


Rituximab-PECC induction followed by ⁹⁰Y-ibritumomab tiuxetan consolidation in relapsed or refractory DLBCL patients who are ineligible for or have failed ASCT: results from a phase II HOVON study

Pieterella J. Lugtenburg,¹  Josee M. Zijlstra,² Jeanette K. Doorduijn,¹ Lara H. Böhmer,³ Mels Hoogendoorn,⁴ Henriette W. Berenschot,⁵ Aart Beeker,⁶ Nicole C. van der Burg-de Graauw,⁷ Harry C. Schouten,⁸ Yavuz M. Bilgin,⁹  Marie-Jose Kersten,¹⁰ Harry R. Koene,¹¹ Alexandra H. E. Herbers,¹² Daphne de Jong,¹³ Nathalie Hijmering,¹³ King H. Lam,¹⁴ Dana Chițu,¹⁵ Rolf E. Brouwer,¹⁶ Gustaaf W. van Imhoff¹⁷ and for the Dutch HOVON group

¹Department of Haematology, Erasmus MC Cancer Institute, Rotterdam, ²Department of Haematology, Amsterdam University Medical Centre VUmc, Amsterdam, The Netherlands, ³Department of Haematology, Haga Teaching Hospital, The Hague, ⁴Department of Internal Medicine, Medical Centre Leeuwarden, Leeuwarden, ⁵Department of Internal Medicine, Albert Schweitzer Hospital, Dordrecht, The Netherlands, ⁶Department of Internal Medicine, Spaarne Gasthuis, Hoofddorp, ⁷Department of Internal Medicine, Bravis Hospital, Roosendaal, ⁸Department of Haematology, Maastricht University Medical Centre, Maastricht, ⁹Department of Internal Medicine, Admiraal de Ruyter Hospital, Goes, ¹⁰Department of Haematology, Amsterdam University Medical Centre AMC, University of Amsterdam, Amsterdam, The Netherlands, ¹¹Department of Internal Medicine, St Antonius Hospital, Nieuwegein, ¹²Department of Haematology and Medical Oncology, Jeroen Bosch Hospital, Den Bosch, ¹³HOVON Pathology Facility and Biobank (HOP), Department of Pathology, Amsterdam University Medical Centre, Amsterdam, ¹⁴Department of Pathology, Erasmus MC, Rotterdam, The Netherlands,

Summary

Patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) after, or ineligible for, autologous stem cell transplantation (ASCT) have a dismal prognosis. This phase II study evaluated treatment with R-PECC (rituximab, prednisolone, etoposide, chlorambucil, lomustine), every 28 days for 4 cycles in 62 patients, followed by radio-immunotherapy consolidation with ⁹⁰Y-ibritumomab tiuxetan in responsive patients. Primary endpoints were failure-free survival (FFS) and incidence of grade ≥ 3 adverse events from start of ⁹⁰Y-ibritumomab tiuxetan. The overall response rate after R-PECC was 50%. Twenty-nine of 31 responsive patients proceeded to ⁹⁰Y-ibritumomab tiuxetan. Five out of 15 partial remission patients converted to complete remission after ⁹⁰Y-ibritumomab tiuxetan. One-year FFS and overall survival (OS) from start of ⁹⁰Y-ibritumomab tiuxetan was 52% (95% confidence interval [CI], 33–68%) and 62% (95% CI, 42–77%), respectively. One-year FFS and OS from start of R-PECC was 28% (95% CI, 17–39%) and 49% (95% CI, 36–61%), respectively. Toxicities of R-PECC and ⁹⁰Y-ibritumomab tiuxetan were mainly haematological. In conclusion, for relapsed DLBCL patients the largely oral R-PECC regimen achieves promising response rates, combined with an acceptable safety profile. Consolidation with ⁹⁰Y-ibritumomab tiuxetan resulted in long-term response durations in approximately one third of the patients that received it.

Keywords: diffuse large B-cell lymphoma, relapse, ⁹⁰Y-ibritumomab tiuxetan, consolidation, PECC.

¹⁵HOVON Data Centre, Department of Haematology, Erasmus MC Cancer Institute, Rotterdam, ¹⁶Department of Haematology, Reinier de Graaf Hospital, Delft and ¹⁷Department of Haematology, University Medical Centre Groningen, Groningen, The Netherlands

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Correspondence: Dr Pieternella Johanna Lugtenburg, Department of Haematology, Erasmus MC Cancer Institute, Wytemaweg 80, 3015 CN, Rotterdam, The Netherlands.
E-mail: p.lugtenburg@erasmusmc.nl

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Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma (NHL) in western countries, and the majority of diagnosed patients are over 65 years of age. The CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy regimen has been the mainstay of therapy since its development in the last century (McKelvey *et al*, 1976). Several randomized trials comparing CHOP with rituximab plus CHOP (R-CHOP) demonstrated that the addition of rituximab to CHOP improved cure rates by 10–15% (Coiffier *et al*, 2002; Pfreundschuh *et al*, 2008, 2011). However, 35–40% of patients still have refractory disease or relapse (Coiffier *et al*, 2002; Pfreundschuh *et al*, 2008; Sehn & Gascoyne, 2015). High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) is the standard salvage treatment for transplant-eligible patients. However, the outcome remains poor with a two-year progression-free survival (PFS) of only 24% (Van Imhoff *et al*, 2017). Elderly patients, or those with co-morbidities precluding ASCT are generally treated with palliative intent and have a dismal outcome (Sarkozy & Sehn, 2018). Thus, the development of tolerable and effective salvage strategies without ASCT remains an important objective for this patient group.

Radioimmunotherapy (RIT) was introduced as a potentially effective treatment for NHL, making use of the high radiosensitivity of lymphoid malignancies. ⁹⁰Y-ibritumomab is a murine monoclonal antibody to CD20 and conjugated to the metal chelator tiuxetan for retention of the beta emitter

⁹⁰Y for therapy. Single dose ⁹⁰Y-ibritumomab tiuxetan demonstrated responses in patients with relapsed or refractory DLBCL, although of relatively short duration (Morschhauser *et al*, 2007). The main toxicity of ⁹⁰Y-ibritumomab tiuxetan is myelosuppression, typically lasting several weeks, with gradual recovery over the ensuing weeks (Morschhauser *et al*, 2007).

The rationale for ⁹⁰Y-ibritumomab tiuxetan as a consolidation therapy comes from its proven efficacy in DLBCL and its relatively moderate toxicity profile (Zinzani *et al*, 2008, 2010; Witzig *et al*, 2015). Several phase 2 studies investigated the role of ⁹⁰Y-ibritumomab tiuxetan consolidation following (R)-CHOP in newly diagnosed patients with DLBCL. ⁹⁰Y-ibritumomab tiuxetan improved response rates, by converting partial remission (PR) to complete remission (CR) in a substantial percentage of patients. In addition, encouraging PFS rates (2-year PFS 75–92%) and overall survival (OS) rates (2-year OS 86–96%) were reported (Zinzani *et al*, 2008, 2010; Witzig *et al*, 2015).

In the Netherlands, the almost completely oral R-PECC combination chemotherapy (rituximab, prednisolone, etoposide, chlorambucil, lomustine), is generally used as the preferred treatment option in relapsed and refractory DLBCL patients who are not eligible for ASCT. Its use started when the experience with PECC in a small cohort of 15 extensively pre-treated patients with advanced Hodgkin lymphoma was published, demonstrating an overall response rate (ORR) of

86% and haematological toxicity as the major side effect (Lennard *et al*, 1990). Our study is the first report regarding the efficacy and toxicity of R-PECC in relapsed/refractory DLBCL.

Here we report the results of a prospective multi-centre phase II study in relapsed/refractory DLBCL patients, evaluating ⁹⁰Y-ibritumomab tiuxetan consolidation in R-PECC responsive disease.

Materials and methods

Patient eligibility

Patients older than 17 years of age with biopsy-proven CD20-positive DLBCL or follicular lymphoma grade 3b, were eligible if they had a first or second relapse or refractory disease after ASCT or were not eligible for ASCT. Refractory disease was defined as no response or PR according to a computed tomography (CT) scan. Patients in PR were only eligible in case of positive fluorodeoxyglucose positron emission tomography (FDG-PET) scan or biopsy. Patients were included according to the local pathology diagnosis. Central review was performed as part of the quality assessment (HOVON Pathology Facility and Biobank). Eligibility criteria included World Health Organisation performance status of 0–2, measurable disease on CT scan, an absolute neutrophil count (ANC) $>1.5 \times 10^9/l$ and platelet count $>100 \times 10^9/l$, unless caused by bone marrow infiltration with lymphoma.

Exclusion criteria included: transformed indolent lymphoma, central nervous system lymphoma, prior ASCT within 12 months of study entry, prior radiotherapy to more than 25% of active bone marrow, concurrent severe and/or uncontrolled medical disease.

Pre-treatment staging comprised clinical examination, CT scanning of neck, thorax, abdomen and pelvis and bone marrow biopsy. A baseline FDG-PET scan was optional.

The study was conducted in accordance with the ethical guidelines mandated by the Declaration of Helsinki and approved by all relevant institutional review boards or ethics committees. Written informed consent was obtained from all participants.

Treatment protocol

Patients were treated with R-PECC every 28 days for two cycles. Rituximab 375 mg/m^2 was administered intravenous (i.v.) on day 1, lomustine 80 mg/m^2 was given orally on day 1, prednisolone 40 mg/m^2 , etoposide 100 mg/m^2 and chlorambucil 8 mg/m^2 were given orally daily on day 1–5 of each cycle. The first cycle was administered at full dose, irrespective of blood cell counts. Subsequent dose reductions for haematological toxicity were specified in the protocol. Haematological growth factors were allowed at the discretion of each individual investigator to prevent neutropenia.

Patients who achieved at least stable disease after two cycles of R-PECC proceeded to receive another two cycles. Patients in CR or PR after four cycles were eligible for consolidation treatment with ⁹⁰Y-ibritumomab tiuxetan, if the ANC was $>1.5 \times 10^9/l$, the platelet count was $>100 \times 10^9/l$ and bone marrow infiltration with lymphoma did not exceed 25%. Six to 12 weeks after start of the fourth R-PECC cycle, eligible patients were treated with ⁹⁰Y-ibritumomab tiuxetan. The ⁹⁰Y-ibritumomab tiuxetan treatment consisted of rituximab 250 mg/m^2 i.v. on day 1 followed by rituximab 250 mg/m^2 i.v. one week later, immediately followed by a single dose of ⁹⁰Y-ibritumomab tiuxetan i.v. (Zevalin[®], provided by Spectrum Pharmaceuticals, Henderson, NV, USA and Bayer Schering Pharma AG, Berlin, Germany). ⁹⁰Y-ibritumomab tiuxetan was given at a dose of 14.8 MBq/kg in patients with no prior ASCT and a platelet count of $\geq 150 \times 10^9/l$ and 11.1 MBq/kg in patients with a prior ASCT or platelet counts between 100 and $149 \times 10^9/l$. In all cases the maximum total dose did not exceed 1184 MBq .

Response and toxicity

All patients underwent restaging with CT scans after completion of the second R-PECC cycle and with FDG-PET and CT scans after completion of the fourth R-PECC cycle and 8 weeks after ⁹⁰Y-ibritumomab tiuxetan. Bone marrow biopsy was repeated only if positive at baseline. Response to therapy was assessed according to the revised Cheson criteria (Cheson *et al*, 2007). Safety and tolerability were assessed by monitoring the incidence, severity, and type of any adverse event. Toxicities were graded using National Cancer Institute Common Toxicity Criteria version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae_v3.pdf).

Statistical analysis

The primary objectives for this study were the feasibility and efficacy of consolidation treatment with ⁹⁰Y-ibritumomab tiuxetan of patients who achieved a PR or CR after R-PECC. The primary endpoint for feasibility was the incidence of grade ≥ 3 adverse events after treatment with ⁹⁰Y-ibritumomab tiuxetan, while the primary endpoint for efficacy was failure-free survival (FFS) measured from the start of ⁹⁰Y-ibritumomab tiuxetan. Secondary endpoints included incidence of adverse events of any grade after treatment with ⁹⁰Y-ibritumomab tiuxetan and after treatment with R-PECC; percentage of patients treated with R-PECC who proceeded to ⁹⁰Y-ibritumomab tiuxetan treatment; conversion to PET-negative CR after ⁹⁰Y-ibritumomab tiuxetan treatment of patients who were PET-positive before treatment (PR); OS measured from start of ⁹⁰Y-ibritumomab tiuxetan; FFS and OS measured from start of R-PECC; response rates to R-PECC and response duration. Patients were considered as failure for FFS by no response, defined as stable disease or

progressive disease (PD) after R-PECC, or at progression or relapse after response or at death, whichever came first.

The sample size was based solely on the primary endpoint for efficacy. The median FFS of patients in CR or PR after a rituximab-containing chemotherapy regimen for relapsed or refractory aggressive B-cell lymphoma who do not qualify for stem cell transplantation is about 6 months. We hypothesized that the ^{90}Y -ibritumomab tiuxetan consolidation treatment would increase this to 12 months, translating into a target number of 30 patients. It was expected that about 50% of the patients treated with R-PECC would achieve a PR or CR and be eligible for treatment with ^{90}Y -ibritumomab tiuxetan. Thus, the expected required number of patients to be entered in the study was 60.

Survival probabilities were calculated by the method of Kaplan and Meier. The median and probabilities at 1 year were calculated together with 95% confidence intervals (CI) and all p-values reported are 2-sided. The trial is registered on the Dutch Trial registry website (www.trialregister.nl), number NT1380.

Results

Patient characteristics

Between November 2008 and February 2012 64 patients were registered in this trial. Two patients were declared ineligible due to misdiagnosis (T-cell lymphoma, $n = 1$) and neutropenia ($n = 1$), and not included for further evaluation (Fig 1). Patient characteristics of the 62 eligible patients are summarized in Table I. Central pathology review could be performed in 56/62 (90%) patients, confirming CD20-positive DLBCL. The majority of patients were elderly and approximately 1 out of 4 patients were refractory to their last prior therapy. All patients had received CHOP chemotherapy as first line. Twelve patients (19%) did not receive rituximab in first line and 10 patients (16%) never received rituximab prior to study enrolment.

Efficacy

Detailed information about the participant progress through the study is listed in Fig 1. One patient refused further treatment after registration, therefore 61 patients started with R-PECC treatment. The median interval between cycles was 28 days (range 24–55). The relative median dose intensity was 95% for chlorambucil (range 20–255) and 94% for both lomustine (range 9–500); one patient had a protocol violation and received lomustine for 5 consecutive days and etoposide (range 20–255). Only 36 out of 62 (58%) eligible patients received all 4 cycles of R-PECC. The main reason for early treatment discontinuation on or after R-PECC was PD in 25 out of 62 patients (40%) (Fig 1). The ORR after R-PECC was 50%, with 14 of 62 (23%) patients achieving a CR and 17 of 62 (27%) patients achieving a PR (Table II).

The ORR of relapsed patients was 30 of 48 patients (63%) and this was significantly higher compared to the 7% ORR (1 of 14 patients) for patients who were refractory to their last prior treatment (63% vs. 7%, $P = 0.0001$). Of 48 patients with relapsed disease, 13 (27%) achieved a CR in contrast to 1 of 14 (7%) refractory patients.

Of 31 patients with responsive disease after $4 \times$ R-PECC, 29 proceeded to ^{90}Y -ibritumomab tiuxetan consolidation. Two patients failed to proceed, because of misinterpretation of response ($n = 1$) and premature death ($n = 1$). One patient received the reduced dose of ^{90}Y -ibritumomab tiuxetan because of persisting thrombocytopenia following R-PECC. Of the 15 patients in PR after $4 \times$ R-PECC, 5 converted to CR after ^{90}Y -ibritumomab tiuxetan. Those starting with CR remained without disease after completing consolidation treatment. The best ORR on protocol at the end of the entire treatment was 50% (31 of 62) with 31% CR (19 of 62) and 19% PR (12 of 62) (Table II). The ORR after R-PECC plus ^{90}Y -ibritumomab tiuxetan was 70% (7 of 10) in patients without prior rituximab exposure versus 46% (24 of 52) in patients with prior rituximab exposure. The median duration of response in the patients that reached a CR or PR after R-PECC was 9 months (range, 3–74 months). The median duration of response of the 5 patients who converted from a PR to a CR with ^{90}Y -ibritumomab tiuxetan was 19 months (range, 13–42 months). For the 14 patients who were already in CR after R-PECC and remained in CR the median duration of response was 42 months (range 3–88 months).

From all the patients that entered the study, 9 are still alive with a median follow-up of 59 months. Events have occurred in 23 out of 29 patients treated with ^{90}Y -ibritumomab tiuxetan, progression or relapse in 18 patients and deaths without progression in 5 patients. Causes of death in 4 of these 5 patients were cerebral vascular accident, pulmonary embolism, sepsis and unknown, all of which were unrelated to ^{90}Y -ibritumomab tiuxetan. The fifth patient experienced a prolonged pancytopenia after ^{90}Y -ibritumomab tiuxetan and died 3 months later due to a pneumonia. The primary endpoint of one-year FFS measured from the start of ^{90}Y -ibritumomab tiuxetan was 52% (95% CI, 33–68%) and two-year FFS post- ^{90}Y -ibritumomab tiuxetan was 38% (95% CI, 21–55%) (Fig 2A). The median FFS after ^{90}Y -ibritumomab tiuxetan consolidation was 15.1 months. An unplanned subgroup analysis showed that the one-year FFS from start of ^{90}Y -ibritumomab tiuxetan was 80% (95% CI, 41–95%) for the group that received no rituximab in first line versus 37% (95% CI, 17–57%) for the group of patients that had received rituximab at first line. We also analysed FFS from start of ^{90}Y -ibritumomab tiuxetan for the different International Prognostic Index (IPI) risk groups. One-year FFS was 71% (95% CI, 26–92%) for the low IPI risk group, 55% (95% CI, 23–78%) for the low-intermediate IPI risk group and 44% (95% CI, 14–72%) for the high-intermediate IPI risk group. There were only two patients in the high IPI

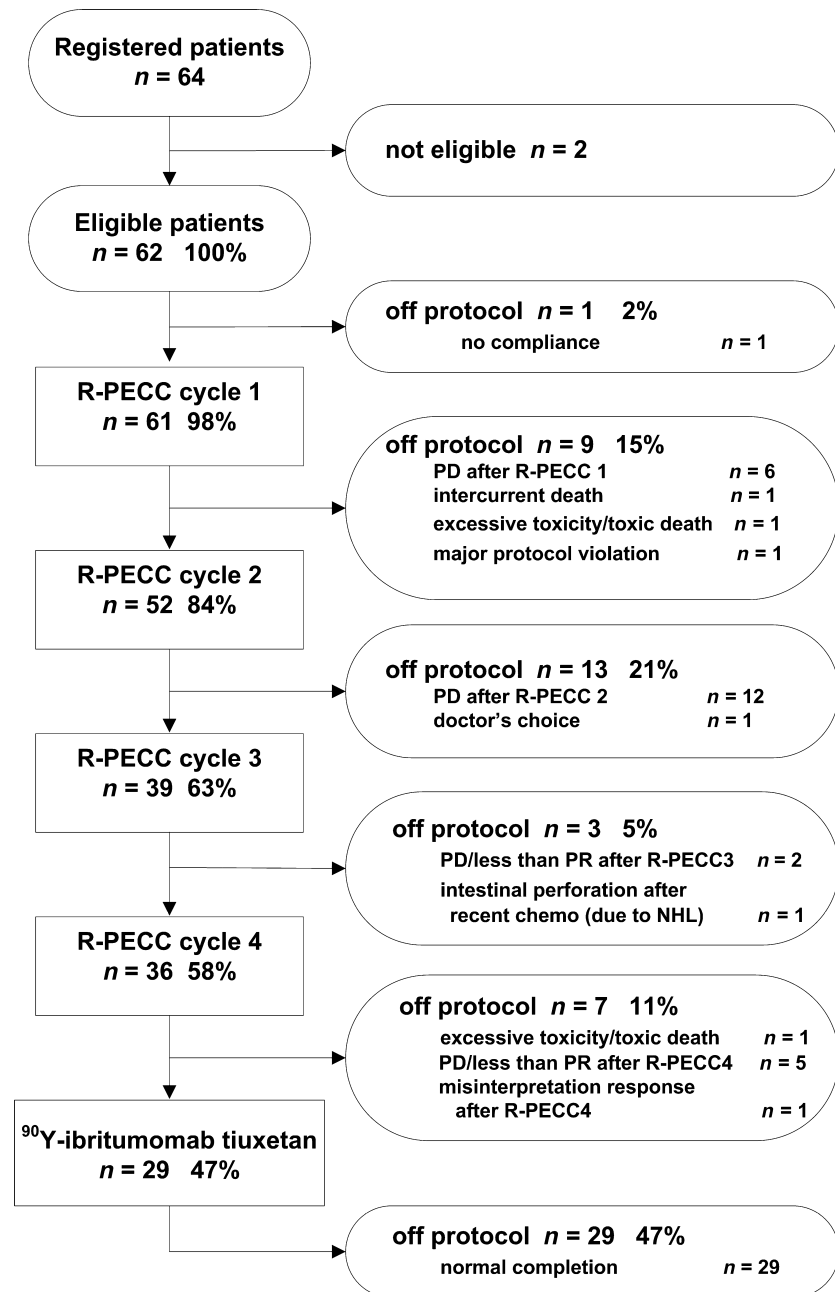


Fig 1. Participant progress through the study. NHL, non-Hodgkin lymphoma; PD, progressive disease; PR, partial remission; R-PECC, rituximab, prednisolone, etoposide, chlorambucil, lomustine.

risk group, who both failed within 2 months. We note that these subgroup analyses were exploratory only. The one-year and two-year OS from start of ⁹⁰Y-ibritumomab tiuxetan were 62% (95% CI, 42–77%) and 48% (95% CI, 29–65%), respectively (Fig 2B). One-year FFS and one-year OS from start of R-PECC were 28% (95% CI, 17–39%) and 49% (95% CI, 36–61%), respectively (Fig 2C,D).

Safety

The R-PECC regimen was well tolerated by most patients. Two toxic deaths occurred. The first patient died due to *Escherichia Coli* sepsis (with normal leucocyte counts) and

multi-organ failure on day 6 after the first R-PECC cycle. The second patient died after the fourth cycle of R-PECC, but the cause of death is unknown. The majority of adverse events comprised reversible haematological toxicities, including grade 3 or higher neutropenia in 15/61 (25%) patients and grade 3 or higher thrombocytopenia in 11/61 patients (18%). Three patients received platelet transfusions and 19 received red blood cell transfusions. Nine/61 (15%) patients developed febrile neutropenia and were hospitalized; an infectious agent could be demonstrated in 7 of these nine patients. Two other patients were hospitalized for proven infections without neutropenia.

Table I. Baseline patient demographics and clinical characteristics

	Total (N = 62)
Sex	
Male	41 (66%)
Female	21 (34%)
Age (years)	
Median (range)	70 (45-82)
≤65	15 (24%)
66–75	27 (44%)
>75	20 (32%)
WHO performance status	
0	25 (40%)
1	28 (45%)
2	8 (13%)
unknown	1 (2%)
Stage	
I	6 (10%)
II	18 (29%)
III	12 (19%)
IV	26 (42%)
B symptoms*	11 (18%)
LDH elevated >1 ULN	37 (60%)
Bulky disease (>10 cm)	4 (6%)
BM involvement	5 (8%)
IPI risk group at study entry	
Low	14 (23%)
Low-intermediate	22 (35%)
High-intermediate	20 (32%)
High	6 (10%)
Histology	
Central review	
DLBCL	55 (89%)
Follicular lymphoma grade 3b	1 (2%)
Not reviewed	
DLBCL	6 (9%)
Previous therapy	
(R)-CHOP only	42 (68%)
(R)-CHOP + R-DHAP/R-VIM	13 (21%)
(R)-CHOP + R-DHAP/R-VIM + ASCT	7 (11%)
No rituximab in first line	12 (19%)
First relapse	47 (76%)
Second relapse	1 (2%)
Refractory to prior therapy	14 (23%)

ASCT, autologous stem cell transplantation; BM, bone marrow; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; DHAP, dexamethasone, cytarabine, cisplatin; DLBCL, diffuse large B-cell lymphoma; IPI, International Prognostic Index; LDH, Lactate dehydrogenase; R, rituximab; ULN, upper limit of normal; VIM, etoposide, ifosfamide, methotrexate; WHO, World Health Organization. *fever, night sweats and >10% weight loss.

Adverse events after ^{90}Y -ibritumomab tiuxetan were also primarily haematological and transient. No infusion-related reactions were observed. Grade 3 or higher thrombocytopenia occurred in 16/29 patients (55%) and grade 4 neutropenia in 8 patients (28%). Eight patients received platelet transfusions and 6 patients received red blood cell

transfusions. Recovery was complete after a median of 7 weeks for grade 4 neutropenia and after a median of 8 weeks for grade 3 or higher thrombocytopenia. Prolonged severe neutropenia and/or thrombocytopenia was observed in 3 patients. Six (21%) patients were hospitalized during the neutropenic period for infections. Five patients developed a second malignancy: myelodysplastic syndrome ($n = 2$); non-small cell lung cancer ($n = 1$); neuroendocrine carcinoma of the liver ($n = 1$); squamous cell carcinoma skin ($n = 1$).

Discussion

This study evaluated treatment with four cycles of R-PECC followed by ^{90}Y -ibritumomab tiuxetan consolidation in responsive patients as salvage therapy in relapsed or refractory DLBCL patients who were not eligible for, or relapsed after, ASCT. There is currently no standard therapy for these patients and the outcome is extremely poor (Sarkozy & Sehn, 2018). Of the 62 eligible patients, 36 (58%) completed 4 cycles of R-PECC and 29 (47%) proceeded to ^{90}Y -ibritumomab tiuxetan consolidation. The one-year FFS measured from the start of ^{90}Y -ibritumomab tiuxetan consolidation was the primary endpoint for efficacy and was 52%. The median FFS after ^{90}Y -ibritumomab tiuxetan consolidation was 15.1 months. With this result, our hypothesis, that ^{90}Y -ibritumomab tiuxetan consolidation treatment could increase the median FFS from 6 to 12 months, was confirmed.

In the present study, ^{90}Y -ibritumomab tiuxetan consolidation improved the quality of response after 2nd or 3rd line salvage chemotherapy by converting PR to CR in one third of the PR cases. After a median follow-up of almost 5 years, progression or relapse has occurred in 18 of 29 patients who received the complete programme of 4 × R-PECC and ^{90}Y -ibritumomab tiuxetan consolidation and 5 patients died without signs of active DLBCL. This has resulted in a promising 3-year FFS of 34% in these patients. At 5 years post-consolidation therapy with ^{90}Y -ibritumomab tiuxetan, the FFS probability was 21% (95% CI, 8–37%), indicating that 1 out of 5 patients with relapsed DLBCL who have chemotherapy-responsive disease and receive RIT are still alive and free of disease 5 years after start of consolidation treatment. Thus, in a small but relevant part of the patients, consolidation therapy resulted in long term response duration. Although it is unlikely that this is the effect of only 4 cycles of R-PECC, it cannot be ruled out, because there are no long-term response data for R-PECC alone.

^{90}Y -ibritumomab tiuxetan consolidation was generally well tolerated, with significant neutropenia and thrombocytopenia being the most important side effects, easily handled with close haematological monitoring and prophylactic platelet support. No major bleeding events occurred. The observed acute toxicity was fully in line with previous experience with ^{90}Y -ibritumomab tiuxetan monotherapy in patients with relapsed and refractory DLBCL (Morschhauser *et al*, 2007). In the monotherapy study, 43% of patients experienced

Table II. Response to therapy

Response	After R-PECC n (%)	After R-PECC + ⁹⁰ Y-ibritumomab tiuxetan n (%)
Complete response	14 (23)	19 (31)
Partial response	17 (27)	12 (19)
Progressive disease	25 (40)	–

R-PECC, rituximab prednisolone, etoposide, chlorambucil, lomustine.

grade 3 or 4 haematological toxicity. Five of our patients (8%) developed a secondary malignancy. As the overall incidence of treatment-related myelodysplastic syndrome/acute myeloid leukaemia and solid tumours has been reported to

range from 0 to 12% with conventional dose chemotherapy or radiotherapy, the 8% observed in our trial is within this range (Stefoni *et al*, 2016).

The 4 cycles of R-PECC also showed a promising efficacy in this unfavourable population of relapsed DLBCL patients, with an ORR of 63% and 27% CR. In contrast, the efficacy of R-PECC was poor in refractory patients. These response rates are comparable to various alternative salvage strategies for relapsed/refractory DLBCL. For example, ORRs ranging from 43% to 59% and CR rates ranging from 34% to 37% have been reported in transplant-ineligible patients for the gemcitabine-oxaliplatin combination (López *et al*, 2008; Corazzelli *et al*, 2009; Mounier *et al*, 2013). Studies with rituximab-bendamustine in patients who were ineligible for, or have failed ASCT reported ORR of 45–62% and CR rates of 15–37% (Ohmachi *et al*, 2013; Vacirca *et al*, 2014).

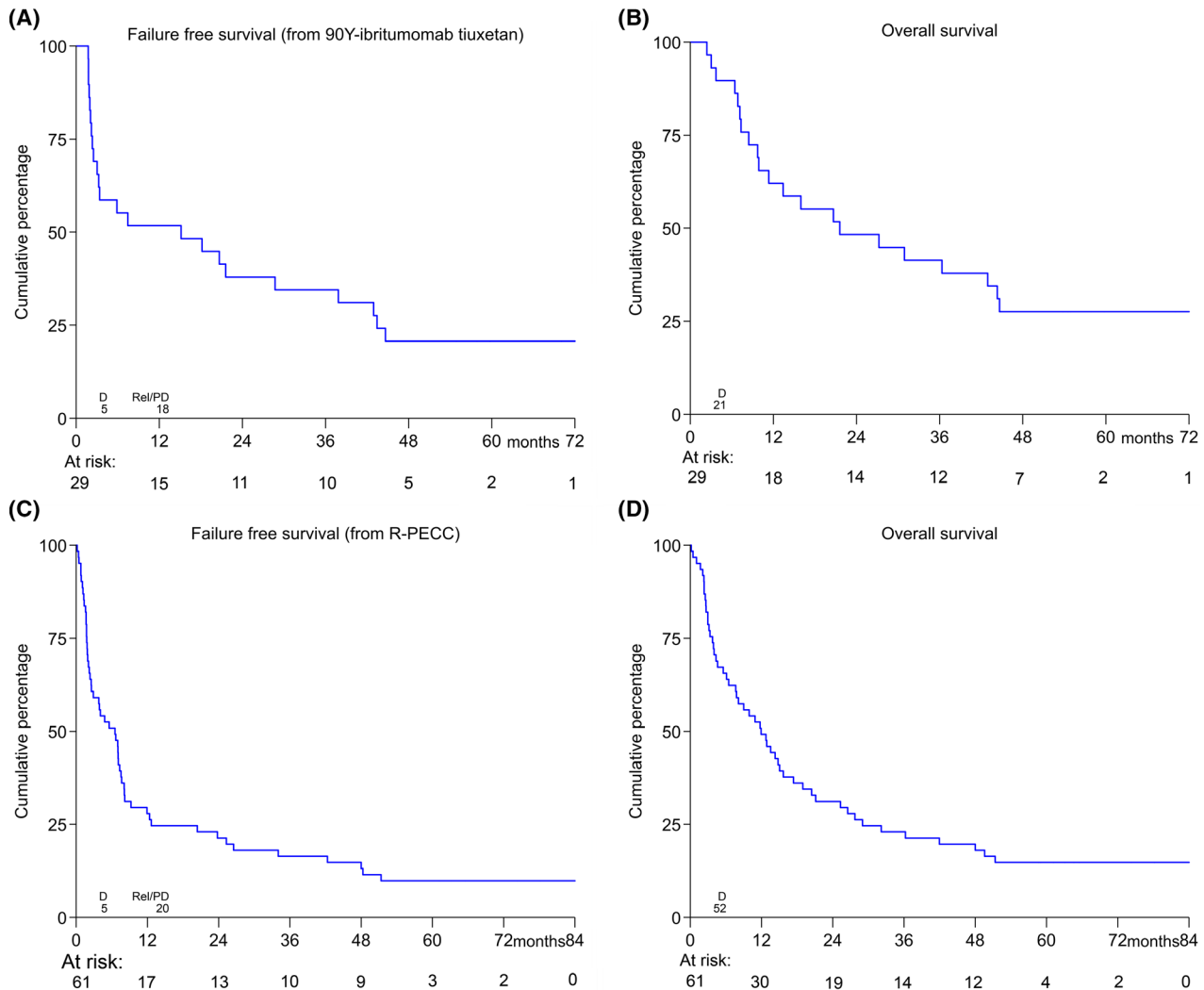


Fig 2. Failure-free survival and overall survival. (A) Failure-free survival (FFS) measured from start of ⁹⁰Y-ibritumomab tiuxetan. (B) Overall survival (OS) measured from start of ⁹⁰Y-ibritumomab tiuxetan. (C) FFS for the whole study population. (D) OS for the whole study population. D, death; PD, progressive disease; R-PECC, rituximab, prednisolone, etoposide, chlorambucil, lomustine; Rel, relapse. [Colour figure can be viewed at wileyonlinelibrary.com]

Lenalidomide with or without rituximab was shown to induce ORR of 27% and CR rates of 10–15% in patients with relapsed/refractory DLBCL, albeit that the benefit of lenalidomide may be seen preferentially in the non-GCB DLBCL subtype (Hernandez-Ilizaliturri *et al*, 2011; Czuczman *et al*, 2017).

The subjective toxicity of the R-PECC regimen was considered very mild in our patient series. The most frequently observed grade 3 or 4 adverse events were haematological. Febrile neutropenia was observed in 15% of the patients, but without prolonged cytopenias. Although the use of granulocyte colony-stimulating factor (G-CSF) was not mandatory in this study, primary prophylaxis with G-CSF in patients above 65 years of age or with other adverse risk factors for febrile neutropenia risk was recommended. Overall the R-PECC regimen is a well-tolerated, mostly oral regimen for patients with DLBCL that has limited efficacy in refractory disease but may enable more than half of the patients with relapsed disease to achieve a remission. Therefore, it is a reasonable treatment option for patients with DLBCL who are deemed to be inappropriate candidates for intensive salvage therapies. Although the outcome for patients with chemotherapy sensitive disease followed by consolidation with ⁹⁰Y-ibritumomab tiuxetan is not bad, the outcome for the whole study population is poor. Despite recent treatment advances in relapsed/refractory DLBCL, the unmet clinical need remains for this predominantly elderly patient population.

In conclusion, the largely oral R-PECC regimen provides patients with relapsed DLBCL who are not eligible for ASCT, a treatment regimen with promising response rates and an acceptable safety profile. However, the efficacy is very disappointing for refractory patients. Consolidation with ⁹⁰Y-ibritumomab tiuxetan was also well tolerated and resulted in

long term response durations in approximately one third of the patients who received ⁹⁰Y-ibritumomab tiuxetan.

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Author contributions

Design of the study: P.J.L, REB, GWvI. Central PET review: JMZ. Pathology review: DdJ, NH, KHL. Analysis and interpretation of the data: P.J.L, REB, DC, GWvI. Acquisition: P.J.L, JMZ, JKD, LHB, MH, HWB, AB, NCvdB-dG, HCS, YMB, MJK, HRK, AHEH, DdJ, NH, KHL, REB, GWvI. Writing of the paper: P.J.L. Revising draft version paper: all authors. Approval of the submitted version: all authors.

References

- Cheson, B.D., Pfistner, B., Juweid, M.E., Gascoyne, R.D., Specht, L., Horning, S.J., Coiffier, B., Fisher, R.I., Hagenbeek, A., Zucca, E., Rosen, S.T., Stroobants, S., Lister, T.A., Hoppe, R.T., Dreyling, M., Tobinai, K., Vose, J.M., Connors, J.M., Federico, M. & Diehl, V. (2007) Revised response criteria for malignant lymphoma. *Journal of Clinical Oncology*, **25**, 579–586.
- Coiffier, B., Lepage, E., Briere, J., Herbrecht, R., Tilly, H., Bouabdallah, R., Morel, P., Van den Neste, E., Salles, G., Gaulard, P., Reyes, F., Lederlin, P. & Gisselbrecht, C. (2002) CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *New England Journal of Medicine*, **346**, 235–242.
- Corazzelli, G., Capobianco, G., Arcamone, M., Ballerini, P.F., Ianitto, E., Russo, F., Frigeri, F., Becchimanzi, C., Marcacci, G., De Chiara, A. & Pinto, A. (2009) Long-term results of gemcitabine plus oxaliplatin with and without rituximab as salvage treatment for transplant-ineligible patients with refractory/relapsing B-cell lymphoma. *Cancer Chemotherapy and Pharmacology*, **64**, 907–916.
- Czuczman, M.S., Trněný, M., Davies, A., Rule, S., Linton, K.M., Wagner-Johnston, N., Gascoyne, R.D., Slack, G.W., Brousset, P., Eberhard, D.A., Hernandez-Ilizaliturri, F.J., Salles, G., Witzig, T.E., Zinzani, P.L., Wright, G.W., Staudt, L.M., Yang, Y., Williams, P.M., Lih, C.J., Russo, J., Thakurta, A., Hagner, P., Fustier, P., Song, D. & Lewis, I.D. (2017) A Phase 2/3 multicenter, randomized, open-label study to compare the efficacy and safety of lenalidomide versus investigator's choice in patients with relapsed or refractory diffuse large B-cell lymphoma. *Clinical Cancer Research*, **23**, 4127–4137.
- Hernandez-Ilizaliturri, F.J., Deeb, G., Zinzani, P.L., Pileri, S.A., Malik, F., Macon, W.R., Goy, A., Witzig, T.E. & Czuczman, M.S. (2011) Higher response to lenalidomide in relapsed/refractory diffuse large B-cell lymphoma in nongerminal center B-cell-like than in germinal center B-cell like phenotype. *Cancer*, **117**, 5058–5066.
- Lennard, A.L., Carey, P.J., Jackson, G.H. & Proctor, S.J. (1990) An effective oral combination in advanced relapsed Hodgkin's disease prednisolone, etoposide, chlorambucil and CCNU. *Cancer Chemotherapy and Pharmacology*, **26**, 301–305.
- Lopéz, A., Gutiérrez, A., Palacios, A., Blancas, I., Navarrete, M., Morey, M., Perelló, A., Alarcón, J., Martínez, J. & Rodríguez, J. (2008) GEMOX-R regimen is a highly effective salvage regimen in patients with refractory/relapsing diffuse large-cell lymphoma: a phase II study. *European Journal of Haematology*, **80**, 127–132.
- McKelvey, E.M., Gottlieb, J.A., Wilson, H.E., Haut, A., Talley, R.W., Stephens, R., Lane, M., Gamble, J.F., Jones, S.E., Grozea, P.N., Gutterman, J., Coltman, C. & Moon, T.E. (1976) Hydroxyldaunomycin (Adriamycin) combination chemotherapy in malignant lymphoma. *Cancer*, **38**, 1484–1493.
- Morschhauser, F., Illidge, T., Huglo, D., Martinelli, G., Zinzani, P.L., Rule, S., Liberati, A.M., Milpied, N., Hess, G., Stein, H., Kalmus, J. & Marcus, R. (2007) Efficacy and safety of yttrium-90

- ibritumomab tiuxetan in patients with relapsed or refractory diffuse large B-cell lymphoma not appropriate for autologous stem-cell transplantation. *Blood*, **110**, 54–88.
- Mounier, N., El Gnaoui, T., Tilly, H., Canioni, D., Sebban, C., Casasnovas, R.O., Delarue, R., Sonet, A., Beaussart, P., Petrella, T., Castaigne, S., Bologna, S., Salles, G., Rahmouni, A., Gaulard, P. & Haioun, C. (2013) Rituximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy. A phase II Lymphoma Study Association trial. *Haematologica*, **98**, 1726–1731.
- Ohmachi, K., Niitsu, N., Uchida, T., Kim, S.J., Ando, K., Takahashi, N., Takahashi, N., Uike, N., Eom, H.S., Chae, Y.S., Terauchi, T., Tateishi, U., Tatsumi, M., Kim, W.S., Tobinai, K., Suh, C. & Ogura, M. (2013) Multicenter phase II study of bendamustine plus rituximab in patients with relapsed or refractory diffuse large B-cell lymphoma. *Journal of Clinical Oncology*, **31**, 2103–2109.
- Pfreundschuh, M., Schubert, J., Ziepert, M., Schmits, R., Mohren, M., Lengfelder, E., Reiser, M., Nickenig, C., Clemens, M., Peter, N., Bokemeyer, C., Eimermacher, H., Ho, A., Hoffman, M., Mertelsmann, R., Trümper, L., Balleiden, L., Liersch, R., Metzner, B., Hartmann, F., Glass, B., Poeschel, V., Schmitz, N., Ruebe, C., Feller, A.C. & Loeffler, M. (2008) Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). *The Lancet Oncology*, **9**, 105–116.
- Pfreundschuh, M., Kuhnt, E., Trümper, L., Osterborg, A., Trnety, M., Shepherd, L., Gill, D.S., Walewski, J., Pettengell, R., Jaeger, U., Zinzani, P.L., Shpilberg, O., Kvaloy, S., de Nully Brown, P., Stahel, R., Milpied, N., López-Guillermo, A., Poeschel, V., Grass, S., Loeffler, M. & Murawski, N. (2011) CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large B-cell lymphoma: 6 year results of an open-label randomised study of the MabThera International Trial (MInT) Group. *The Lancet Oncology*, **12**, 1013–1022.
- Sarkozy, C. & Sehn, L.H. (2018) Management of relapsed/refractory DLBCL. *Best Practice & Research: Clinical Hematology*, **31**, 209–216.
- Sehn, L.H. & Gascoyne, R.D. (2015) Diffuse large B-cell lymphoma optimizing outcome in the context of clinical and biological heterogeneity. *Blood*, **125**, 22–32.
- Stefoni, V., Casadei, B., Bottelli, C., Gaidano, G., Ciochetto, C., Cabras, M.G., Ansuinelli, M., Argnani, L., Broccoli, A., Gandolfi, L., Pellegrini, C. & Zinzani, P.L. (2016) Short-course R-CHOP followed by ⁹⁰Y-Ibritumomab tiuxetan in previously untreated high-risk elderly diffuse large B-cell lymphoma patients: 7-year long-term results. *Blood Cancer Journal*, **6**, e425.
- Vacirca, J.L., Acs, P.L., Tabbara, I.A., Rosen, P.J., Lee, P. & Lynam, E. (2014) Bendamustine combined with rituximab for patients with relapsed or refractory diffuse large B cell lymphoma. *Annals of Hematology*, **93**, 403–409.
- Van Imhoff, G.W., Mc Millan, A., Matasar, M.J., Radford, J., Ardeshta, K.M., Kuliczowski, K., Kim, W., Hong, X., Goerloev, J.S., Davies, A., Barrigón, M.D., Ogura, M., Leppä, S., Fennessy, M., Liao, Q., Van der Holt, B., Lisby, S. & Hagenbeek, A. (2017) Ofatumumab versus rituximab salvage immunochemotherapy in relapsed or refractory diffuse large B-cell lymphoma: the ORCHARD study. *Journal of Clinical Oncology*, **35**, 544–551.
- Witzig, T.E., Hong, F., Micallef, I.N., Gascoyne, R.D., Dogan, A., Wagner, H. Jr, Kahl, B.S., Advani, R.H. & Horning, S.J. (2015) A phase II trial of RCHOP followed by radioimmunotherapy for early stage (stages I/II) diffuse large B-cell non-Hodgkin lymphoma: ECOG3402. *British Journal of Haematology*, **170**, 679–686.
- Zinzani, P.L., Tani, M., Fanti, S., Stefoni, V., Musuraca, G., Castellucci, P., Marchi, E., Farsad, M., Fina, M., Pellegrini, C., Alinari, L., Derenzini, E., de Vivo, A., Bacci, F., Pileri, S. & Baccarani, M. (2008) A phase II trial of CHOP chemotherapy followed by yttrium 90 ibritumomab tiuxetan (Zevalin) for previously untreated elderly diffuse large B-cell lymphoma patients. *Annals of Oncology*, **19**, 769–773.
- Zinzani, P.L., Rossi, G., Franceschetti, S., Botto, B., Di Rocco, A., Cabras, M.G., Petti, M.C., Stefoni, V., Broccoli, A., Fanti, S., Pellegrini, C., Montini, G.C., Gandolfi, L., Derenzini, E., Argnani, L., Fina, M., Tucci, A., Bottelli, C., Pileri, S. & Baccarani, M. (2010) Phase II trial of short-course R-CHOP followed by ⁹⁰Y-Ibritumomab tiuxetan in previously untreated high-risk elderly diffuse large B-cell lymphoma patients. *Clinical Cancer Research*, **16**, 3998–4004.