Efficacy and safety of MIL62, a novel glycoengineered type II anti-CD20 monoclonal antibody, combined with lenalidomide in patients with relapsed/refractory follicular lymphoma or marginal zone lymphoma: a multicentre, single-arm, phase 1b/2 trial

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Summary

Background MIL62, a novel glycoengineered type II anti-CD20 monoclonal antibody, with a nearly completely afucosylated N-glycans in Fc region, has demonstrated superior activity compared with rituximab and obinutuzumab in vitro and in vivo, respectively.

Methods This multicentre, single-arm, phase 1b/2 trial aimed to explore the efficacy, pharmacokinetics, and safety of MIL62 combined with lenalidomide in patients with relapsed/refractory (R/R) follicular lymphoma (FL) or marginal zone lymphoma (MZL). Eligible patients included those who had histopathologically confirmed CD20 positive FL (grade 1–3a) or MZL and failed to be treated with rituximab. Patients received intravenously infused MIL62 1000 mg (cycle 1: day 1, 15; cycles 2–8: day 1, cycles 10 and 12: day 1) combined with oral lenalidomide (once a day, days 2–22, the initial dose was 10 mg, and the maximum dose was 20 mg) for 12 cycles, 28 days as a cycle. The primary endpoint was objective response rate (ORR) assessed by investigator per Lugano 2014 criteria every 3 cycles. This study was registered in ClinicalTrials.gov (NCT04110301).

Findings Between November 22, 2019 and December 22, 2020, 54 patients were enrolled from 11 hospitals in China and received study treatment. Fifty patients were included in the efficacy analysis set, and 43 patients (86%, 95% CI: 73, 94) achieved objective response, meeting the pre-specified primary endpoint. Disease control rate was 96% (48/50, 95% CI: 86, 100), proportion of patients with duration of response (DoR) > 6 months was 77% (33/43). The median follow-up for survival was 12.3 months (IQR 12.0–12.6). The 1-year progression-free survival rate was 72% (95% CI: 57, 83), 9-month DoR rate was 74% (95% CI: 58, 85), and 1-year overall survival rate was 98% (95% CI: 85, 100). Most common TRAEs were neutropenia (93%, 50/54), leukopenia (85% 46/54), thrombocytopenia (61% 33/54), lymphopenia (32% 17/54), and alanine aminotransferase increased (20% 11/54).

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Interpretation MIL62 combined with lenalidomide showed promising efficacy in patients with R/R FL and MZL. A multicentre, randomized, open-label, phase III trial of MIL62 combined with lenalidomide versus lenalidomide in anti-CD20 monoclonal antibody refractory FL patients is ongoing (NCT04834024).

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Keywords: MIL62; Type II anti-CD20 monoclonal antibody; Relapsed/refractory follicular lymphoma; Relapsed/refractory marginal zone lymphoma

Research in context

Evidence before this study

Patients with follicular lymphoma (FL) or marginal zone lymphoma (MZL) have few treatment options after failure of immunochemotherapy regimens such as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) and RB (rituximab and bendamustine). We searched PubMed for all clinical trial publications up to May 2nd 2024 on second or further-line therapy in patients with FL or MZL, published in any language, with the terms ("indolent non-Hodgkin lymphoma" or "follicular lymphoma" or "marginal zone lymphoma") and ("lenalidomide") and ("CD20") and ("relapsed or refractory"), and found 2 matched articles. Prior to this study, 2 published studies supported the notion that lenalidomide combined with anti-CD20 monoclonal antibody was well tolerated and effective in relapsed or refractory (R/R) FL or MZL.

Added value of this study

The results of this study suggest that MIL62, a novel glycoengineered type II anti-CD20 monoclonal antibody combined with lenalidomide have promising efficacy in patients with R/R FL and MZL, including those with progression of disease within 24 months (POD24) and rituximab refractory.

Implications of all the available evidence

These results may indicate the potential use of chemo-free combination therapy of MIL62 combined with lenalidomide in patients with FL and MZL. The clinical outcomes of MIL62 combined with lenalidomide will be further assessed in an ongoing phase III trial (NCT04834024).

Introduction

Follicular lymphoma (FL) and marginal zone lymphoma (MZL) are common pathological subtypes of non-Hodgkin lymphoma (NHL), which belong to indolent lymphoma. In China, FL accounts for about 8% of B-cell NHL, while MZL accounts for about 12%.[1] The early progression of indolent lymphoma patients is directly related to the poor prognosis, with approximately 20% of patients experiencing recurrence or progression of disease within 24 months (POD24) after diagnosis.[2] These patients often have poor prognosis, therefore new treatment options are urgently needed to address unmet clinical needs.

The treatment schemes of FL and MZL are roughly in common. Chemotherapies are based on anti-CD20 monoclonal antibody (mAb) such as rituximab, and obinutuzumab, combined with chemotherapy (CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone]/CVP [cyclophosphamide, vincristine, and prednisone]), or bifunctional alkylating agents (chlorambucil and bendamustine), or immunomodulator (lenalidomide); anti-CD20 mAb monotherapy is also used for maintenance therapy. In addition, phosphoinositide 3′-kinase (PI3K) inhibitors are used only for third-line and above of patients with relapsed or refractory (R/R) FL or MZL. Although several PI3K inhibitors (duvelisib, linperlisib, and copanlisib) have recently been approved by the China National Medical Products Administration (NMPA) for R/R FL patients received at least two prior systemic therapies through single-arm, registration clinical trials, the long-term safety and survival benefits of PI3K inhibitors remain to be further investigated.[3–6]

Lenalidomide is an immunomodulatory agent, which exerts anti-tumor activity by directly acting on lymphocytes and immune microenvironment, and improves antibody-dependent cell-mediated cytotoxicity (ADCC) activity, regulates B-cell signal pathway as well as enhances T-cell function.[7] When combined with rituximab, lenalidomide has synergistic effects, increasing apoptosis and cell-mediated cytotoxicity.[8] The combination of lenalidomide and rituximab shows potential efficacy in patients with R/R FL and MZL. It was approved by the US Food and Drug Administration (FDA) for this indication in May 28, 2019 and approved by the China NMPA in November 17, 2020.

The chemo-free combination therapy of lenalidomide and rituximab (R2) for B-NHL patients has been widely applied since the positive results released from the AUGUMENT and REVELANCE studies.[8,9] MIL62, a novel glycosylated type II anti-CD20 mAb with enhanced affinity for the FcγRIIIa receptors and direct B-cell killing effects, developed by Beijing Mabworks Biotech Co Ltd., Beijing, China, has shown the improved ADCC function than rituximab in vivo and in vitro.[10]

MIL62 has been demonstrated that the ADCC activity is obviously superior to rituximab and obinutuzumab in vitro pharmacodynamic studies; furthermore, it can significantly inhibit the growth of CD20-positive human B-cell lymphoma transplanted subcutaneously in Daudi nude mice, causing tumor regression, and its activity is equivalent to obinutuzumab, obviously stronger than rituximab, as shown in vivo pharmacodynamic studies. The objective response rate (ORR) is similar to obinutuzumab when MIL62 is used alone for CD20-positive NHL in the phase I and phase II study (NCT04103905).[10–12] It was shown that MIL62 had a manageable safety profile and had a favourable efficacy in patients with FL and MZL in the phase I study (data unpublished).

Therefore, we suppose that the combination of MIL62 and lenalidomide might be even more effective than rituximab combined with lenalidomide. Based on this assumption, we conducted this multicentre, single-arm, phase 1b/2 trial to explore the efficacy and safety of MIL62 combined with lenalidomide in patients with previously treated R/R FL and MZL in China.

Methods

Study design and participants

This multicentre, single-arm phase 1b/2 trial enrolled patients with R/R FL or MZL from 11 hospitals in China. Eligible patients aged 18 years or older with histopathologically confirmed CD20-positive FL (grade 1–3a) or MZL; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0–2; ≥1 measurable lesion (Lugano 2014 criteria) on computed tomography (CT) scan or magnetic resonance imaging (MRI) (longest diameter >15 mm and shortest diameter >10 mm); the estimated life expectancy ≥ 6 months. Patients had received adequate treatment with rituximab-containing regimens or progressed during the rituximab-containing treatments; patients had disease relapsed or refractory to one to four prior lines of treatment, including at least one line rituximab-containing treatments. Required initial laboratory values included platelet count ≥75 × 10^9/L, absolute neutrophil count (ANC) ≥1.5 × 10^9/L, hemoglobin ≥90 g/L, creatinine clearance ≥60 mL/min, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × upper limit of normal (ULN), and serum total bilirubin ≤1.5 × ULN. Patients were excluded if they had transformed lymphoma; central nervous system (CNS) lymphoma or leukemia; Positive human immunodeficiency virus (HIV) or hepatitis B or C serology; serious comorbidities (eg, severe cardiac disease or lung diseases including obstructive pulmonary disease and bronchospasm); other previous malignancies in the past 3 years. Previous treatment with any mAb (except rituximab) within 3 months, or use of obinutuzumab within 12 months were additional exclusion criteria.

Ethics

The protocol of this study was approved by the Independent Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College and all the ethics committees of all participating hospitals (reference number, 19/183-1967), and the trial was performed in accordance with the Declaration of Helsinki, Guidelines for Good Clinical Practice, and applicable laws and regulations. All patients provided written informed consent prior to any trial-related activity.

Procedures

Patients received intravenously infused MIL62 in 28-day cycles at 1000 mg given on days 1, 15 of cycle (C) 1, on day (D) 1 only of cycles 2–8, and then on D1 of C10 and C12, respectively. MIL62 dose was not reduced, but postponed in cases of toxicity until resolution of adverse events (AEs).

Lenalidomide was given as an initial 10 mg oral dose once daily on days 2–22 of C1. After C1, the lenalidomide dose could be increased to 15 mg once daily on Days 2–22 of C2. After C2, the lenalidomide dose could be increased to 20 mg once daily on Days 2–22 of repeating 28-day cycles for a total maximum of 12 cycles until disease progression or intolerable toxicity. The dose of lenalidomide could be adjusted according to the principle of dose adjustment. Doses were successively reduced from 20 mg to 15 mg, 10 mg, and 5 mg, with no dose re-escalation permitted, and the 5 mg was minimum dose and 20 mg was maximum dose. The daily administration time of lenalidomide was relatively fixed, either with or without food. If the patients miss a dose of lenalidomide, they may still take it up to 12 h after the time they would normally take it. If more than 12 h have elapsed, they should skip the dose for that day. The next day, they should take lenalidomide at the usual time. They should not take 2 doses to make up for the one that they missed.

Premedication for MIL62 was allowed to avoid infusion related reaction, including anti-histamines (e.g. diphenhydramine with 40 mg), acetaminophen (650–1000 mg) and glucocorticoid (e.g. dexamethasone with 10 mg or methylprednisolone with 40 mg). HBsAg-positive or HBcAb-positive but HBV DNA negative

patients were allowed to be enrolled, but should take appropriate doses of entecavir during study treatment, or could continue to take antiviral treatment more than 6 months after the last administration of MIL62 based on the investigators' assessment of the patients' condition to prevent reactivation of hepatitis B virus. If there are intolerable AEs during study treatment, MIL62 and/or lenalidomide may be delayed, or the dosage of lenalidomide may be decreased.

Efficacy

Tumor assessments were performed once every 3 cycles during treatment and once at the end of treatment (EOT) or until disease progression or relapse. Response was assessed by investigators through enhanced CT/MRI (neck, chest, abdomen, and pelvis) according to the Lugano 2014 criteria.[13] To confirm a complete response (CR), patients with positive bone marrow (BM) at screening were required to have a post-screening BM biopsy within 28 days of first achieving CR or unconfirmed CR (uCR).

Pharmacokinetic (PK)/Pharmacodynamic

Serum samples for PK and pharmacodynamic analysis were collected pre-dose and at prespecified post-dose time points, respectively. Concentrations of MIL62 were evaluated using a specific and validated enzyme-linked immunosorbent assay (ELISA) method. PK parameters of MIL62 were calculated using non-compartmental analysis (NCA).

For pharmacodynamic analysis, the absolute cell counts of peripheral blood immune-cell subsets (phenotyping of T cells, B cells) were measured by flow cytometry. Lymphocytes were gated as high CD45 fluorescence intensity and low side scatter intensity; B cells were defined as $CD3^{-}CD19^{+}$ lymphocytes, CD4 T cells were defined as $CD3^{+}CD4^{+}$ lymphocytes, and CD8 T cells were defined as $CD3^{+}CD8^{+}$ lymphocytes.

Safety

Safety was reviewed once a week during the first two cycles, once every two weeks from the third to the fourth cycle, then once every cycle and once after treatment. Safety evaluations included AEs, serious adverse events (SAEs), laboratory tests, physical examination, vital signs and electrocardiogram, etc. AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0, and were categorized by study treatment relatedness. SAEs were those causing significant disability, hospitalisation, life-threatening status, or death.

Outcomes

The primary endpoint was ORR, defined as the proportion of patients with CR and partial response (PR).

The secondary endpoints were duration of response (DoR), defined as the time from the date of first response to the date of disease progression or death of any reason; proportion of patients with DoR > 6 months; disease control rate (DCR), defined as the proportion of patients with CR, PR and stable disease (SD); 1-year progression-free survival (PFS) rate, defined as the percentage of patients who have no tumor progression or death after receiving the first dose of study drug for one year; safety, and PK/pharmacodynamic characteristics.

Statistics

The sample size was based on a Simon's two-stage design. The first stage will recruit 30 patients, if there are >14 responders (CR or PR), the trial will continue to the second stage, otherwise will stop for efficacy. The second stage will recruit further 23 patients, if there is a total of > 31 responders in both the first and the second stage, then can continue to the phase III trial.

The analysis was per-protocol, the efficacy population included all those who had completed ≥ 2 cycles study treatment, had a valid baseline, and had ≥ 1 efficacy assessment after study treatments. Safety was assessed in all patients enrolled in the study who received ≥ 1 dose of either study drug, and had ≥ 1 safety assessment after study treatments. Safety analyses were summarized descriptively. Time-to-event endpoints were assessed using the Kaplan–Meier method. Responses were reported as percentages of patients, with Clopper-Pearson 95% confidence intervals (CIs). Median time to event and response rates were calculated with 95% CIs. Post hoc analyses included outcomes within patient subgroups with age, sex, ECOG PS, elevated lactate dehydrogenase (LDH) at baseline, extranodal involvement, baseline BM involvement, number of prior treatments, Follicular Lymphoma International Prognostic Index 2 (FLIPI-2) score,[14] POD24, and rituximab refractory. SAS version 9.4 (SAS Institute, Cary, NY, USA) was used for all analyses.

This study was registered with ClinicalTrials.gov, number NCT04110301.

Role of funding source

This study was initiated by Beijing Mabworks Biotech Co Ltd., Beijing, China and partly supported by the National Science and Technology Major Project for Key New Drug Development (2017ZX09304015). The funders and the principle investigator professor Yuankai Shi of this study had roles in study design, data collection, data analysis, data interpretation, and in the writing, revision, and approval of the article.

Results

Patient disposition and demographics

The flowchart of this study is presented in Fig. 1. Between November 22, 2019 and December 22, 2020, 54

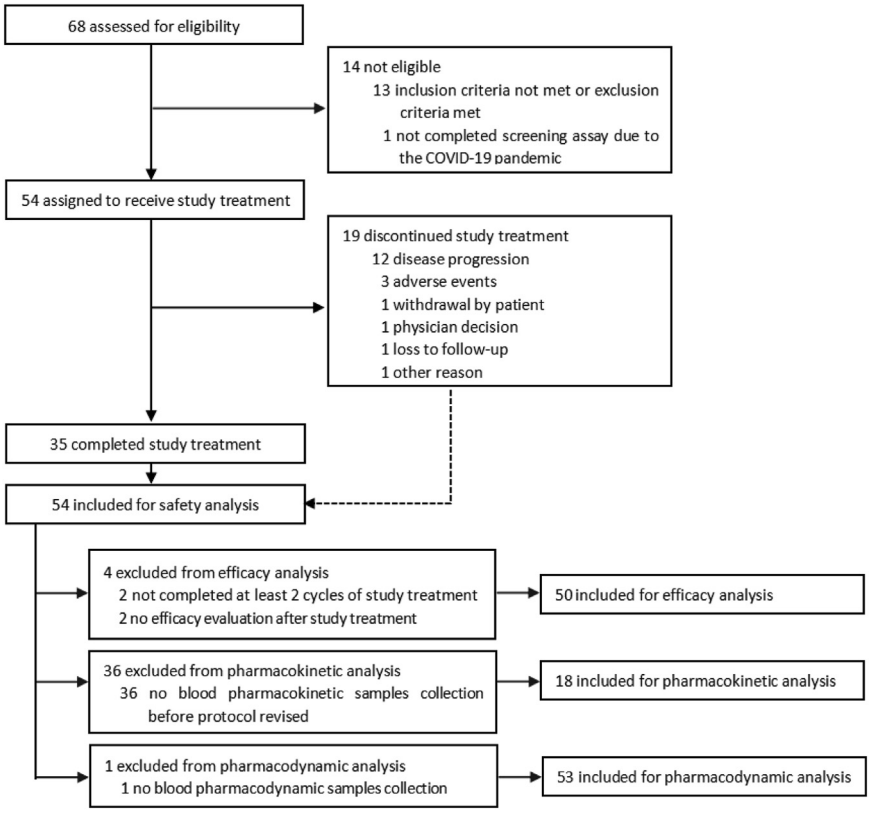

Fig. 1: **Consort flowchart**.

patients were enrolled from 11 hospitals in China and received the study treatment. Fifty-four patients were in the safety population and 50 patients were in the efficacy population.

The baseline characteristics of the patients are shown in Table 1. The median age of patients was 50.0 years (IQR 42–57), and 31 patients (57%) were male. A total of 51 patients (94%) had FL, and 3 patients (6%) had MZL. Most patients had Ann Arbor stage of III-IV (87%, 47/54). The median number of prior treatments was 1 (IQR 1–2). Thirty-five patients (65%) had POD24, 20 patients (37%) were refractory to rituximab, and 25 patients (46%) had high tumor burden per GELF criteria.[15] Twenty-three patients (43%) were intermediate or high risk according to the FLIPI-2.[14]

Efficacy

The median study treatment time of MIL62 and lenalidomide was 10.5 months (IQR 5.1–10.8) and 11.1 months (IQR 5.8–11.4), respectively. Thirty-nine patients (72%) received MIL62 treatment for more than 6 cycles, 6 (11%) for 5–6 cycles, 7 (13%) for 3–4 cycles, and 2 (4%) with less than 2 cycles. For the lenalidomide treatment, 34 (63%) patients had at least one dose adjustment (including delay, interruption and dose reduction), 35 (65%) patients had a dose reduction, and 44 (82%) patients had an interruption of administration. The median cumulative exposure of lenalidomide was 3045 mg (IQR 1380–4090). The percentage of patients with average relative dose intensity (ARDI) of lenalidomide was 85% (46/54, range: 80%, 120%). Fifty patients were included in the efficacy analysis population, with a median follow-up time of 12.3 months (IQR 12.0–12.6), and 43 (86%, 95% CI: 73, 94) patients achieved objective response, including 13 (26%) with CR and 30 (60%) with PR. DCR was 96% (48/50, 95% CI: 86, 100), proportion of patients with DoR > 6 months was 77% (33/43), 9-month DoR rate was 74% (95% CI: 58, 85), and 12-month PFS rate was 72% (95% CI: 57, 83) (Table 2, Figs. 2, and 3A and B). The ORR was 86% (43/50), which exceeded the original statistical assumptions (> 31 patients, ≥ 65%), supporting the role for MIL62 combined with lenalidomide treatment for this patient population and worth further investigation in phase III study.

In the post-hoc analyses, among 31 patients with POD24, 26 (84%) patients had an objective response, including 9 (29%) with CR and 17 (55%) with PR. DCR was 97% (30/31, 95% CI: 83, 100). Proportion of patients with DoR > 6 months was 73% (19/26). 9-month DoR rate and 12-month PFS rate were 68% (95% CI: 46,

	All patients (n = 54)
Age, years; median (IQR)	50 (42–57)
Sex	
Male	31 (57%)
Female	23 (43%)
ECOG PS	
0	27 (50%)
1	26 (48%)
2	1 (2%)
Histology	
FL	
Grade 1–2	40 (74%)
Grade 3a	11 (20%)
MZL	3 (6%)
Ann Arbor stage	
I-II	6 (11%)
III-IV	47 (87%)
Unknown	1 (2%)
Bone marrow involvement	13 (24%)
Bulk disease (≥6 cm)	16 (30%)
Extranodal involvement	22 (41%)
LDH > ULN	16 (30%)
FLIPI-2 score	
0–1	30 (56%)
2	11 (20%)
3–5	12 (22%)
Unknown	1 (2%)
No. of prior treatments	
Median (IQR)	1 (1, 2)
1	34 (63%)
2–4	20 (37%)
POD24	35 (65%)
Refractory to rituximab	20 (37%)
High tumor burden per GELF[a]	25 (46%)

Data are n (%) or median (IQR), unless otherwise specified. ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; FLIPI-2, follicular lymphoma international prognostic index 2; GELF, Groupe d'Etude des Lymphomes Folliculaires; LDH, lactate dehydrogenase; MZL, marginal zone lymphoma; POD24, progression of disease within 24 months; PS, performance status; ULN, upper limit of normal; IQR, interquartile range. The definition of refractory to rituximab: progressive disease during or within 6 months after last rituximab-containing regimen treatment, or no response for ≥4 rituximab-containing regimen treatment cycles. [a]GELF criteria were defined according to previously published report.[15]

Table 1: **Baseline characteristics.**

83) and 68% (95% CI: 47, 82), respectively. Similarly, among 20 patients who were refractory to rituximab, 16 (80%) patients had an objective response (Table 2 and Fig. 2), including 5 (25%) with CR and 11 (55%) with PR. DCR was 100% (20/20, 95% CI: 83, 100). Proportion of patients with DoR > 6 months was 75% (12/16). 9-month DoR rate and 12-month PFS rate were 69% (95% CI: 41, 86) and 72% (95% CI: 46, 87), respectively. The results for PFS, and DoR in the proportion of patients with refractory or non-refractory to rituximab are presented in Fig. 3A and B, respectively.

Subgroup analysis was also performed on efficacy population showing consistent response across different age, sex, ECOG PS, extranodal involvement, baseline BM involvement, number of prior treatments and FLIPI-2 score. LDH level at baseline was adversely correlated with patient response (ORR, 94% versus 69%, $p = 0.016$) (Appendix, Figure S3).

PK/Pharmacodynamic

Eighteen patients were included in the PK analysis. The mean serum concentration–time profiles of MIL62 for patients from cycle 1 to cycle 12 are shown in Appendix, Figure S1. Following intravenous infusion, MIL62 serum concentrations peak was reached at the end of each infusion. After repeated administration, MIL62 serum concentration reached a stable state at C4D1 (Appendix, Figure S1), and appears to be eliminated with a $t_{1/2}$ of about 20 days. There was no significant accumulation of drug after repeated intravenous infusion with MIL62 (Appendix, Figure S1).

Fifty-three patients were included for pharmacodynamic analysis. B-cells ($CD3^{-}CD19^{+}$ lymphocytes) were almost completely depleted (< 5 cells/μL) at 24 h after the first dose administration of MIL62 and remained depleted during the study treatment (Appendix, Figure S2A). MIL62 administration resulted in a rapid and transient reduction in T cells ($CD3^{+}CD4^{+}$ lymphocytes and $CD3^{+}CD8^{+}$ lymphocytes) in the peripheral blood circulation in all patients. Later, it is noticeable that after the first cycle of MIL62 combined with lenalidomide, the T-cell numbers were quickly recovered and slightly above baseline and then remained a relatively stable state (Appendix, Figure S2B–D).

Safety

Among 54 safety evaluable patients, all experienced at least one treatment-emergent adverse events (TEAEs), and at least one treatment-related adverse events (TRAEs). Grade 3 or above TEAEs and TRAEs were observed in 46 (85%) and 43 (80%) patients, respectively.

SAEs were observed in 17 (32%) patients and recovered with appropriate supportive care. SAEs of 13 (24%) patients were related to MIL62 and/or lenalidomide. No treatment-related deaths occurred during the study period. Two (4%) patients had AEs that led to MIL62 permanent treatment discontinuation and 16 (30%) patients had AEs that led to MIL62 interruption. Twelve (22%) patients had AEs that modified lenalidomide dose and 24 (44%) patients had AEs that suspended lenalidomide administration. Three (6%) patients had AEs that led to MIL62 or lenalidomide permanent treatment discontinuation, one patient had pulmonary toxicity and dyspnea, one patient had neutropenia and leukopenia, and one patient had infusion related reaction.

Efficacy	Efficacy population (n = 50)	Rituximab refractory (n = 20)	POD24 (n = 31)
CR	13 (26%)	5 (25%)	9 (29%)
PR	30 (60%)	11 (55%)	17 (55%)
SD	5 (10%)	4 (20%)	4 (13%)
PD	2 (4%)	0 (0%)	1 (3%)
ORR	43 (86% [73, 94])	16 (80% [56, 94])	26 (84% [66, 95])
DCR	48 (96% [86, 100])	20 (100% [83, 100])	30 (97% [83, 100])
Proportion of patients with DoR > 6 months	33/43 (77%)	12/16 (75%)	19/26 (73%)
9-month DoR rate	74% (58, 85)	69% (41, 86)	68% (46, 83)
12-month PFS rate	72% (57, 83)	72% (46, 87)	68% (47, 82)
12-month OS rate	98% (85, 100)	100% (100, 100)	100% (100, 100)

Data are n (% [95% CI]) or n (%). Responses were assessed in the efficacy analysis population (n = 50) according to the Lugano 2014 criteria.[13] CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; POD24, progression of disease within 24 months; PR, partial response; SD, stable disease.

Table 2: **Best overall response.**

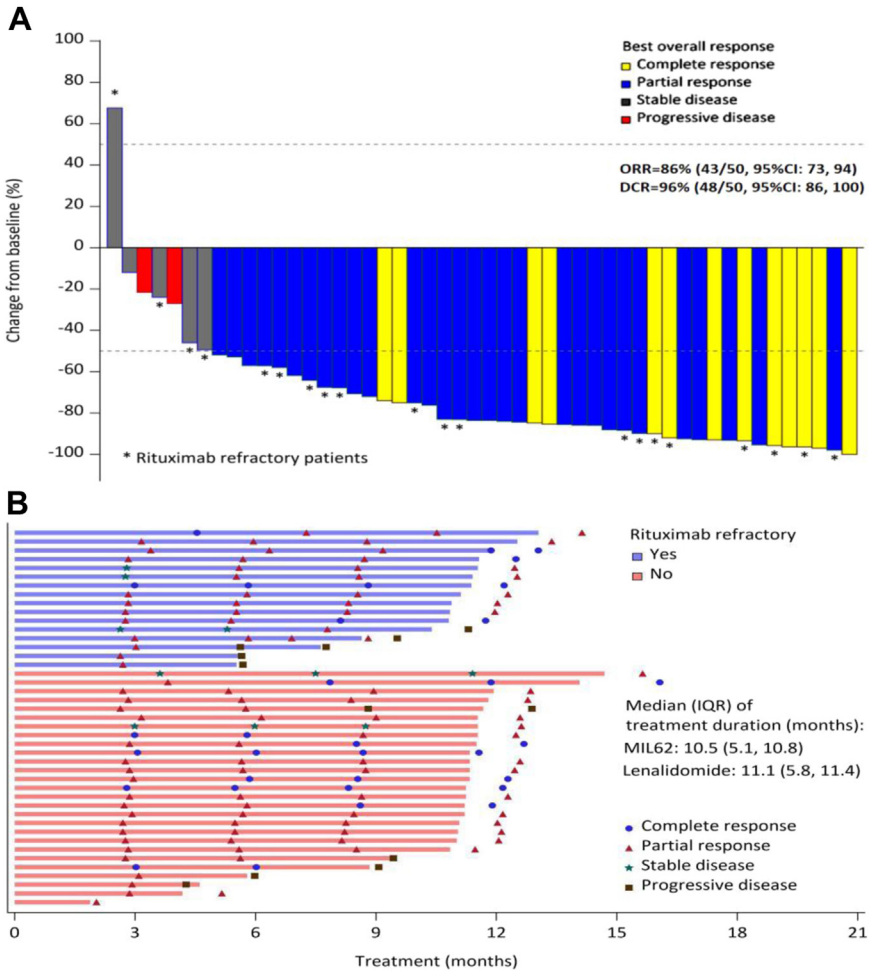

***Fig. 2:* A. Waterfall plot of best percentage change of target lesions for the efficacy analysis population (n = 50)**. Grey dotted lines represent 50% decrease and 50% increase from baseline in total sum of target lesion diameters. CI, confidential interval; DCR, disease control rate; ORR, objective response rate. **B. Swimmer plot for responders (n = 43, complete response or partial response)**. IQR, interquartile range.

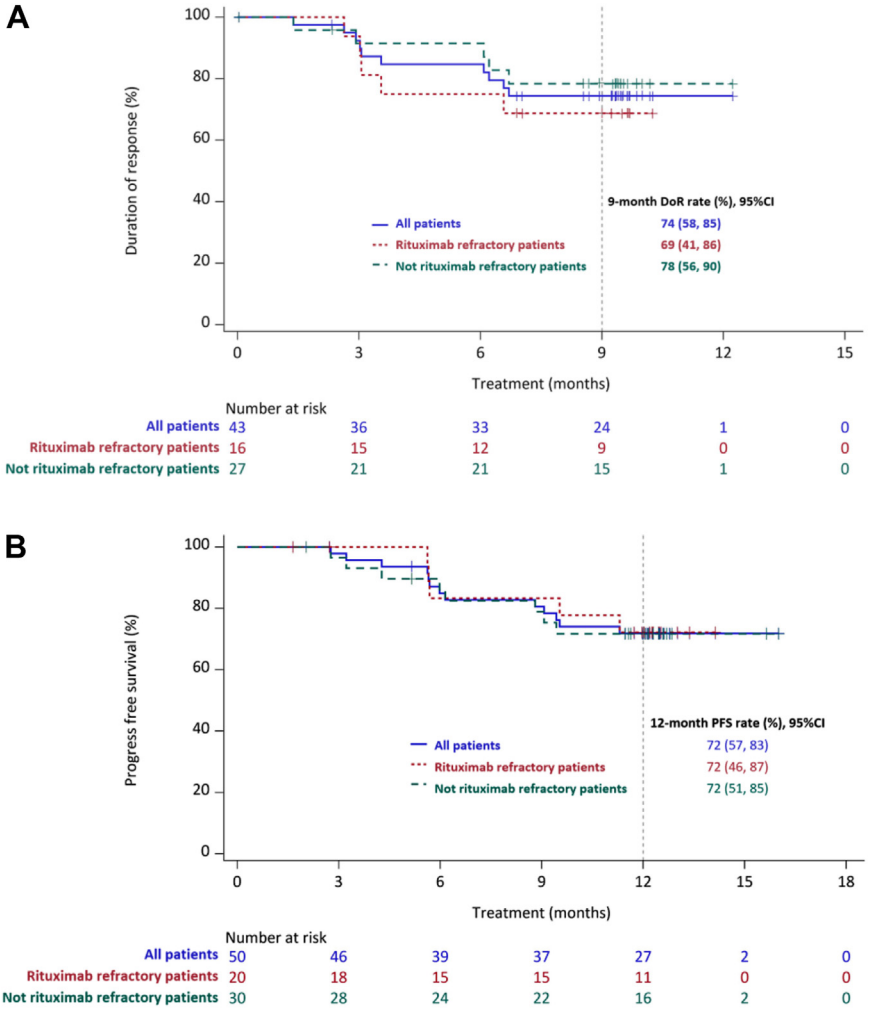

***Fig. 3*: A. Kaplan–Meier estimates of DoR for responders (n = 43, complete response or partial response)**. CI, confidence interval; DoR, duration of response. **B. Kaplan–Meier estimates of PFS for the efficacy analysis population (n = 50)**. CI, confidence interval; PFS, progression-free survival.

Most common TRAEs occurring in ≥ 10% of patients were neutropenia (93%, 50/54), leukopenia (85%, 46/54), thrombocytopenia (61%, 33/54), lymphopenia (32%, 17/54), ALT increased (20%, 11/54), rash (19%, 10/54), infusion related reaction (17%, 9/54), pneumonia (13%, 7/54), AST increased (11%, 6/54), asthenia (11%, 6/54), and hyperbilirubinemia (11%, 6/54). Grade 3 or above TRAEs observed in ≥ 10% of patients consisted of neutropenia (59%, 32/54), leukopenia (22%, 12/54), thrombocytopenia (20%, 11/54), and lymphopenia (11%, 6/54). Thirty-one (57%) patients received recombinant human granulocyte colony-stimulating factor (rhG-CSF) support, and the median dose of rhG-CSF was 300 μg/d (IQR 150–300). The incidence of MIL62 infusion related reaction was 17% (9/54), most of which was grade 1–2 (Table 3).

Discussion

The results of this phase 1b/2 trial demonstrated that the efficacy and safety profile of MIL62 combined with lenalidomide treatment is inspiring in R/R FL or MZL patients. The primary endpoint was met with the proportion of patients who achieved an objective response at 86% (43/50), with 26% (13/50) achieving CR, meeting the pre-specified primary endpoint.

This study has several limitations. Anti-tumor responses assessment did not use an Independent Review Committee; this is a single-arm non-randomization study, and did not have a control group. Thus, only historical cross-comparisons and subgroup analysis comparisons with other studies could be made. In the GALEN study or MAGNIFY study,[12,16] rituximab-refractory patients accounted for 26% (23/88) and

TRAEs	All grades	Grade 3/4
Neutropenia	50 (93%)	32 (59%)
Leukopenia	46 (85%)	12 (22%)
Thrombocytopenia	33 (61%)	11 (20%)
Lymphopenia	17 (32%)	6 (11%)
ALT increased	11 (20%)	0
Rash	10 (19%)	1 (2%)
Infusion related reaction	9 (17%)	3 (6%)
Pneumonia	7 (13%)	1 (2%)
AST increased	6 (11%)	0
Asthenia	6 (11%)	0
Hyperbilirubinemia	6 (11%)	0

Data are n (%). All grades and all grade 3/4 TRAEs reported in ≥ 10% of patients were shown. ALT, alanine aminotransferase; AST, aspartate aminotransferase; TRAEs, treatment related adverse events.

***Table 3*: Most common TRAEs (≥ 10%) reported during the entire study in the safety population (n = 54).**

35.5% (140/394), respectively. By contrast, in this study, rituximab-refractory patients accounted for 40% (20/50) in the efficacy analysis population.

Although the proportions of rituximab-refractory patients and POD24 patients were higher in this study, the ORR of overall population (86%, 43/50) was still slightly higher than that in the GALEN study (84%, 24/88) or MAGNIFY study (71%, 133/394).[12,16] Additionally, in the subgroup of patients with rituximab-refractory, the ORR in this study (80%, 16/20) is higher than that of GALEN study (69.6%, 16/23) or MAGNIFY study (60%, 84/140),[12,16] but similar with GADOLIN study (79%, 151/192).[17] And in the POD24 subset, the ORR in this study (84%, 26/31) also is higher than that of GALEN study (70.8%, 17/24) or MAGNIFY study (65%, 86/133).[12,16]

In the published PI3K inhibitors studies, the ORR of the idelalisib,[18] copanlisib,[19] and duvelisib[20] for patients with R/R indolent NHL (copanlisib and duvelisib were in FL or MZL) was 57% (71/125), 61% (77/127), and 42% (42/101), respectively. The ORR of these studies was lower than that in this study. It is worth noting that in recent years, PI3K inhibitors have exposed an increasing number of safety issues, and a limited number of approved drugs have suffered delisting or abandonment of marketing applications due to safety issues.[21,22]

Response rates in this study are more similar to those observed in studies evaluating chimeric antigen receptor T-cell (CAR-T) therapies and CD3 × CD20 bi-specific mAbs in patients with R/R FL, in which similar ORR (86% versus 86%–94%), but lower CR rates (26% versus 60%–79%) were reported. However, cytokine release syndrome (CRS) did not occur in this study, but it was very common in CAR-T therapies and bi-specific mAbs, with an incidence rate of 44%–59%.[23–26]

Subgroup analysis showed that the efficacy of patients with other baseline characteristics, including age, sex, ECOG PS, and so on, was similar except for LDH baseline levels.

Of the 54 patients enrolled, 4 (7%) were not included in the efficacy analysis population. The first patient experienced a grade 2 TEAE (herpes zoster) after cycle 2 study treatment, and after 1-week active treatment for this AE, the patient loss follow-up without efficacy evaluation. The second patient was permanently discontinue the study treatment due to a grade 4 infusion related reaction during the first infusion, although recovered after symptomatic treatment. The third patient failed to return to the hospital for examination due to the COVID-19 pandemic, and then voluntarily withdrew from this study. The fourth patient had a high tumor burden at baseline, with 3/6 target lesions diameter > 6 cm, SPD of 13441.81 mm^2, and 7 non-target lesions. Unplanned imaging (C1D4) showed disease progression after C1D1 administration. So this patient was not included in the efficacy analysis population due to have less than 2 cycles.

The AEs and ≥ grade 3 AEs of this study were similar to the GALEN study,[12] MAGNIFY study,[16] and GADOLIN study,[17] with acceptable safety profile and no unexpected toxicity.

As an immunomodulator, lenalidomide functions through many mechanisms, such as immunomodulation, directly killing tumor cells, inhibiting angiogenesis, and changing tumor microenvironment. Studies have shown that lenalidomide can enhance T-cell and NK-cell function, and it had a synergistic effect with anti-CD20 mAb on promoting immune-mediated cytotoxicity against B-NHL cells, thus further increasing the innate immunity and adaptive immune activity of anti-CD20 mAb. In agreement with the data in this study, the $CD3^+CD4^+$ T cell, and $CD3^+CD8^+$ T cell numbers in patients were quickly returned to or slightly above baseline after the first cycle of MIL62 combined with lenalidomide treatment, and then remained stable. It may be that lenalidomide indirectly assisted MIL62 in inducing B-cells apoptosis from FL and MZL patients through the activation of these immune cells. Therefore, the combination of MIL62 and lenalidomide can more effectively activate the immune killing effect of MIL62 on CD20-positive B-cell lymphoma, obtaining better clinical efficacy.[7,11]

In summary, the chemo-free combination therapy of MIL62 and lenalidomide showed promising efficacy and manageable safety profile in Chinese patients with CD20-positive R/R FL or MZL, especially in those who were POD24 and rituximab refractory. Based on previously published studies, the combination of MIL62 and lenalidomide appears potentially similar efficacy or slightly higher response to the current standard post-line treatments for R/R FL, including obinutuzumab

combined with bendamustine, PI3K inhibitors, and lenalidomide combined with rituximab, without additional safety concerns, making this regimen a valuable second-line treatment option.

Therefore, we have carried out a multicentre, randomized, open-label phase III trial of MIL62 in combination with lenalidomide versus lenalidomide alone in patients with anti-CD20 mAb refractory FL, which is underway (NCT04834024).

Contributors

YKS was the leading principal investigator of this study, contributed to study conception and design with input from YQ, JJL and MW, and data analysis and interpretation, manuscript writing, review and editing. YKS, KSZ, HZ, YQ, HMJ, YX, ZW, ZW, AMZ, OB, ZYL, HLZ and YPS were involved in patient recruitments and data acquisition. JJL and MW conducted the data curation and statistical analysis. MW wrote the first draft of the manuscript. KSZ and JJL contributed to manuscript review and editing. YKS and JJL had directly accessed and verified the underlying study data. All authors had full access to all the data in this study and had final responsibility for the decision to submit for publication. All authors read and approved the final version of the manuscript.

Data sharing statement

Anonymous data are shared with centres participating in this study, based on research questions mentioned in this study protocol. Selected anonymous data collected in the study and additional documents can be made available to others not involved in this study upon reasonable request.

Declaration of interests

All the authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102702.

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