A Phase II Study of Acimtamig (AFM13) in Patients with CD30-Positive, Relapsed, or Refractory Peripheral T-cell Lymphomas

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ABSTRACT

Purpose: Patients with relapsed or refractory (R/R) peripheral T-cell lymphoma (PTCL) generally have poor prognoses and limited treatment options. This study evaluated the efficacy of a novel CD30/CD16A bispecific innate cell engager, acimtamig (AFM13), in patients with R/R PTCL.

Patients and Methods: Patients included those with CD30 expression in ≥1% of tumor cells and who were R/R following ≥1 prior line of systemic therapy. Acimtamig (200 mg) was administered once weekly in 8-week cycles. The primary endpoint was the overall response rate by fluorodeoxyglucose-PET per independent review committee; secondary and exploratory endpoints included duration of response, safety, progression-free survival, and overall survival.

Results: The overall response rate in 108 patients was 32.4% [95% confidence interval (CI), 23.7, 42.1] with a complete response rate of 10.2% (95% CI, 5.2, 17.5); the median duration of response was 2.3 months (95% CI, 1.9, 6.5). Patients with R/R angioimmunoblastic T-cell lymphoma exhibited the greatest number of responses [53.3% (95% CI, 34.3, 71.7)]. Responses were independent of CD30 expression level, prior brentuximab vedotin treatment, or steroid premedication. Acimtamig exhibited a tolerable safety profile; the most common treatment-related adverse events were infusion-related reactions in 27 patients (25.0%) and neutropenia in 11 patients (10.2%). No cases of cytokine release syndrome or acimtamig-related deaths were reported. Despite exhibiting promising clinical activity and tolerable safety in a heavily pretreated PTCL population, the study did not meet the criteria for the primary endpoint.

Conclusions: The promising clinical efficacy observed warrants further investigation, and development of acimtamig for patients with R/R CD30$^+$ lymphomas continues in combination with allogeneic NK cells.

Introduction

Peripheral T-cell lymphomas (PTCL) are a heterogeneous group of hematological malignancies arising from mature postthymic T cells, accounting for 10%–15% of all new cases of non-Hodgkin lymphomas worldwide (1–4). Initial response rates to standard first-line therapies, including cytotoxic chemotherapy regimens, autologous hematopoietic stem cell transplant in first remission, and chemotherapy in combination with the CD30-targeting antibody–drug conjugate brentuximab vedotin (BV) for the treatment of anaplastic large cell lymphoma (ALCL), are generally favorable; however, long-term disease control is limited (5, 6). A significant proportion of patients relapse or are refractory (R/R) to first-line therapies. The prognosis for these patients is poor; the median overall survival (OS) is 5.5 months (7–10).

Of note, ALCL has two distinct types: one that affects the skin (cutaneous ALCL) and one that affects other organs [systemic ALCL (sALCL)] with the systemic version also existing in two types based on being anaplastic lymphoma kinase-positive or anaplastic lymphoma kinase-negative. Although they have immunophenotypical similarities, such as high CD30 expression, they differ by clinical presentation and prognosis (11). Despite BV providing an efficacious treatment option for patients with R/R sALCL (12), therapeutic options are generally limited for patients with R/R PTCL (13). Molecular targeted therapies, including pralatrexate, belinostat, and duvelisib, are approved or in development for patients with R/R PTCL; however, the efficacy of the majority of these therapies is limited, and undesirable adverse events (AE) are common (12, 14–19). Novel, broadly efficacious, well-tolerated therapies for R/R PTCL are therefore required.

CD30 remains an attractive therapeutic target for R/R PTCL, with 37% to 100% of patients exhibiting expression of CD30 on tumor cells depending on the subtype (20). Acimtamig (AFM13), a novel,

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Translational Relevance

High unmet need for patients with relapsed or refractory (R/R) peripheral T-cell lymphoma (PTCL) remains, as few therapeutic options are available. Acimtamig offers a new mechanism of action by redirecting and engaging innate immune cells to kill CD30-positive tumor cells. In the presented study, acimtamig monotherapy has exhibited promising efficacy and safety in patients with R/R PTCL. Subgroup analyses revealed pronounced efficacy in patients with angioimmunoblastic T-cell lymphoma, a subtype characterized by a highly immune-reactive microenvironment, higher lymphocyte counts, or a higher number of circulating mature lymphocytes at baseline. Interestingly, a phase I/II study of acimtamig in combination with allogeneic NK cells in patients with R/R CD30$^+$ lymphomas reported a high overall response rate and complete response rate. Hence, the addition of allogeneic NK cells to acimtamig might boost the efficacy of acimtamig in less immunogenic PTCL subtypes. A phase II study (NCT05883449) is enrolling patients with R/R Hodgkin lymphomas and R/R CD30$^+$ PTCL subtypes for treatment with acimtamig in combination with allogeneic NK cells.

bispecific Innate Cell Engager (ICE), binds to CD30 on CD30$^+$ tumor cells and CD16A on innate effector cells, such as NK cells and macrophages, enhancing and redirecting antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cell-mediated phagocytosis, respectively, toward CD30$^+$ tumor cells (21–23). Previous studies have demonstrated the clinical activity of acimtamig as a monotherapy. In a phase I trial, heavily pretreated patients with R/R Hodgkin lymphomas showed an overall response rate (ORR) and a disease control rate of 11.5% and 61.5%, respectively (24). A further phase II trial showed an ORR of 16.7% (25). In a phase Ib/IIa study of patients with T-cell lymphomas with cutaneous involvement, acimtamig exhibited an ORR of 40% (26). Correlative science data have shown enhanced activation of NK cells following acimtamig infusion (24), as well as an increased tumor infiltration of NK cells, compared with values prior to infusion (26), suggesting augmentation of the innate immune system in response to acimtamig.

Acimtamig exhibited a well-managed safety profile across previous trials. The most common treatment-related AE (TRAE) has been infusion-related reactions (IRR; refs. 24–26). However, no cases of cytokine release syndrome (CRS) have been reported, and no correlation between acimtamig immunogenicity and the safety profile was found in patients exhibiting anti-acimtamig antibodies (24–26). Based on the tolerability and pharmacokinetics (PK) observed in previous studies, a dose of 200 mg acimtamig once weekly was determined to reach exposures likely to achieve clinical benefit and was established as the recommended phase II dose (24–26).

Based on preclinical and clinical data, it was hypothesized that acimtamig may provide clinical benefit for patients with R/R CD30$^+$ PTCL. The study detailed here (REDIRECT, NCT04101331) was a phase II, open-label study investigating the safety and efficacy of acimtamig monotherapy in these patients.

Patients and Methods

The study was initiated at 69 sites across Australia, France, Germany, Italy, South Korea, Poland, the Russian Federation, Spain, Turkey, and the United States; of these, 42 sites enrolled patients. The protocol was registered under the ClinicalTrials.gov number NCT04101331. The study was approved by the institutional review board/ethics committee at each participating center and performed in accordance with good clinical practice and local regulatory requirements. The informed consent form contained all the Essential Elements of Informed Consent set forth in 21 CFR, Part 50, the International Council for Harmonization Guideline for Good Clinical Practice, and the terms of the Declaration of Helsinki.

Patient population

Full inclusion and exclusion criteria are provided as Supplementary Materials. Patients enrolled were ≥18 years old and had histologically confirmed CD30$^+$ PTCL, centrally assessed by Ber-H2 targeted IHC, with CD30 expression confirmed in ≥1% of tumor cells. Patients were R/R to at least one prior line of systemic therapy; patients with sALCL had relapsed following or were intolerant to, BV treatment. Patients were required to have an Eastern Cooperative Oncology Group performance score of 0 or 1 and have demonstrated adequate organ function within the protocol-specified laboratory function values. Written informed consent was obtained from all patients or their legal representatives and consent could be withdrawn at any time.

Study endpoints

The primary endpoint was to evaluate the antitumor efficacy of acimtamig by fluorodeoxyglucose-PET (FDG-PET)-based ORR by independent review committee (IRC) assessment. Secondary endpoints were IRC-confirmed complete response (CR) and partial response (PR) rates, CT scan-based ORR, investigator-assessed ORR (ORR-2), duration of response (DoR), safety and tolerability, PK, immunogenicity of acimtamig, and patient quality of life while on acimtamig. Exploratory endpoints were progression-free survival (PFS), OS, and any potential relationship between CD30 expression in patient tumor samples at baseline and acimtamig response and between various pretreatment biomarkers in the peripheral blood and acimtamig response.

Study design

The study design is outlined in **Fig. 1**. Patients were originally enrolled into two cohorts based on measured CD30 expression. Patients recruited to cohort A had CD30 on ≥10% tumor cells, and patients recruited to cohort B had CD30 expression on ≥1% to <10% tumor cells. Following a protocol-specified planned interim analysis (after enrollment of 21 patients into cohort A and 20 patients into cohort B) showing comparability between the two cohorts, they were combined into a single cohort with CD30$^+$ defined as ≥1% by centrally assessed IHC.

Acimtamig was administered at a dose of 200 mg intravenously, once weekly in 8-week cycles until disease progression, intolerable toxicity, termination at the investigator's discretion, or withdrawal of patient consent; patients could remain on treatment beyond confirmed progression if clinical benefit was still being derived at the discretion of the investigator. All doses of acimtamig were infused over 4 hours (50 mg/hour) unless the rate was modified because of treatment-related IRRs. From cycle 2, day 50 onward, patients exhibiting recurrent IRRs who had achieved an objective response could be dosed once every 2 weeks, at the discretion of the investigator. Following a protocol update to reduce the incidence of IRRs observed early in the study, a mandatory premedication regimen consisting of dexamethasone (20 mg), or an equivalent steroid

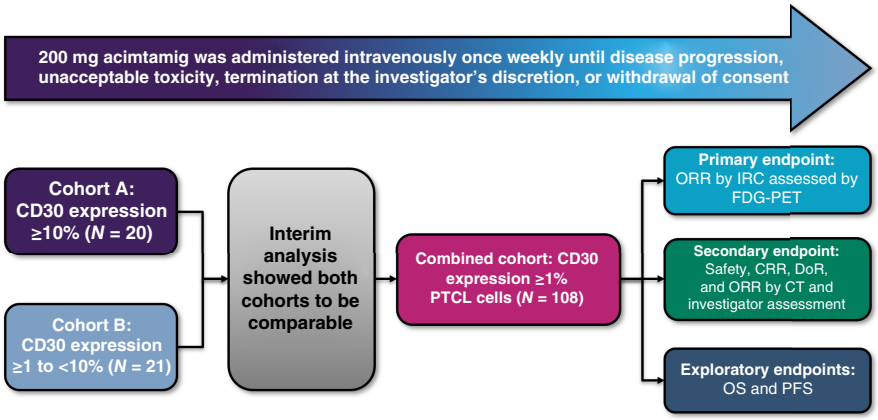


Figure 1.
Study design for the phase II trial of acimtamig in patients with CD30-positive, R/R PTCL. The study began with a 28-day prescreening phase starting from the time of informed consent, during which the tumor sample was tested for CD30 expression, and ALK expression in patients with sALCL. This was followed by a screening period lasting up to 21 days in which evaluations were carried out as per the protocol to assess eligibility to proceed to the treatment phase. Patients were initially recruited into two cohorts based on CD30 expression as indicated. Following a planned interim analysis, the cohorts were combined into a single cohort. Key endpoints for the study are shown. ALK, anaplastic lymphoma kinase.

dose, was introduced, to be given 1 hour prior to each acimtamig infusion. Investigators could taper steroid prophylaxis after the first cycle (8 weeks) if the patients did not develop IRRs of Grade 2 or higher. Premedication also included intravenous H1 antagonist [such as diphenhydramine (50 mg) or equivalent] with or without an H2 antagonist (e.g., famotidine or equivalent) and oral acetaminophen (500–600 mg) or equivalent.

Efficacy

For the primary endpoint, tumor responses were evaluated using FDG-PET and assessed by IRC (27). For secondary endpoints, disease responses were evaluated using CT and assessed by the investigator and IRC assessment, as well as FDG-PET evaluation per investigator assessment. For both the primary and secondary efficacy endpoints, the modified Lugano Classification Revised Staging System for malignant lymphoma was used to determine responses (27). Disease assessments were performed during the screening period, then every 8 weeks for the first three assessments (cycle 2 day 1, cycle 3 day 1, and cycle 4 day 1), and then every 12 weeks thereafter.

Safety

AEs and serious AEs (SAE) were collected from the time of informed consent up to and including the 30-day +7 follow-up (final study visit) and were graded using the NCI Common Terminology Criteria for Adverse Events, v5.0. An independent safety review committee was established to review the safety data obtained from the study, including treatment-emergent AEs (TEAE) in all cohorts.

Safety was assessed by monitoring of AEs, vital signs, physical examinations, clinical laboratory assessments, Eastern Cooperative Oncology Group performance score, and 12-lead electrocardiograms predose and immediately postdose. Immunogenicity was assessed by observing the development of anti-drug antibodies (ADA) before and twice every cycle throughout acimtamig treatment.

PK profile

Summary statistics for acimtamig PK parameters are provided in Supplementary Table S1. Serum trough levels of acimtamig were assessed in all patients. In a subset of patients (PK group 1, $n = 20$), additional serum acimtamig concentrations were assessed 1 hour after the start of infusion, end of infusion (EOI), and 1, 2, 3, 24, and 48 hours after EOI on cycle 1 days 1, 8, and 29; cycle 2 day 1; and cycle 3 day 1. In another subset of patients, an additional serum acimtamig level was assessed at the EOI on cycle 1 days 1, 8, and 29; cycle 2 day 1; and cycle 3 day 1 (PK group 2, $n = 20$). The subsets of patients were selected independently of the subject cohorts defined by CD30 expression. A noncompartmental analysis was carried out on the acimtamig concentrations obtained from PK group 1 only. PK parameters investigated included maximum concentration (C_{max}), AUC, volume of distribution at steady state (V_{ss}), and half-life ($t_{1/2}$).

Immunophenotyping

Whole-blood samples were collected in BD Vacutainer CPT Mononuclear cell preparation tubes (BD Biosciences, #362753) from patients at baseline. Peripheral blood mononuclear cells (PBMC) were isolated following the manufacturer's instructions. Isolated PBMCs were then stained using antibodies for CD45 (RRID AB_2888654), CD45RA (RRID AB_3665076), CD3 (RRID AB_130860), CD20 (RRID AB_3665077), CD7 (RRID AB_10375171), CD4 (RRID AB_3665078), CD8 (RRID AB_3665079), CD16 (RRID AB_3665080), CD69 (RRID AB_2801272), CD56 (RRID 10645063), HLA-DR (RRID AB_399988), CD14 (RRID AB_3665082), CD127 (RRID AB_3665083), and CD25 (AB_10643226) across two panels; DAPI was used as the live/dead exclusion dye. Samples were measured on a Beckman Coulter Navios EX flow cytometer and analyzed using Beckman Coulter Kaluza analysis software V1.2. Further information on the antibody clones used is provided in Supplementary Table S2.

Bioanalysis

Serum concentrations of acimtamig were measured using a ligand binding assay with a sensitivity of 20 ng/mL. The determination of anti-acimtamig antibodies was performed with an ADA assay and

determination of neutralizing antibodies was evaluated by competitive ligand binding assay. Both immunogenicity assessment methods are sensitive (<100 ng/mL) and sufficiently drug and target tolerant.

Statistical analysis

The full analysis set consisted of all patients who received at least one dose of acimtamig; this was the primary population for all efficacy-related endpoints. The safety set consisted of all patients who received at least one dose of acimtamig and had at least one postbaseline safety assessment; the safety set was the primary population for all safety-related endpoints.

The overall response (CR and/or PR) rate was described using descriptive statistics and corresponding 95% confidence intervals (CI). An ORR of ≥40% in R/R PTCL patients with CD30 ≥1% was benchmarked to be considered promising based on previous studies of pralatrexate, belinostat, and romidepsin, in which the highest ORR was observed with pralatrexate [ORR 29.0%, 95% CI, 21.0%, 39.0% ($n = 111$); ref. 15]. DoR, PFS, and OS are summarized using descriptive statistics and Kaplan–Meier estimates.

Preplanned subgroup analyses were performed for CD30 expression level, prior BV treatment, PTCL subtypes, and receipt of steroid premedication at cycle 1 day 1 (C1D1) as well as *post hoc* subgroup analyses based on common subgrouping variables.

Logistical regression analyses were performed using multiple combinations of baseline patient variables to determine their influence on the primary outcome variable (ORR). The association of various baseline biomarkers and disease response was also analyzed.

Data availability

The data generated in this study are available within the article and its Supplementary Data files; additional information is available upon request from the corresponding author.

Results

Patients

Baseline characteristics are reported in **Table 1**. A total of 136 patients were enrolled and prescreened; 134 underwent screening, and 108 patients were treated in the study. Most patients were male and of White ethnicity. The three main PTCL subtypes investigated were PTCL-not otherwise specified (38.0%), AITL (27.8%), and sALCL (24.1%); 11 patients (10.2%) presented with other subtypes. Most patient tumors exhibited ≥10% CD30 expression. Most patients had advanced-stage disease (Ann Arbor stages III or IV). The median (range) number of prior lines of therapy was 2 (1–7); 46.3% of patients had previously received BV.

Most (85.2%) patients received 200 mg acimtamig at all infusions, and 88.9% of patients did not require a dose modification or adjustment. Reasons for dose adjustment in 11.1% of patients were IRRs in nine patients, a different AE in two patients, or other reasons (not specified) in one patient. The median (range) number of infusions was 9.0 (1–116). The mean relative acimtamig dose intensity was 91.4%.

Antitumor response

A summary of responses to acimtamig is provided in **Fig. 2**. The ORR by FDG-PET assessed per IRC was 32.4% (95% CI, 23.7, 42.1); the CR rate (CRR) was 10.2% (95% CI, 5.2, 17.5). Most patients who exhibited CR or PR showed responses within the first cycle of acimtamig treatment. Furthermore, based on CT evaluations (per IRC assessed change in the sum of the products of diameters) tumor shrinkage was observed in >50% of evaluable patients (**Fig. 3**).

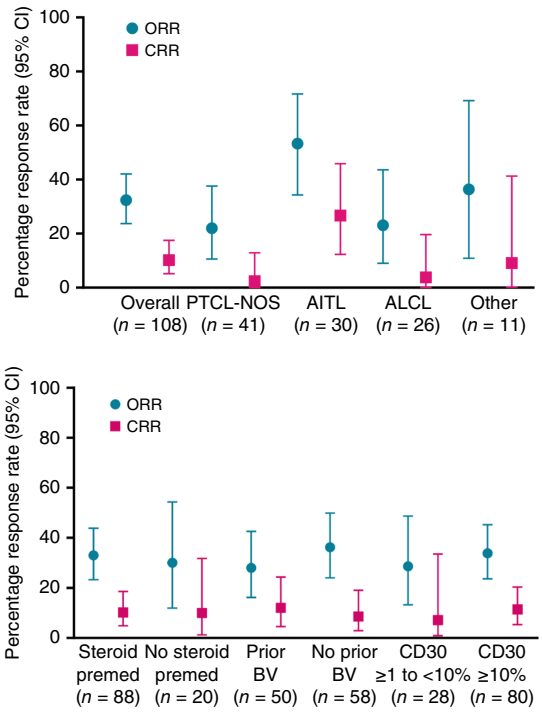
Table 1. Baseline patient characteristics and demographics.

Characteristic	Total ($N = 108$)
Median (range) age, years	63 (21–93)
Sex, *n* (%)	
Male	66 (61.1)
Female	42 (38.9)
Race, *n* (%)	
White	75 (69.4)
Asian	15 (13.9)
Black or African American	5 (4.6)
ND	12 (11.1)
Missing	1 (0.9)
Cancer subtypes, *n* (%)	
PTCL-NOS	41 (38.0)
AITL	30 (27.8)
ALCL	26 (24.1)
Other	11 (10.2)
Ann Arbor stage, *n* (%)	
I	1 (0.9)
II	13 (12.0)
III	36 (33.3)
IV	56 (51.9)
NR	2 (1.9)
ECOG PS, *n* (%)	
0	42 (38.9)
1	66 (61.1)
Number of prior lines, *n* (%)	
Median	2.0
1	23 (21.3)
2	35 (32.4)
≥3	50 (46.3)
CD30 expression at baseline, *n* (%)	
≥1 to <5	15 (13.9)
≥5 to <10	13 (12.0)
≥10 to <50	39 (36.1)
≥50	36 (33.3)
Missing	5 (4.6)
Number of patients having received prior BV, *n* (%)	50 (46.3)
Number of patients having received prior auto-HSCT, *n* (%)	19 (17.6)

Abbreviations: auto-HSCT, autologous hematopoietic stem cell transplant; *N*, number; ND, not disclosed; NR, not recorded; PTCL-NOS, PTCL-not otherwise specified.

In preplanned subgroup analyses (**Fig. 2**), the greatest ORR by FDG-PET assessed by IRC was observed in patients with R/R AITL [ORR 53.3% (95% CI, 34.3, 71.7); CRR 26.7% (95% CI, 12.3, 45.9)]. No meaningful differences in ORR by FDG-PET assessed by IRC were observed based on CD30 expression level, prior BV treatment, or receipt of steroid premedication at C1D1.

In *post hoc* subgroup analyses based on results from logistical regression analyses (Supplementary Table S3), greater ORR correlated with baseline patient characteristics including lower than/equal to median lactate dehydrogenase levels, above median albumin levels, above median lymphocytes, lower than/equal to median levels of CRP, and lower than/equal to median body weight. Female patients also exhibited a greater ORR per FDG-PET when compared with male patients. No meaningful differences were detected based on the number of prior systemic therapies, age groups, ethnicity, and best response to the last line of therapy (Supplementary Table S4).



	ORR, % (95% CI)	CRR, % (95% CI)	DoR, months Median (min, max)
Total	32.4 (23.7, 42.1)	10.2 (5.2, 17.5)	2.3 (1.9, 6.5)
PTCL-NOS	22.0 (10.6, 37.6)	2.4 (0.1, 12.9)	2.1 (1.8, 5.6)
AITL	53.3 (34.3, 71.7)	26.7 (12.3, 45.9)	3.6 (1.9, 11.9)
ALCL (ALK$^+$ and ALK$^-$)	23.1 (9.0, 43.6)	3.8 (0.1, 19.6)	9.0 (1.8, 9.0)
Other	36.4 (10.9, 69.2)	9.1 (0.2, 41.3)	1.8 (1.4, 1.9)

	ORR, % (95% CI)	CRR, % (95% CI)	DoR, months Median (min, max)
Patients who received steroid premedication on C1D1	33.0 (23.3, 43.8)	10.2 (4.8, 18.5)	2.0 (1.9, 5.6)
Patients who did not receive steroid premedication on C1D1	30.0 (11.9, 54.3)	10.0 (1.2, 31.7)	NE (NE, NE)
Patients who received prior BV	28.0 (16.2, 42.5)	12.0 (4.5, 24.3)	2.4 (1.9, 9.0)
Patients who did not receive prior BV	36.2 (24.0, 49.9)	8.6 (2.9, 19.0)	2.1 (1.9, 6.5)
Patients with tumor CD30 expression levels ≥1 to <10%	28.6 (13.2, 48.7)	7.1 (0.9, 33.5)	7.3 (1.9, 11.9)
Patients with tumor CD30 expression levels ≥10%	33.8 (23.6, 45.2)	11.3 (5.3, 20.3)	2.1 (1.9, 5.6)

Figure 2.

Objective responses stratified by PTCL subtype, steroid premedication, prior BV, and tumor CD30 expression level. Top, ORR, CRR, and DoR in the overall cohort and stratified by PTCL subtype. Bottom, ORR, CRR, and DoR stratified by steroid premedication, prior BV, and tumor CD30 expression level. ALK, anaplastic lymphoma kinase; max, maximum; min, minimum; *N*, number; NE, not estimable; PTCL-NOS, PTCL-not otherwise specified.

Median DoR (**Fig. 2**) and PFS (**Fig. 4**) per FDG-PET by IRC were 2.3 months (95% CI, 1.9, 6.5) and 3.5 months (95% CI, 1.9, 3.6), respectively. The median duration of CR was 3.6 months (95% CI, 1.9, not estimable). One patient exhibited sufficient DoR to enable subsequent allogeneic stem cell transplant. The median OS was 13.8 months (95% CI, 7.6, not estimable; **Fig. 4**). A total of 46 and 62 patients were censored for PFS and OS analysis, respectively.

Correlative analyses on PBMCs from 22/108 patients revealed that patients who responded to acimtamig (overall response by PET-CT assessed by IRC) exhibited a higher percentage of circulating mature lymphocytes compared with nonresponders at baseline, whereas the opposite was observed for CD4$^+$ CD25$^+$ CD45RA$^+$ CD127$^-$ regulatory T cells (Supplementary Fig. S1).

Safety profile

A summary of TEAEs observed in the study is provided in **Table 2**. TRAEs were reported in 79 (73.1%) patients, with the majority of these patients reporting mild or moderate events.

The most common TRAEs were IRRs and neutropenia. IRRs considered related to acimtamig occurred in 27 (25.0%) patients; most were Grade 1/2 (21 patients, 19.4%), with 12 Grade 3 events observed in six patients (5.6%). IRRs were well managed with symptomatic treatment, steroid premedication, and infusion rate reduction. In 88 patients who received steroid premedication at C1D1, a reduced incidence of IRRs [14 (15.9%)] was observed at C1D1 compared with 20 patients who did not receive steroids at C1D1 [12 (60.0%)]. No CRS events were reported. Neutropenia was reported in 14 (13.0%) patients and was considered treatment related in 11 patients (10.2%). Of those 11 patients, six exhibited Grade 3 events, and two exhibited Grade 4 events. One case of febrile neutropenia was observed, unrelated to acimtamig. All other TRAEs occurred in less than 10% of patients.

Serious TRAEs occurred in nine patients (8.3%, 14 events); serious IRRs accounted for eight events in five patients. Other serious TRAEs were pneumonia (two events in two patients), and chills, pyrexia, hepatic enzyme increase, and pulmonary embolism (one event in one patient, each). TEAEs leading to acimtamig discontinuation were observed in 13 patients (12.0%, 19 events); only three events in two patients (1.9%) were related to acimtamig treatment (all IRRs). Although 11 TEAEs leading to on-study deaths occurred in six patients (5.6%), none were considered related to acimtamig.

ADAs were detected in 45 samples in 19 patients (17.6%). Two of these patients already had detectable ADAs prior to the first acimtamig administration, of which one did not develop on-treatment ADAs. Of 45 ADA-positive samples, 38 were measured as being neutralizing antibodies.

PK profile

Noncompartmental PK analysis was performed using all available acimtamig data in subjects belonging to PK group 1. Summary statistics for the PK parameters are presented for cycle 1 by cycle day in Supplementary Table S1. No marked differences were observed between cycle days for C_{max} and exposure (no formal statistical analysis was performed). The geometric mean [coefficient of variation (CV)

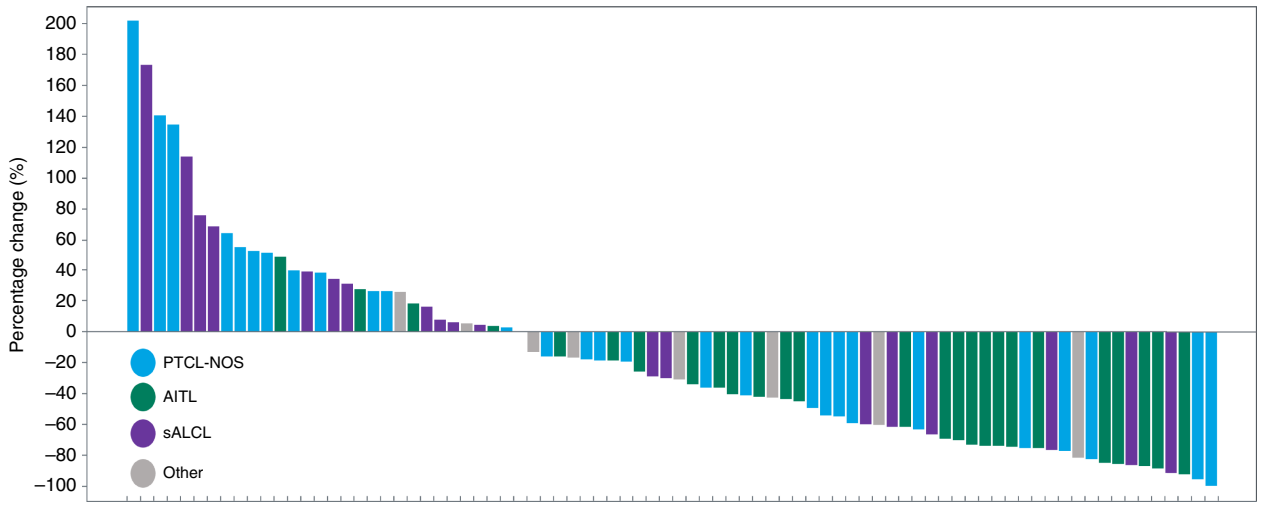


Figure 3.

Greatest percentage tumor change from baseline in sum of the products of diameters (SPD) based on CT per IRC assessment in individual patients. Each bar represents one patient. Only patients with a measurable postbaseline assessment are included. PTCL-NOS, PTCL-not otherwise specified.

geomean, %] acimtamig C_{max}, for cycle 1 by cycle day, was estimated to be 26,232 ng/mL (270%), 29,014 ng/mL (272%), and 24,435 ng/mL (364%) for days 1, 8, and 29, respectively. The CV geomean (%) acimtamig $AUC_{0\text{-}168\ hours}$, for cycle 1 by cycle day, was estimated to be 608,104 ng·h/mL (60.1%), 708,765 ng·h/mL (41.6%), and 759,038 ng·h/mL (35.0%) for days 1, 8, and 29, respectively. The CV geomean (%) $t_{1/2}$, for cycle 1 by cycle day, was estimated to be 20.7 hours (35.9%), 19.1 hours (36.5%), and 19.6 hours (47.4%) for days 1, 8, and 29, respectively.

Discussion

Patients with R/R PTCL generally have a poor prognosis, with limited therapy options and long-term disease control; a high unmet need for novel therapies to treat patients with R/R PTCL remains (7, 8). The innate cell engager acimtamig potentiates the activity of a patient's endogenous NK cells, redirecting and enhancing ADCC toward $CD30^+$ tumor cells. This phase II monotherapy study established the efficacy of acimtamig in patients with $CD30^+$ R/R PTCL.

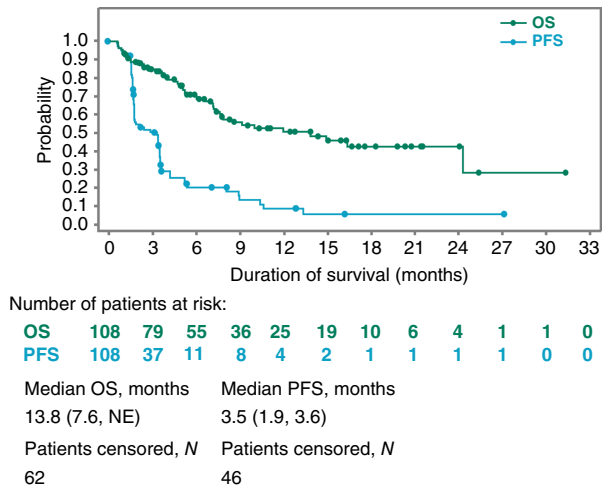


Figure 4.

Kaplan–Meier estimate of OS and PFS. PFS was assessed by FDG-PET per IRC. *N*, number; NE, not estimable.

With the exception of BV, which is approved for patients with R/R sALCL, having exhibited an ORR of 86.0% in a pivotal phase II trial (12), currently approved and available therapies for R/R PTCL have limited efficacy and/or tolerability (12, 14–19). Response rates to BV in $CD30^+$ R/R PTCL subtypes, such as PTCL-not otherwise specified and AITL, seem to be lower than those observed in sALCL, with patients exhibiting ORRs of 33.0% and 54.0%, respectively (14). Moreover, pralatrexate and belinostat, both approved for use in the R/R setting, have previously exhibited ORRs of 29.0% and 25.8%, respectively (15, 16). Romidepsin showed similar efficacy to pralatrexate and belinostat in R/R PTCL but was withdrawn in May 2021 because of a lack of increased clinical benefit in a phase III trial of romidepsin combined with standard chemotherapy versus standard chemotherapy alone, in untreated patients (17, 18). An upcoming therapy, the PI3K inhibitor duvelisib, has exhibited promising clinical efficacy in R/R PTCL, with a recent phase II trial reporting an ORR of 49.0%; however, this class of drug has been associated with high rates of SAEs (19, 28). Similarly, the upcoming targeted therapies valemetostat (an EZH1/EZH2 inhibitor) and golidocitinib (a JAK1 tyrosine kinase inhibitor) have shown promising efficacy for patients with PTCL, with ORRs of 43.7% and 44.3%, respectively (29, 30).

In this study, acimtamig exhibited an ORR of 32.4% (95% CI, 23.7, 42.1) and a CRR of 10.2% (95% CI, 5.2, 17.5), showing promising efficacy in 108 patients, most of whom had received two or more prior lines. This ORR is comparable with those observed with pralatrexate, belinostat, and romidepsin (15, 16, 18). The ORR observed with acimtamig was unaffected by the number of prior lines, prior treatment with BV, and the last previous therapy line. Patients with R/R AITL ($n = 30$) exhibited the greatest response, with an ORR of 53.3% (95% CI, 34.3, 71.7) and a CRR of 26.7% (95% CI, 12.3, 45.9), making the ORR comparable with that

Table 2. Summary of all TEAEs and acimtamig-related TEAEs by grade (≥5% patients).

Category	Total *N* = 108 *n* (%)
TEAE	105 (97.2)
Related TEAE	79 (73.1)
TEAE grade ≥3	58 (53.7)
Related TEAE with grade ≥3	33 (30.6)
Serious TEAE	43 (39.8)
Related serious TEAE	9 (8.3)
Fatal TEAE	6 (5.6)
Related fatal TEAE	0
TEAEs leading to study drug discontinuation	13 (12.0)
Related TEAEs leading to study drug discontinuation	2 (1.9)
Related TEAEs by grade (≥5% patients)	
IRRs	27 (25.0)
Grade 1/2	21 (19.4)
Grade 3/4	6 (5.6)
Neutropenia	11 (10.2)
Grade 1/2	3 (2.8)
Grade 3/4	8 (7.4)
Pyrexia	9 (8.3)
Grade 1/2	8 (7.4)
Grade 3/4	1 (0.9)
Nausea	8 (7.4)
Grade 1/2	7 (6.5)
Grade 3/4	1 (0.9)
Anemia	7 (6.5)
Grade 1/2	3 (2.8)
Grade 3/4	4 (3.7)
Chills	7 (6.5)
Grade 1/2	6 (5.6)
Grade 3/4	1 (0.9)
Thrombocytopenia	7 (6.5)
Grade 1/2	5 (4.6)
Grade 3/4	2 (1.9)
Rash	6 (5.6)
Grade 1/2	5 (4.6)
Grade 3/4	1 (0.9)

Only related events in ≥5% of patients shown.

previously reported for BV (54.0%, $n = 13$; ref. 14). AITL originates in T follicular helper cells and is characterized by a highly immune-reactive microenvironment, exhibiting high numbers of immunoblasts, histiocytes, and plasma cells (31). As the mechanism of action of acimtamig relies on potentiating the immune response to tumor cells, a highly immune-reactive environment in AITL may enable greater responses compared with other PTCL subtypes. This may be congruent with the observations in this study that patients with higher than median lymphocytes (0.9×10^9 cells/L) at baseline exhibited a greater ORR with acimtamig than those with equal to/lower than median lymphocytes at baseline; a significantly higher number of circulating mature lymphocytes at baseline was also observed in those patients who responded to acimtamig. The latter data, however, must be caveated as only 22 of 108 samples were available for analysis and yielded reliable data because of poor quality and viability of PBMCs obtained.

No new or unexpected safety results were observed compared with previous studies with acimtamig (24, 32). Acimtamig had a tolerable safety profile and most TEAEs observed were Grade 1/2. A relatively low number of patients discontinued because of TEAEs, and a dose intensity of 91% indicated high exposure. No treatment-related deaths were observed. Consistent with previous studies of acimtamig and other mAbs and constructs (33), IRRs were the most frequently observed TRAE, accounting for most serious TRAEs (8 of 14 events in 5 patients) and the only three TRAEs in two patients leading to discontinuation. No CRS events were observed. IRRs were generally well managed with symptomatic treatment. Furthermore, the inclusion of a mandatory steroid premedication seemed to reduce the frequency of IRRs. As the regimen was introduced early in the study, there were large differences in sample size between patients who did not receive steroid premedication at C1D1 ($n = 20$) versus those who did ($n = 88$), potentially influencing this conclusion. It was noted that the most frequently reported SAEs unrelated to acimtamig were infections; however, infections have been noted previously in patients with T-cell lymphomas and may arise because of confounding factors within this population, such as poor immune function (34).

The half-life of acimtamig determined in this study (~19.1–20.7 hours) was similar to that determined for acimtamig in a previous study (24). No PK correlation of ADAs could be ascertained in 19 patients who were ADA positive. Moreover, no impact on the efficacy of acimtamig was observed in the 17 patients with anti-acimtamig neutralizing antibodies that remained consistent for patients with transient and persistent ADAs. No clinical correlations could be attributed to low titers of ADAs.

Median (95% CI) PFS was 3.5 months (1.9, 3.6), comparable with that observed for approved therapies in patients with R/R PTCL (14–16). However, a high number of patients ($n = 46$) were censored in this study for the PFS analysis, which may have influenced the findings.

DoR was notably shorter with acimtamig than for approved therapies for R/R PTCL (12, 14–16, 18). This could be attributed to potential mechanisms that may limit acimtamig-induced ADCC, including low NK cell numbers, impaired NK cell functionality, the presence of immunosuppressive cytokines, low NK cell CD16 expression, or co-treatment with immunosuppressive doses of dexamethasone (35, 36). As the mechanism of action of acimtamig relies on stimulating NK cell-mediated antitumor ADCC toward $CD30^+$ lymphoma cells, likely impairment of endogenous NK cells in heavily pretreated patients may impact the efficacy of acimtamig therapy (37, 38). Previous studies have shown that patients with hematological malignancies exhibit impaired NK cell function and downregulation of CD16A, which may limit their capacity for ADCC (22, 39, 40).

A median OS of 13.8 months with acimtamig indicates an improvement to the 5.5 months previously seen in population-based studies (7) and is comparable with other therapies in patients with R/R PTCL (15, 16, 18). However, a relatively short follow-up period (median: 10.8 months) and a high censoring rate (57%) at the time of data analyses suggest that these data should be interpreted with caution.

Despite signs of clinical activity in a pretreated cohort of patients, and a tolerable safety profile, the criteria for meeting the primary endpoint of this study were not met. The antitumor activity of acimtamig may be enhanced in combination with adoptive NK cell therapies, with the aim of synergistically enhancing the innate immune response to $CD30^+$ tumors. A phase I/II study of acimtamig in combination with cord blood-derived NK cells in patients with R/R $CD30^+$ lymphomas (majority R/R Hodgkin lymphomas) treated at the recommended phase II dose achieved an ORR of 94% (41). Following this, a phase II, open-label, multicenter, multicohort

study (NCT05883449) began enrolling patients in October 2023 and aims to evaluate the efficacy and safety of acimtamig in combination with allogeneic NK cells (AlloNK) in patients with R/R Hodgkin lymphomas and certain R/R CD30$^+$ PTCL subtypes.

In conclusion, acimtamig provides a potential treatment option with a novel mechanism of action, enhancing the activity of the innate immune response, and shows promise in a pretreated cohort of patients with R/R PTCL. This study provides a basis for further development of acimtamig, including in combination with allogeneic NK cells, in patients with R/R PTCL.

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