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# Safety and efficacy of amulirafusp alfa (IMM0306), a fusion protein of CD20 monoclonal antibody with the CD47 binding domain of SIRPα, in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: a phase 1/2 study

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## Abstract

**Background** Amulirafusp alfa (IMM0306) is a fusion protein of CD47 binding domain of signal-regulatory protein alpha (SIRPα) with CD20 monoclonal antibody on both heavy chains. This study aimed to evaluate the safety and preliminary efficacy of amulirafusp alfa in relapsed or refractory (r/r) B-cell non-Hodgkin lymphoma (B-NHL).

**Methods** We enrolled patients with CD20 + r/r B-NHL who had previously received at least two lines of therapy to receive a single-dose of amulirafusp alfa in the first 2 weeks, followed by a multiple-dose period, in which the patients received the same intravenous dose every week in 4-week cycles. The primary endpoints were to evaluate the safety, determine the maximum tolerated dose (MTD) and the recommended phase 2 dose (RP2D) of amulirafusp alfa.

**Results** Between May 22, 2020 and February 10, 2022, 48 patients with r/r B-NHL were enrolled and received amulirafusp alfa at the doses of 40–2000 μg/kg. As of the data cut-off date of April 18, 2024, no dose-limiting toxicity was observed, and the MTD was not reached. The dose of 2000 μg/kg was identified as the RP2D. All grades and ≥ grade 3 treatment-related adverse events (TRAEs) occurred in 48 (100%) and 33 (68.8%) patients, respectively. The most common ≥ grade 3 TRAEs were lymphocyte count decreased (28/48, 58.3%), white blood cell count decreased (10/48, 20.8%), absolute neutrophil count decreased (9/48, 18.8%) and anemia (5/48, 10.4%). At the doses of 800–2000 μg/kg, objective response rate in follicular lymphoma and marginal zone lymphoma was 41.2% (7/17, 95% confidence interval [CI] 18.4–67.1) and 33.3% (2/6, 95% CI 3.7–71.0), respectively.

**Conclusion** Amulirafusp alfa showed favorable safety profile and preliminary efficacy in patients with r/r B-NHL, meriting further investigation.

*Trial registration* NCT05805943.

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## Introduction

Non-Hodgkin lymphoma (NHL) occurs with an incidence rate of 5.73 per 100 000 population and an mortality rate of 3.19 per 100 000 population in 2019, according to the Global Burden of Disease study [1]. CD20 monoclonal antibodies (mAbs) in combination with conventional chemotherapy remains the standard treatment for virtually all subtypes of B-cell non-Hodgkin lymphoma (B-NHL), achieving long lasting survival benefit in most patients [2]. However, the prognosis is poor among patients who have primary refractory disease or have a relapse following treatment initiation, typically within the first 2 years [3–5]. The emergence of chimeric antigen receptor T-cell (CAR-T) therapy [6–8] and CD3xCD20 bispecific antibodies [9–11] represent important advances in the treatment of relapsed or refractory (r/r) B-NHL. However, both treatments potentially lead to severe toxicity associated with T-cell activation, especially cytokine release syndrome [12, 13]. What's more, CAR-T therapy, as a complex and specialist treatment, is currently available in certain highly expertized treatment centers [14]. Therefore, the development of novel therapies is still urgent to provide safe and effective treatment options for patients with r/r B-NHL.

Targeting the CD47 protein represents a novel therapeutic strategy for human cancers. The CD47 protein, overexpressed on various cancer cells, plays a pivotal role in delivering a "don't eat me" signal upon binding to the signal-regulatory protein alpha (SIRPα) receptor on myeloid cells [15]. Both CD47 mAb, magrolimab (Hu5F9-G4) and SIRPα fusion protein, TTI-621 were well-tolerated and have demonstrated efficacy as monotherapy in patients with r/r B-NHL [16, 17]. The phagocytosis and NHL cell eradication mediated by CD47 antibody could be augmented through combinations with rituximab [18]. The combination of magrolimab and rituximab also showed promising activity in patients with r/r B-NHL in a phase 1b study [19].

Amulirafusp alfa (IMM0306) is a fusion protein of CD47 binding domain of SIRPα with CD20 mAb on both heavy chains, developed by ImmuneOnco Biopharmaceuticals (Shanghai) Inc., Shanghai, China [20]. Amulirafusp alfa has a high affinity for the simultaneous binding of CD20-positive cells and CD47-positive cells [20]. Furthermore, amulirafusp alfa has a much higher affinity for CD20 compared with CD47, so that it will preferentially combine with lymphoma cells expressing both CD20 and CD47, thus reducing the side effects related to CD47-positive normal cells, such as anemia and thrombocytopenia related to CD47 targets [15, 20]. In pre-clinical studies, amulirafusp alfa exerts excellent anti-tumor activity in different mouse xenograft tumor models, by activating both macrophages and NK cells via CD47-SIRPα blockade and FcγR engagement [20].

Overall, these findings led to the initiation of a first in human phase 1/2 dose escalation and expansion study of intravenous administration amulirafusp alfa in patients with r/r B-NHL. We report findings from the phase 1 dose escalation part of this ongoing study, where the primary endpoints were to evaluate the safety, establish the maximum tolerated dose (MTD) and the recommended phase 2 dose (RP2D) of amulirafusp alfa.

## Methods

### Study design and patients

This multicenter, open-label,first-in-human phase 1/2 study aimed to evaluate the safety, tolerability, pharmacokinetic, immunogenicity, and preliminary efficacy of amulirafusp alfa. The phase 1 part of this study used two consecutive dose-escalation designs, which began with an accelerated titration design at the 40, 100, and 250 μg/kg dose levels, and transitioned to a "3 + 3" design at higher dose levels.

Eligible patients were aged 18 years or older; histologically diagnosed with B-NHL that was either relapsed or refractory after one or more lines of therapy; had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2 and adequate organ function; at least one measurable or evaluable lesion; life expectancy of at least 3 months. Patients who had any of the following were excluded from the study: active central nervous system lymphoma; history of allogeneic hematopoietic stem cell transplantation or organ transplantation, and autologous hematopoietic stem cell transplantation within 100 days before the first dose of amulirafusp alfa; active autoimmune diseases or a history of autoimmune diseases with potential recurrence; previous exposure to any CD47 mAbs or SIRPα fusion proteins; long term administration of anti-platelet drugs, such as clopidogrel, aspirin or other nonsteroidal anti-inflammatory drugs; required systemic administration of corticosteroid (> 10mg/day prednisone or equivalent) or other immunosuppressive drugs within 7 days before the first dose of amulirafusp alfa or during the study period. The study protocol, detailed inclusion and exclusion criteria are provided in the Supplementary Appendix.

This study was conducted in accordance with good clinical practice standards and the Declaration of Helsinki. The protocol and its amendments were approved by the relevant institutional review boards or ethics committees of each participating hospital. Written informed consent was obtained from each patient. This

study was registered with ClinicalTrials.gov, number NCT05805943.

### Procedures

The phase 1 dose-escalation part of this phase 1/2 study consisted of a single-dose period in the first 2 weeks and followed by a multiple-dose period, in which the patients received the same dose intravenous administration once a week in 4-week cycles, until unacceptable toxicity, disease progression, death, patient informed consent withdrawal, investigator judgement, initiation of new anti-tumor treatments, maximum treatment duration of 50 weeks or study termination, whichever occurred first. The dose-limiting toxicity (DLT) observation period was the first 4 weeks. DLTs were defined as hematological toxicities (grade 3 febrile neutropenia, grade 4 neutropenia persists for more than 5 days, grade 3 thrombocytopenia with bleeding or bleeding events requiring platelet transfusion, grade 4 thrombocytopenia, ≥ grade 3 hemolysis, or any other grade 4 hematological toxicities) and non-hematological toxicities (all ≥ grade 4 non-hematological toxicities, ≥ grade 3 toxicities related to important organs, including heart, lung, gastrointestinal, liver, kidney, and nervous system, grade 3 cytokine release syndrome and no recovered to grade 1 or baseline within 7 days, grade 3 fatigue lasting for more than 14 days), respectively.

The primary endpoints were safety, MTD and RP2D of amulirafusp alfa. The secondary endpoints included pharmacokinetics, immunogenicity and efficacy. The exploratory endpoints included pharmacodynamic, immune biomarkers, CD47 receptor occupancy rate, and so on.

Adverse events (AEs) were encoded based on Medical Dictionary for Regulatory Activities (MedDRA) version 27.0 and graded with National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The MTD was the highest dose at which no more than one of every six patients had a DLT. A RP2D was chosen on the basis of integrated evidence, such as safety, pharmacokinetic, pharmacodynamic, and efficacy.

Serial blood samples were collected for pharmacokinetic analysis after amulirafusp alfa administration at cycle 0 day 1 (C0D1), cycle 0 day 2 (C0D2), cycle 0 day 3 (C0D3), cycle 0 day 4 (C0D4), cycle 0 day 5 (C0D5), cycle 0 day 8 (C0D8) during single-dose period, and cycle 1 day 1 (C1D1), cycle 1 day 8 (C1D8), cycle 1 day 15 (C1D15), cycle 1 day 22 (C1D22) and same timepoints in subsequent cycles during multiple-dose period. The pharmacokinetic parameters of single-dose period included maximum concentration ($C_{max}$), time to reach $C_{max}$ ($T_{max}$), area under the curve of serum concentration versus time from 0 to the last quantifiable time point ($AUC_{0\text{-last}}$). If data permits, area under the curve of serum concentration versus time from 0 to infinity ($AUC_{0\text{-inf}}$), elimination half-life ($t_{1/2}$), volume of distribution (V), total plasma clearance (CL) would also be calculated. The pharmacokinetic parameters of multiple-dose period included minimum concentration at steady state ($C_{min,ss}$), maximum concentration at steady state ($C_{max,ss}$), average concentration at steady state ($C_{av,ss}$), area under the curve of serum concentration versus time during dosing intervals ($AUC_{0\text{-tau}}$), $T_{max}$, accumulation ratio calculated from the $C_{max}$ ($R_{ac\_Cmax}$), accumulation ratio calculated from the $AUC_{0\text{-tau}}$ ($R_{ac\_AUC0\text{-tau}}$). If data permits, volume of distribution at steady state ($V_{SS}$), total plasma clearance at steady state ($CL_{ss}$), and $t_{1/2}$ would also be calculated.

Immunogenicity was assessed with the incidence rate of anti-drug antibodies (ADAs). ADA titers and neutralizing antibodies (Nabs) were further measured after confirming ADA positivity.

Tumor response of chronic lymphocytic leukemia (CLL) / small lymphocytic lymphoma (SLL) was assessed by investigators according to the 2008 International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria [21]. Tumor response of other histological subtypes was assessed by investigators according to the Lugano criteria [22]. The best objective response (BOR) is defined as the optimal efficacy achieved across all visits from study treatment initiation till confirmed progressive disease (PD), death or initiation of new anti-tumor treatments, whichever occurred first. The objective response rate (ORR) was defined as the percentage of patients with BOR of complete response (CR) or partial response (PR). The disease control rate (DCR) was defined as the percentage of patients with BOR of CR, PR or stable disease (SD). If PD happened at the first efficacy assessment, considering pseudoprogression or overall clinical benefit, study treatment may be continued until PD is confirmed by the lymphoma response to immunomodulatory therapy criteria (LYRIC) [23]. Progression free survival (PFS) was defined as the time from the first dose of amulirafusp alfa to first documented PD or death due to any reason, whichever occurred earlier. Duration of response (DoR) was defined as the time from achieving CR or PR to first documented PD. Overall survival (OS) was defined as the duration from the first dose of amulirafusp alfa to death due to any reason.

An exploratory analysis of pharmacodynamic and potential biomarkers associated with clinical response and safety profile to amulirafusp alfa was performed based on peripheral blood samples obtained at screening and during study treatment. Flow cytometric assay was used to measure the CD47 receptor occupancy on peripheral lymphocyte and to detect the absolute CD19 positive B cell count for evaluation of B cell depletion.

Enzyme-linked immunosorbent assay was used to detect serum cytokine concentrations.

### Statistical analysis

All statistical analyses for safety, pharmacokinetic and efficacy were primarily descriptive. No formal hypothesis testing was conducted. Categorical variables were summarized and presented as frequencies and percentages of patients within each classification. Continuous data were summarized by the number of non-missing values and presented as median and range (minimum–maximum). The 95% confidence intervals (CIs) of ORR were determined by the Clopper-Pearson exact method. Time to event parameters were estimated using Kaplan–Meier method and presented as median time and 95% CIs. Subgroup analyses of tumor response and survival time based on baseline characteristics were performed using the same method as for the overall population.

All patients who had received at least one dose of amulirafusp alfa were included in the full analysis set (FAS), which was used for baseline data summarization. Safety analyses were done on the safety set (SS), which consisted of all patients in the FAS who had safety evaluation data after amulirafusp alfa administration. The pharmacokinetic concentration set (PKCS) consisted of all patients in the FAS who had at least one valid serum drug concentration data. The pharmacokinetic parameter set (PKPS) consisted of all patients in the FAS who had at least one valid pharmacokinetic parameter during the study period and excluded those who seriously violated the protocol and therefore affected the results of pharmacokinetic parameters. The anti-drug antibody set (ADAS) consisted of all patients in the SS who had at least one valid immunogenicity result and excluded those with baseline ADA positive. The dose-limiting toxicity set (DLTS) consisted of all patients in the FAS who had completed the DLT observation period or who had experienced DLT. Treatment response was evaluated in the efficacy set (EFS), which consisted of all patients in the FAS who had measurable or evaluable lesions at baseline and at least one post baseline disease assessment.

All analyses were conducted using SAS version 9.4 (SAS Institute Inc., North Carolina, US). Pharmacokinetic parameters were calculated using non-compartmental analysis (NCA) with Phoenix software version 8.2 (Certara L.P., New Jersey, US).

## Results

### Patient baseline characteristics

Between May 22, 2020 and February 10, 2022, a total of 48 patients with B-NHL from 7 hospitals in China were enrolled in this study and received amulirafusp alfa treatment across eight escalating doses (Fig. 1). The first 9 patients enrolled were treated at fixed doses of 40 μg/kg (n = 1), 100 μg/kg (n = 2) or 250 μg/kg (n = 6), using the accelerated titration dose-escalation design. Dose-escalation cohorts were then expanded at 1200 μg/kg (n = 10), 1600 μg/kg (n = 9) or 2000 μg/kg (n = 13) to further investigate the safety, pharmacokinetics, pharmacodynamic, and preliminary efficacy.

Patient demographics and baseline characteristics are summarized in Table 1. Of the 48 patients, 20 (41.7%) had follicular lymphoma (FL), 15 (31.3%) had diffuse large B-cell lymphoma (DLBCL), 7 (14.6%) had marginal zone lymphomas (MZL), 3 (6.3%) had mantle cell lymphoma (MCL). The remaining 3 (6.3%) patients had blastoid variant of MCL, histologic transformation of indolent B-cell lymphoma to DLBCL, and CLL/SLL based on the 2016 revision of the World Health Organization classification of lymphoid neoplasms [24]. Thirty (62.5%) patients were male. The median age of patients was 56 (range, 27–76). Most (46/48, 93.9%) patients had an ECOG PS of 0–1. All patients had received anti-CD20 mAbs treatmentmonoclonal antibodies. The patients had received a median of 3 (range, 1–8) previous lines of therapy and most (25/48, 52.1%) patients were refractory to their last line of systemic therapy. One (2.1%) patient with histologic transformation of indolent B-cell lymphoma to DLBCL had received previous autologous hematopoietic stem cell transplantation therapy, 2 patients with FL had received previous CD3xCD19 bispecific antibody therapy, and 1 patient with DLBCL had received previous CAR-T therapy. Patients with FL (20/48, 41.7%) had received a median of 2 (range, 1–7) lines of previous systemic therapy. Patients with DLBCL (15/48, 31.3%) had received a median of 4 (range, 2–6) previous lines of systemic therapy. Patients with MZL (7/48, 14.6%) had received a median of 2 (range, 1–2) previous lines of systemic therapy.

### Safety

As of the data cutoff date of April 18, 2024, all (48/48, 100%) patients had received at least one dose of amulirafusp alfa treatment and were included in the SS. Thirty-eight (79.2%) patients were included in the DLTS. Patients received a median 7.5 doses (range, 1–87) of amulirafusp alfa treatment with a median 1.6 months (range, 0.03–21.8) of exposure and a median 98.9% (range, 50.0–107.5) relative dose intensity, during the multiple-dose period. Amulirafusp alfa was well tolerated and no DLT was observed across all dose levels. The MTD was not reached. All (48/48, 100%) patients had completed the study treatment. The reasons for treatment completion were PD (25/48, 52.1%), completion of protocol treatment (10/48, 20.8%), investigator assessment (4/48, 8.3%), treatment refusal (3/48, 6.3%), ≥ 4

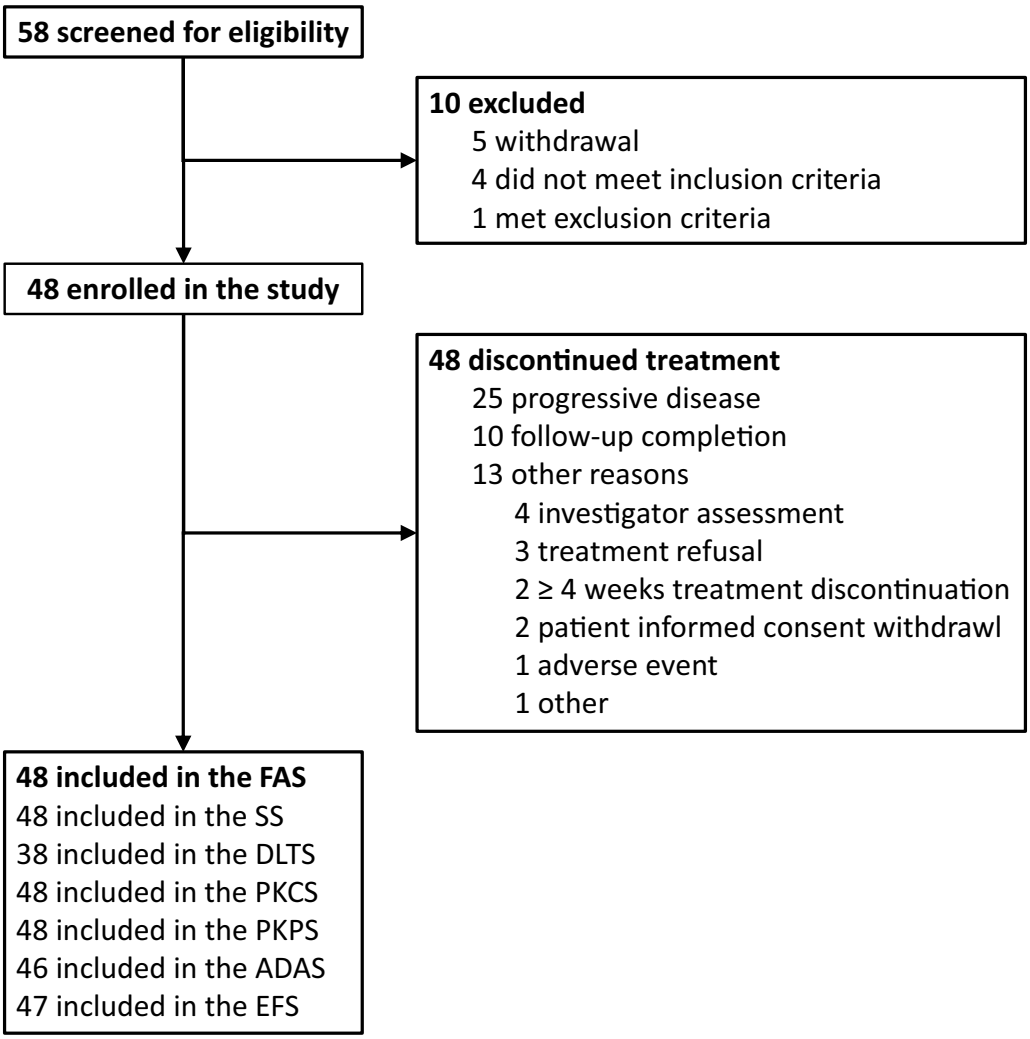


**Fig. 1** Flowchart of the study. ADAS, anti-drug antibody set; DLTS, dose-limiting toxicity set; EFS, efficacy set; FAS, full analysis set; PKCS, pharmacokinetic concentration set; PKPS, pharmacokinetic parameter set; SS, safety set

weeks amulirafusp alfa discontinuation (2/48, 4.2%), patient informed consent withdrawal (2/48, 4.2%), AE (1/48, 2.1%) and other (1/48, 2.1%).

Both treatment-emergent adverse events (TEAEs) and treatment-related adverse event (TRAEs) occurred in all (48/48, 100%) patients (Table 2 and Supplementary Table 1). The most common TRAEs were white blood cell (WBC) count decreased (32/48, 66.7%), anemia (31/48, 64.6%), lymphocyte count decreased (29/48, 60.4%), absolute neutrophil count (ANC) decreased (23/48, 47.9%), platelet count decreased (23/48, 47.9%), and infusion related reaction (17/48, 35.4%). Thirty-eight (79.2%) patients had at least one ≥ grade 3 TEAE, and 33 (68.8%) patients had at least one ≥ grade 3 TRAE. The most common ≥ grade 3 TRAEs included lymphocyte count decreased (28/48, 58.3%), WBC count decreased (10/48, 20.8%), ANC decreased (9/48, 18.8%), anemia (5/48, 10.4%), infectious pneumonia (3/48, 6.3%), gamma-glutamyltransferase increased (2/48, 4.2%), platelet count decreased (2/48, 4.2%) and sinus tachycardia (1/48, 2.1%). One (2.1%) patient discontinued the study treatment due to grade 4 thrombocytopenia related to amulirafusp alfa. Severe adverse events occurred in 14 (29.2%) patients and were considered amulirafusp alfa-related in 6 (12.5%) patients, including pneumonia (4/48, 8.3%), platelet count decreased (1/48, 2.1%) and chest pain (1/48, 2.1%). Most patients with TEAEs recovered or symptom recovered with no sequelae through symptom management, treatment interruption, or both.

No death occurred on the study treatment and 11 (22.9%) patients died during follow up after study treatment discontinuation. Disease progression (7/11, 63.6%) was the most common cause of death. Other causes of death were cardiac arrest (1/11, 9.1%) and severe

**Table 1** Demographic and clinical characteristics at baseline of patients in the FAS (n = 48)

| Characteristic | FL (n = 20) | DLBCL[a] (n = 15) | MZL[b] (n = 7) | Total[c] (n = 48) |
|---|---|---|---|---|
| Median age, years (range) | 59 (35–76) | 57 (27–69) | 56 (41–64) | 56 (27–76) |
| Sex, no. (%) | | | | |
| Female | 9 (4.5.0) | 6 (40.0) | 2 (28.6) | 18 (37.5) |
| Male | 11 (55.0) | 9 (60.0) | 5 (71.4) | 30 (62.5) |
| ECOG PS, no. (%) | | | | |
| 0 | 5 (25.0) | 3 (20.0) | 5 (71.4) | 15 (31.3) |
| 1 | 14 (70.0) | 11 (73.3) | 2 (28.6) | 31 (64.6) |
| 2 | 1 (5.0) | 1 (6.7) | 0 | 2 (4.2) |
| Lugano stage at enrollment[d] | | | | |
| I | 0 | 0 | 0 | 0 |
| II | 3 (15.0) | 6 (40.0) | 2 (28.6) | 12 (25.5) |
| II with bulky lesions | 0 | 0 | 0 | 0 |
| III | 8 (40.0) | 3 (20.0) | 2 (28.6) | 13 (27.7) |
| IV | 9 (45.0) | 6 (40.0) | 3 (42.9) | 22 (46.8) |
| Time since diagnosis, months (range) | 39.3 (6.7–97.1) | 18.8 (7.9–86.2) | 78.00 (10.8–99.9) | 38.2 (6.7–103.8) |
| Previous lines of therapy, median (range) | 2.0 (1–7) | 4.0 (2–6) | 2.0 (1–2) | 2.5 (1–8) |
| ≤ 2 previous lines, no. (%) | 13 (65.0) | 3 (20.0) | 7 (100) | 24 (50.0) |
| ≥ 3 previous lines, no. (%) | 7 (35.0) | 12 (80.0) | 0 | 24 (50.0) |
| CD20 positive, no. (%) | 20 (100) | 14 (93.3) | 7 (100%) | 47 (97.9)[e] |
| Relapsed or refractory status, no. (%) | | | | |
| Relapsed | 12 (60.0) | 5 (33.3) | 3 (42.9) | 23 (47.9) |
| Refractory | 8 (40.0) | 10 (66.7) | 4 (57.1) | 25 (52.1) |

[a] Including 1 patient with primary bone DLBCL; [b]Including 1 patient with MALT-L; [c]Including 3 (6.3%) patients with MCL and 3 (6.3%) patients with blastoid variant of MCL, histologic transformation of indolent B-cell lymphoma to DLBCL, and CLL/SLL, respectively, except for patients with FL, DLBCL, and MZL; [d]One patient with CLL/SLL was not suitable for Lugano staging system; [e]One patient was diagnosed with CD20-positive at the initial pathological diagnosis while CD20-negative at the last pathology diagnosis before enrollment

*CLL/SLL* chronic lymphocytic leukemia/small lymphocytic lymphoma, *DLBCL* diffuse large B-cell lymphoma, *FAS* full analysis set, *FL* follicular lymphoma, *MALT-L* mucosa-associated lymphoid tissue lymphoma, *MCL* mantle cell lymphoma, *MZL* marginal zone lymphomas, *n* number of patients included in statistical analyses, *no.* number of patients

**Table 2** TRAEs that occurred in at least 10% of patients in the SS (n = 48)

| Event | All grades, no. (%) | Grade 1 or 2, no. (%) | Grade 3, no. (%) | Grade 4, no. (%) |
|---|---|---|---|---|
| Any AE | 48 (100%) | 15 (31.3%) | 10 (20.8%) | 23 (47.9%) |
| WBC decreased | 32 (66.7%) | 22 (45.8%) | 10 (20.8%) | 0 |
| Anemia | 31 (64.6%) | 26 (54.2%) | 5 (10.4%) | 0 |
| Lymphocyte count decreased | 29 (60.4%) | 1 (2.1%) | 6 (12.5%) | 22 (45.8%) |
| Platelet count decreased | 23 (47.9%) | 21 (43.8%) | 1 (2.1%) | 1 (2.1%) |
| ANC decreased | 23 (47.9%) | 14 (29.2%) | 8 (16.7%) | 1 (2.1%) |
| Infusion-related reaction | 17 (35.4%) | 17 (35.4%) | 0 | 0 |
| LDH increased | 9 (18.8%) | 9 (18.8%) | 0 | 0 |
| ALT increased | 8 (16.7%) | 8 (16.7%) | 0 | 0 |
| Pyrexia | 8 (16.7%) | 8 (16.7%) | 0 | 0 |
| γ-GT increased | 8 (16.7%) | 6 (12.5%) | 2 (4.2%) | 0 |
| α-HBDH increased | 7 (14.6%) | 7 (14.6%) | 0 | 0 |
| AST increased | 7 (14.6%) | 7 (14.6%) | 0 | 0 |
| Hypercholesterolemia | 6 (12.5%) | 6 (12.5%) | 0 | 0 |
| C-reactive protein increased | 5 (10.4%) | 5 (10.4%) | 0 | 0 |

*AE* adverse event, *ALT* alanine aminotransferase, *ANC* absolute neutrophil count, *AST* aspartate aminotransferase, *α-HBDH* alpha hydroxybutyrate dehydrogenase, *γ-GT* Gamma-glutamyltransferase, *LDH* Lactate dehydrogenase, *n* number of patients included in statistical analyses, *no.* number of patients, *SS* safety set, *TRAEs* Treatment-related adverse events, *WBC* White blood cell

pneumonia (1/11, 9.1%). The causes of death were unknown in 2 (18.2%) patients who died during survival follow-up.

### Pharmacokinetic

All 48 patients were included in the PKCS and PKPS. Amulirafusp alfa single-dose exposure increased with the doses from 100 to 2000 μg/kg (Supplementary Fig. 1A, B), with an average $t_{1/2}$ of 18.8–46.3 h, an average $V_{SS}$ of 9.65–34.5 L, and an average CL of 0.255–1.08 L/h, which decreased against with increasing doses (Supplementary Table 2). After multiple-dose administration of amulirafusp alfa, exposure increased with the doses from 100 to 2000 μg/kg (Supplementary Fig. 1C, D), with an average $t_{1/2}$ of 15.8–42.2 h, an average $CL_{ss}$ of 0.234–1.17 L/h, an average $V_{SS}$ of 8.51–24.6 L, an average $R_{ac\_Cmax}$ of 0.665–1.47 and an average $R_{ac\_AUC0\text{-}tau}$ of 1.03–18.7 (Supplementary Table 3), indicating no significant accumulation of amulirafusp alfa with the dose frequency of once a week (Supplementary Fig. 1E, F). After 4 consecutive doses of once a week administration of amulirafusp alfa, the average trough concentration of each dose group tended to reach a steady state. The results of dose-exposure analysis indicated nonlinear pharmacokinetic characteristics of amulirafusp alfa within the studied dose range (Supplementary Fig. 2, Supplementary Tables 4, and 5).

### Immunogenicity

Forty-six (95.8%) patients were included in the ADAS. Two patients (1 at 250 μg/kg and 1 at 2000 μg/kg) were positive for ADA. There was no significant effect of ADA on the safety, PK and efficacy of amulirafusp alfa.

### Efficacy

Forty-seven (97.9%) patients were included in the EFS, in which 46 patients were in the Lugano EFS and 1 patient was in the CLL/SLL EFS. The efficacy of patients in each dose level and histology for Lugano EFS was detailed in Supplementary Tables 6 and 7. The BOR of the patient (1200 μg/kg group) in the CLL/SLL EFS was PD.

Of 46 patients across all dose levels in the Lugano EFS, 5 patients achieved CR, 5 patients achieved PR, and 14 patients achieved SD (Table 3). The ORR was 21.7% (10/46, 95% CI 10.9–36.4). The DCR was 52.2% (24/46, 95% CI 36.9–67.1). Among the 5 patients achieved CR, 1 patient with MZL was in the 800μg/kg dose level, 3 patients with FL were in the 1200μg/kg dose level, 1 patient with FL was in the 2000 μg/kg dose level. Among the 5 patients achieved PR, 1 patient with mucosa-associated lymphoid tissue lymphoma was in the 1200 μg/kg dose level, 1 patient with FL was in the 1600 μg/kg dose level, 2 patients with FL and 1 patient with primary bone DLBCL were in the 2000 μg/kg. The sum of the product of the diameters of 11 patients ≥ 50% (Fig. 2A, B).

For 46 patients in the Lugano EFS, the median follow-up time for DoR was 9.36 months (95% CI 0.03–12.29). The median DoR was not available (NA, 95% CI NA-NA, Fig. 2C, D) among the 10 patients achieved objective response. The 6-month DoR rate was 100% (95% CI 100–100). The median follow-up time for PFS was 11.07 months (95% CI 5.26–11.63). The median PFS was 2.23 months (95% CI 1.84–10.58, Fig. 2E). The 6-month, 12-month and 18-month PFS rate was 38.5% (95% CI 23.5–53.5), 34.2% (95% CI 19.3–49.7), and 34.2% (95% CI 19.3–49.7), respectively. The median follow-up time for OS was 18.30 months (95% CI 16.20–19.94, Fig. 2F). The median OS was not reached (95% CI 7.13–NR). The 6-month, 12-month, 18-month and 24-month OS rate was 93.0% (95% CI 79.7–97.7), 78.5% (95% CI 62.8–88.2), 78.5% (95% CI 62.8–88.2), 75.0% (95% CI 12.8–96.1), respectively.

**Table 3** Objective responses to amulirafusp alfa in the Lugano EFS (n = 46)

| Response | FL (n = 20), n (%) | DLBCL (n = 14), n (%) | MZL (n = 7), n (%) | Total (n = 46), n (%) |
|---|---|---|---|---|
| Objective response | 7 (35.0) | 1 (7.1) | 2 (28.6) | 10 (21.7) |
| Disease control | 13 (65.0) | 5 (35.7) | 5 (71.4) | 24 (52.2) |
| CR | 4 (20.0) | 0 | 1 (14.3) | 5 (10.9) |
| PR | 3 (15.0) | 1 (7.1)[a] | 1 (14.3)[b] | 5 (10.9) |
| SD | 6 (30.0) | 4 (28.6) | 3 (42.9) | 14 (30.4) |
| PD | 7 (35.0) | 9 (64.3) | 2 (28.6) | 22 (47.8) |

[a] This is a patient with primary bone DLBCL; [b]This is a patient with MALT-L

*CR* complete response, *DLBCL* diffuse large B-cell lymphoma, *EFS* efficacy set, *FL* follicular lymphoma, *MALT-L* mucosa-associated lymphoid tissue lymphoma, *MZL* marginal zone lymphomas, *n* number of patients included in statistical analyses, *PD* progressive disease, *PR* partial response, *SD* stable disease

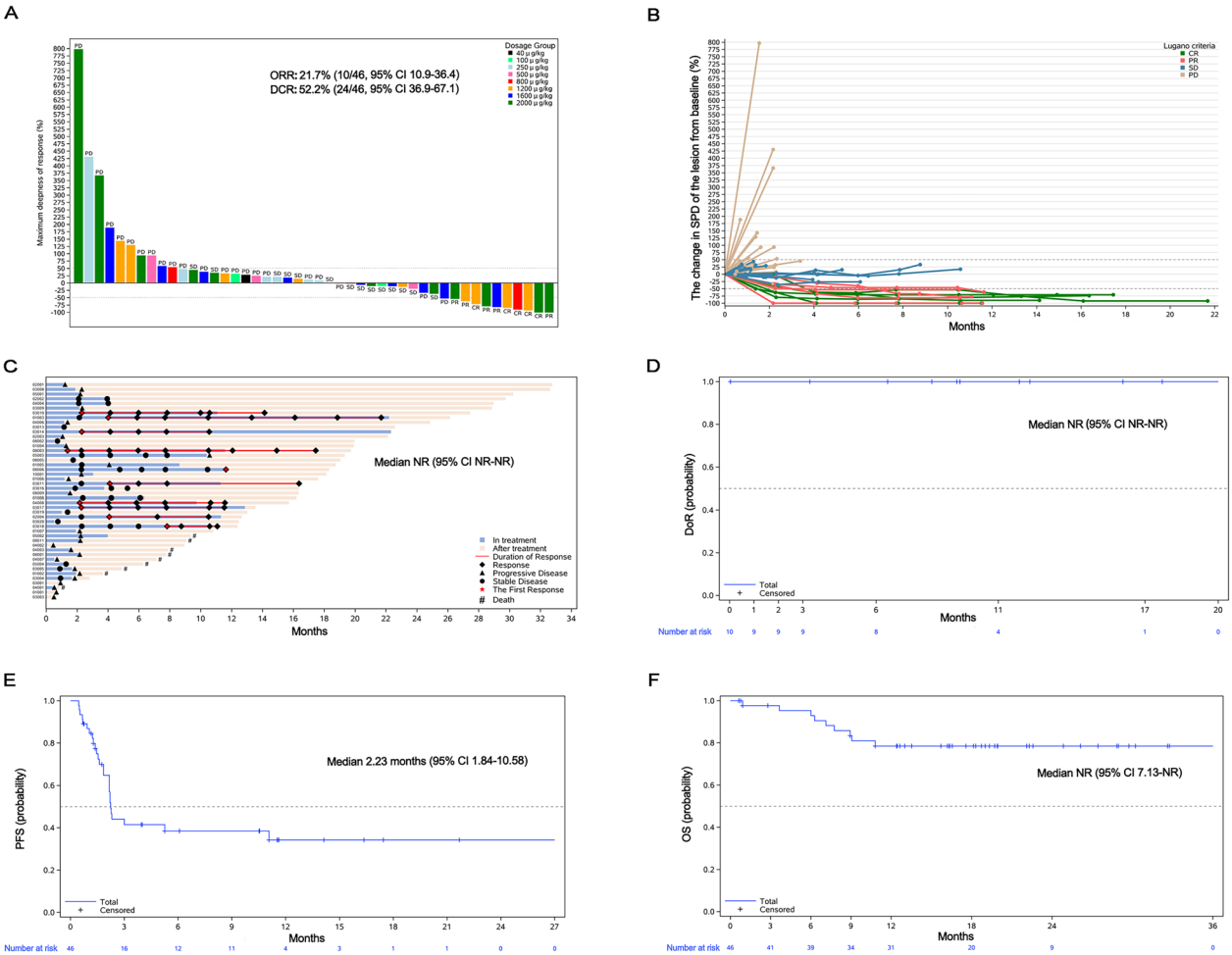


**Fig. 2** **A**–**F** Efficacy of amulirafusp alfa in the Lugano EFS assessed by investigators. **A** waterfall plot for the best percentage change from baseline measurable lesions. **B** spider plot for the relative change from baseline measurable lesions. **C** swimmer plot for the treatment duration and tumor response. **D** The Kaplan–Meier curve of DoR. **E** The Kaplan–Meier curve of PFS. **F** The Kaplan–Meier curve of OS. CR: complete response; CI: confidence interval; DCR: disease control rate; DoR: duration of response; EFS: efficacy set; NE: not evaluable; NR: not reached; ORR: objective response rate; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PR: partial response; SD: stable disease; SPD: sum of the product of the diameters

Amulirafusp alfa showed preliminary anti-tumor activity across 800–2000 μg/kg for CD20 positive r/r B-NHL, especially for FL and MZL (Table 3 and Supplementary Table 6). The ORR of FL patients and MZL patients across 800–2000μg/kg dose levels was 41.2% (7/17, 95% CI 18.4–67.1) and 33.3% (2/6, 95% CI 4.3–77.7), respectively. The median PFS of 17 FL patients across 800–2000μg/kg was 10.58 months (95% CI 2.20–NA).

### Recommended phase 2 dose

The RP2D was 2000 μg/kg based on integrated evaluation of safety, pharmacokinetic, pharmacodynamic, and efficacy in the dose escalation phase.

### Pharmacodynamic and exploratory analysis

Amulirafusp alfa administration resulted significantly B cell depletion in patient peripheral blood. There was a rapid depletion of CD19 positive B cells after the first administration of amulirafusp alfa across all dose levels, with the absolute B cell counts reaching its lowest level at C1D1. At the 500 μg/kg dose level, there was a gradual restoration of B cells since C1D22, and resolved to baseline at the end of treatment (EOT) (Supplementary

Fig. 3A). At the 800 and 1200 μg/kg dose levels, there was a slight increase in the absolute B cell counts since C1D22, while remained a relatively low level on the study treatment. At the 1600 and 2000 μg/kg dose levels, the absolute B cell counts remained a very low level, nearly to 0, since C1D22 until the EOT, indicating the greatest effect of B cell depletion.

There was no significant correlation between the degree of cytokine increase and the dose of study drug for all 48 patients in the FAS. It showed similar trends for the level changes of interleukin-6, interferon-γ, tumor necrosis factor-α and interferon-γ-induced protein 10 (Supplementary Fig. 3B–E). The levels of cytokines increased significantly after study drug administration and reach the peak after 4 h. Thereafter, cytokine levels decreased and returned to baseline after around 24 h. No significant cytokine activation was observed in the subsequent multiple-dose period. We divided patients into responder (CR and PR) group and non-responder (SD and PD) group according to their best objective response efficacy. However, there was no significant correlation between cytokine levels and amulirafusp alfa efficacy (Supplementary Fig. 3F–I). The transient cytokine release after amulirafusp alfa administration did not trigger cytokine release syndrome, as no cytokine release syndrome occurred in this study.

The CD47 receptor occupancy rate reached to peak after a single dose administration of amulirafusp alfa and decreased significantly after 24 h (Supplementary Fig. 3J). The peaks of CD47 receptor occupancy during multiple-dose period were close to single-dose period. Therefore, the mild binding of amulirafusp alfa to CD47 protein of peripheral lymphocytes supporting its good tolerability and safety profile.

## Discussion

Despite recent advances in the treatment of r/r B-NHL, there is an unmet need for novel therapeutic strategies that are safe, efficacious, and conveniently delivered to patients. Antibodies that target CD47-SIRPα axis offer an off the shelf therapy option with potential advantages to patients with r/r B-NHL who are ineligible for or do not have access to CAR-T therapy, bispecific antibodies or other treatments.

CD47-SIRPα, serving as a "don't eat me" signal in the innate immune system, inhibits the macrophage phagocytosis of tumor cells and has become a novel immune checkpoint in cancer immunotherapy [25]. Targeting CD47-SIRPα not only destroys the cross talk of CD47 and SIRPα and enhances the phagocytosis of tumor cells by macrophages, but also results in tumor cell killing through NK cell-modulated antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity, even directly inducing tumor cell apoptosis [26]. CD47 mAbs could also promote phagocytosis and antigen presentation of tumor cells by dendritic cells, eliciting the activation of an anti-tumor adaptive immune response [27]. Magrolimab is the first humanized antibody targeting CD47 and was well tolerated patients with various tumor types in a phase 1 trial [16]. Magrolimab combined with rituximab resulted in augmented therapeutic efficacy in patients with DLBCL or FL [19]. The combination of magrolimab and azathioprine has also exhibited a safe and curative effect in a phase 1b study of acute myeloid leukemia, including patients with *TP53* mutations [28]. Considering that CD47 is widely expressed in the hematopoietic system, especially in red blood cells and platelets, dual antigen targeting binds to not only CD47 but also tumor-specific antigens may achieve specific clearance of tumor cells and reduce potential off-target toxicity [25]. Different bispecific antibodies or fusion proteins targeting both CD47-SIRPα and other tumor-specific antigens were generated to target and deplete tumor cells via multiple antibody mediated mechanisms.

To our knowledge, amulirafusp alfa is the first fusion protein of CD47 binding domain of SIRPα with CD20 mAb on both heavy chains in clinical trial. This study revealed that amulirafusp alfa was safe and well tolerated at doses up to 2000 μg/kg every week in patients with B-NHL. Amulirafusp alfa had a manageable safety profile, with no TRAE leading to death, no case of cytokine release syndrome. Importantly, no DLT was observed and the MTD was not reached. There was a good compliance to the study treatment. Of 48 (100%) patients completed administration during single-dose period, no dose adjustment was needed. Of 42 (87.5%) patients completed administration during multiple-dose period, dose adjustment was needed in 1 (2.4%) patient according to body weight change. TRAEs were manageable through symptom management, treatment interruption, or both. The most common ≥ grade 3 TRAEs were mainly expected on-target hematological toxicity, including lymphocyte count decreased (28/48, 58.3%), WBC decreased (10/48, 20.8%), ANC decreased (9/48, 18.8%), anemia (5/48, 10.4%). The lymphocyte count decreased is associated with the anti-tumor effect of amulirafusp alfa. Of 10 (20.8%) patients had grade 3 WBC decreased, 9 (18.8%) patients had ≥ grade 3 neutropenia, 5 (10.4%) patients had grade 3 anemia, and 2 (4.2%) patients had ≥ grade 3 platelet decreased, 5 (50%), 6 (66.7%), 2 (40%), and 2 (100%) patients needed symptomatic treatment, respectively. The patients received symptomatic treatment recovered or symptom disappeared with no sequelae mostly within 3 days, while those with no measure taken mostly within a month. Furthermore, compared with the high occurrence rate of cytokine release syndrome

among CD3xCD20 bispecific antibodies [9, 10, 29–32], the transient cytokine release within 24 h after the first dose administration of amulirafusp alfa did not trigger a cytokine release syndrome event in this study.

Amulirafusp alfa exhibited favorable pharmacokinetic properties, with a half-life time of 1.5 days, which allowed the intermittent recovery of platelet in once a week dosing, and meanwhile, maintained a completely depletion of B cell when dose above 800 μg/kg. In this study, only one (2.1%) patient had TRAE of grade 4 thrombocytopenia leading to treatment discontinuation. All (33/48, 68.8%) patients in the 800–2000 μg/kg dose cohorts showed a rapid and transient decrease in platelet cell count at 4 h, recovered gradually on the third day, and returned to baseline or grade 1 level around one week after first dose of amulirafusp alfa.

Although not powered for efficacy analysis, amulirafusp alfa showed anti-tumor activity as a single agent in heavily pretreated patients with r/r B-NHL, including those with r/r FL, MZL, MCL, and DLBCL. In 10 patients with objective response, the 26-week DoR rate was 100% (95% CI 100–100). Patients with FL appeared to derive particular benefit, with 13 of 20 patients experiencing stable disease or better, including 3 confirmed PR and 4 CR. In 17 patients with FL received amulirafusp alfa at the dose range of 800–2000μg/kg, the median PFS was 10.58 months (95% CI 2.20–NA). Meanwhile, one CR and one PR were observed in two patients with MZL. Disease stabilization was observed in patients with various tumor types, including 6 (30.0%) patients with FL, 4 (30.8%) patients with DLBCL, 3 (50.0%) patients with MZL and 2 (66.7%) patients with MCL. Therefore, the reported data from this study, though preliminary, provided an indication of the potentially broader application of amulirafusp alfa among various histological subtypes of B-NHL.

Taken together, this first in human phase 1 study of amulirafusp alfa, met its primary endpoints, establishing the RP2D in patients with r/r B-NHL, a population for whom there are few effective treatment options. The safety profile of amulirafusp alfa, together with pharmacokinetic, pharmacodynamic modelling, and the efficacy, suggested the dose level of 2000 μg/kg once a week as the RP2D for amulirafusp alfa monotherapy across the B-NHL histological subtypes. The optimal amulirafusp alfa dose regimen is undergoing investigation in the phase 2 dose-expansion part of this study to provide rationale for efficacy studies in subsequent clinical trials. This phase 1 dose escalation study of amulirafusp alfa only enrolled 2 FL patients with treatment failure from CD3xCD19 bispecific antibody and 1 DLBCL patient with treatment failure from CAR-T therapy. There would be further evidence for the ideal timing and sequencing among amulirafusp alfa and other therapies from the results of subsequent clinical studies of amulirafusp alfa.

## Supplementary Information

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Additional file 1.

Additional file 2.

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**Author contributions**
Y.S. was the leading principal investigator and designed the trial with the sponsor, and was responsible for the administrative support. All authors contributed to patient recruitment and data acquisition, accessed and verified the data. Y.S., J.Y., Q.L., and W.M. involved in data analysis and data interpretation. Y.S. did the manuscript writing. All authors reviewed and approved the final version of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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**Availability of data and materials**
The data and materials that support the findings of this study are available from the corresponding author upon reasonable request.

## Declarations

**Competing interests**
W.M. and Q.L. are employees in Biopharmaceuticals (Shanghai) Inc., Shanghai, China. W.T. is the founder of ImmuneOnco Biopharmaceuticals (Shanghai) Inc., Shanghai, China. All other authors declare no competing interests.

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