

Phase 1/2a study of ^{177}Lu -lilotomab satetraxetan in relapsed/refractory indolent non-Hodgkin lymphoma

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Key Points

- There is a high unmet need for new treatment options, particularly in elderly patients with relapsed/refractory FL.
- Radioimmunotherapy is an underused option, and ^{177}Lu -lilotomab satetraxetan may offer a safe and effective treatment for relapsed FL.

For patients with indolent non-Hodgkin lymphoma who fail initial anti-CD20-based immunochemotherapy or develop relapsed or refractory disease, there remains a significant unmet clinical need for new therapeutic approaches to improve outcomes and quality of life. ^{177}Lu -lilotomab satetraxetan is a next-generation single-dose CD37-directed radioimmunotherapy (RIT) which was investigated in a phase 1/2a study in 74 patients with relapsed/refractory indolent non-Hodgkin B-cell lymphoma, including 57 patients with follicular lymphoma (FL). To improve targeting of ^{177}Lu -lilotomab satetraxetan to tumor tissue and decrease hematologic toxicity, its administration was preceded by the anti-CD20 monoclonal antibody rituximab and the “cold” anti-CD37 antibody lilotomab. The most common adverse events (AEs) were reversible grade 3/4 neutropenia (31.6%) and thrombocytopenia (26.3%) with neutrophil and platelet count nadirs 5 to 7 weeks after RIT. The most frequent nonhematologic AE was grade 1/2 nausea (15.8%). With a single administration, the overall response rate was 61% (65% in patients with FL), including 30% complete responses. For FL with ≥ 2 prior therapies (n = 37), the overall response rate was 70%, including 32% complete responses. For patients with rituximab-refractory FL ≥ 2 prior therapies (n = 21), the overall response rate was 67%, and the complete response rate was 24%. The overall median duration of response was 13.6 months (32.0 months for patients with a complete response). ^{177}Lu -lilotomab satetraxetan may provide a valuable alternative treatment approach in relapsed/refractory non-Hodgkin lymphoma, particularly in patients with comorbidities unsuitable for more intensive approaches. This trial was registered at www.clinicaltrials.gov as #NCT01796171.

Introduction

Non-Hodgkin lymphoma (NHL) comprises indolent and aggressive hematologic malignancies. Follicular lymphoma (FL) is the most common indolent subtype, alongside marginal zone lymphoma, small lymphocytic

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lymphoma and lymphoplasmacytic lymphoma (Waldenström macroglobulinemia). FL has an annual incidence of 3.4 to 5 per 100 000 in Europe and in the United States.¹ With a median age at diagnosis of 65 years, FL has a protracted course with multiple remissions and relapses. Consequently, many patients in later-stage disease will be elderly or frail, limiting feasible treatment options.

The anti-CD20 monoclonal antibody rituximab, alone or in combination with chemotherapy, has revolutionized the treatment of B-cell NHL.^{2,3} However, refractory disease or early relapse (within 2 years) is observed in $\leq 20\%$ of patients receiving immunochemotherapy, with early relapse in FL associated with particularly poor overall survival.⁴ Effective treatment options other than autologous stem cell transplant for patients with relapsed and rituximab-refractory disease are needed. The anti-CD20 antibody obinutuzumab is approved for rituximab-resistant FL in combination with bendamustine,^{5,6} and with very promising early data in combination with lenalidomide.⁷ Approaches such as B-cell receptor pathway-targeting agents (including phosphatidylinositol 3-kinase [PI3K] and Bruton tyrosine kinase [BTK] inhibitors) have yielded modest response rates^{8,9} but remain among the few available alternatives for heavily pretreated patients.

New options for relapsed/refractory FL are urgently needed, especially for the large cohort of elderly patients with comorbidities who cannot tolerate intensive chemotherapy. In this context, radioimmunotherapy (RIT) is underutilized. CD20-directed RIT via ¹³¹I-tositumomab (Bexxar) and ⁹⁰Y-ibritumomab tiuxetan (Zevalin), with predosing comprising cold antibody and rituximab, has proved effective.^{10,11} In patients with relapsed or refractory NHL, ⁹⁰Y-ibritumomab tiuxetan was superior to rituximab (overall response rate [ORR] 80% vs 56% [$P = .002$] and complete response rate [CRR] 30% vs 16% [$P = .04$], respectively). In rituximab-refractory patients, the ORR was 74%, CRR was 15%, and time to progression was 8.7 months for responders.¹²

Alternative targets are necessary to overcome resistance to anti-CD20-based therapy. CD37 is a highly glycosylated transmembrane protein selectively expressed by normal B cells and the majority of B-cell lymphomas,¹³⁻¹⁵ making it an attractive therapeutic target. ¹⁷⁷Lu-lilotomab satetraxetan (Betalutin) consists of the anti-CD37 murine monoclonal antibody lilotomab conjugated to the chelator satetraxetan (*p*-SCN-benzyl-DOTA) that conjugates the β -emitting isotope ¹⁷⁷Lu. ¹⁷⁷Lu-lilotomab satetraxetan has been extensively investigated in preclinical models,¹⁵⁻¹⁷ and the radionuclide ¹⁷⁷Lu has shown efficacy in clinical trials with various tumor types.¹⁸⁻²²

This phase 1/2a dose-escalation and expansion study (LYMRIT-37-01; NCT01796171) investigated the safety, biodistribution, and pharmacokinetics (PK) of single-dose RIT with ¹⁷⁷Lu-lilotomab satetraxetan in patients with relapsed indolent NHL. The most appropriate dosing regimen and maximum tolerated dose were assessed, and recommended doses and regimens for expansion into phase 2 were established to further evaluate the safety and efficacy of ¹⁷⁷Lu-lilotomab satetraxetan.

Methods

Patients

Patients ≥ 18 years old with histologically confirmed (World Health Organization classification) relapsed/refractory indolent non-Hodgkin

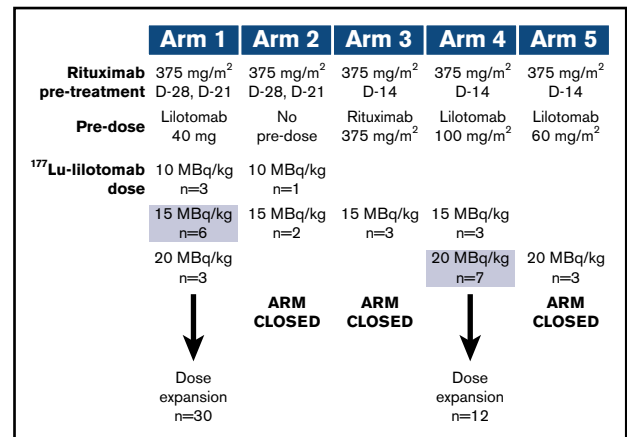


Figure 1. Dose-escalation and expansion cohorts. Shaded doses selected for dose expansion. D, day.

B-cell lymphoma (follicular grade I-IIIa, marginal zone, small lymphocytic or lymphoplasmacytic) or mantle cell lymphoma were included. The main inclusion criteria were prestudy World Health Organization performance status of 0 to 1 and life expectancy ≥ 3 months; $< 25\%$ tumor cells in bone marrow biopsy; measurable disease by radiological methods; platelet count $\geq 150 \times 10^9/L$, absolute neutrophil count $\geq 1.5 \times 10^9/L$; and no central nervous system lymphoma, transformed disease, or prior stem cell transplantation. Patients with human anti-mouse antibodies (HAMA⁺) at baseline were excluded. CD37 expression in tumor collected prior to treatment was tested by immunohistochemistry using the antibody clone CT1 (mIgG1, Leica). No biopsy specimens were collected after administration of lilotomab and ¹⁷⁷Lu-lilotomab satetraxetan.

The lilotomab satetraxetan conjugate was manufactured by conjugating lilotomab with the chelator satetraxetan (*p*-SCN-bezyl-DOTA, Macrocyclics, Plano, TX). For each patient, the conjugate is mixed with noncarrier added ¹⁷⁷Lu (ITG, Garching, Germany) to produce the final ¹⁷⁷Lu-lilotomab satetraxetan radioimmunoconjugate, supplied ready to use to centers. Doses were calculated using patients' bodyweight on the day of administration and corrected for physical decay of ¹⁷⁷Lu.

Study design

Initially, the study regimen was based on experiences from previous RIT and included pretreatment with rituximab for B-cell depletion to potentially optimize the biodistribution of ¹⁷⁷Lu-lilotomab satetraxetan. The first (index) patient entered into the study received rituximab (Roche, Basel, Switzerland) 250 mg/m² on days -7 and 0, with 10 MBq/kg ¹⁷⁷Lu-lilotomab satetraxetan on day 0. Using dosimetry and safety data for the index patient, arm 1 and subsequent arms were designed to assess different pretreatment and predose regimens in a standard 3 + 3 study design (Figure 1). The dose of ¹⁷⁷Lu-lilotomab satetraxetan was escalated if 0 out of 3 or 1 out of 6 dose-limiting toxicities (DLTs) were recorded for a cohort, and the cohort was expanded if 1 out of 3 DLTs were reported. Dose escalation was halted for ≥ 2 DLTs and arm closure decided by the safety review committee (SRC).

Rituximab pretreatment was administered at either days -28 and -21 (arms 1 and 2) or day -14 (arms 3, 4, and 5). Predosing

on day 0 with lilotomab (arms 1, 4, and 5) or rituximab (arm 3) or no predosing (arm 2) was tested to assess the impact of pre-emptively blocking the CD37 antigens (CD20 antigens in arm 3) of normal B lymphocytes on the biodistribution of ^{177}Lu -lilotomab satetraxetan. Arm 4 was initiated to confirm whether a higher lilotomab predose would enable an increased ^{177}Lu -lilotomab satetraxetan dose to be tolerated, and arm 5 was added to characterize the 20 MBq/kg dose and fully characterize the PK of ^{177}Lu -lilotomab satetraxetan in addition to existing PK and dosimetry data.

Two dosing regimens from arms 1 and 4 were eventually selected for further investigation and patient enrollment in phase 2a. In the arm 1 phase 2a cohort an interim analysis was performed to review safety after 9 patients had been treated with 15 MBq/kg ^{177}Lu -lilotomab satetraxetan.

Dosimetry

Serial whole-body or thorax/abdominal/other areas of known lesions single-photon emission computerized tomography (SPECT)/computed tomography (CT) was performed at intervals from 2 hours up to 7 days postdosing with ^{177}Lu -lilotomab satetraxetan, with the aim of studying 3 patients at each dose level for the different pretreatment regimens. Tumor and bone marrow–absorbed doses were calculated from SPECT/CT images. A detailed description of the dosimetry methods has already been published.²³⁻²⁶ Volumes taken from CT images and radioactivity in tumors and lumbar vertebrae 2 to 4 derived from SPECT were used for the calculations.

Pharmacokinetics

^{177}Lu -lilotomab satetraxetan PK was assessed by measuring the total radioactivity in blood using a γ counter. Blood samples were collected according to various schedules. For the first 2 patients, samples were collected before and 2.5, 5, 15, 30, 60, 90, and 120 minutes, 4, 8, and 20 hours, and 2, 3, 4, 7, and 28 days after administration of ^{177}Lu -lilotomab satetraxetan). For subsequent patients, samples were collected before and 5, 60, and 120 minutes, 24 hours, and 2, 3, 4, 7, 14, 21, and 28 days after administration of ^{177}Lu -lilotomab satetraxetan. Patients participating in the serial whole-body SPECT/CT study had additional samples collected 4 and 8 hours after ^{177}Lu -lilotomab satetraxetan administration.

Total radioactivity in blood versus time was analyzed by PKxpert AB (Sweden) by noncompartmental analysis in Phoenix WinNonLin 64 version 8.1 build 8.1.0.3530 (Certara), using the “linear up log down” area under the curve method, and the 200-202 blood model. Maximum serum concentration and time to maximum serum concentration were taken directly from the activity-time profile.

Safety and DLTs

The SRC was responsible for dose-escalation decisions throughout the study. Adverse events (AEs) and serious AEs were collected via electronic case report forms from the signing of informed consent to 12 weeks after administration of ^{177}Lu -lilotomab satetraxetan and then as reported to the investigator thereafter. AEs were graded according to NCI-CTCAE version 4.0.

DLTs were assessed during the first 12 weeks after administration and were initially defined as grade 4 hematologic toxicity that did not recover after 7 days, grade 3 hematologic toxicity that did not recover after 2 weeks, or grade ≥ 3 nonhematologic AEs at the

discretion of the SRC. DLT criteria were later revised by the SRC to comprise grade 4 hematologic toxicity that did not recover to grade 3 within 7 days or bleeding due to thrombocytopenia, febrile neutropenia, failure of platelets or neutrophils to recover to grade 1 by 12 weeks after treatment, or grade ≥ 3 nonhematologic AEs per SRC review.

Immunogenicity assessment

Patients were monitored for the development of HAMAs after lilotomab and ^{177}Lu -lilotomab satetraxetan administration using an in-house bridging assay, which used biotinylated and Eu-labeled lilotomab as solid-phase and tracer proteins, respectively, or the Milenia QuickLine HAMA test (Milenia Biotec). Blood samples were collected at 7 days and 1, 3, 6, and 12 months after lilotomab and ^{177}Lu -lilotomab satetraxetan administration for patients enrolled in phase 1. Day 7 specimens were not collected for patients enrolled in phase 2a.

Efficacy

Responses were assessed periodically up to 5 years by fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT²⁷ and contrast-enhanced CT²⁸ (or magnetic resonance imaging for patients with allergy to CT contrast media). Baseline contrast-enhanced CT and FDG PET/CT scans were taken within 4 weeks prior to first rituximab infusion, and responses were assessed at 3 and 6 months after treatment by contrast-enhanced CT and FDG PET/CT. Repeat bone marrow biopsy was performed to confirm complete response (CR) if bone marrow biopsy was positive at baseline; progressive disease (PD) was confirmed by CT only. Follow-up CT scans were taken at 9, 12, 18, and 24 months and then every 6 months up to 5 years. Efficacy was assessed in terms of ORR (CR or partial response [PR]) at 3 months, and best ORR, progression-free survival (PFS), duration of response (DoR) and overall survival.

Ethics statement

The study protocol was approved by each hospital's ethics committee and independent review board and/or regional ethics committees. All patients gave written, informed consent, and the study was conducted in accordance with the Declaration of Helsinki.

Results

Patients

Patients were enrolled to the study between December 2012 and December 2017 (phase 1) and October 2015 and March 2018 (phase 2a). All pretreatment biopsy specimens that were available for testing (65/74) stained positive for CD37. Patient demographics and baseline disease characteristics are shown in Table 1. The majority of patients in phase 1 and 2a had FL, and a considerable proportion (34% in phase 1 and 55% of additional patients in phase 2a) were rituximab-refractory. Patients had received a median of 2 prior therapies, including rituximab ($n = 67$ [91%]), alkylating agents ($n = 60$ [81%]), and bendamustine ($n = 23$ [31%]). Overall, 21 patients (28%) were refractory to their last line of therapy before study entry ($n = 17$ [30%] for patients with FL).

Table 1. Patient baseline characteristics

	Phase 1 dose escalation	Phase 2a dose expansion	All FL patients
n	32	42	57
Median age at study entry (range), y	69.0 (38-88)	68.0 (51-80)	69.0 (38-80)
≥65 y, n (%)	24 (75.0)	30 (71.4)	41 (71.9)
Male, n (%)	23 (71.9)	18 (42.9)	32 (56.1)
NHL subtype, n (%)			
FL grade I	10 (31.3)	5 (11.9)	15 (26.3)
FL grade II	18 (56.3)	15 (35.7)	33 (57.9)
FL grade IIIa	0 (0)	9 (21.4)	9 (15.8)
MZL	1 (3.1)	8 (19.0)	—
SLL	0 (0)	1 (2.4)	—
MCL	3 (9.4)	4 (9.5)	—
Bulky disease (>6 cm), n (%)	10 (31.3)	17 (40.5)	22 (38.6)
BM involvement, n (%)	7 (21.9)	9 (21.4)	11 (19.3)
Prior therapies			
Median prior treatments, n (range)	3 (1-6)	2 (1-8)	2 (1-7)
≥2 prior regimens, n (%)	23 (71.9)	26 (61.9)	38 (66.7)
Prior bendamustine, n (%)	13 (40.6)	10 (23.8)	15 (26.3)
Refractory (SD or PD) to last therapy, n (%)	9 (28.1)	12 (28.6)	17 (29.8)
Rituximab refractory, n (%)	12 (37.5)	19 (45.2)	26 (45.6)

BM, bone marrow; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PD, progressive disease; SD, stable disease; SLL, small lymphocytic lymphoma.

Dosimetry

Some dosimetry and PK data have already been published for patients included in phase 1 of this study.²³⁻²⁶

Figure 2 shows fused SPECT/CT images of activity at day 4 after ¹⁷⁷Lu-lilotomab satetraxetan administration for 5 representative patients, the correlation between absorbed dose in red marrow and tumor, and PK profiles for ¹⁷⁷Lu-lilotomab satetraxetan. Arms 1 and 4 showed the largest differences between tumor- and red marrow-absorbed dose. In contrast, arms 2 and 3 demonstrated the necessity of lilotomab as a predose; although arm 2 (with no predose) showed similar tumor absorption to arm 1, red marrow absorption was significantly higher, which correlated with the increased hematological toxicity reported for patients in arm 2. In arm 3 (rituximab predose), absorbed dose to red marrow was higher than that to tumor tissue. The differences in splenic uptake intensity with different lilotomab predoses vs no predose or rituximab are particularly noticeable, supporting the beneficial effect of predosing with lilotomab. These data correlate with the occurrence of DLTs observed in phase 1.

PK

¹⁷⁷Lu-lilotomab satetraxetan PK was assessed as measurements of total radioactivity in blood for the index patient and patients enrolled in arm 1 (n = 9), arm 2 (n = 3), arm 3 (n = 3), arm 4 (n = 10), and arm 5 (n = 3) in the phase 1 part of the study. ¹⁷⁷Lu-lilotomab satetraxetan blood clearance profiles of mean activity-adjusted radioactivity in blood are shown in supplemental Figure 1. Lilotomab predosing appeared to dose-dependently increase the activity-adjusted exposure (as area under the curve) of ¹⁷⁷Lu-lilotomab

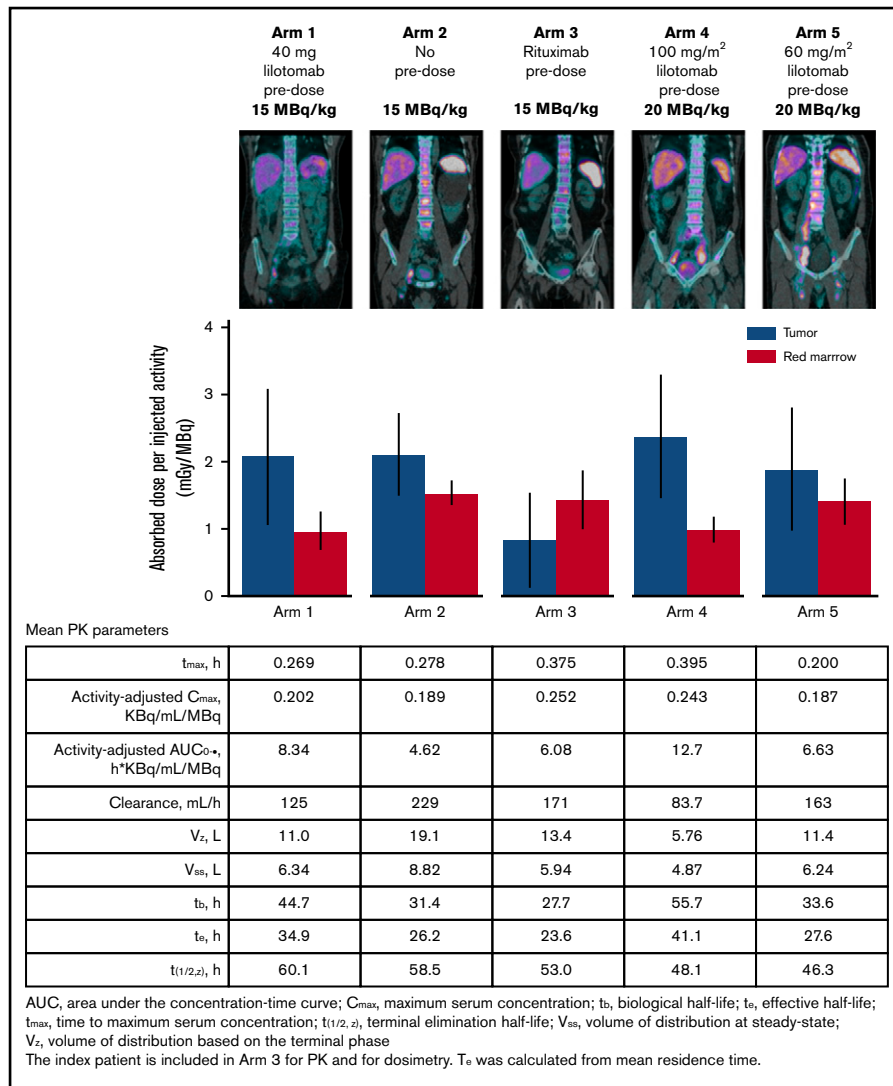
satetraxetan (arm 4 > arm 1 > arm 5 > arm 3 > arm 2), with a direct impact on volume of distribution and blood clearance (Figure 2). Activity-adjusted exposure was highest (12.7 [KBq/mL]/MBq), and clearance lowest (83.7 mL/h), for arm 4. Furthermore, the biological half-life (t_b) and effective half-life (t_e) were longest for arm 4, at 55.7 hours and 41.1 hours, respectively.

Phase 1 hematologic AEs and DLT

¹⁷⁷Lu-lilotomab satetraxetan dose was escalated as far as 20 MBq/kg in arm 1 (with 40 mg lilotomab predosing) before being deescalated to 15 MBq/kg. DLTs during dose escalation for all study arms are shown in Table 2; arms 2 and 3 were closed due to occurrence of hematologic AEs, although only 1 patient in arm 3 experienced a DLT. For arm 4 with elevated lilotomab predosing (100 mg/m²), there was 1 DLT with 20 MBq/kg ¹⁷⁷Lu-lilotomab satetraxetan. In conclusion, the biodistribution, tumor targeting, and hematologic toxicity profile of ¹⁷⁷Lu-lilotomab satetraxetan was improved with lilotomab predosing compared with rituximab predosing or no predosing.

Mean neutrophil and platelet counts after dosing with ¹⁷⁷Lu-lilotomab satetraxetan in phase 1 are shown in Figure 3. Nadirs for neutrophils (Figure 3A) and platelets (Figure 3B) with 15 MBq/kg ¹⁷⁷Lu-lilotomab satetraxetan but no predose lilotomab (arms 2 and 3) were similar to those with 20 MBq/kg ¹⁷⁷Lu-lilotomab satetraxetan in arm 1, and characteristic of grade 4 neutropenia and thrombocytopenia. Results for 15 MBq/kg in arm 1 and 20 MBq/kg in arm 4 were similar, for both platelets and absolute neutrophil counts. In all study arms, blood cell counts began to decrease from 2 weeks (platelets) and 4 weeks (neutrophils) after dosing, with recovery over the 4 to 5 weeks following the nadir.

Figure 2. SPECT, dosimetry, and PK comparison by study arm.



Two regimens were selected for dose expansion in phase 2a: lilotomab 40 mg + ¹⁷⁷Lu-lilotomab satetraxetan 15 MBq/kg (arm 1) and lilotomab 100 mg/m² + ¹⁷⁷Lu-lilotomab satetraxetan 20 MBq/kg (arm 4).

Phase 2a/overall AEs

Confirmatory safety data from the interim analysis of the first 15 patients to receive 15 MBq/kg ¹⁷⁷Lu-lilotomab satetraxetan in arm 1 supported continuation of this regimen, and the general safety profile was consistent between phase 1 and phase 2a across both arms 1 and 4.

Grade 3 and 4 study drug-related treatment-emergent AEs occurring in ≥2 patients are shown in supplemental Table 1 and, as expected, primarily consisted of hematologic events. Non-hematologic events were predominantly of grade 1 or 2, with the most frequent being nausea (15.8%), upper respiratory tract infections (10.5%), and urinary tract infections (10.5%). The median duration of grade ≥3 neutropenia and thrombocytopenia was 14.0 days each. Although the overall frequencies of grade ≥3 neutropenia and thrombocytopenia were 31.6% and 26.3%,

respectively, these were predominantly grade 3 events; clinically relevant grade 4 neutropenia and thrombocytopenia occurred in 11% and 8% of patients, respectively. Overall, 5 patients received platelet transfusions (2 for active bleeding and 3 as prophylaxis), and 3 patients received granulocyte colony-stimulating factor.

Fourteen patients experienced serious AEs; serious AEs in ≥2 patients comprised thrombocytopenia, atrial fibrillation, lymphoma progression, and sepsis (all n = 2), and there were no reports of febrile neutropenia. Thrombocytopenia events were considered related to study treatment. Both incidences of atrial fibrillation were of grade 2 and resolved within 24 hours with oral therapy (1 occurred 9 months after study drug administration). These events were considered possibly related to study treatment.

Two patients experienced AEs of special interest. One case of chronic myelomonocytic leukemia occurred 24 months after ¹⁷⁷Lu-lilotomab satetraxetan administration (and 18 months after 6 courses of bendamustine-rituximab) and was fatal; this event was considered possibly related to study treatment. One case of prostate cancer diagnosed 6 months after ¹⁷⁷Lu-lilotomab satetraxetan was not considered to be related.

Table 2. DLTs in phase 1 dose escalation

Arm	Predose	¹⁷⁷ Lu-lilotomab dose (MBq/kg)	DLT	Disease
Index patient	Rituximab 250 mg/m ²	10	Thrombocytopenia	FL
1	Lilotomab 40 mg	10	—	FL
		10	—	FL
		10	—	FL
		15	—	FL
		15	—	FL
		15	—	FL
		15	Thrombocytopenia, neutropenia	FL
		15	—	FL
		15	Hyponatremia	FL
		20	Neutropenia	FL
		20	Epistaxis	MCL
		20	Neutropenia	FL
2	No predose	10	—	FL
		15	Thrombocytopenia, neutropenia	FL
		15	Thrombocytopenia	FL
3	Rituximab 375 mg/m ²	15	Thrombocytopenia, neutropenia	MZL
		15	—	FL
		15	—	MCL
4	Lilotomab 100 mg/m ²	15	—	FL
		15	—	FL
		15	—	FL
		20	—	FL
		20	—	FL
		20	Hematuria with platelet count $40 \times 10^9/L$	FL
		20	—	MCL
		20	—	FL
		20	—	FL
		20	—	FL
5	Lilotomab 60 mg/m ²	20	—	FL
		20	—	FL
		20	—	FL

Immunogenicity results

The development of a HAMA response after administration of lilotomab and ¹⁷⁷Lu-lilotomab satetraxetan was reported for 7 out of 74 subjects overall. Five of the observed responses were detected 1 month after treatment; 3 had resolved at the 3-month visit and 1 at the 6-month visit (data not available for one patient). Two additional immune responses were detected at 12-month follow-up visits. No reported side effects could be associated with the development of HAMA.

Treatment efficacy

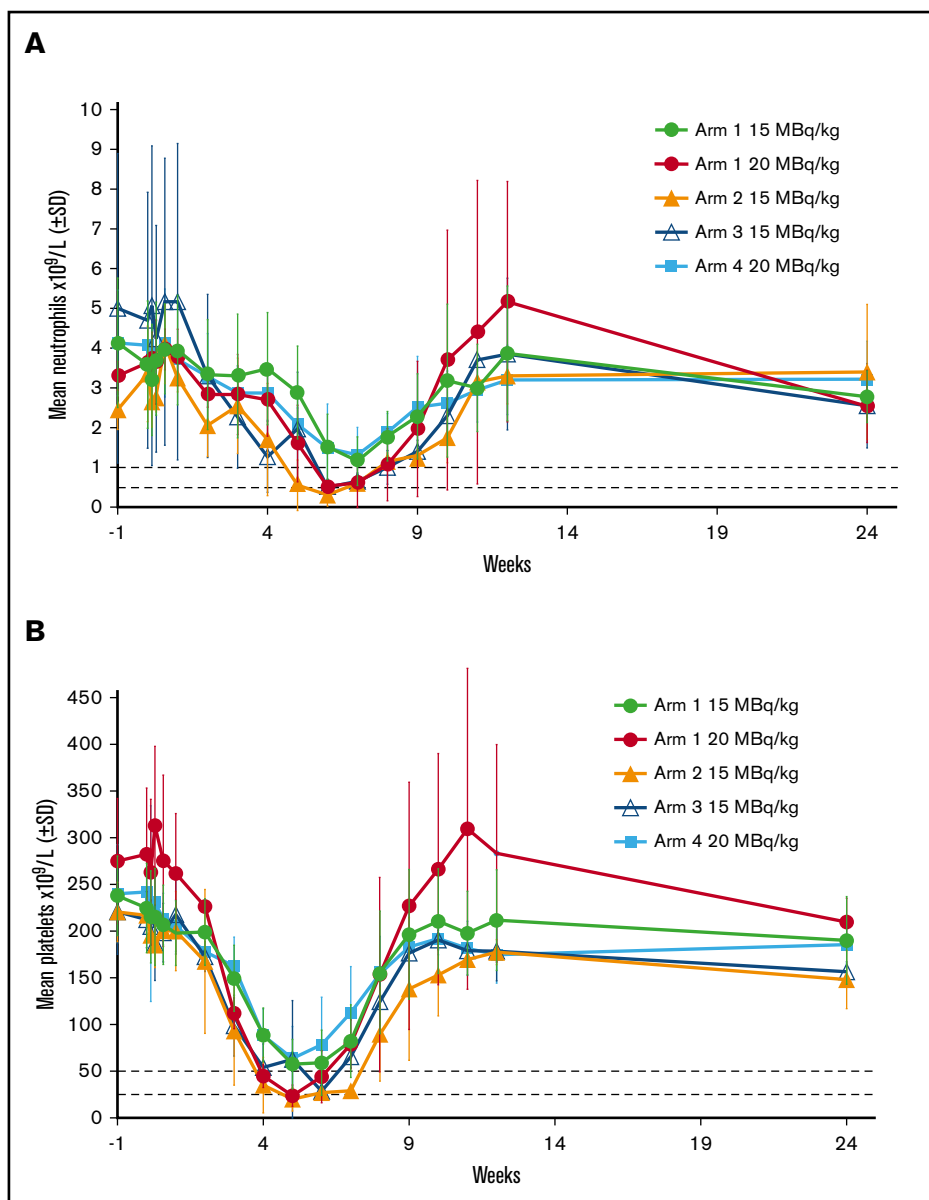
With a median follow-up of 24.5 months (range, 0.4-60.7 months), best ORR for all patients (N = 74) was 61% (n = 45; 22 CR [30%], 23 PR [31%], and 14 SD [19%]). For patients with FL (n = 57), ORR was 65% (n = 37; 17 CR [30%], 20 PR [35%], and 10 SD [18%]). Notably, nearly half of the clinical responses observed were CR in both the overall and FL populations. Patients with bulky

disease (>6 cm; n = 27) had an ORR of 56%. For FL with ≥2 prior therapies (n = 37 evaluable), the ORR was 70% and the CRR 32%.

Of the total of 74 patients, 31 were classified as rituximab-refractory. Rituximab-refractoriness was defined as no response to single-agent rituximab (n = 6) or a rituximab-containing regimen (n = 8) or relapse/progression within 6 months (n = 3) or relapse/progression during rituximab maintenance (n = 14). For rituximab-refractory FL (n = 26), the ORR was 58%, with a CRR of 19%. For rituximab-refractory FL with ≥2 prior therapies (n = 21), the ORR was 67% and the CRR was 24%.

Response rates were similar in patients enrolled to phase 2a (n = 42), who received ¹⁷⁷Lu-lilotomab satetraxetan 15 MBq/kg per arm 1 or 20 MBq/kg per arm 4; ORR was 64.3% (n = 27; 13 CR [31%], 14 PR [33%], and 7 SD [17%]). In rituximab-refractory patients (n = 19), the ORR was 53%, with a CRR of 21%. In patients with rituximab-refractory FL (n = 15), the ORR was 67%

Figure 3. Effect of different phase 1 regimens on mean neutrophil and platelet counts. Horizontal dotted lines show cut-offs for grade 3 and 4 neutropenia (A) and thrombocytopenia (B).



and the CRR was 27%. The majority of patients experienced a reduction in tumor size (Figure 4).

Figure 5A shows DoR for all patients with PR or CR ($n = 45$) and those with CR only ($n = 22$). With a median follow-up time for responders of 30.0 months (range, 12.0-60.7 months), median DoR was 13.6 months (95% confidence interval [CI], 6.1, 20.5) for all responders and 32.0 months (95% CI, 14.5, 46.0) in patients achieving a CR. PFS is shown in Figure 5B. Median PFS was 8.8 months (95% CI, 6.0, 12.0) overall ($n = 74$) and 9.0 months (95% CI, 6.0, 15.7) in patients with FL ($n = 57$). Median PFS in patients without documented disease progression or death was 9.2 months overall (95% CI, 6.2, 17.7; $n = 74$) and 9.1 months in patients with FL (95% CI, 6.0, 17.3; $n = 57$).

Discussion

This study evaluated the safety and recommended ^{177}Lu -lilotomab satetraxetan/lilotomab regimen for further phase 2 evaluation.

The single-administration regimen was administered safely with manageable toxicity. Hematologic AEs correlated well with both dosimetry and ^{177}Lu -lilotomab satetraxetan PK data for the different study arms in phase 1 and were managed using standard therapy.

To optimize the delivery schedule for this novel RIT compound, we rigorously tested different regimens in the phase 1 part of this study and monitored PK, dose distribution, hematologic toxicity, and safety. Predosing with lilotomab was essential to mitigate hematologic toxicity; PK and dosimetry data showed reduced clearance and volume of distribution with lilotomab predosing, resulting in greater ^{177}Lu -lilotomab satetraxetan targeting to tumor tissue. The nadir for blood cell counts occurred 5 to 7 weeks after dosing, later than would be expected with chemotherapy or immunochemotherapy. Mean neutrophil and platelet counts for patients in arms 1 (15 MBq/kg) and 4 (20 MBq/kg) remained above cutoffs indicative of grade 3 neutropenia and thrombocytopenia, while for arms 2 and 3, and the 20 MBq/kg dose in arm 1, neutrophil and platelet nadirs

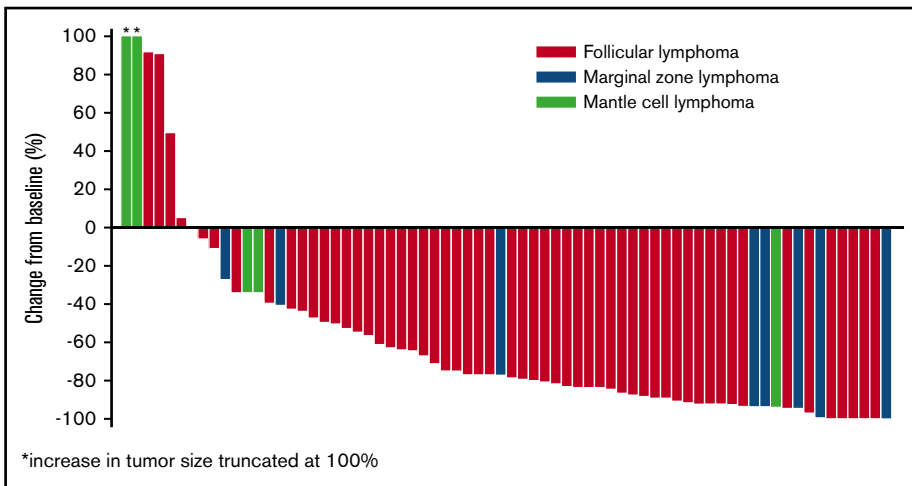


Figure 4. Best percentage change in tumor size from baseline for evaluable patients in phases 1 and 2a.

were near or below the levels defining grade 4 events. Correspondingly, grade 4 neutropenia and thrombocytopenia were relatively unusual in the phase 2a population, which received the arm 1 and 4 regimens.

One case of chronic myelomonocytic leukemia was observed in the study population occurring 24 months after ¹⁷⁷Lu-lilotomab satetraxetan administration. The cumulative incidence of myelodysplastic syndrome/secondary leukemia reported for patients enrolled

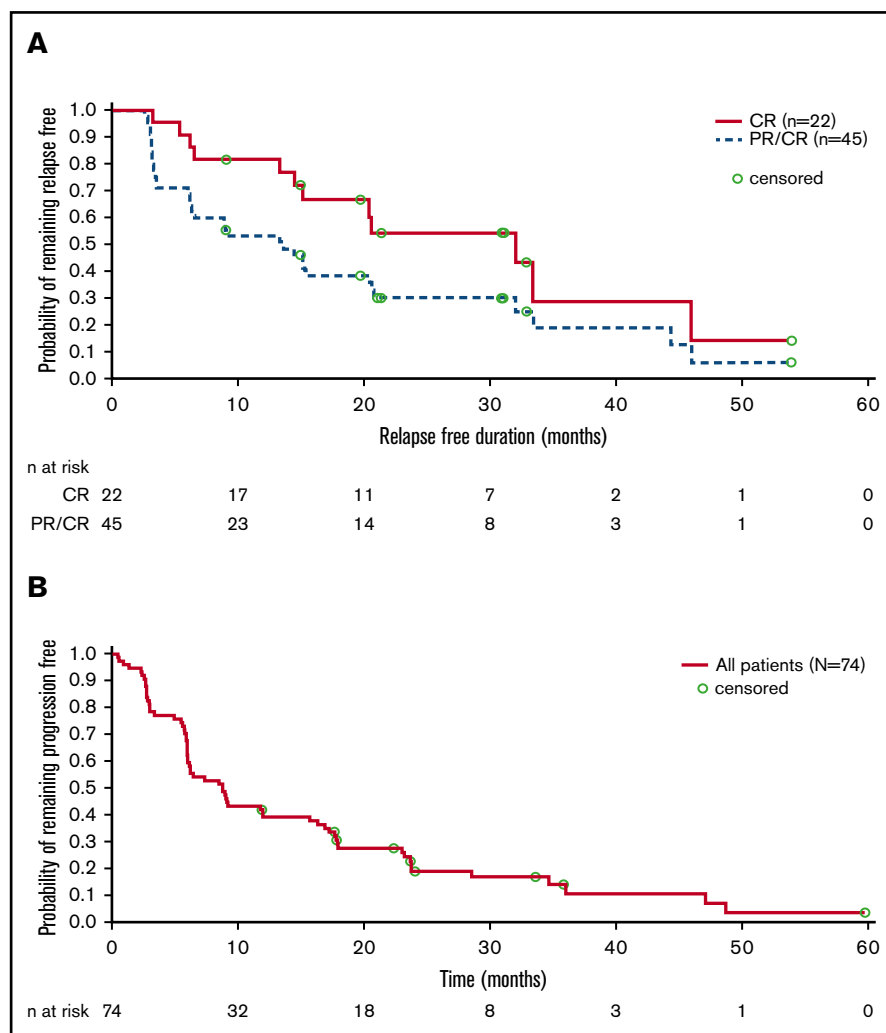


Figure 5. Duration of response and progression-free survival. (A) Kaplan-Meier estimate of DoR. (B) Kaplan-Meier estimate of PFS.

in Zevalin and Bexxar clinical trials is 5% to 10%.²⁹ Since the majority of patients who received RIT had also received cytotoxic therapies, it is difficult to determine which of these treatments has primarily contributed to the occurrence of myelodysplastic syndrome and acute myeloid leukemia. However, continuous focus needs to be kept on this serious toxicity in patients treated with RIT, including ¹⁷⁷Lu-lilotomab satetraxetan.

The ORR to ¹⁷⁷Lu-lilotomab satetraxetan (61% in all patients and 65% in FL), particularly the high CRR (30% overall and in FL), were impressive in a cohort of heavily pretreated patients with recurrent indolent NHL, especially for those with FL histology. The importance of achieving a CR is clear given that median DoR for patients with CR (32 months) was considerably longer than the overall median DoR (13.6 months).

The ORR and CRR with ¹⁷⁷Lu-lilotomab satetraxetan in the present study compare well with data for ⁹⁰Y-ibritumomab tiuxetan RIT. In rituximab-naïve patients with relapsed/refractory NHL, an ORR of 80% and CRR of 30% were reported,¹¹ with an ORR of 74% and a CRR of 15% reported in a similar study in patients with rituximab-refractory FL.¹² In these studies, although the ORR was maintained between populations, the reduction in CRR in rituximab-refractory disease was particularly noticeable, as reflected in a median DoR of 14.2 months in rituximab-naïve patients and an estimated time to progression of 8.7 months in rituximab-refractory patients. Importantly, a combined analysis of 211 patients from 4 trials of ⁹⁰Y-ibritumomab tiuxetan in relapsed/refractory NHL demonstrated long-term responses, with median DoR of 29 months in patients with CR or unconfirmed CR and a median time to progression of ≥ 12 months in 37% of patients.³⁰ In this context, the median DoR of 13.6 months in the present study, with a mixed population of rituximab sensitivity, is noteworthy.

¹⁷⁷Lu-lilotomab satetraxetan was granted Fast Track designation for relapsed/refractory FL by the US Food and Drug Administration in June 2018 based on efficacy and safety data from the present study³¹ and has since received a similar designation for relapsed/refractory marginal zone lymphoma.³² Alternative postchemotherapy options for patients with relapsed/rituximab-refractory NHL are currently limited. PI3K inhibitors have been associated with an ORR of 40% to 60%³³ but with lower rates of CR ($\leq 20\%$) than reported in the current study and significant nonhematologic toxicity. More recently, an ORR of 59% was shown with the pan-PI3K inhibitor copanlisib in relapsed indolent NHL and CRR of 12% to 14%.³⁴ Similarly, overall responses to EZH2 inhibition in 76 heavily pretreated patients with FL have been promising (35%), but with low CRR (6%); in the cohort of 22 patients with an activating EZH2 mutation, ORR and CRR were 82% and 5%, respectively.³⁵ The BTK inhibitor ibrutinib has also been investigated in relapsed/refractory FL with an ORR of 21% and CRR of 11%.³⁶ These data highlight that deep responses with postchemotherapy agents are uncommon. Consequently, the comparatively high CRR to ¹⁷⁷Lu-lilotomab satetraxetan and the high CRR and ORR reported for the combination of obinutuzumab and lenalidomide⁷ are potentially very important for this difficult-to-treat population. ¹⁷⁷Lu-lilotomab satetraxetan therefore represents an attractive, well-tolerated alternative for a patient population that needs additional options. Furthermore, targeted RIT such as ¹⁷⁷Lu-lilotomab satetraxetan would be an interesting partner in combinations with small-molecule inhibitors of EZH2, PI3K, BTK, and others for future

development. ¹⁷⁷Lu-lilotomab satetraxetan has been tested in combination with a panel of 384 small-molecule inhibitors, and cell-cycle kinase, topoisomerase, and histone deacetylase inhibitors emerged as potential combination partners.³⁷ The cell-cycle kinase inhibitors JNJ-7706621, MK-1775, and PD-166285 increased the *in vitro* and *in vivo* therapeutic effect of ¹⁷⁷Lu-lilotomab satetraxetan.^{37,38}

RIT presents the possibility of long-term efficacy and a vital alternative option for patients with relapsed or refractory disease. ¹⁷⁷Lu-lilotomab satetraxetan differs from prior RIT by using a different therapeutic isotope and, importantly, targeting CD37 rather than CD20. It is well placed to meet 2 current clinical needs: potential long-term efficacy in patients with recurrent disease and limited treatment options (in particular for patients refractory to CD20-directed therapy) and a highly convenient treatment with manageable and predictable toxicity. Single-dose treatment offers a meaningful improvement in quality of life for patients, especially older patients, for whom frequent hospital or clinic visits are challenging and who may have already experienced several lengthy cyclical cytotoxic regimens. The long half-life of ¹⁷⁷Lu-lilotomab satetraxetan compared with ⁹⁰Y-ibritumomab tiuxetan also simplifies logistical considerations, as this compound is prepared off site and delivered ready to use, unlike ⁹⁰Y-ibritumomab, which must be coupled on site.

Two dose regimens were selected for further study: a lilotomab pre-dose of 40 mg plus 15 MBq/kg ¹⁷⁷Lu-lilotomab satetraxetan and a lilotomab pre-dose of 100 mg/m² plus 20 MBq/kg ¹⁷⁷Lu-lilotomab satetraxetan. The global randomized phase 2b PARADIGME study is ongoing in patients with relapsed rituximab/anti-CD20 refractory FL who have received ≥ 2 prior therapies and will provide further data to inform the use of this novel drug.

In conclusion, ¹⁷⁷Lu-lilotomab satetraxetan was demonstrated to be a promising, ready-to-use, single-dose RIT in heavily pretreated patients with B-cell NHL with low bone marrow infiltration and was well tolerated, with reversible uncomplicated grade 3/4 neutropenia and thrombocytopenia as the most common AEs, with limited nonhematologic toxicity. Encouraging responses, DoR, and PFS were observed in phases 1 and 2a. In particular, the preliminary efficacy observed in rituximab-refractory patients with FL warrants further investigation. RIT with ¹⁷⁷Lu-lilotomab satetraxetan could represent an effective and convenient alternative treatment for patients with relapsed/refractory indolent NHL, a population that urgently needs effective and tolerable therapy options.

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Authorship

Contribution: A.K. and T.I. contributed to study conception and design, data collection and analysis, and manuscript preparation and review; H.H. contributed to study design, data collection, and manuscript review; C.S. and J.B. contributed to data collection and analysis and manuscript review; N.B., S.S., U.M., A.L., N.O., M. Beasley, W.J., U.-M.F., M.K., M. Bayne, and A.O. contributed to data collection, manuscript review; J.D. contributed to study conception and design, data collection and analysis (PK, immunogenicity, and dosimetry), and manuscript preparation and review; L.R. contributed to manuscript preparation and review; and V.P. contributed to bio-analytics data analysis and collection (PK and immunogenicity) and manuscript preparation and review.

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References

1. Matasar MJ, Luminari S, Barr PM, et al. Follicular lymphoma: recent and emerging therapies, treatment strategies, and remaining unmet needs. *Oncologist*. 2019;24(11):e1236-e1250.
2. McLaughlin P, Grillo-López AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. *J Clin Oncol*. 1998;16(8):2825-2833.
3. Mohammed R, Milne A, Kayani K, Ojha U. How the discovery of rituximab impacted the treatment of B-cell non-Hodgkin's lymphomas. *J Blood Med*. 2019;10:71-84.
4. Casulo C, Byrtek M, Dawson KL, et al. Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: an analysis from the National Lymphocare Study. *J Clin Oncol*. 2015;33(23):2516-2522.
5. Sehn LH, Chua N, Mayer J, et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. *Lancet Oncol*. 2016;17(8):1081-1093.
6. Food and Drug Administration. Gazyva prescribing information revised 3/2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125486s025lbl.pdf. Accessed April 2020.
7. Fowler NH, Nastoupil LJ, Chin C, et al. A phase I/II study of lenalidomide plus obinutuzumab in relapsed indolent lymphoma [abstract]. *Blood*. 2019;134(suppl 1):348. Abstract 623.
8. Rodgers TD, Reagan PM. Targeting the B-cell receptor pathway: a review of current and future therapies for non-Hodgkin's lymphoma. *Expert Opin Emerg Drugs*. 2018;23(2):111-122.
9. Valla K, Flowers CR, Koff JL. Targeting the B cell receptor pathway in non-Hodgkin lymphoma. *Expert Opin Investig Drugs*. 2018;27(6):513-522.
10. Kaminski MS, Zelenetz AD, Press OW, et al. Pivotal study of iodine I 131 tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. *J Clin Oncol*. 2001;19(19):3918-3928.
11. Witzig TE, Gordon LI, Cabanillas F, et al. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. *J Clin Oncol*. 2002;20(10):2453-2463.
12. Witzig TE, Flinn IW, Gordon LI, et al. Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. *J Clin Oncol*. 2002;20(15):3262-3269.
13. Link MP, Bindl J, Meeker TC, et al. A unique antigen on mature B cells defined by a monoclonal antibody. *J Immunol*. 1986;137(9):3013-3018.
14. Schwartz-Albiez R, Dörken B, Hofmann W, Moldenhauer G. The B cell-associated CD37 antigen (gp40-52). Structure and subcellular expression of an extensively glycosylated glycoprotein. *J Immunol*. 1988;140(3):905-914.
15. Dahle J, Repetto-Llamazares AHV, Mollatt CS, et al. Evaluating antigen targeting and anti-tumor activity of a new anti-CD37 radioimmunoconjugate against non-Hodgkin's lymphoma. *Anticancer Res*. 2013;33(1):85-95.
16. Repetto-Llamazares AH, Larsen RH, Patzke S, et al. Targeted cancer therapy with a novel anti-CD37 beta-particle emitting radioimmunoconjugate for treatment of non-Hodgkin lymphoma. *PLoS One*. 2015;10(6):e0128816.

17. Repetto-Llamazares AHV, Malenge MM, O'Shea A, et al. Combination of ^{177}Lu -lilotomab with rituximab significantly improves the therapeutic outcome in preclinical models of non-Hodgkin's lymphoma. *Eur J Haematol*. 2018;101(4):522-531.
18. Forrer F, Chen J, Fani M, et al. In vitro characterization of (^{177}Lu)Lu-radiolabelled chimeric anti-CD20 monoclonal antibody and a preliminary dosimetry study. *Eur J Nucl Med Mol Imaging*. 2009;36(9):1443-1452.
19. Sierra ML, Agazzi A, Bodei L, et al. Lymphocytic toxicity in patients after peptide-receptor radionuclide therapy (PRRT) with ^{177}Lu -DOTATATE and $^{90\text{Y}}$ -DOTATOC. *Cancer Biother Radiopharm*. 2009;24(6):659-665.
20. Claringbold PG, Brayshaw PA, Price RA, Turner JH. Phase II study of radiopeptide ^{177}Lu -octreotate and capecitabine therapy of progressive disseminated neuroendocrine tumours. *Eur J Nucl Med Mol Imaging*. 2011;38(2):302-311.
21. Kunikowska J, Królicki L, Hubalewska-Dydejczyk A, Mikołajczak R, Sowa-Staszczak A, Pawlak D. Clinical results of radionuclide therapy of neuroendocrine tumours with $^{90\text{Y}}$ -DOTATATE and tandem $^{90\text{Y}}$ / ^{177}Lu -DOTATATE: which is a better therapy option? *Eur J Nucl Med Mol Imaging*. 2011;38(10):1788-1797.
22. Forrer F, Oechslein-Oberholzer C, Campana B, et al. Radioimmunotherapy with ^{177}Lu -DOTA-rituximab: final results of a phase I/II Study in 31 patients with relapsing follicular, mantle cell, and other indolent B-cell lymphomas. *J Nucl Med*. 2013;54(7):1045-1052.
23. Blakkisrud J, Løndalen A, Martinsen AC, et al. Tumor-absorbed dose for non-Hodgkin lymphoma patients treated with the anti-CD37 antibody radionuclide conjugate ^{177}Lu -lilotomab satetraxetan. *J Nucl Med*. 2017;58(1):48-54.
24. Blakkisrud J, Løndalen A, Dahle J, et al. Red marrow-absorbed dose for non-Hodgkin lymphoma patients treated with ^{177}Lu -lilotomab satetraxetan, a novel anti-CD37 antibody-radionuclide conjugate. *J Nucl Med*. 2017;58(1):55-61.
25. Blakkisrud J, Holtedahl JE, Løndalen A, et al. Biodistribution and dosimetry results from a phase 1 trial of therapy with the antibody-radionuclide conjugate ^{177}Lu -lilotomab satetraxetan. *J Nucl Med*. 2018;59(4):704-710.
26. Stokke C, Blakkisrud J, Løndalen A, et al. Pre-dosing with lilotomab prior to therapy with ^{177}Lu -lilotomab satetraxetan significantly increases the ratio of tumor to red marrow absorbed dose in non-Hodgkin lymphoma patients. *Eur J Nucl Med Mol Imaging*. 2018;45(7):1233-1241.
27. Cheson BD, Pfistner B, Juweid ME, et al; International Harmonization Project on Lymphoma. Revised response criteria for malignant lymphoma. *J Clin Oncol*. 2007;25(5):579-586.
28. Cheson BD, Horning SJ, Coiffier B, et al; NCI Sponsored International Working Group. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. *J Clin Oncol*. 1999;17(4):1244.
29. Sachpekidis C, Jackson DB, Soldatos TG. Radioimmunotherapy in non-Hodgkin's lymphoma: Retrospective adverse event profiling of Zevalin and Bexxar. *Pharmaceuticals (Basel)*. 2019;12(4):E141.
30. Witzig TE, Molina A, Gordon LI, et al. Long-term responses in patients with recurring or refractory B-cell non-Hodgkin lymphoma treated with yttrium 90 ibritumomab tiuxetan. *Cancer*. 2007;109(9):1804-1810.
31. Nordic Nanovector. 2018. Regulatory designations. <https://www.nordicnanovector.com/node/324>. Accessed March 2020.
32. Nordic Nanovector. 2020. Press releases. <https://www.nordicnanovector.com/investors-and-media/press-releases?page=/en/pressreleases/nordic-nanovector%2527s-betalutin%2528r%2529-receives-fast-track-designation-from-us-fda-for-marginal-zone-lymphoma-1822545>. Accessed July 2020.
33. Batlevi CL, Younes A. Revival of PI3K inhibitors in non-Hodgkin's lymphoma. *Ann Oncol*. 2017;28(9):2047-2049.
34. Krause G, Hassenrück F, Hallek M. Copanlisib for treatment of B-cell malignancies: the development of a PI3K inhibitor with considerable differences to idelalisib. *Drug Des Devel Ther*. 2018;12:2577-2590.
35. Morschhauser F, Tilly H, Chaidos A, et al. Interim update from a phase 2 multicenter study of tazemetostat, an EZH2 inhibitor, in patients with relapsed or refractory (R/R) follicular lymphoma (FL) [oral presentation at EHA23 2018]. Abstract S100. https://library.ehaweb.org/eha/2018/stockholm/214434/gilles.salles.interim.update.from.a.phase.2.multicenter.study.of.tazemetostat.html?f=topic=1574*media=3%27. Accessed April 2020.
36. Gopal AK, Schuster SJ, Fowler NH, et al. Ibrutinib as treatment for patients with relapsed/refractory follicular lymphoma: Results from the open-label, multicenter, phase II DAWN study. *J Clin Oncol*. 2018;36(23):2405-2412.
37. Rødland GE, Melhus K, Generalov R, et al. The dual cell cycle kinase inhibitor JNJ-7706621 reverses resistance to CD37-targeted radioimmunotherapy in activated B cell like diffuse large B cell lymphoma cell lines. *Front Oncol*. 2019;9:1301.
38. Pichard A, Marcatili S, Karam J, et al. The therapeutic effectiveness of ^{177}Lu -lilotomab in B-cell non-Hodgkin lymphoma involves modulation of G2/M cell cycle arrest. *Leukemia*. 2020;34(5):1315-1328.