Safety and activity of lenalidomide in combination with obinutuzumab in patients with relapsed indolent non-Hodgkin lymphoma: a single group, open-label, phase 1/2 trial

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eClinicalMedicine
2024;74: 102747
Published Online xxx
https://doi.org/10.1016/j.eclinm.2024.102747

Summary

Background Rituximab and lenalidomide is a preferred option for relapsed indolent B cell non-Hodgkin lymphoma. Obinutuzumab may be a superior combination partner with lenalidomide given enhanced antibody dependent cellular cytotoxicity and phagocytosis compared to rituximab. Our aim was to determine the recommended phase 2 dose, safety, and activity of lenalidomide in combination with fixed dose of obinutuzumab in relapsed and refractory indolent B cell non-Hodgkin lymphoma.

Methods In this single-arm, open-label, phase 1/2 trial, we enrolled patients with relapsed or refractory WHO Grade 1–3A follicular lymphoma, marginal zone lymphoma and small lymphocytic lymphoma and adequate performance status (ECOG 0–2) at the MD Anderson Cancer Center. We excluded patients with evidence of ongoing transformation to aggressive lymphoma. During phase 1, 1000 mg intravenous obinutuzumab was administered with three predefined levels of oral lenalidomide in a 3 + 3 dose escalation design to establish lenalidomide 20 mg as the recommended phase 2 dose. During phase 2, patients received induction therapy with six 28-day cycles of lenalidomide 20 mg with intravenous obinutuzumab 1000 mg. In accordance with our prior experience with lenalidomide plus rituximab, patients who were responding to the combination could receive up to 6 additional cycles (up to 12 cycles in total) of combination therapy. Dosing of obinutuzumab was continued in all responding patients after cycle 6 every 2 months for a total of 30 months from the start of therapy. The decision of number of cycles of combination therapy beyond 6 was at discretion of the investigator and was included to allow individualisation of therapy to maximise response while minimising exposure. The co-primary objectives were to evaluate the safety and overall response, defined as the proportion of patients who achieved a complete or partial response in relapsed and refractory indolent non-Hodgkin lymphoma at the end of induction therapy, according to Cheson and colleagues (2007 criteria). The secondary endpoints were complete response after induction therapy and time to event endpoints including time to progression, progression free survival, and overall survival. Analyses were intent to treat in the efficacy cohort and per-treated in the safety population in all patients who received at least one dose of either investigational agent. This trial is registered with ClinicalTrials.gov, NCT01995669.

Findings Between June 03, 2014, and 07 March 2019, we completed planned enrolment, and 66 patients started therapy including 9 patients in phase 1 and 57 patients in phase 2. All patients were evaluated for safety and the 60 patients treated at the recommended phase 2 dose of lenalidomide 20 mg were evaluable for activity. Grade 3–4 haematological toxicities included neutropenia 21% (14/66) and thrombocytopenia 11% (7/66) with no cases of febrile neutropenia. Grade 3–4 non-haematological toxicities included lung infection 8% (5/66), fatigue 8% (5/66) and rash 6% (4/66). By Cheson 2007 criteria, 90% (54/60, 95% CI: 79–96) achieved an overall response at the end of induction meeting the prespecified activity endpoint. Complete responses were seen in 33% (20/60, 95% CI: 22–47) at the end of induction. Median progression free survival, time to progression and overall survival have

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not been reached after median follow-up of 41.7 months. Estimated 4-year progression free survival rates were 55% (95% CI: 42–73), time to progression of 56% (95% CI: 43–74) and overall survival of 84% (95% CI: 74–95).

Interpretation Our findings suggest that oral lenalidomide with obinutuzumab is safe and highly active in patients with relapsed and refractory indolent B cell non-Hodgkin lymphoma and is associated with prolonged remission duration. The study is limited by the lack of a control arm leading to cross-trial comparisons to evaluate activity. Future randomised trials comparing this regime to rituximab and lenalidomide are warranted.

Funding Genentech and an MD Anderson Core grant.

Keywords: Follicular lymphoma; Lenalidomide; Obinutuzumab; Relapsed

Research in context

Evidence before this study

We designed this study in an era where there were limited treatment options for relapsed indolent B cell non-Hodgkin lymphoma particularly follicular lymphoma. We used our own experience with the combination of rituximab and lenalidomide in indolent lymphoma to select the combination of obinutuzumab and lenalidomide based on improved antibody dependent cellular cytotoxicity with obinutuzumab. We searched PubMed on October 31, 2017, for publications without any language restrictions using the search terms, "lenalidomide", "obinutuzumab", "lymphoma" and found no clinical trials incorporating this combination in lymphoma. Since then, the landscape of relapsed indolent B cell lymphoma has dramatically changed with the approval of rituximab and lenalidomide in 2019 based on the AUGMENT trial as well as the availability of multiple targeted agents. We aimed to evaluate the safety and long-term efficacy of the combination of lenalidomide with obinutuzumab in relapsed or refractory indolent lymphoma to best identify optimal sequencing of therapies.

Added value of this study

Our trial met its primary safety and efficacy endpoints with an overall response rate of 90% and complete response of 33% with the combination of obinutuzumab and lenalidomide at the end of six months of induction therapy. High risk groups such as patients with progressive disease within 24 months of diagnosis and patients refractory to last therapy benefited. The safety profile of our combination was consistent with the reported toxicities with lenalidomide and rituximab in the AUGMENT trial. We observed no instances of febrile neutropenia and low rates of grade 3 or higher haematological toxicity.

Implications of all the available evidence

Although our primary endpoint was overall response rate, the better endpoint in relapsed indolent lymphoma is progression free survival after an adequately long follow-up period. Results of our study demonstrate the durability of the combination of obinutuzumab and lenalidomide with median progression free survival, time to progression and overall survival not reached in the relapse setting after a median follow-up of 3.5 years. These findings warrant further exploration in a randomized controlled trial comparing it to the current preferred strategy of rituximab and lenalidomide to prove superiority.

Introduction

Indolent B cell non-Hodgkin lymphomas (NHL) are comprised of slowly progressive malignancies with variable outcomes including follicular lymphoma (FL), marginal zone lymphoma (MZL) and small lymphocytic lymphoma (SLL).[1] Most indolent B cell lymphomas have a prolonged natural history coupled with multiple disease relapses and the need for several lines of therapy. There is no single standard of care for relapsed FL or MZL which tend to be treated in a similar fashion at relapse.[2] A common approach is to pursue multiple lines of chemoimmunotherapy which can inadvertently result in significant morbidity. This highlights a need for novel, well tolerated approaches. A promising targeted approach at relapse is the combination of the anti-CD20 monoclonal antibody, rituximab, and immunomodulator (IMiD) drug, lenalidomide (R^2) which has been demonstrated to be a safe and effective combination in the AUGMENT phase 3 randomised trial. R^2 was approved by the United States (US) Food and Drug Administration in 2019.[3]

Lenalidomide is a second generation IMiD drug and a derivative of thalidomide. Lenalidomide has effects on both the tumour and the tumour microenvironment by enhancing the proliferative and functional capacity of T cells, repairing effector T-cell synapses, increasing natural killer (NK)-cell mediated antibody-dependent cellular cytotoxicity (ADCC) and upregulating

co-stimulatory molecules on the tumour cell surface.[4–6] Additionally, lenalidomide modulates activated signalling pathways within the tumour cells involving transcription factors, including interferon regulatory factor 4, NFκB, Ikaros and Aiolos.[7] Lenalidomide in combination with rituximab is synergistic in-vivo and in-vitro by enhancing rituximab-induced apoptosis and rituximab-dependent NK-cell mediated cytotoxicity.[4,8]

Obinutuzumab is a glycosylated type II anti-CD20 antibody with enhanced affinity for the FcγRIIIα receptor leading to improved ADCC. Obinutuzumab in combination with bendamustine was evaluated in relapsed and refractory indolent B cell lymphoma in the phase 3 GADOLIN trial[9] and found to be highly active in rituximab-refractory patients. Preclinical studies confirm the advantage of obinutuzumab over rituximab is due to enhanced ADCC and antibody dependent cellular phagocytosis, decreased complement dependent cytotoxicity and increased induction of direct cell death.[9] This preclinical data led us to build on the R^2 combination by combining obinutuzumab with lenalidomide in relapsed indolent B cell lymphomas. Herein we present long term follow-up of the phase 1/2 trial we undertook to assess the safety and activity of lenalidomide and obinutuzumab in patients with relapsed and refractory indolent B-cell lymphoma.

Methods

Study design

Patients were enrolled into an investigator initiated, open-label, phase 1/2 trial at a single institution, MD Anderson Cancer Center, Houston, TX, US. The study was approved by our institutional review board, and it was performed in accordance with the Declaration of Helsinki and good clinical practice guidelines (ClinicalTrials.gov identifier: NCT01995669). All patients provided written informed consent. This study adheres to CONSORT reporting guidelines.

Participants

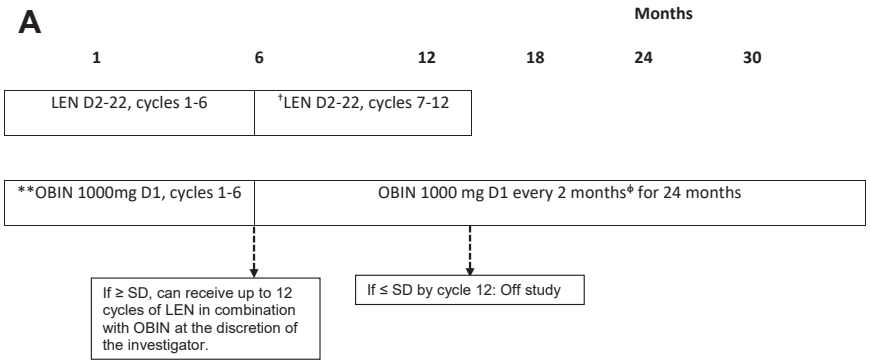
Eligible patients were at least 18 years old with histologically confirmed CD20-positive World Health Organization grade 1–3A FL, MZL, or SLL; relapsed or refractory disease after at least 1 prior therapy; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; measurable disease of at least one node greater than 1.5 cm in short axis dimension; willingness to comply with lenalidomide requirements for pregnancy prevention; adequate haematologic function defined by: haemoglobin ≥9.0 g/dL, absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$ cells per L and platelet count $\geq 75 \times 10^9$ cells per L. We allowed lower blood counts if cytopenia is due to extensive bone marrow lymphomatous involvement as determined by the treating physician.

Patients were ineligible if they had evidence of transformation to aggressive lymphoma; significant laboratory abnormalities unless due to lymphoma (calculated creatinine clearance <40 mL/min, aspartate aminotransferase or alanine aminotransferase >2.5 times upper limit of normal, bilirubin >1.5 times upper limit of normal); history of severe allergic or anaphylactic reactions to monoclonal antibody therapy; known hypersensitivity to thalidomide or lenalidomide; history of prior malignancy within the last 5 years; uncontrolled serious illness; known active infection; human immunodeficiency virus; hepatitis B or hepatitis C infection. Regular treatment with corticosteroids during the 4 weeks prior to the start of cycle 1 was an additional exclusion criterion unless it was administered for indications other than lymphoma at a dose equivalent to ≤30 mg/day prednisone.

Procedures

Phase 1 was a traditional 3 + 3 dose escalation design using a fixed dose of obinutuzumab (1000 mg) and three predefined levels of lenalidomide as outlined in Fig. 1. Patient enrolment began at dose level 1 (DL1) of lenalidomide 10 mg with escalation to DL2 of lenalidomide 15 mg and finally to DL3 of lenalidomide 20 mg. DL3 of lenalidomide at 20 mg was chosen as the maximum dose of lenalidomide to be tested based on efficacy and tolerability in previous combination studies with rituximab in FL.[10] The recommended phase 2 dose (RP2D) was established at the maximum tolerated dose (MTD) of lenalidomide from phase 1. Two cohorts were initially planned for phase 2: FL (cohort A; n = 30); SLL and MZL (cohort B; n = 30). However, due to slow recruitment into cohort B, it was expanded to enrol patients with FL as well.

Treatment schedule (Fig. 1) comprised of six 28-day cycles of induction treatment with combination of daily lenalidomide for 21 days with obinutuzumab 1000 mg as an intravenous infusion on day 1, 2, 8, 15 and 22 of cycle one (obinutuzumab was given 100 mg IV on day 1 and 900 mg on day 2) and on day 1 of each subsequent cycle up to 6 cycles. Lenalidomide was administered orally on days 2–22 each cycle for cycles 1 to 6. At the end of induction phase, patients who did not progress (complete response, partial response, or stable disease) and were deriving benefit in the opinion of the treating physician could receive up to 6 more cycles of lenalidomide therapy. Obinutuzumab was given every 2 months after cycle 6 for a total 30 months from the start of therapy. The maximum number of doses of obinutuzumab that a patient could receive is 21. The number of cycles of combination therapy beyond cycle 6 is at the discretion of the treating team and investigator to allow individualization to maximise response while minimising exposure. Patients who demonstrated at least partial response following 12 cycles were eligible to continue obinutuzumab monotherapy.



B

Dose level	Lenalidomide	Obinutuzumab
-1	5mg	1000mg
0	10mg	1000mg
+1	15mg	1000mg
+2	20mg	1000mg

Fig. 1: A) Treatment schedule. B) Dose level cohorts for phase I dose finding component. **OBIN administered intravenously on days 1, 8, 15 and 22 on cycle 1. †LEN administered orally from cycles 7–12 if responding to treatment (complete response, partial response, or stable disease) at investigator discretion. $OBIN monotherapy continued for patients in at least partial response after C12. LEN, lenalidomide; OBIN, obinutuzumab; D, day.

For patients with bulky disease (tumour >5 cm), prophylactic daily aspirin 81 mg or 325 mg daily was recommended. Individuals received prophylaxis for venous thromboembolism with aspirin or an anticoagulant tailored to their thrombotic and bleeding risk.

Tumour assessments were performed using computed tomography (CT) imaging at study entry and every 3 months during combination treatment. Positron emission tomography scan at study entry was recommended but not mandated. Bone marrow biopsies were performed at screening and repeated to document complete remission if the screening biopsy was positive. Responses were assessed every 4 months on maintenance obinutuzumab monotherapy. Responses were assessed according to the Response Criteria for Malignant Lymphoma reported by Cheson and colleagues (2007 criteria).[11] Post treatment evaluation was for at least 6 months after last dose of therapy and included CT imaging every 3 months for 1 year followed by every 6 months for 1 year and then yearly. Follow-up evaluation was ceased after starting next line of lymphoma therapy.

Adverse events (AE) were graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. AE and laboratory assessments were carried out at each treatment visit. Dose limiting toxicities (DLT) were monitored during the first cycle in the phase 1 cohort. Non-haematological DLT were defined as any grade 3 or grade 4 toxicity felt to be related to study drug, except for transient grade 3 or higher infusion reaction that completely resolved within 24 h. Haematological DLT included any grade 4 haematological toxicity, grade 3 neutropenia with fever or grade 3 thrombocytopenia with bleeding. Treatment delay of greater than 2 weeks due to treatment-related toxicity was an additional DLT.

For any grade 3 or higher non-haematological AE due to lenalidomide, we interrupted lenalidomide until resolution to ≤ grade 2 severity except for any allergic reaction/hypersensitivity or sinus bradycardia/other cardiac arrhythmia AE for which we required resolution to ≤ grade 1 severity. For haematological AE, we considered only grade 3 neutropenia with fever, grade 4 neutropenia or ≥ grade 3 thrombocytopenia to be significant enough to interrupt lenalidomide dosing and we required resolution to ≤ grade 2 severity. Lenalidomide was re-introduced in these circumstances at one dose level reduction from the starting dose. We permitted use of myeloid growth factors for isolated grade 3 neutropenia with fever or grade 4 neutropenia at the discretion of the investigator.

Outcomes

The primary objective of phase 1 was to determine the MTD of lenalidomide in combination with obinutuzumab for subsequent evaluation in phase 2. The co-primary objectives of phase 2 were to evaluate the safety and overall response defined as the proportion of patients who achieved a complete or partial response in

relapsed and refractory indolent NHL at the end of induction therapy according to Cheson and colleagues (2007 Criteria).[11] The secondary objectives were to determine the complete response (CR) at the end of induction, time to progression (TTP) defined as time from treatment administration to lymphoma progression, progression free survival (PFS) assessed from treatment administration to disease progression or death and overall survival (OS) from treatment administration to death.

Statistical analysis

The co-primary outcomes of overall response rate after induction of 6 cycles with combination therapy and DLT after 1 cycle were monitored simultaneously using the Bayesian approach of Thall, Simon, Estey (1995, 1996)[12,13] as extended by Thall and Sung (1998).[14] The null hypothesis predicted overall responses in no more than 23% of patients based on expected response rate of lenalidomide alone.[15] We hypothesised that our two-drug combination therapy will improve the overall response by 20% to 43% and maintain DLT at or below 30%. The sample size of 30 in each cohort was calculated to ensure that a 43% overall response rate will have a posterior 90% credible interval with a width of 0.283 at most.

We evaluated the association between various categorical patient characteristics: age, sex, stage, B symptoms, ECOG performance score, FLIPI score against response rates and survival. Descriptive statistics including mean, standard deviation, median and range for continuous variables, and frequency, counts and percentages for categorical variables are provided.

Responses are reported as percentages of patients using the Clopper Pearson method with 95% confidence intervals (CI). Chi square test or Fisher's exact test was used to evaluate the association between patient prognostic factors and response.

Time to event analyses were done with the method of Kaplan and Meier. The log-rank test was used to compare the differences in time-to-event endpoints in important subgroups including progression of disease within 24 months (POD24) and receiving 6 cycles of lenalidomide vs more than 6 cycles. Intent to treat analysis was used for efficacy endpoints and per-treated analysis used for toxicity endpoints. The Statistical software SAS 9.4 (SAS, Cary, NC) and TIBCO Spotfire S+ 8.2 (TIBCO Software Inc., Palo Alto, CA) were used for all the analyses.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to the data in the study and had final responsibility for the decision to submit for publication.

Results

From June 03, 2014, to December 2, 2014, 9 patients were enrolled in the phase 1 component of the study and 57 patients were enrolled in the phase 2 component from 22 December 2015 to 07 March 2019. There was no dose expansion in the phase 1 study. Safety was evaluated in all patients and activity was evaluated in the population treated at the RP2D (n = 60). The flow of patients through the study is displayed in Fig. 2.

All patients in the phase 1 component had FL with a median age of 65 years (range, 35–72 years), 67% were male with 1 (range 1–2) median prior line of therapy and only one patient was rituximab refractory. Responses to varying dose levels of lenalidomide in the phase 1 component are displayed in the Supplementary Appendix Table S1. As no DLT were encountered, lenalidomide 20 mg dose in combination with obinutuzumab was established as the RP2D.

Demographics and disease characteristics are displayed in Table 1. Of the 60 patients evaluated for activity, 51 (85%) had FL, 5 patients (8%) had SLL and 4 patients (7%) had MZL. The median age was 65 years (range, 40–82), 52% were age ≥65, 50% were male and median prior line of therapy was 1 (range, 1–7). At screening, 35 (58%) patients had ECOG performance status of 0, 56 (93%) patients had advanced stage disease, 63% of patients had high FLIPI score and 20% had bone marrow involvement. Twenty-seven (45%) of 60 patients had POD24, 12 (20%) patients were refractory to last line of therapy, 15 (25%) patients were rituximab-refractory and 75% of our patients had received prior therapy with a chemotherapy backbone. Among these, 19 received obinutuzumab-lenalidomide on this protocol as their second-line of therapy.

Sixty-four (97%) of 66 patients completed six cycles of induction therapy and were eligible for maintenance. Twenty-seven (41%) patients received only 6 cycles of combination therapy and moved onto maintenance obinutuzumab monotherapy. Twenty-five (38%) patients completed 12 cycles of combination lenalidomide with obinutuzumab therapy as demonstrated on the CONSORT diagram (Fig. 2). There were no differences in baseline variables between those who completed 6 cycles compared to those who completed more than 6 cycles of lenalidomide.

There was no dose modification of obinutuzumab; lenalidomide dose reduction occurred due to 34 adverse events in 23 patients (35%). This includes neutropenia in 11 patients (17%), thrombocytopenia in 7 (11%), fatigue in 5 (8%), infection in 5 (8%), rash in 3 (5%), cough in 2 (3%) and sinus bradycardia in 1 patient (2%). The adverse events for the cohort are summarised in Table 2. The most common non-haematological adverse events were mainly grade 1 to 2 including fatigue (83%), rash (58%) and cough (53%). The most common haematological adverse effects were neutropenia with grade 3 or higher seen in 21% and grade 3 or higher thrombocytopenia in

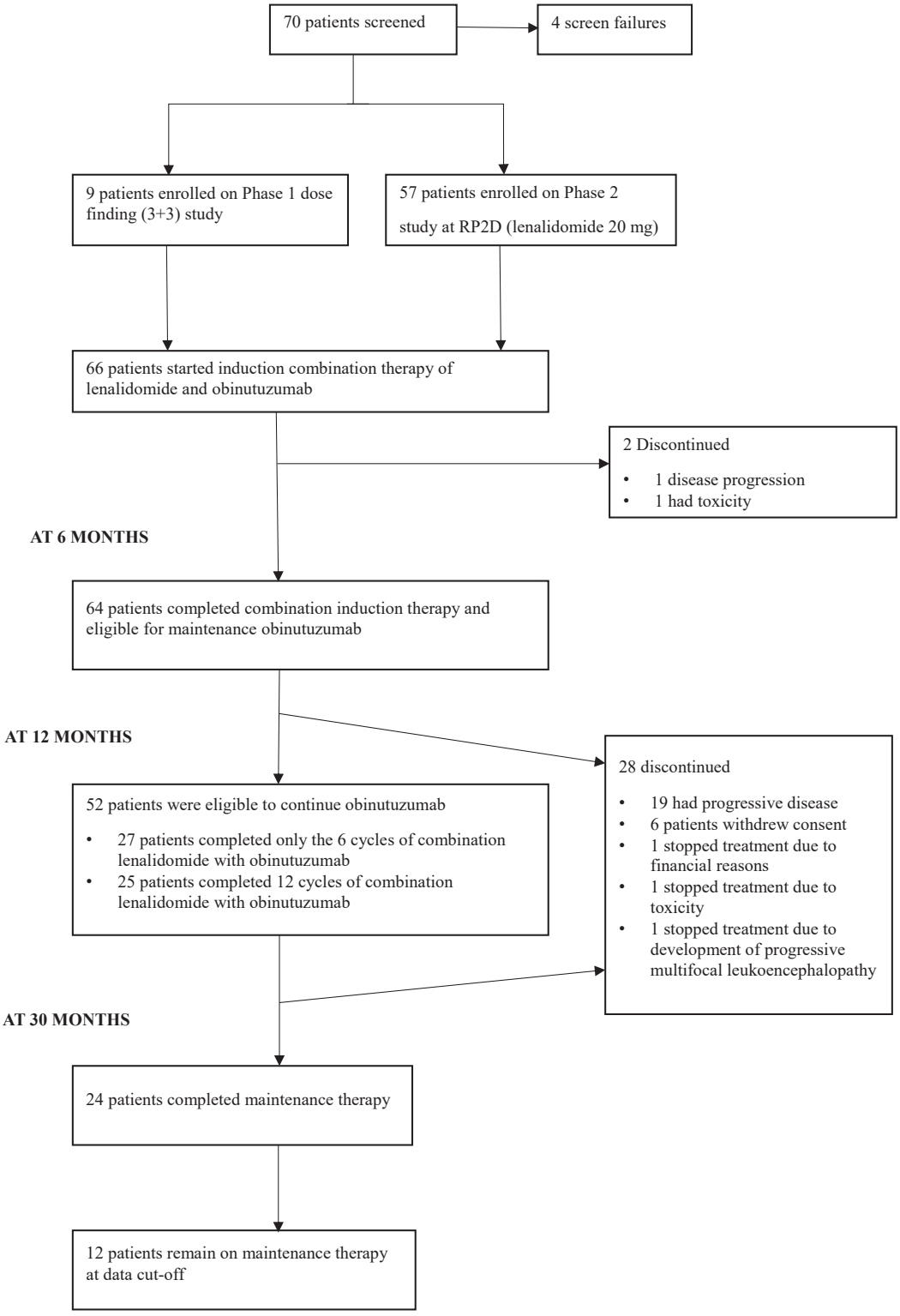


Fig. 2: Trial profile at last follow-up. RP2D, recommended phase 2 dose.

	Safety evaluable population	Activity evaluable population (RP2D Cohort of Lenalidomide 20 mg dose)
	n = 66	(n = 60)
Age, years		
Median	64.5	65
Range	35–82	40–82
Sex		
Female	31 (47%)	30 (50%)
Male	35 (53%)	30 (50%)
Diagnosis		
Follicular lymphoma	57 (86%)	51 (85%)
SLL	5 (8%)	5 (8%)
Marginal zone lymphoma	4 (6%)	4 (7%)
Ann Arbor Stage		
II	4 (6%)	4 (7%)
III	17 (26%)	16 (27%)
IV	45 (68%)	40 (67%)
ECOG Score		
0	40 (61%)	35 (58%)
1	25 (38%)	24 (40%)
2	1 (2%)	1 (2%)
FLIPI score		
0–1	11 (17%)	9 (15%)
2	14 (21%)	13 (22%)
3–5	41 (62%)	38 (63%)
Bone marrow involvement		
Negative	51 (77%)	48 (80%)
Positive	15 (23%)	12 (20%)
Number of prior therapies		
1	35 (53%)	31 (52%)
2	16 (24%)	14 (23%)
3 or more	15 (23%)	15 (25%)
First-line:		
Chemo-immunotherapy	49 (74%)	44 (73%)
Rituximab alone	7 (11%)	1 (2%)
Rituximab + targeted tx	10 (15%)	0
Rituximab-refractory		
No	50 (76%)	45 (75%)
Yes	16 (24%)	15 (25%)
POD24 status		
POD ≤24 months	38 (58%)	27 (45%)
POD >24 months	28 (42%)	33 (55%)
Refractory to Last Therapy		
No	53 (80%)	47 (78%)
Yes	12 (18%)	12 (20%)

Date are n (%). RP2D, recommended phase 2 dose; SLL, small lymphocytic lymphoma; ECOG, Eastern Cooperative Oncology Group; FLIPI, Follicular Lymphoma International Prognostic Index; POD24, progression of disease within 24 months; tx, therapy.

Table 1: **Patient demographics and clinical characteristics.**

11%. Lenalidomide rash was mild except for 6% with ≥grade 3 events and one case of erythroderma. There were no grade 5 events and no treatment related deaths.

Serious adverse events (SAE) were reported in 18 (27%) of 66 patients and the most common were lung infections (n = 5, 8%), sepsis (n = 3, 5%), fever (n = 2, 3%) and sinus bradycardia (n = 2, 3%). Adverse events of special interest during follow-up included 1 case of tumour lysis syndrome and 1 case of unintended pregnancy. The unintended pregnancy occurred in the female partner of a male patient at 19 months after last dose of lenalidomide due to failure to comply with contraception advice during obinutuzumab monotherapy. Of the 16 patients that experienced any grade neutropenia, there were no cases of febrile neutropenia with 14 patients experiencing ≥ grade 3 neutropenia of whom 13 received myeloid growth factor support. We interrupted lenalidomide for neutropenia in 9 patients and discontinued in 1 patient due to repeated episodes of grade 3 neutropenia needing growth factor support. The incidence of ≥ grade 3 neutropenia was similar in those receiving 6 cycles vs those receiving >6 cycles of lenalidomide at 11%.

Second primary malignancies were seen in 3 patients including one skin squamous cell carcinoma, one clear cell renal cell carcinoma and a case of therapy related acute myeloid leukemia (AML) after trial completion. The patient with secondary AML had a history of 3 prior lines of chemotherapy as well as high dose therapy with autologous stem cell transplant consolidation, was lymphoma free and had been off lenalidomide for 8 months at the time of diagnosis.

There were 83 instances of therapy interruptions due to adverse events in 29 (44%) of 66 patients and these were mostly grade 1; only 2 (3%) patients permanently discontinued therapy due to SAEs of sick sinus syndrome and lung infection, respectively. Nine (14%) deaths occurred during the trial period, two of these may be attributable to therapy. These include the patient with therapy related acute myeloid leukemia which may be attributable to lenalidomide and a patient with progressive multifocal leukoencephalopathy after cycle 15 that may be attributable to obinutuzumab. These patients passed away 2 months and 1 year after coming off study, respectively. The remaining cases all had progressive disease, came off study and died during follow-up from: infection (n = 3), progressive lymphoma after 6–12 months of subsequent therapy (n = 2) and unknown cause (n = 2).

The overall response rate at the end of induction of 6 cycles of combination therapy was 90% (95% CI: 79–96) with a CR of 33% (95% CI: 22–47) by Cheson 2007 criteria[11] (Table 3) meeting the primary objective (i.e. lower bound of 95% CI excluding 43%). At 12 months, there is a deepening of the CR to 50% due to conversions from partial response with a slight decrement in overall response rate to 78%. The best overall response rate during treatment was 97% (95% CI: 91–99%) with 68% CR (95% CI: 59%–76%) by Cheson 2007 criteria.[11] Post hoc analysis per the Lugano 2014 Criteria[16]

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	All grades
Haematological events					
Neutropenia	1 (2%)	1 (2%)	10 (15%)	4 (6%)	16 (24%)
Thrombocytopenia	7 (11%)	2 (3%)	6 (9%)	1 (2%)	16 (24%)
Anaemia	14 (21%)	–	1 (2%)	–	15 (23%)
Leukopenia	–	2 (3%)	1 (2%)		3 (5%)
Non-haematological events					
Fatigue	33 (50%)	17 (26%)	5 (8%)	–	55 (83%)
Rash	32 (48%)	2 (3%)	4 (6%)	–	38 (58%)
Cough	26 (39%)	7 (11%)	2 (3%)	–	35 (53%)
Diarrhea	13 (20%)	18 (27%)	–	–	31 (47%)
Myalgia	23 (35%)	7 (11%)	–	–	30 (45%)
Constipation	21 (32%)	9 (14%)	–	–	30 (45%)
Peripheral edema	23 (35%)	3 (5%)	–	–	26 (39%)
Dyspnea	17 (26%)	6 (9%)	1 (2%)	–	24 (36%)
Nausea	20 (30%)	3 (5%)	–	–	23 (35%)
Dizziness	20 (30%)	2 (3%)	–	–	22 (33%)
Dry Eye	16 (24%)	2 (3%)	–	–	18 (27%)
Fever	15 (23%)	1 (2%)	1 (2%)	–	17 (26%)
Peripheral sensory neuropathy	15 (23%)	1 (2%)	–	–	16 (24%)
Memory impairment	13 (20%)	1 (2%)	1 (2%)	–	15 (23%)
Back pain	9 (14%)	5 (8%)	1 (2%)	–	15 (23%)
Blurred Vision	13 (20%)	1 (2%)	–	–	14 (21%)
Mucositis—oral	9 (14%)	3 (5%)	–	–	12 (18%)
Sinusitis	–	12 (18%)	–	–	12 (18%)
Pruritus	9 (14%)	2 (3%)	–	–	11 (17%)
Upper respiratory infection	–	11 (17%)	–	–	11 (17%)
Allergic rhinitis	10 (15%)	–	–	–	10 (15%)
Headache	8 (12%)	2 (3%)			10 (15%)
Infection—other	1 (2%)	5 (8%)	4 (6%)	–	10 (15%)
Nasal Congestion	7 (11%)	2 (3%)	–	–	9 (14%)
Vomiting	8 (12%)	1 (2%)			9 (14%)
Lung infection	–	1 (2%)	5 (8%)	–	6 (9%)
Hyperglycaemia	5 (8%)	–	1 (2%)	–	6 (9%)
Sepsis	–	–	–	3 (5%)	3 (5%)
Urinary tract infection	–	2 (3%)	1 (2%)	–	3 (5%)
ALT or AST increased	3 (5%)	–	1 (2%)	–	4 (6%)
Atrial fibrillation	–	–	1 (2%)	–	1 (2%)
Erythroderma	–	–	1 (2%)	–	1 (2%)
Heart failure	–	–	1 (2%)	–	1 (2%)
Hypotension	–	–	1 (2%)	–	1 (2%)
Sick sinus syndrome	–	–	1 (2%)	–	1 (2%)
Sinus Tachycardia	–	–	1 (2%)	–	1 (2%)
Chest pain–cardiac	–	–	1 (2%)	–	1 (2%)
Gastrointestinal reflux	–	–	1 (2%)	–	1 (2%)
Syncope	–	–	1 (2%)	–	1 (2%)
Vertigo	–	–	1 (2%)	–	1 (2%)
Gallbladder obstruction	–	–	1 (2%)	–	1 (2%)
Appendicitis	–	–	1 (2%)	–	1 (2%)
Testicular Pain	–	–	1 (2%)	–	1 (2%)

Data are n (%). All grade 3 to 4 events are reported. There were no grade 5 toxicities.

Table 2: **Summary of adverse events occurring in at least 10% of patients in the safety cohort of the phase 1/2 study (n = 66).**

	RP2D of LEN 20 mg (N = 60)
First assessment (post 3 cycles)	
Overall Response	50 (83%; 71–92)
CR/CRu	12 (20%; 11–32)
PR	38 (63%)
SD	9 (15%)
PD	1 (2%)
After induction (post 6 cycles)	
Overall Response	54 (90%; 79–96)
CR/CRu	20 (33%; 22–47)
PR	34 (57%)
SD	2 (3%)
PD	4 (7%)
After 12 cycles	
Overall Response	47 (78%; 66–88)
CR/CRu	30 (50%; 37–63)
PR	17 (28%)
SD	0
PD	12 (20%)
Best Overall Response during treatment	
Overall Response	58 (97%; 91–99)
CR/CRu	41 (68%; 59–76)
PR	17 (28%)
SD	1 (2%)
PD	1 (2%)

RP2D, recommended phase 2 dose; CR/CRu, complete response and complete response unconfirmed; PR, partial response; SD, stable disease; PD, progressive disease.

Table 3: **(A) Response outcomes for Activity evaluable population at RP2D of Lenalidomide 20 mg (n = 60) using Cheson 2007 Criteria.**

demonstrated an overall response rate of 98% (95% CI: 94%–100%) and 75% CR (95% CI: 66%–82%).

The secondary objectives of median PFS, TTP and OS have not been reached after a median follow-up of 41.7 months (range 16.8 months–71.1 months). The median time to response was 2.8 months (range, 2–12.2 months). Estimated 4-year rates for PFS were 55% (95% CI: 42–73), TTP of 56% (95% CI: 43–74) and OS of 84% (95% CI: 74–95) as demonstrated in Fig. 3.

The POD24 subgroup demonstrated an overall response rate of 93% (95% CI: 76–99) and 33% CR (95% CI: 17–54) at the end of induction. Their best overall response rate was 100% (95% CI: 87–100) with CR of 67% (95% CI: 46–84%), median PFS was 44.2 months (95% CI: 22.5–NA) by Cheson 2007 criteria, median TTP was 44.2 months (95% CI: 26.6–NA), and median OS had not been reached with a median follow up time of 42.7 months for the 23 censored observations as demonstrated in Supplementary Appendix Fig. S1.

In the post-hoc analysis, ECOG score >1 (p = 0.0003) and prior chemotherapy treatment (p = 0.013) were significantly associated with inferior PFS and TTP. Elevated FLIPI score ≥3, POD24 and rituximab-refractory disease were associated with a trend towards inferior PFS and TTP which did not reach statistical significance.

The following factors were not associated with inferior PFS or TTP: age ≥65 years, male sex, non-FL histology, bone marrow involvement, advanced Ann Arbor stage, receiving 6 cycles vs > 6 cycles of lenalidomide (Fig. 4), ≥2 prior lines of therapy, and use of growth factor support.

Discussion

In this single centre, phase 1/2 study, the combination of lenalidomide and obinutuzumab was highly active in relapsed and refractory indolent B cell lymphoma. We established lenalidomide 20 mg as the RP2D with the absence of any DLT when given with obinutuzumab during the phase 1 component of our study. The phase 2 component met its co-primary endpoints of safety and activity with a 90% overall response rate and 33% CR (Cheson 2007 Criteria)[11] at the end of induction. Long term follow-up of 3.5 years confirms benefit with median PFS, TTP and OS not reached. High risk subgroups of POD24 and rituximab refractory had good responses but appeared to have a trend to inferior survival that did not reach statistical significance. Although post hoc analysis found similar benefit in non-FL histology such as MZL and SLL, given our population mainly comprised of FL histology (85%), conclusions are mainly applicable to FL.

There is currently no single standard of care for relapsed FL. There are multiple approaches available that can only be evaluated through cross trial comparisons. Many of these trials focused on highly pre-treated populations with two or more prior lines of therapy. Copanlisib, the PI3K inhibitor, can be associated with significant toxicity with low rates of CR. The oral EZH2 inhibitor, tazemetostat, is well tolerated but has low rates of CR and median PFS of only 14 months among EZH2 mutated cases.[17,18] The ROSEWOOD study demonstrated the combination of obinutuzumab with zanubrutinib had an overall response rate of 69% with CR of 39% and median PFS of 28 months; however this approach is limited by the use of indefinite zanubrutinib exposing the patient to potential financial toxicity and adverse effects.[19] Chimeric antigen receptor T (CAR T) cell therapies have demonstrated high response rates in FL with 74% CR with Axi-cel in ZUMA-5 with a median PFS of 40 months and 68% CR with Tisa-cel in ELARA.[20,21] Although toxicities such as cytokine release syndrome and neurological toxicity are milder in indolent lymphomas compared to aggressive lymphomas, CAR T remains limited by infectious complications in the COVID era and heavy resource utilisation.[22–24] Mosunetuzumab, a recently approved bispecific T-cell engaging antibody (BiAb), for a fixed duration demonstrated an 80% overall response with 60% CR but durability was more limited with a median PFS of 18

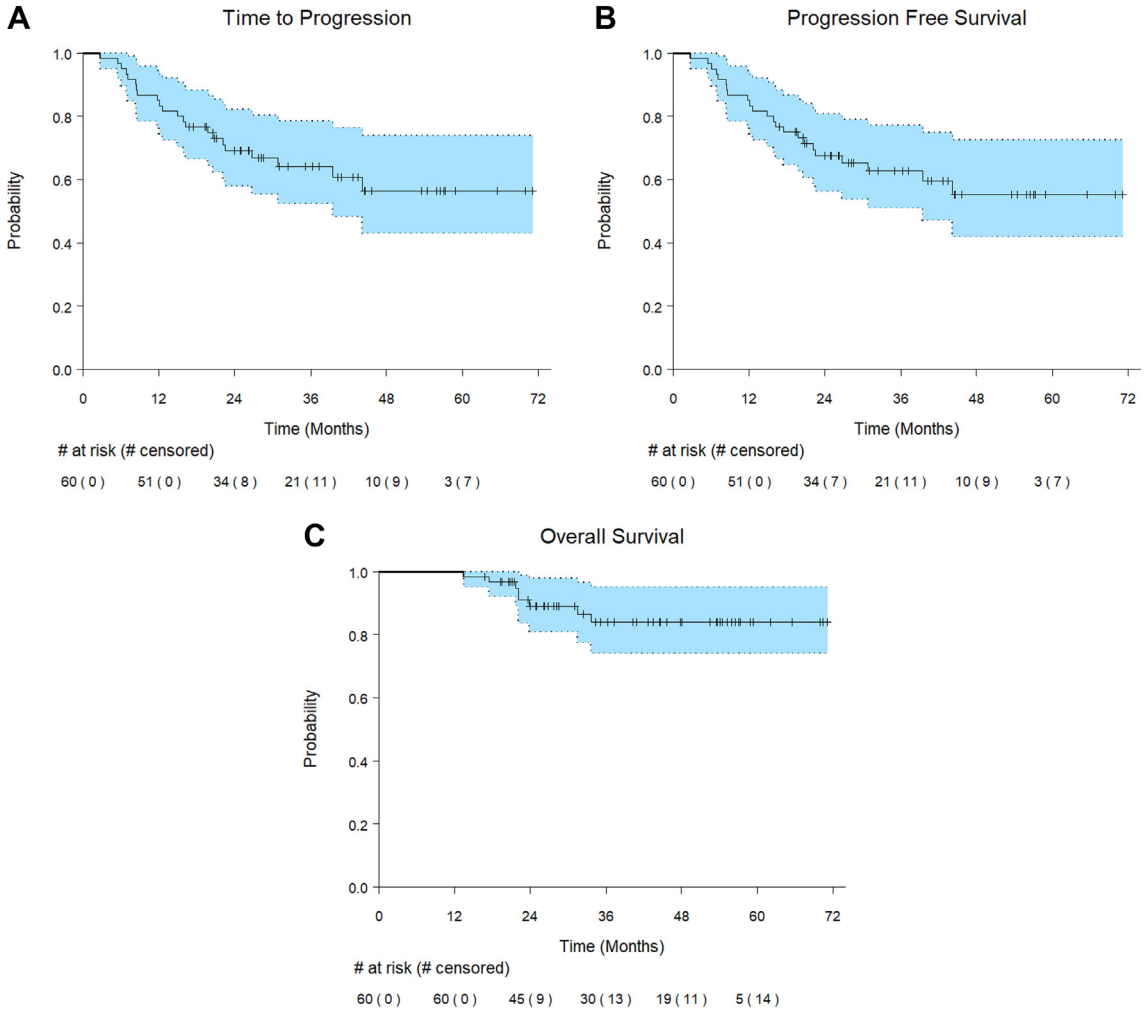


Fig. 3: Kaplan Meir survival curves for RP2D patients (n = 60). Blue shaded area provides the 95% CI. A) Time to progression. B) Progression for survival. C) Overall Survival. RP2D, recommended phase 2 dose.

months.[24] This is likely due to a more heavily pre-treated population with a median of 3 prior lines of therapy. Although this regime was well tolerated with low rates of high-grade cytokine release syndrome or neurological symptoms, ≥ grade 3 neutropenia was common at 26% and 69% of patients received growth factor support.

In contrast to these approaches, R^2 from the AUGMENT study is often accepted as a standard in relapsed FL given this trial had a placebo controlled arm, the regimen is safe, well tolerated and highly active with a median PFS of 39.4 months in relapsed FL after 1 prior line of therapy.[3] The AUGMENT trial was enriched for patients sensitive to rituximab, whereas in our trial, nearly a quarter of patients were refractory to rituximab, and 45% experienced POD24; despite this we observed the median PFS was not reached at median follow up of 41.7 months.[3] This supports an approach favouring lenalidomide and obinutuzumab at first relapse of FL adding further evidence to the GALEN trial with our longer follow-up establishing durability.[25]

The optimal duration and dose for the combination of lenalidomide and obinutuzumab immunotherapy in relapsed indolent lymphoma has not been established. The GALEN trial used extended duration lenalidomide for 18 months with 20 mg for 6 months followed by 10 mg for the remaining period as opposed to our trial using the same uniform dosing of 20 mg for 6–12 months depending on response, tolerability, and investigator discretion. The baseline characteristics of the GALEN trial and our trial are broadly similar except we had a higher proportion of FL POD24 patients at 36% compared to 27% in the GALEN trial.[25] The GALEN trial reported more than double the rate of Grade 3 to 4 neutropenia at 44% compared to our own rate at 20%. It also reported 5% febrile neutropenia compared to no febrile neutropenia in our cohort. We interrupted

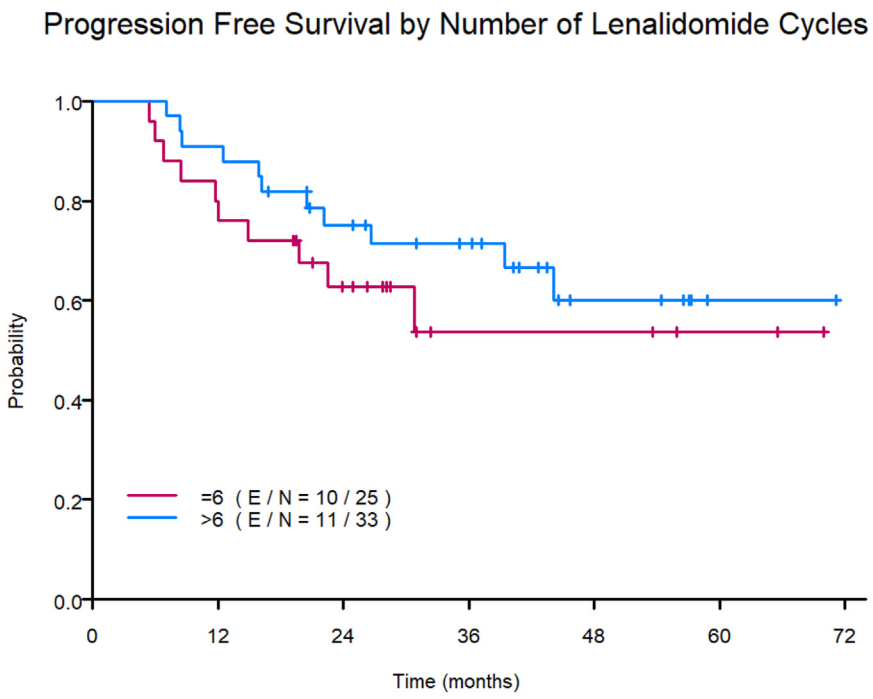


Fig. 4: Kaplan Meir progression free survival Curves for RP2D patients. Red line indicates progression free survival for patients who received 6 cycles of lenalidomide. Blue Line indicates progression free survival for patients who received more than 6 cycles of lenalidomide. Data provided as number of progression events (E) over number of patients receiving lenalidomide (N). RP2D, recommended phase 2 dose.

lenalidomide in 14% of our patients due to neutropenia as opposed to 28% in the GALEN trial. The marked neutropenia seen in the GALEN trial is likely due to the longer duration of lenalidomide use in the GALEN trial as compared to our trial. Despite 42% of our efficacy cohort only receiving a 6-month duration of lenalidomide, we report high overall response rates. Interestingly there were no significant differences in PFS or TTP by whether there were 6 cycles compared to >6 cycles of lenalidomide completed with median survival times not reached for both groups. Based on these findings, we postulate that a shorter duration of lenalidomide similar to our schedule may be adequate to achieve response, more tolerable and safer in preventing neutropenia and treatment discontinuation.

The limitations of our trial include a single institutional study and the absence of a control arm restricting us to cross trial comparisons to evaluate the clinical impact of our therapy. Comparing objective response rates across trials is limited by the use of different response criteria. Primary endpoints for our trial were measured using the Cheson 2007 Criteria,[11] GALEN used Cheson 1999[26] and Cheson 2007 criteria.[11] The other limitation of our study was that it comprised of less heavily pre-treated patients; only 25% of our patients had three or more prior lines of therapy.

The main strength of our study is the long follow-up period in the relapsed setting for indolent B cell lymphoma. Many trials use response rate as the primary endpoint but the better endpoint in indolent lymphomas like FL is median survival particularly PFS and TTP. Our long median follow-up of 3.5 years gave an estimated 4-year PFS of 55% which is impressive in the relapse setting for this combination given it is well tolerated and safe.

Except for high-risk disease such as POD24, indolent lymphoma, particularly FL, has a similar overall survival to age matched controls. The aim of therapy should be on maintaining quality of life by maximising remission free periods, minimising toxicity from therapy, and increasing the time spent off therapy. Obinutuzumab in combination with lenalidomide sequenced at first relapse is favoured given it is time limited to 6–12 months with manageable toxicity and median PFS in this study has not been reached. CAR T-cell therapies have demonstrated high response rates and particularly impressive survival times in the third line setting of heavily pre-treated patients. However, this is unlikely to lead to earlier sequencing of CAR T-cell therapy except in high-risk groups due to the significant toxicities associated with therapy and the societal cost. BiAb therapies have shown high response rates in trials but their durability in terms of survival have been limited and this is likely due to their later use in the relapse setting. Current trials incorporating BiAb in earlier lines and in combination with anti-CD20 or with R2 are

promising. For example, epcoritamab, a BiAb, with R2 in relapsed FL after 1 prior line of therapy reported a preliminary response rate of 95% with 73% CR among 41 evaluable patients at a median follow up of 4 months.[27] Longer follow-up is necessary to evaluate durability and safety, especially given high grade neutropenia was common with other bispecifics like mosunetuzumab and is a well-recognised side effect of R2. Alternative options including polatuzumab, tazemetostat, or zanubrutinib with obinutuzumab have a place in later therapeutic sequence given questions about efficacy and concerns regarding toxicity given continuous drug exposure. Most patients with indolent NHL will likely have several courses of therapy, therefore, we should prioritise those with fixed duration of treatment, manageable toxicity, coupled with durability of response.

Contributors

AG and LJN have access to and verify the underlying study data.

Conception and Design: NHF, LF, SSN.

Investigation: CKC, CO, JA, LJN, Formal Analysis: AG, CKC, LF, LJN.

Manuscript Writing: All authors.

Resources: LJN, NHF, PS, FBH, LF, JRW, RN, RES, SSN provided study materials and patients.

Supervision: LJN.

Data sharing statement

Data will not be shared at this point with results available on Clinicaltrials.gov; however, readers are welcome to contact the corresponding author.

Declaration of interests

AG: Received honorarium for participation in advisory board for Kite Pharma.

CKC: has received honorarium for participation in advisory boards with Kite/Gilead.

LF: No competing interests.

NF: has received research support from Celgene for undertaking the preclinical and clinical trials of lenalidomide.

PS: consultancy for Kite, a Gilead Company, Roche-Genentech, Hutchinson MediPharma, ADC Therapeutics, Incyte Morphosis and TG Therapeutics; research funding from Sobi Pharmaceuticals, AstraZeneca-Acerta, ALX Oncology, and ADC Therapeutics.

Research: Salary support from the Leukemia Lymphoma Society Scholar in Clinical Research Career Development Program, the Sabin Fellowship Award, and by Gilead Scholar in Clinical Research Award.

FJH: No competing interests.

LEF: No competing interests.

JRW: Consulting and Research Funding—BMS ADC Therapeutics, AstraZeneca, Genentech, Kite, Janssen, Kymera, Merck, Morphosys/Incyte, Novartis.

Consulting: Abbvie, GenMab, Regeneron, and SeaGen.

CO: No competing interests.

JA: No competing interests.

RN: Consulting–Abbvie, Incyte.

Honorarium for Educational Events—AstraZeneca, ScienciaCME, MedPage, Curio Science.

Travel Support for Attending Meetings–Viracta Therapeutics, Inc. Studio E.R. Congressi s.r.l. World Health Communications, Ltd.

RES: Grants–Seagen, BMS, GSK and Rafael Pharmaceuticals.

SSN—has received research support from Kite/Gilead, Cellectis, Poseida, Merk, Acerta, Karus, BMS, Unum Therapeutics, Allogene, and Precision Biosciences; served as consultant and advisory board member for Kite/Gliead, Celgene, Novartis, Unum Therapeutics, Pfizer, Merck, Precision Biosciences, Cell Medica, Incyte, Allogene, Calibr, and Legend Biotech; has patents related to cell therapy.

CF: Consultant: Abbvie, Bayer, BeiGene, Celgene, Denovo Biopharma, Foresight Diagnostics, Genentech/Roche, Genmab, Gilead, Karyopharm, N-Power Medicine, Pharmacyclics/Janssen, SeaGen, Spectrum.

Stock Options: Foresight Diagnostics, N-Power MedicineResearch Funding: 4D, Abbvie, Acerta, Adaptimmune, Allogene, Amgen, Bayer, Celgene, Cellectis EMD, Gilead, Genentech/Roche, Guardant, Iovance, Janssen Pharmaceutical, Kite, Morphosys, Nektar, Novartis, Pfizer, Pharmacyclics, Sanofi, Takeda, TG Therapeutics, Xencor, Ziopharm, Burroughs Wellcome Fund, Eastern Cooperative Oncology Group, National Cancer Institute, V Foundation, Leukemia and Lymphoma Sociery, Cancer Prevention and Research Institute of Texas: CPRIT Scholar in Cancer Research.

LJN: has received honorarium for participation in advisory boards/consulting from Abbvie, ADC Therapeutics, BMS/Celgene, Caribou Biosciences, Daiichi Sankyo, Epizyme, Genentech/Roche, Genmab, Janssen, Incyte, Ipsen, Novartis, and Takeda; research support from BMS/Celgene, Caribou Biosciences, Daiichi Sankyo, Epizyme, Genentech/Roche, Genmab, Gilead/Kite, IGM Biosciences, Ipsen, Janssen, Novartis, and Takeda.

Acknowledgements

This study was financially funded by Genentech as well as an MD Anderson Core grant NCI # CA16672.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102747.

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