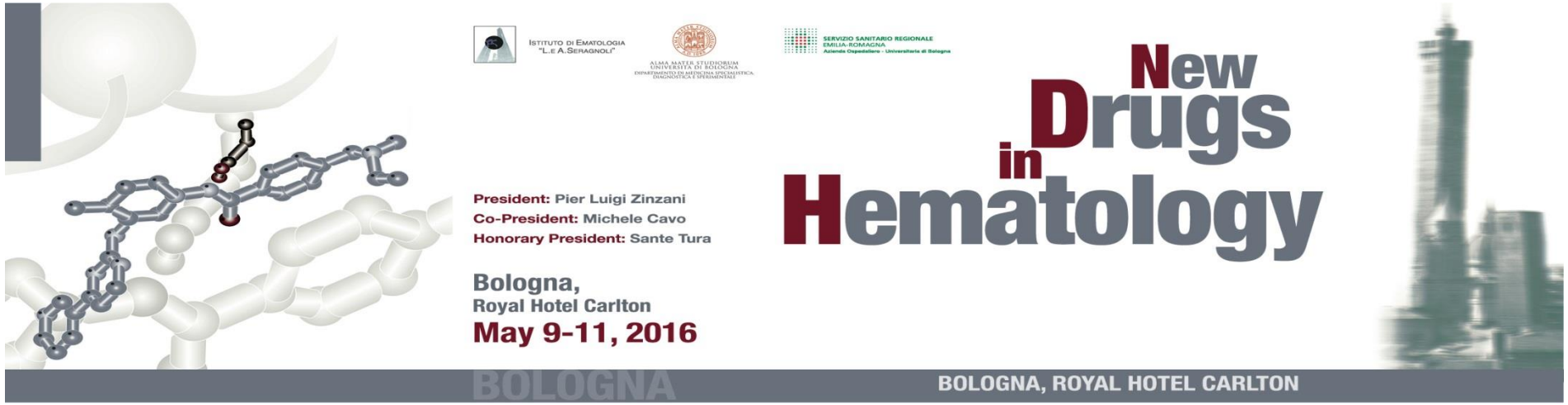
Betalutin (177Lu-Lilotomab)

Arne Kolstad

Oslo University Hospital Norway

May 10, 2016



Disclosures of: Arne Kolstad

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

Background

- Two anti-CD20 radioimmunotherapy (RIT) agents (Zevalin® and Bexxar®) are currently approved for non-Hodgkin`s lymphoma.

- These drugs are not extensively used in treatment of NHL.
  Preference for naked anti-CD20 antibody

- They may not be as effective in patients who have been treated with anti-CD20 antibodies.

- A novel RIT agent, Lu177-Lilotomab (Betalutin) is developed at Oslo University Hospital and targets CD37 on B cell NHL.

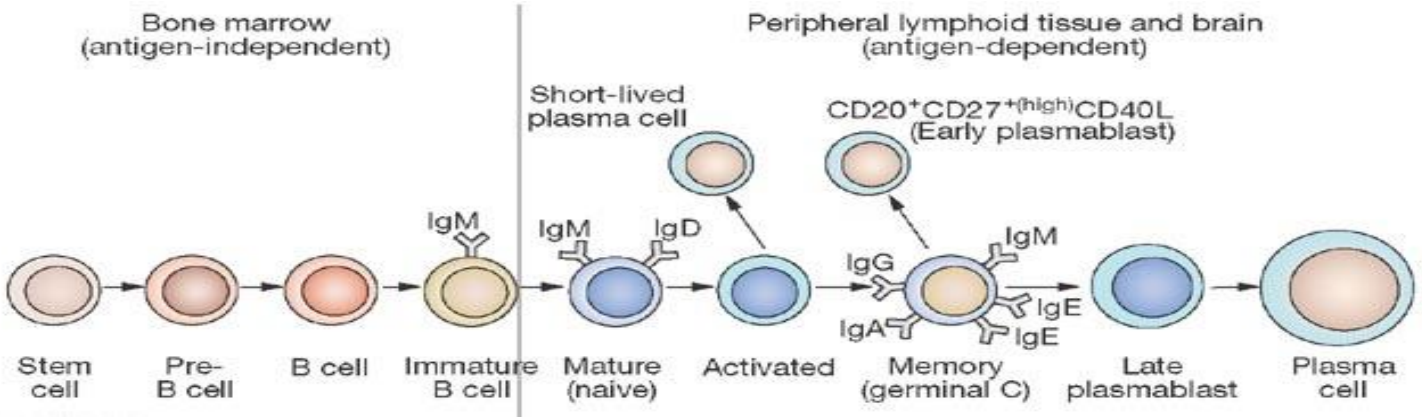
HH1 (Lilotomab): anti-CD37 antibody

- Developed at the Norwegian Radium Hospital in the mid 1980's.

Radiumhospitalet
Comprehensive Cancer Center

- Nordic Nanovector has obtained exclusive rights.

CD37 is expressed on the same B-cell subsets as CD20



Cell surface antigens

CD19

CD20

CD27

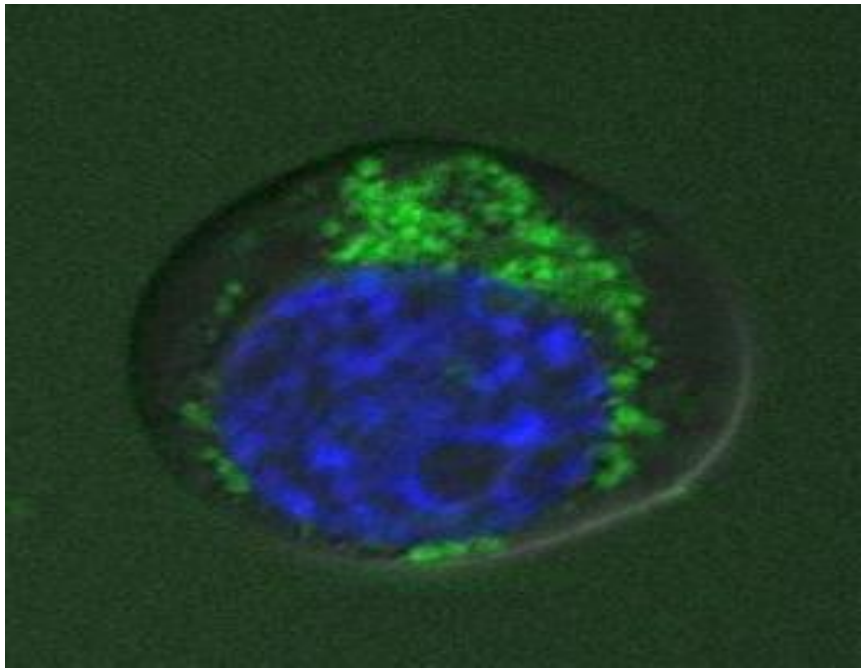
CD37

CD38

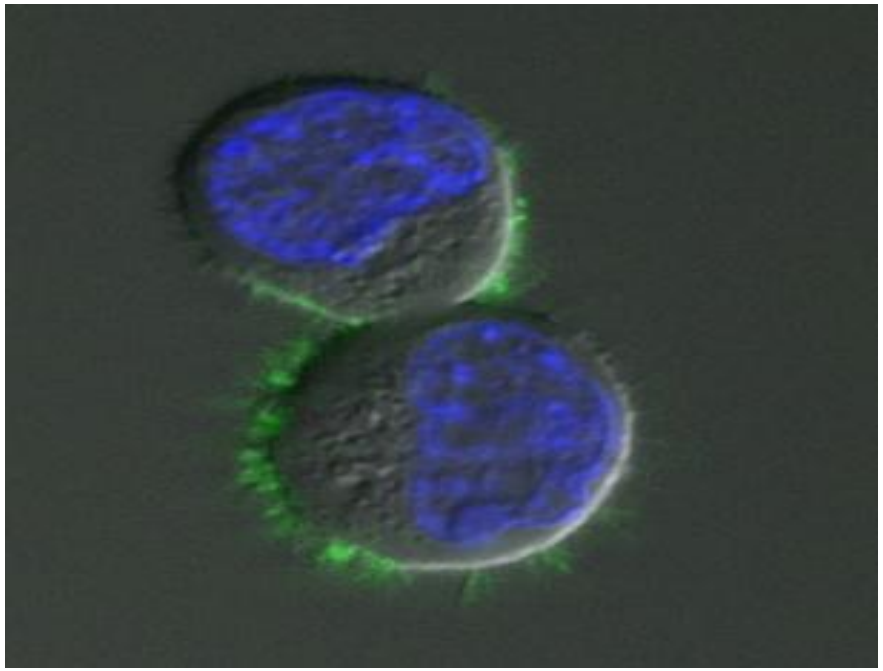
CD138

CD22

Anti-CD37 (Lilotomab) is internalized while anti-CD20 (Rituximab) is not internalized.

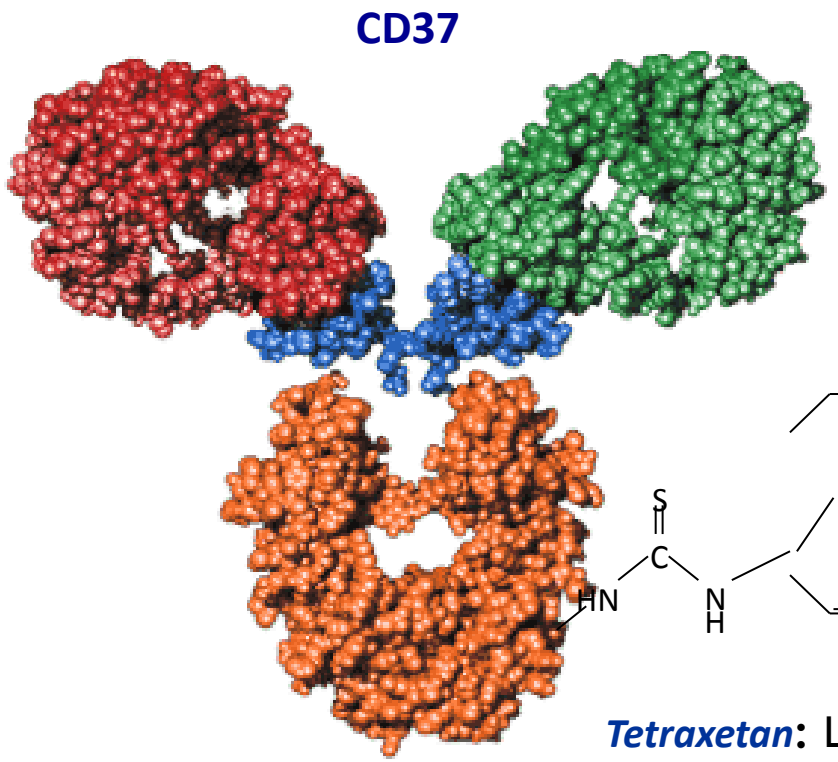


Ant-CD37

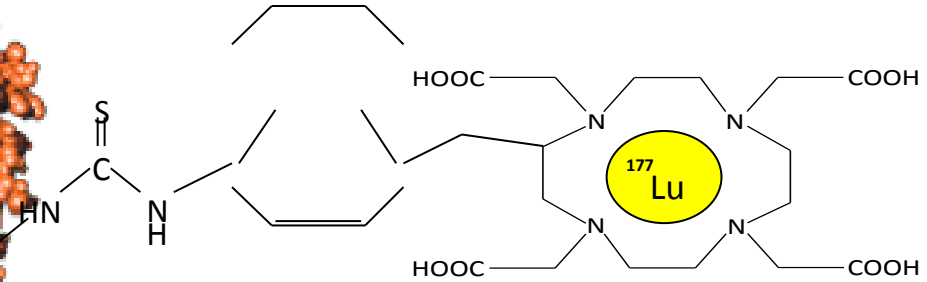


Anti-CD20

Structure of Betalutin



***Lilotomab*: antibody that targets the CD37 antigen that is expressed on B-cell lymphocytes and corresponding NHLs**



***Tetraxetan*: Linker that binds to lysine residues on tetulomab and that chelates Lutetium-177**

***Lutetium-177*: Beta-particle emitting radioactive nuclide with 6.7 days half-life.**

Comparison of RIT agents

	Betalutin™	Zevalin®	Bexxar®
Radioisotope	^{177}Lu	^{90}Y	^{131}I
$T_{½}$	6.7 d	2.7 d	8.0 d
Mean gamma-energy	0.13 MeV	0.93 MeV	0.18 MeV
Mean range in tissue	0.67 mm	3.6 mm	0.7 mm
ICRP radiotox.	3 (moderate)	3 (moderate)	2 (high)
ɣ-yield	17 %	0 %	94 %
ɣ-energies	110 & 210 keV	Bremsstrahlung	280, 360 & 640 keV
Imaging possible?	Yes	No	Yes
Antigen	CD37	CD20	CD20
Antibody	tetulomab, murine IgG_1	ibritumomab, murine IgG_1	tositumomab, murine IgG_{2a}
Pre-treatment	rituximab	rituximab	tositumomab

Radiochemical aspects

- Carrier-free
- "Ready to use” formulation
- Specific activity (100-500MBq/mg)
- Clinical dosage: 10mg/patient

LYMRIT-37-01 phase 1/2 study

- Betalutin as single agent for treatment of relapsed indolent NHL

- A total of 24 patients have been enrolled in to the LYMRIT-37-01 Phase 1/2 study, including 8 patients in Phase 2. **21 evaluable** patients so far.

- The latest trial data were presented at the AACR congress in April 2016

Kolstad A, et al. Poster version of the Abstract LB-252. Presented at AACR Annual Meeting, New Orleans, April 16-20, 2016.

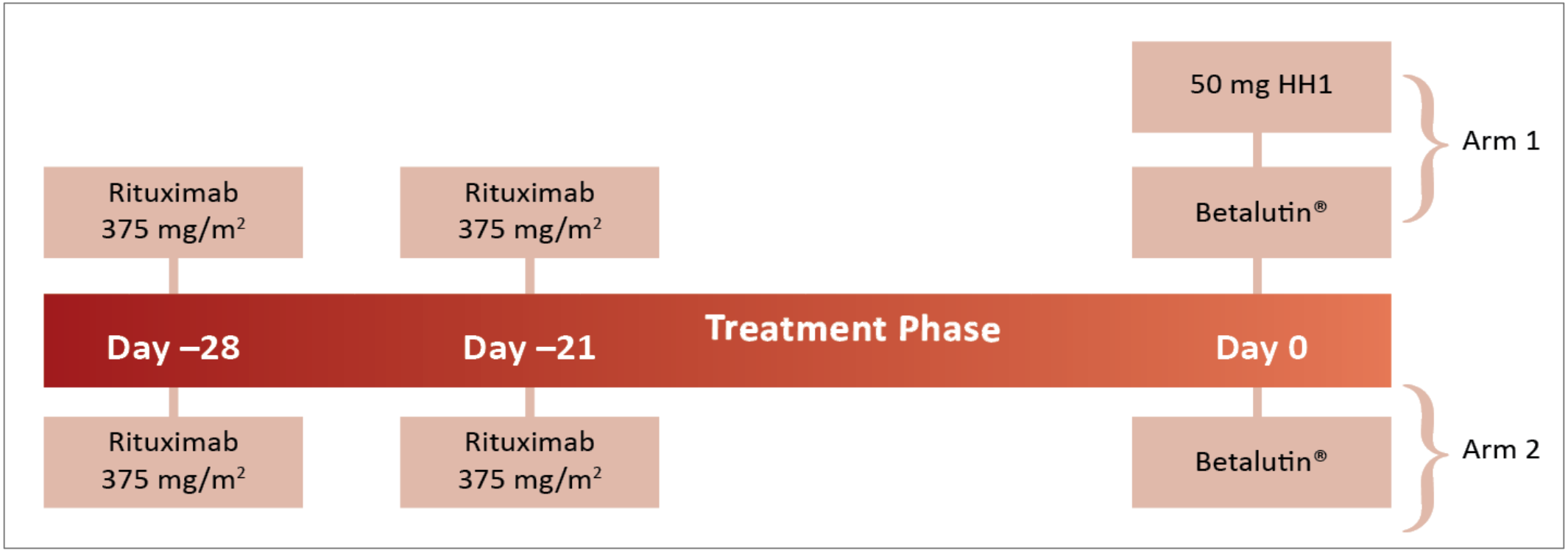
Major inclusion criteria

1. Histologically confirmed (by WHO classification) **relapsed** incurable non-Hodgkin B-cell lymphoma of following subtypes; follicular grade I-IIIA, marginal zone, small lymphocytic, lymphoplasmacytic and mantle cell
2. Age > 18 years
3. A pre-study WHO performance status of 0-1
4. Life expectancy should be ≥ 3 months
5. <25% tumour cells in bone marrow biopsy
6. CD37+, re-biopsy or test on existing tumour material if not known
7. Measurable disease by radiological methods

Major exclusion criteria

1. Medical contraindications, including uncontrolled infection, severe cardiac, pulmonary, neurologic, psychiatric or metabolic disease, steroid requiring asthma/allergy, known HIV positive
2. Laboratory values:
   a. Absolute Neutrophil Counts ≤ 1.5 x 10^9 /l
   b. Platelet count ≤ 150 x 10^9 /l
   c. Total bilirubin ≥ 30 mmol/l
   d. ALP and ALAT ≥ 4x normal level
   e. Creatinine ≥ 110 µmol/l (men), 90 µmol/l (women)
   f. IgG ≤ 3 gr/l
3. Known CNS involvement of lymphoma

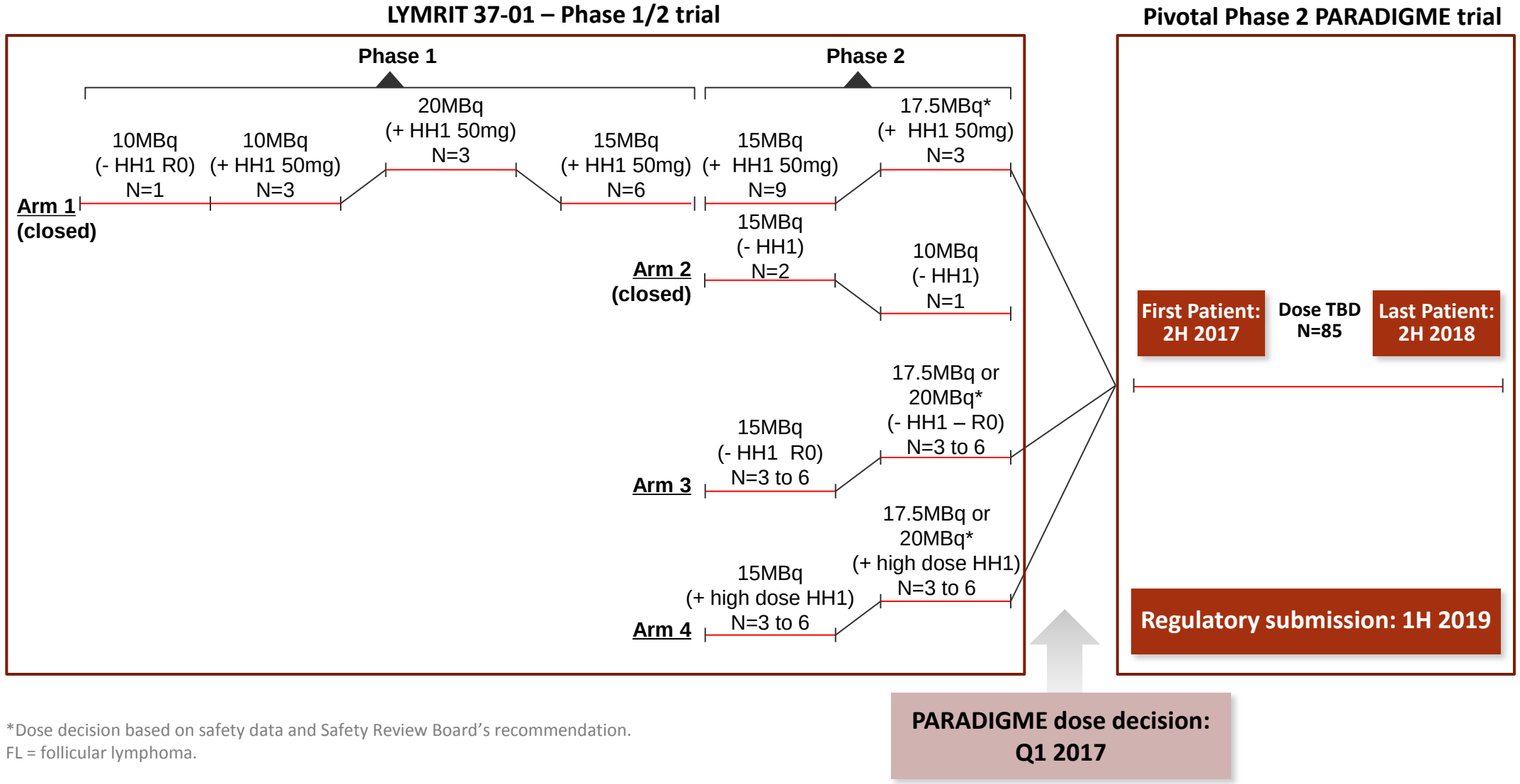
Treatment schedule



Treatment schedule. In Arm 1 patients received rituximab (375 mg/m^2) on day -28 and -21 to deplete circulating B cells. On day 0 pre-dosing with 50 mg HH1 (cold CD37 antibody) was administered before Betalutin injection. In Arm 2 Betalutin was administered without HH1 pre-dosing on day 0. The first patient received 250 mg/m^2 rituximab on day -7 and day 0 prior to Betalutin and was included in Arm 2 in the presented poster.

Kolstad A, et al. Poster version of the Abstract LB-252. Presented at AACR Annual Meeting, New Orleans, April 16-20, 2016.

Betalutin's clinical development plan - Targeting approval in third line for follicular lymphoma



*Dose decision based on safety data and Safety Review Board's recommendation.
FL = follicular lymphoma.

Kolstad A, et al. Poster version of the Abstract LB-252. Presented at AACR Annual Meeting, New Orleans, April 16-20, 2016.

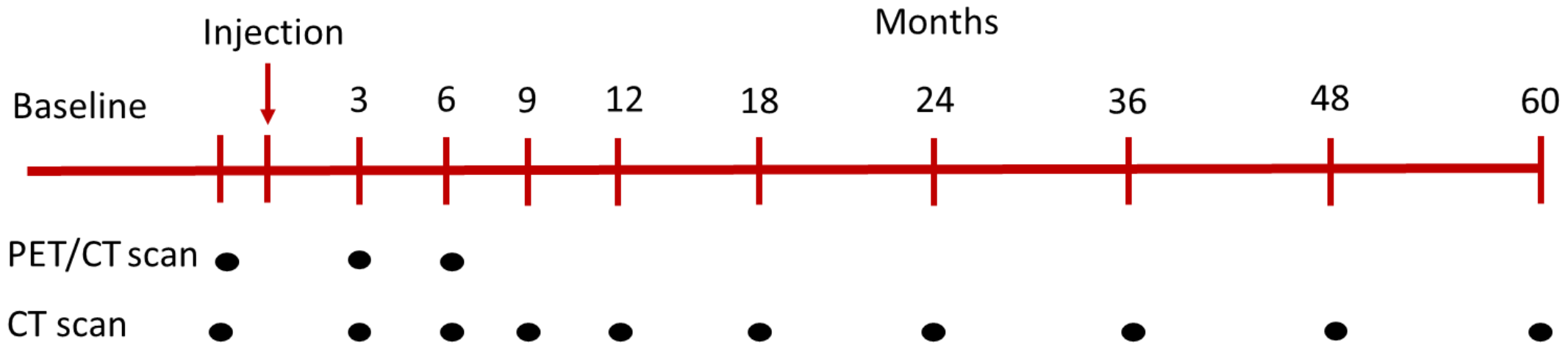
Summary of demographics and baseline characteristics

Characteristics	Arm 1			Arm 2		Phase 2	Total
Dose level	10 MBq/kg N=3	15 MBq/kg N=6	20 MBq/kg N=3	10 MBq/kg N=2*	15 MBq/kg N=2	15 MBq/kg N=5	**N=21**
Median age (years)	68	66.5	68	63	71.5	70	**68**
Range	50-69	49-78	41-69	58-68	71-72	61-74	**41-78**
Male	3 (100%)	5 (83%)	1 (50%)	1 (50%)	1 (50%)	1 (20%)	**14 (67%)**
Female	0	1 (17%)	1 (50%)	1 (50%)	1 (50%)	4 (80%)	**7 (33%)**
Primary diagnosis							
- FL	3 (100%)	5(83%)	2 (100%)	2 (100%)	2 (100%)	4 (80%)	**19 (90%)**
- MCL	0	1 (17%)	0	0	0	1 (20 %)	**2 (10%)**
Prior treatments, range	1-8	1-5	2-2	2-2	2-4	1-3	**1-8**

*First patient received 250 mg/m^2 rituximab on day -7 and day 0 prior to Betalutin and is included in this group.
FL = follicular lymphoma, MBq = megabecquerel, MCL = mantle cell lymphoma.

Kolstad A, et al. Poster version of the Abstract LB-252. Presented at AACR Annual Meeting, New Orleans, April 16-20, 2016.

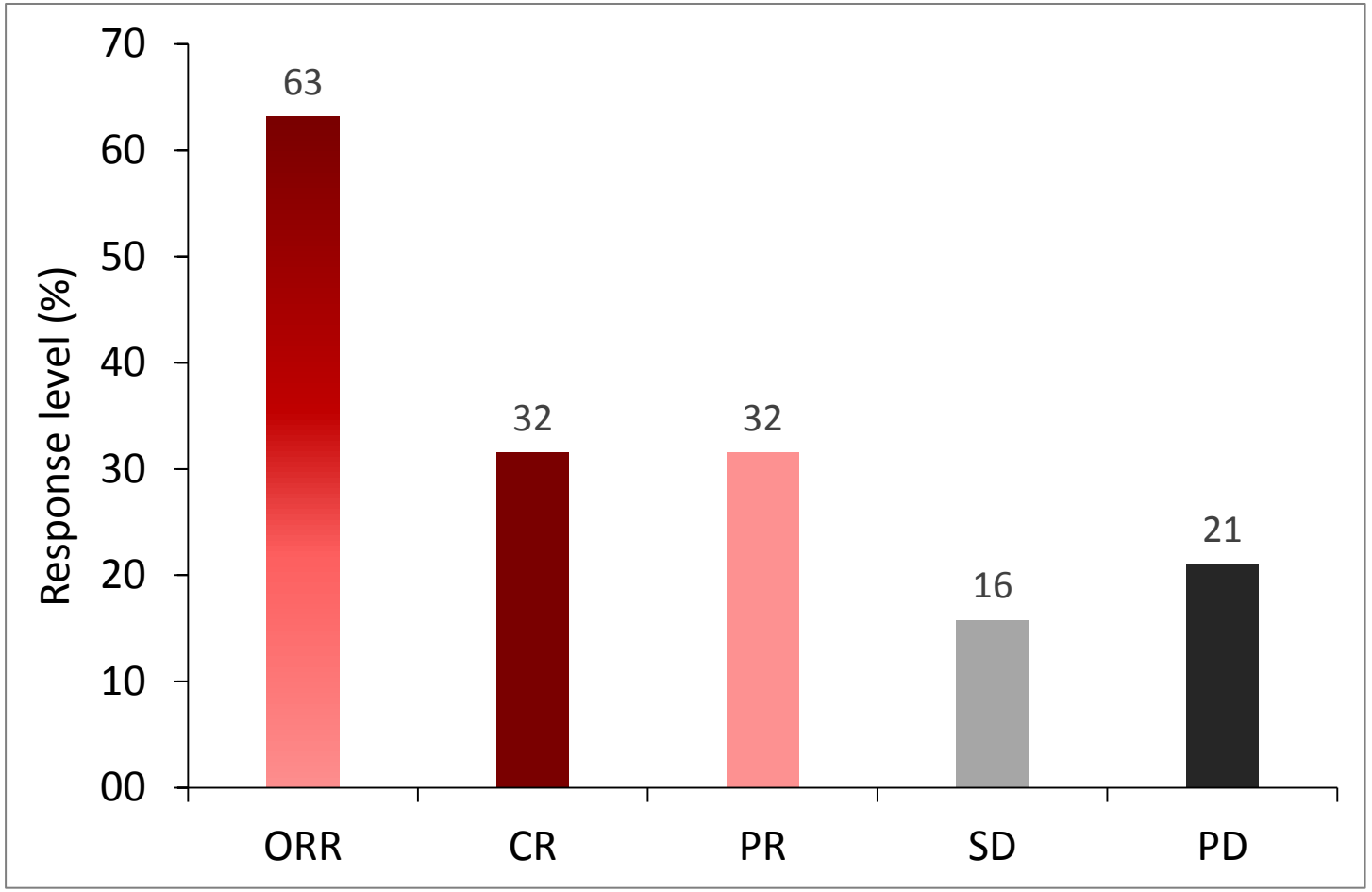
Imaging schedule



FDG PET/CT = fluorodeoxyglucose positron emission tomography-computer tomography.

Kolstad A, et al. Poster version of the Abstract LB-252. Presented at AACR Annual Meeting, New Orleans, April 16-20, 2016.

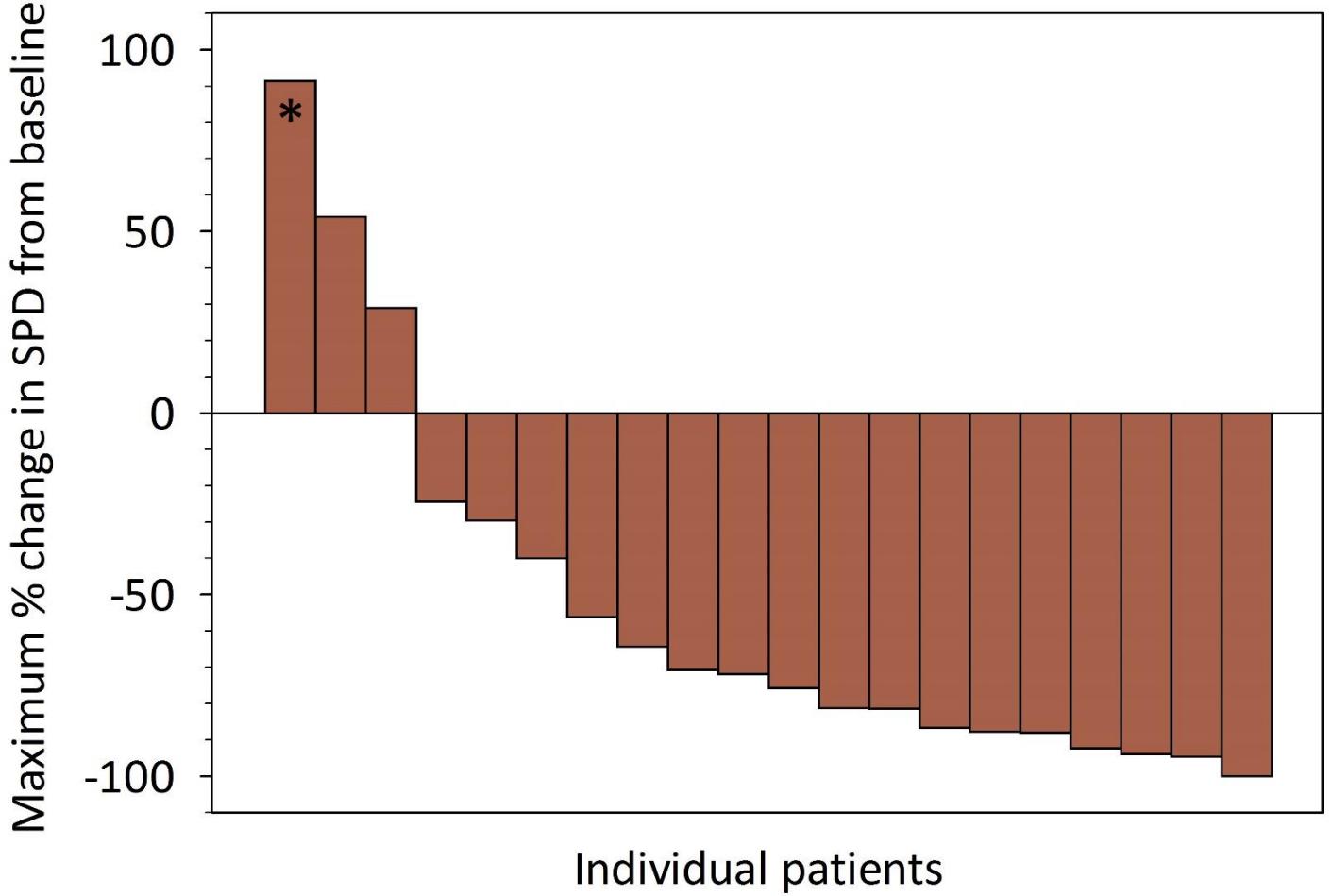
Total best response levels



One patient had confirmed transformed lymphoma at 3 months.
Tumour response was assessed according to Cheson criteria 2007.
ORR = Overall response rate, CR = Complete response, PR = Partial response, SD = Stable disease, PD = Progressive disease.

Kolstad A, et al. Poster version of the Abstract LB-252. Presented at AACR Annual Meeting, New Orleans, April 16-20, 2016.

Maximum tumour volume reduction

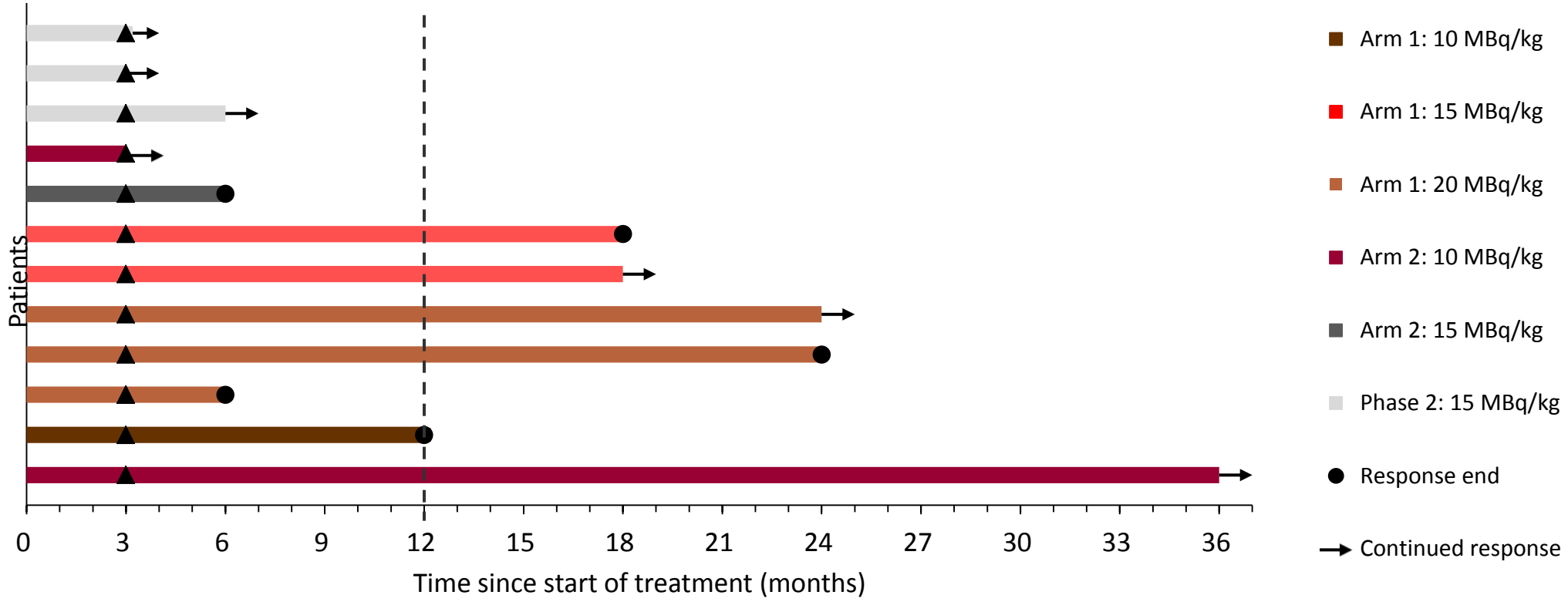


Maximum change in the sum of products of the diameters (SPD) of up to six of the largest tumour nodules for each patient from baseline.

*Patient with transformed disease.

Kolstad A, et al. Poster version of the Abstract LB-252. Presented at AACR Annual Meeting, New Orleans, April 16-20, 2016.

Duration of response



Duration of response of all patients with response assessment (12/21). Triangles represent start of response (partial and complete).

MBq = megabecquerel.

Kolstad A, et al. Poster version of the Abstract LB-252. Presented at AACR Annual Meeting, New Orleans, April 16-20, 2016.

Incidence of grade 3 (> 2 weeks) and grade 4 (> 1 week) hematolgical adverse events

Adverse events	Arm 1						Arm 2				Phase 2		Total	
Dose levels	10 MBq/kg N=3		15 MBq/kg N=6		20 MBq/kg N=3		10 MBq/kg N=2*		15 MBq/kg N=2		15 MBq/kg N=5		N=21	
CTCAE grade**	3	4	3	4	3	4	3	4	3	4	3	4	3	**4**
Platelet count decrease	0	0	2	1	0	3	1	0	0	2	0	0	**3**	**6**
Neutrophil count decrease	1	0	1	1	1	2	1	0	1	1	0	0	**5**	**4**

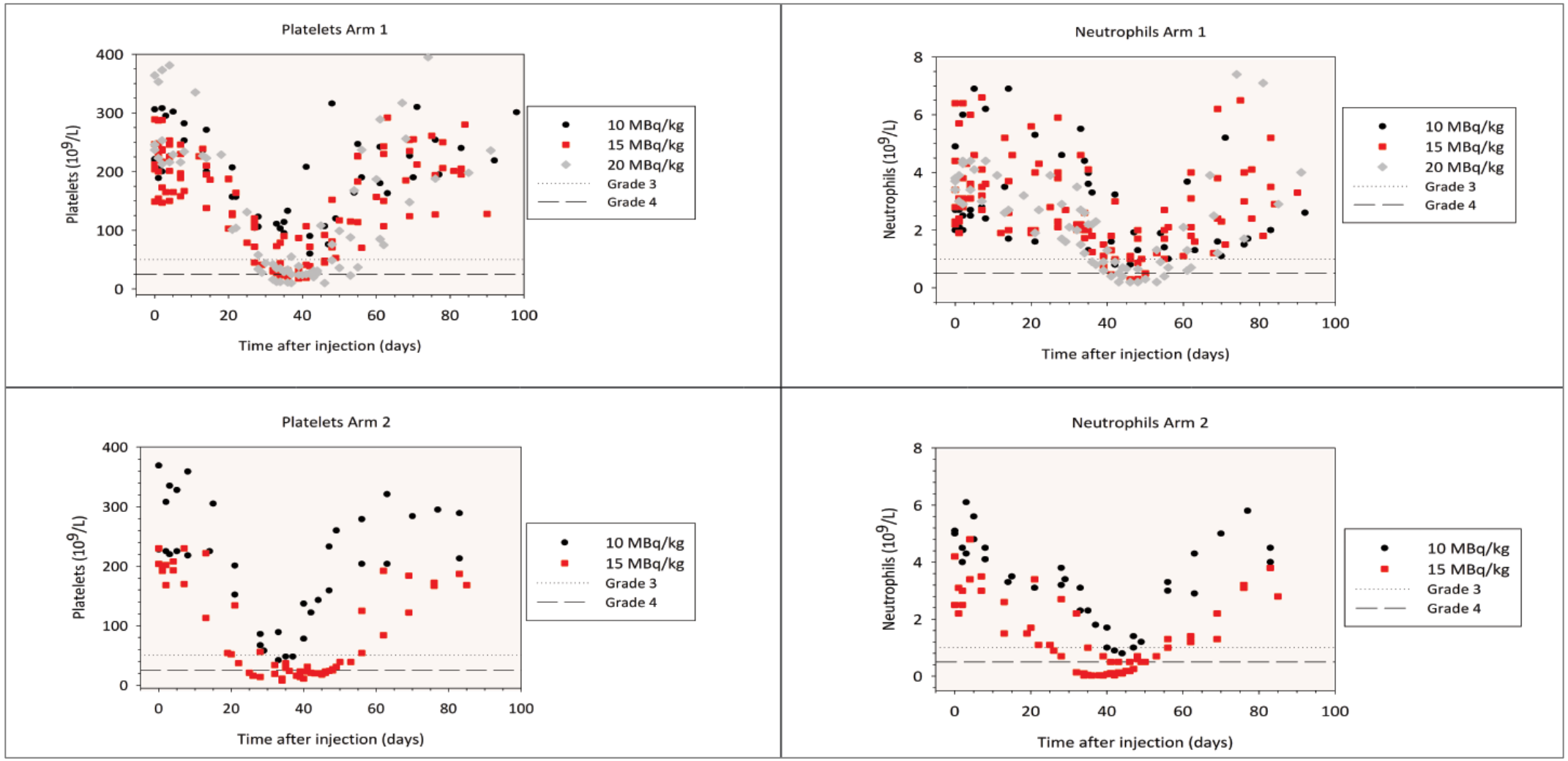
*First patient received 250 mg/m^2 rituximab on day -7 and day 0 prior to Betalutin and is included in this group. **CTCAE grade version 4.

SAEs rated as possibly or probably related to Betalutin: epistaxis, pulmonary infection and febrile neutropenia were reported in one patient each and two cases of atrial fibrillation.

MBq = megabecquerel.

Kolstad A, et al. Poster version of the Abstract LB-252. Presented at AACR Annual Meeting, New Orleans, April 16-20, 2016.

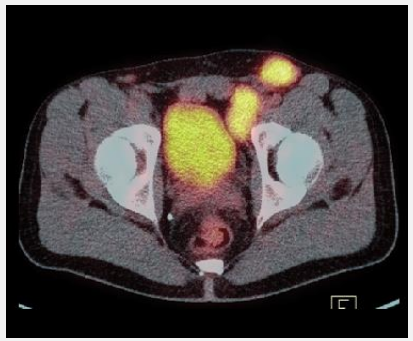
Hematological toxicity phase 1

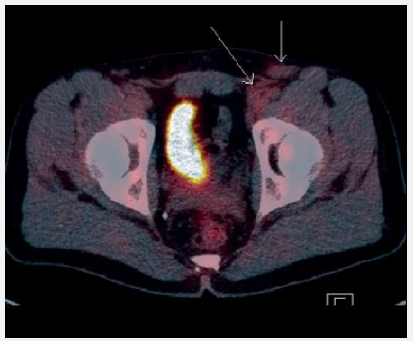


Haematology data. Platelet counts and neutrophil counts of all patients in arm 1 and 2 of phase 1. The phase 2 patients were not included in these plots.

Imaging results: FDG PET/CT scan

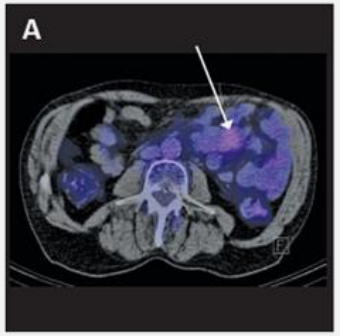
Complete metabolic response (FDG PET/CT) at 3 months in patient with follicular lymphoma at 20 MBq/kg



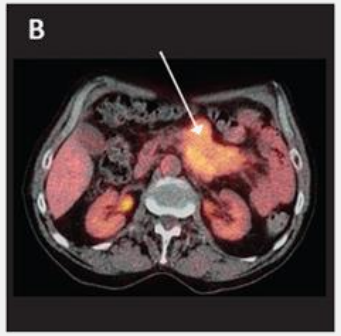


Patient is still in complete remission 24 months after Betalutin treatment

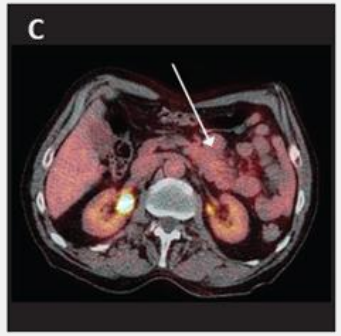
Complete metabolic response (FDG PET/CT) at 6 months in patient with follicular lymphoma at 15 MBq/kg



SPECT/CT at day 4 showed uptake of Betalutin® in tumour.



Baseline FDG PET/CT.



6 months FDG PET/CT complete metabolic response.

Patient is still in complete remission 24 months after Betalutin treatment

FDG PET CT = fluorodeoxyglucose positron emission tomography-computer tomography; MBq = megabecquerel; SPECT = single-photon emission computerized tomography.

Summary

- Betalutin, a single dose, ***ready-to-use formulation***, that binds to a novel target, CD37 for the treatment of NHL.

- Most AEs were hematological (thrombocytopenia and neutropenia), all transient and reversible.

- Promising efficacy and durable responses have been observed.

- Betalutin as single agent may become a good alternative for patients with indolent NHL, relapsed/refractory to anti-CD20 therapy and chemotherapy.

Participating centres

Phase I & II – 11 centers

- Norway
  - Oslo – Dr Kolstad
  - Trondheim - Dr. Fagerli
  - Bergen – Prof Bjørn
- Croatia
  - Zagreb – Dr Aurer
- Italy
  - Bologna - Prof. Zinzani
  - Milan – Dr Ciceri
- Poland
  - Warsaw – Dr Walewski
- Spain
  - Madrid - Dr Provencio Pulla
  - Salamanca - Dr Garcia-Sancho
- Sweden
  - Umeå - Dr. Erlansson
- UK
  - Manchester - Prof. Illidge

Phase II – 14 centres

- Austria
  - Innsbruck - Dr. Willenbacher
  - Linz - Dr. Welterman
  - Vienna - Prof. Raderer
- Czech Republic
  - Ostrava - Prof. Hajek
  - Olomouc - Prof. Papajik
  - Prague - Prof. Trnený
- Italy
  - Firenze - Prof. Bosi
- Poland
  - Kraków - Prof. Jurczak
  - Warsaw - Prof. Jedrzejczak
- Sweden
  - Linkøping - Dr. Lagerløf
  - Borås - Dr. Andersson
- UK
  - Poole - Dr. Bayne
  - Glasgow - Dr. O'Rourke
  - Bristol - Dr. Beasley