Evorpacept plus rituximab for the treatment of relapsed or refractory non-Hodgkin lymphoma: results from the phase I ASPEN-01 study

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Abstract

CD47 overexpression has been associated with tumor cell survival. We present the safety, pharmacokinetics, pharmacodynamics, and preliminary anti-tumor activity of evorpacept, a novel fusion protein comprising a high-affinity CD47–SIRPα immune checkpoint inhibitor to promote tumor cell phagocytosis and inactive Fc domain to spare healthy cells, plus rituximab in patients with relapsed/refractory B-cell non-Hodgkin lymphoma (NHL) from the phase I ASPEN-01 study. Thirty-three patients received intravenous evorpacept (10 mg/kg [N=22] or 15 mg/kg [N=11] once weekly) until disease progression, in combination with fixed-duration intravenous rituximab (375 mg/m^2 once weekly for 4 weeks, then every 4 weeks for 8 months). Evorpacept plus rituximab was well tolerated, with no dose-limiting toxicities; no maximum tolerated dose was identified. The most common treatment-related adverse events (TRAE) were rash (24.2%) and fatigue (15.2%); most TRAE (70.0%) were mild-to-moderate in severity. Four (12.1%) patients reported grade 3 TRAE: anemia, neutropenia, decreased neutrophil count, increased alanine aminotransferase, decreased lymphocyte count, and decreased platelet count (1 of each). Two (6.1%) patients experienced grade 4 TRAE (neutropenia, decreased neutrophil count). Six (18.2%) patients experienced serious AE (not treatment-related): asthma, dyspnea, respiratory failure, gastrointestinal infection, pneumonia, cardiac failure, and disease progression (1 of each). Two (6.1%) deaths occurred (not treatment-related). Pharmacokinetics/pharmacodynamics were consistent with previous studies, with complete CD47 target occupancy (≥85%) achieved at both doses. In response-evaluable patients (N=32), objective response rate was 50.0% (95% confidence interval: 33.1-69.8%). The safety, tolerability, and promising anti-tumor activity of evorpacept plus rituximab support continued evaluation of this combination in NHL (*clinicaltrials gov. Identifier: NCT03013218*).

Introduction

The transmembrane protein CD47 is widely expressed on the surface of normal, healthy cells and acts as a major checkpoint in the innate immune system, analogous to the programmed cell death checkpoint (programmed death-1 and its ligand-1).[1-4] By binding to the receptor signal-regulatory protein α (SIRPα) on the surface of macrophages, CD47 triggers a "don't eat me" signal, thereby inhibiting phagocytosis.[1,3,4] Conversely, cells that express low levels of CD47, such as apoptotic or abnormal cells, are susceptible to phagocytosis and clearance by the innate immune system. However, CD47 has been shown to be overexpressed by many hematologic and solid tumors, enabling them to exploit the "don't eat me" function of CD47, evade phagocytosis, and survive as a consequence.[1,4-12] The CD47–SIRPα axis has therefore become a promising therapeutic target in various cancers, including non-Hodgkin lymphoma (NHL). Evorpacept (ALX148) is a novel engineered fusion protein comprising a high-affinity CD47-blocking domain linked to an inactive human immunoglobulin G1 Fc region.[13-15] While CD47 blockade alone is not usually sufficient to trigger macrophage anti-tumor activity,[4] studies have shown that the targeted antibody-dependent cellular phagocytosis (ADCP) of therapeutic antibodies containing an active Fc region (e.g., rituximab) may be enhanced with evorpacept

through its simultaneous disruption of the CD47–SIRPα antiphagocytic signal via CD47 blockade.[8,13,15-17] This was demonstrated in an *in vitro* flow cytometry assay, in which evorpacept significantly and dose-dependently increased phagocytosis induced by multiple therapeutic antibodies, including trastuzumab, cetuximab, daratumumab, and the CD20 targeted antibody, obinutuzumab, compared to the negative control.[13] Consistent with the lack of Fc effector function, phagocytosis was neither expected nor occurred with evorpacept in the absence of a combination anti-tumor antibody, which is required to provide a prophagocytic signal. These findings were supported by *in vivo* data from murine xenograft models of human cancers (B-cell lymphomas, gastric cancer, and colon cancer) in which evorpacept in combination with rituximab, obinutuzumab, or trastuzumab significantly increased tumor growth inhibition and improved survival compared with the anti-tumor antibody alone, whereas single-agent evorpacept demonstrated minimal efficacy.[13] Similarly, while single-agent evorpacept showed limited efficacy in immunocompetent syngeneic tumor models, combining evorpacept with anti-PD-L1 or anti-4-1BB significantly enhanced anti-tumor activity *versus* anti-PD-L1 or anti-4-1BB treatment alone, indicating that evorpacept also enhances the adaptive immune response.[13] In addition, flow cytometric analysis of CT26 tumors has shown that the ratio of pro-inflammatory to suppressive tumor-associated macrophages (TAM) increases 3-fold after treatment with evorpacept, causing a shift towards an anti-tumor phenotype.[13]

Although CD47 blockers with an active Fc domain are capable of providing both components required for tumor cell phagocytosis, off-tumor/on-target toxicities due to the ubiquitous expression of CD47 has limited their development.[8,18] The inactive Fc region of evorpacept is designed to minimize off-tumor phagocytotic activity and improve tolerability compared with CD47 blockers that contain an active Fc region by sparing healthy cells from CD47-targeted ADCP destruction.[8,16] Non-clinical studies have shown that evorpacept lacks hematologic toxicity due to the absence of Fc effector function.[13] *In vitro* assays showed that evorpacept did not induce hemagglutination of human erythrocytes whereas other anti-CD47 antibodies did cause hemagglutination.[13] In a mouse model, levels of red blood cells, platelets, or white blood cells after treatment with evorpacept remained similar to predose levels, while a control protein with an active Fc region induced significant reductions in levels of blood cells.[13] In addition, evorpacept did not affect levels of red blood cells, white blood cells, or platelets in cynomolgus monkeys in a toxicity study.[13]

The first-in-human, open-label, multicenter, two-part, phase I ASPEN-01 study (*clinicaltrials gov. Identifier: NCT03013218*) was designed to evaluate the safety and preliminary anti-tumor activity of evorpacept as a single-agent and in combination with pembrolizumab, rituximab, or trastuzumab in advanced solid tumors and lymphomas.[16] Initial results of ASPEN-01 showed that single-agent evorpacept had a favorable safety profile, with maximum tolerated dose (MTD) not reached (maximum doses administered: 10 mg/kg once weekly; 30 mg/kg every other week), and promising preliminary anti-tumor activity, when combined with pembrolizumab or trastuzumab in patients with advanced solid tumors.[16]

Here, we present findings from the relapsed/refractory (R/R) B-cell NHL cohort of patients from the ASPEN-01 study, who were treated with evorpacept plus rituximab.

Methods

Study design and participants

ASPEN-01 was conducted between March 2017 and February 2022 at ten centers across the United States and South Korea. Study methodology was published previously,[16] with further details in the *Online Supplementary Appendix*. Briefly, the study comprised a single-agent dose-escalation phase and a combination-therapy dose-escalation and dose-expansion phase (*Online Supplementary Figure S1*). In the single-agent phase, intravenous evorpacept was administered once weekly in 21-day cycles (0.3, 1, 3, or 10 mg/kg) or once every other week in 28-day cycles (30 mg/kg), using a standard 3+3 design,[19] in patients with advanced solid tumors or R/R NHL. Although eligible, no R/R NHL patients enrolled in the single-agent phase. The rationale for dosing frequency was based upon pharmacokinetic (PK) and pharmacodynamic data for evorpacept in non-human primates.[13] The MTD was not reached so the combination-therapy phase evaluated doses of evorpacept (10 and 15 mg/kg once weekly) not exceeding the maximum administered dose in the single-agent phase in combination regimens for solid tumors and NHL. Data for the NHL combination-therapy cohort are presented. The study was approved by institutional review boards and conducted in accordance with ethical guidelines and the Declaration of Helsinki. Participants provided written informed consent before study participation.

Patients were aged ≥18 years with indolent or aggressive R/R $CD20^+$ B-cell NHL who had received ≥1 prior line of anti-cancer therapy, ≥1 measurable lesion per Lugano 2014 criteria,[20] adequate bone marrow, renal, and liver function, and Eastern Cooperative Oncology Group performance status score of 0 or 1. CD20 eligibility was based on local assessment.

Study treatments

Evorpacept (10 or 15 mg/kg once weekly) was administered intravenously until disease progression, voluntary study withdrawal, unacceptable toxicity, dose-limiting toxicity (DLT), or study termination. A fixed-duration dose-intensification regimen of rituximab (375 mg/m^2 once weekly for 4 weeks, then once every 4 weeks for 8 months) was administered intravenously.[21,22]

Study outcomes

The main objective was to establish the MTD of evorpacept when administered with rituximab, measured by DLT occurrence during the first treatment cycle. Adverse events (AE) were monitored and recorded throughout evorpacept treatment. Secondary outcomes included safety, PK, immunogenicity, best objective tumor response (using Lugano criteria[20]), objective response rate (ORR), duration of response, progression-free survival, and overall survival. Predefined exploratory endpoints included CD47 target occupancy and immune-related biomarkers.

Statistical analysis

The sample size in the combination-therapy phase depended on the safety observed in the single-agent phase and determined the number of patients at each dose level and the number of dose levels investigated. With 20 patients in the combination-therapy expansion cohort, there was an 88% chance of detecting a toxic effect in 10% of patients, and a >96% chance of identifying responders if the true ORR was >15%. Safety was analyzed in all patients who received ≥1 dose of study medication; adequate baseline disease assessment and ≥1 post-baseline tumor assessment (or death before post-baseline assessment) were required to assess anti-tumor activity. PK was analyzed in patients with sufficient information to estimate ≥1 parameter, and pharmacodynamic parameters were analyzed in patients with ≥1 pre-/post-dose measurement.

Results

Study participants

In total, 33 patients with R/R NHL were enrolled in the study and received at least one dose of study medication; 11 patients had indolent NHL (follicular lymphoma [FL] or marginal zone lymphoma [MZL]) and 22 had aggressive NHL (diffuse large B-cell lymphoma [DLBCL] or mantle cell lymphoma [MCL]). Twenty-two (66.7%) patients received evorpacept 10 mg/kg, and 11 (33.3%) received evorpacept 15 mg/kg. The median duration of treatment was 16 (range, 0-118) weeks for evorpacept and 15 (range, 0-39) weeks for rituximab. One patient was still receiving treatment at the data cutoff date.

Baseline patient demographics and disease characteristics are summarized in Table 1. In brief, the median age was 64 years (range, 32-80 years), and the majority of patients were male (69.7%), Asian (81.8%), had an Eastern Cooperative Oncology Group performance status score of 1 (72.7%), had stage IV disease (69.7%), and had DLBCL (51.5%).

Patients received a median of three prior regimens (range, 1-7; Table 1). All patients received prior rituximab therapy, which was also the most recent therapy in 12 (36.4%) patients. Eight (24.2%) patients were known to have progressed during the most recent rituximab treatment for their disease. In the subgroup with indolent NHL, most patients (82%) received initial treatment with rituximab, cyclophosphamide, vincristine, and prednisone; rituximab retreatment was the basis of second-line regimens for all nine patients who received subsequent therapy, either as monotherapy (N=5) or in combination (N=4, with: bendamustine; bendamustine + copanlisib; lenalidomide; or cyclophosphamide, doxorubicin, vincristine, and prednisolone [CHOP]). Regimens used in the third-line setting and beyond included obinutuzumab with or without bendamustine, rituximab plus bendamustine with/without copanlisib, and etoposide alone or in combination. One patient with FL had received prior treatment with a bispecific antibody (in the sixth-line setting). In the subgroup with aggressive NHL, rituximab with CHOP (R-CHOP) was the first-line regimen in 88% of patients with DLBCL, while 60% of patients with

Table 1. Demographic and disease characteristics of the study population.

Characteristic	Evorpacept + rituximab N=33
Age, years	
Mean ± SD	63±11.1
Median (range)	64 (32-80)
Sex, N (%)	
Male	23 (69.7)
Female	10 (30.3)
Race, N (%)	
White	6 (18.2)
Asian	27 (81.8)
ECOG performance status score, N (%)	
0	9 (27.3)
1	24 (72.7)
Histopathologic classification, N (%)	
Diffuse large B-cell lymphoma[a]	17 (51.5)
Follicular lymphoma[b]	8 (24.2)
Mantle cell lymphoma[a]	5 (15.2)
Marginal zone lymphoma[b]	3 (9.1)
Current diagnosis staging, N (%)	
Stage II	2 (6.1)
Stage III	8 (24.2)
Stage IV	23 (69.7)
Median number of prior regimens for NHL, N (range)	3 (1-7)
Prior rituximab therapy, N (%)	33 (100)
Most recent therapy was rituximab, N (%)	12 (36.4)
Disease progression, N (%)	
Known progression during most recent therapy	14 (42.4)
Known progression during most recent rituximab therapy	8 (24.2)
Known progression <6 months after completing most recent rituximab therapy	2 (6.1)

[a]Aggressive and [b]indolent non-Hodgkin lymphoma (NHL). subtypes. ECOG: Eastern Cooperative Oncology Group; SD: standard deviation.

MCL received rituximab with cyclophosphamide, vincristine, doxorubicin, methotrexate, and cytarabine (R-HYPER CVAD). A range of different regimens were given in the second-line setting for DLBCL, including rituximab with ifosfamide, carboplatin, and etoposide (R-ICE), R-CHOP, and combination therapy with gemcitabine, dexamethasone, and cisplatin (GDP). Four patients with MCL received at least one further line of therapy, which included single-agent ibrutinib, dexamethasone, cisplatin, and cytarabine (DHAP), and etoposide with DHAP, and bendamustine plus rituximab. Prior chimeric antigen receptor (CAR) T-cell therapy was reported in three patients with DLBCL in the third-line setting. Two patients with aggressive NHL (1 with DLBCL, 1 with MCL) had received autologous peripheral blood stem cell transplants.

Safety outcomes

There was no DLT reported in either the 10 or 15 mg/kg evorpacept treatment groups, and the MTD was not reached. Overall, 28 (84.8%) patients reported at least one treatment-emergent AE (TEAE), most frequently infusion-related reactions (30.3%), rash (27.3%), fatigue (24.2%), and pyrexia (24.2%). The most common grade 3 TEAE were anemia (12.1%) and increased alanine aminotransferase (9.1%); the only grade 4 TEAE reported by more than one patient was decreased neutrophil count (9.1%). Two patients reported grade 5 TEAE (disease progression and respiratory failure secondary to disease progression). Further details on TEAE are provided in *Online Supplementary Table S1*.

Evorpacept treatment-related AE (TRAE) were reported by 20 (60.6%) patients, most frequently rash (24.2%) and fatigue (15.2%) (Table 2). The most common rituximab TRAE were infusion-related reactions (30.3%) and pyrexia (12.1%). Overall, grade 3 evorpacept TRAE were reported by four (12.1%) patients and comprised anemia, neutropenia, decreased neutrophil count, increased alanine aminotransferase, decreased lymphocyte count, and decreased platelet count (one of each event). Grade 4 TRAE were experienced by two (6.1%) patients (neutropenia and decreased neutrophil count). There were no grade 5 TRAE.

Table 2. Summary of safety outcomes and adverse events occurring in >5% of patients.

Safety outcomes	Evorpacept 10 mg/kg N of patients (%) N=22	Evorpacept 15 mg/kg N of patients (%) N=11	Total N of patients (%) N=33
TEAE	19 (86.4)	9 (81.8)	28 (84.8)
SAE	4 (18.1)	2 (18.2)	6 (18.2)
SAE possibly related to evorpacept	0	0	0
SAE possibly related to rituximab	0	0	0
Discontinuation of evorpacept due to TEAE	2 (9.1)	0	2 (6.1)
Discontinuation of rituximab due to TEAE	1 (4.5)	0	1 (3.0)
TRAE			
Any grade	14 (63.6)	6 (54.5)	20 (60.6)
Grade 1	4 (18.1)	3 (27.3)	7 (21.2)
Grade 2	6 (27.3)	1 (9.1)	7 (21.2)
Grade 3	2 (9.1)	2 (18.2)	4 (12.1)
Grade 4	2 (9.1)	0	2 (6.1)
Grade 5	0	0	0
TRAE by system organ class and preferred term			
Skin and subcutaneous disorders	6 (27.3)	3 (27.3)	9 (27.3)
Rash	6 (27.3)	2 (18.2)	8 (24.2)
Pruritus	2 (9.1)	0	2 (6.1)
General disorders and administration-site conditions	4 (18.2)	3 (27.3)	7 (21.2)
Fatigue	3 (13.6)	2 (18.2)	5 (15.2)
Investigations	3 (13.6)	1 (9.1)	4 (12.1)
Decreased neutrophil count	2 (9.1)	0	2 (6.1)
Gastrointestinal disorders	3 (13.6)	0	3 (9.1)
Nausea	2 (9.1)	0	2 (6.1)
Blood and lymphatic system disorders	3 (13.6)	1 (9.1)	4 (12.1)
Anemia	2 (9.1)	0	2 (6.1)
Neutropenia	1 (4.5)	1 (9.1)	2 (6.1)
Musculoskeletal and connective tissue disorders	3 (13.6)	0	3 (9.1)
Myalgia	2 (9.1)	0	2 (6.1)

SAE: serious adverse event; TEAE: treatment-emergent adverse event; TRAE: treatment-related adverse event.

One TEAE leading to study treatment discontinuation was reported (infusion-related reaction during rituximab administration). No patients required evorpacept dose reductions due to a TEAE. Two (6.1%) patients withdrew from the study treatment due to TEAE: one event was considered to be unrelated to evorpacept or rituximab (respiratory failure) and one was described as possibly related to evorpacept or rituximab (infusion-related reaction). Six (18.2%) patients experienced serious AE due to any cause, comprising asthma, dyspnea, respiratory failure, gastrointestinal infection, pneumonia, cardiac failure, and disease progression (1 of each event); none were attributed to evorpacept or rituximab. Two (6.1%) patients died during the study (1 each of respiratory failure and disease progression); neither death was considered to be related to evorpacept or rituximab.

Pharmacokinetics

Concentration-time profiles following the first evorpacept infusion are shown in Figure 1. For the evorpacept 10 and 15 mg/kg groups, respectively, mean (± standard deviation) maximum serum concentration was 175 (±36.2) μg/mL and 326 (±91.8) μg/mL, area under the concentration-time curve from time 0 to infinity was 13,300 (±2,170) μg·h/mL and 26,400 (±8,600) μg·h/mL, clearance was 0.767 (±0.108) mL/h/kg and 0.655 (±0.335) mL/h/kg, and the volume of distribution at steady state was 83.8 (±20.9) and 72.6 (±23.6) mL/kg. Steady-state PK parameters remained stable for the duration of the study (*data not shown*).

Immunogenicity

The incidence of anti-evorpacept antibodies was low (<5%), with most cases being weakly positive and having a low titer. In addition, the presence of anti-evorpacept antibodies did not appear to have a clinically significant impact on PK or pharmacodynamic parameters, or on clinical signs or symptoms.

Anti-tumor activity and treatment outcomes

In total, 32 (97.0%) patients were evaluable for anti-tumor activity, 22 patients in the 10 mg/kg cohort and ten patients in the 15 mg/kg cohort. Tumor response and survival data are summarized in Figure 2A-D and Table 3. The overall ORR was 50.0% (95% CI: 33.1-69.8%): 40.9% (95% CI: 21.8-66.0%) in the 10 mg/kg group, and 70.0% (95% CI: 34.8-93.3%) in the 15 mg/kg group. Eight (25.0%) patients achieved a complete response (in FL [N=4], MCL [N=2], and MZL [N=2]), and eight (25.0%) achieved a partial response (in DLBCL [N=4], MCL [N=2], and FL [N=2]). Hence, for evorpacept overall (both doses), ORR were 72.7% in the indolent NHL group and 38.1% in the aggressive NHL group. The median duration of response was 20.6 months (95% CI: 5.59-not calculable), and median time to response was 1.89 months (range, 1.51-5.43). Median progression-free survival was 9.28 months (95% CI: 2.11-16.6) after a median follow-up of 24.0 months (95% CI: 20.3-24.0). Median overall survival was not calculable (95% CI: 8.95-not calculable) after a median follow-up of 29.3 months (95% CI: 27.2-32.1).

Of the 22 evaluable patients in the evorpacept 10 mg/kg group, 15 had aggressive NHL and seven had indolent NHL (Table 3). CR was reported in one patient (6.7%) with aggressive NHL and three patients (42.9%) with indolent NHL, and PR was reported in four patients (26.7%) and one patient (14.3%), respectively. The ORR was 33.3% and 57.1% for patients with aggressive and indolent NHL, respectively. Median progression-free survival was 2.53 months (95% CI: 1.38-7.47) in the aggressive NHL group and 18.7 months (95% CI: 7.53-not calculable) in the indolent NHL group. Median overall survival was 8.95 months (95% CI: 2.50-23.4) in the aggressive NHL group but was not calculable in the indolent NHL group.

Of the ten evaluable patients in the evorpacept 15 mg/kg group, six had aggressive NHL and four had indolent NHL (Table 3). Complete response was reported in one patient (16.7%) with aggressive NHL and three patients (75.0%) with indolent NHL, and partial response was reported in two patients (33.3%) and one patient (25.0%), respectively. The ORR was 50.0% and 100% for patients with aggressive and indolent NHL, respectively. Median progression-free survival was not calculable in the aggressive and indolent NHL groups. Median overall survival was 13.2 months (95% CI: 4.28-not calculable) in the aggressive NHL group but was not calculable in the indolent NHL group.

Pharmacodynamics

All 33 patients were included in the pharmacodynamics analysis (all had pre- and post-dose assessments available). Complete CD47 target occupancy (≥85%) was achieved at both doses of evorpacept for peripheral blood T lymphocytes and erythrocytes (Figure 3A, B). A moderate correlation

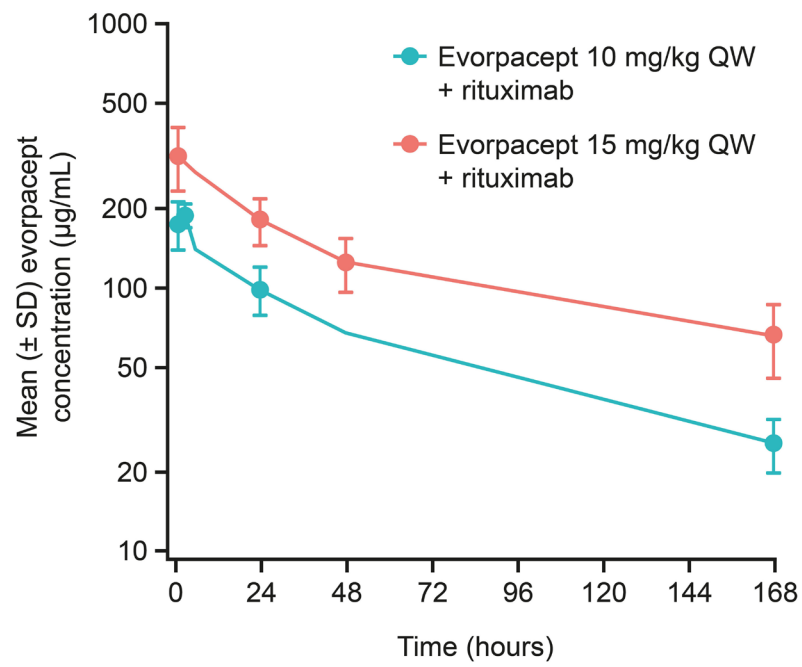

Figure 1. Mean serum concentration-time profiles after the first evorpacept infusion. QW: once weekly; SD: standard deviation.

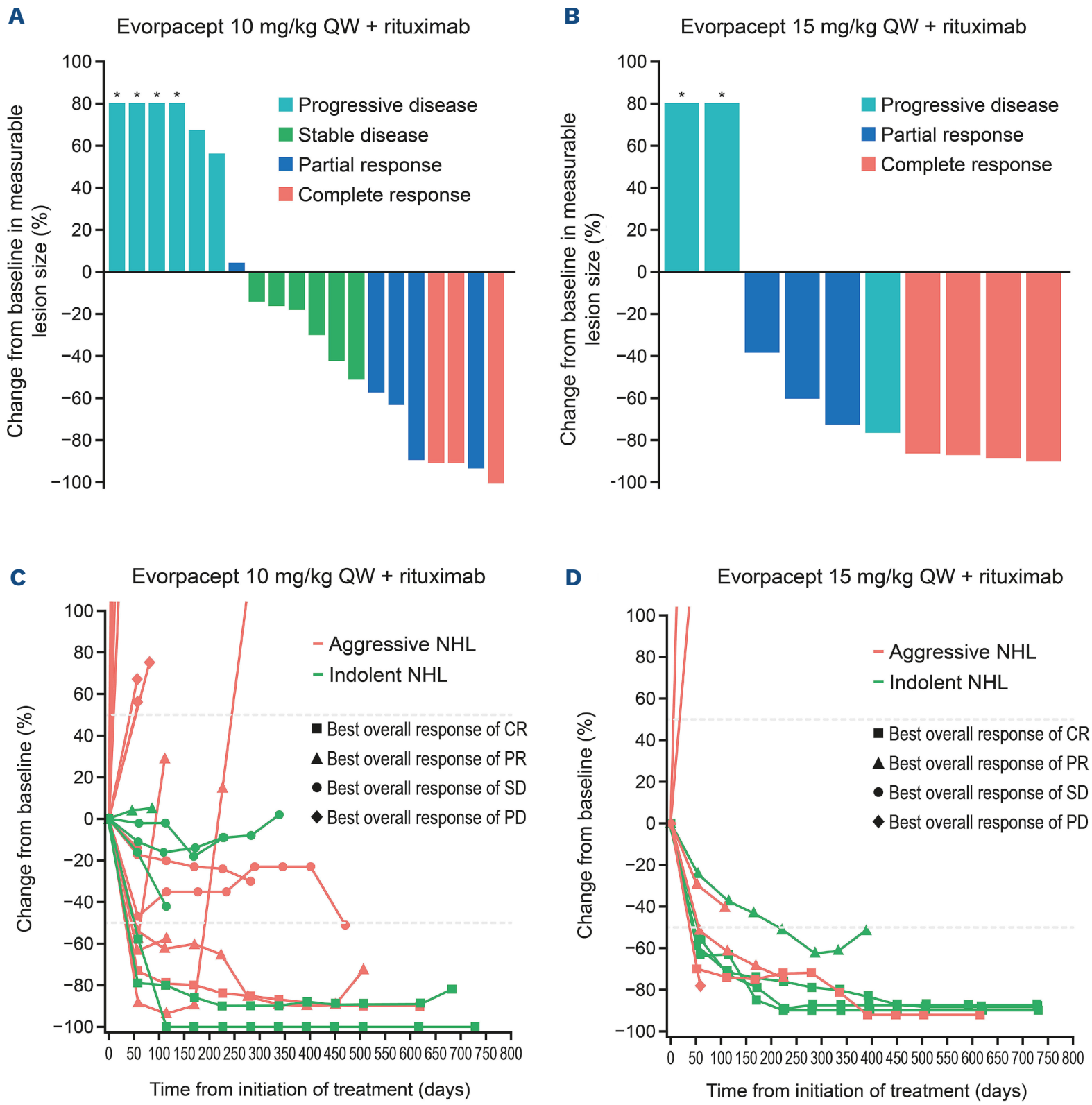

Figure 2. Tumor response data (best overall response). Best percentage change from baseline in measurable lesion size (sum of product [mm]). Baseline is defined as the last measurement before treatment initiation. *Denotes ≥80% increase from baseline. (A) Data for evorpacept 10 mg/kg plus rituximab (2 patients - 1 with metabolic complete response, 1 with rapidly progressive disease - are not represented). (B) Data for evorpacept 15 mg/kg plus rituximab. (C) Data for aggressive and indolent non-Hodgkin lymphoma (NHL) subtypes for evorpacept 10 mg/kg plus rituximab. (D) Data for aggressive and indolent NHL subtypes for evorpacept 15 mg/kg plus rituximab. CR: complete response; PD: progressive disease; PR: partial response; QW: once weekly; SD: stable disease.

was observed between baseline intratumoral CD163$^+$ cells and poor response (r=0.4763; *P*<0.05 [Spearman non-parametric correlation]), but no significant correlations were observed between intratumoral CD8$^+$ and CD68$^+$ immune cell populations and tumor responses (Figure 4A-C). However, the distribution of responses (complete response/partial response) with CD68$^+$ cells did appear to follow a similar trend to CD163$^+$, albeit with a weaker correlation (r=0.3040; *P*>0.05).

Discussion

This first-in-human, phase I ASPEN-01 study demonstrated that evorpacept 10 or 15 mg/kg once weekly in combination with rituximab at the dose administered was well tolerated and the MTD was not reached in patients with R/R NHL. These findings are consistent with those from the analyses of evorpacept in combination with pembrolizumab or trastuzumab in patients with solid tumors in the same

Table 3. Anti-tumor clinical activity: tumor response and survival data.

Cohort	N	ORR % (95% CI)	Median DOR in months (95% CI)	Median time to response in months (range)	Median PFS in months (95% CI)	Median OS in months (95% CI)
All patients, both 10 and 15 mg/kg cohorts	32[a]	50.0 (33.1-69.8)	20.6 (5.59-NC)	1.89 (1.51-5.43)	9.28 (2.11-16.6)	NC (8.95-NC)
10 mg/kg, all patients	22	40.9 (21.8-66.0)	15.8 (1.84-NC)	1.91 (1.51-2.07)	7.47 (1.91-13.2)	23.4 (7.34-NC)
10 mg/kg, aggressive[b] NHL	15	33.3 (12.8-64.9)	5.59 (NC-NC)	1.88 (1.81-1.97)	2.53 (1.38-7.47)	8.95 (2.50-23.4)
10 mg/kg, indolent[c] NHL	7	57.1 (18.4-90.1)	20.6 (NC-NC)	1.92 (1.51-2.07)	18.7 (7.53-NC)	NC (NC-NC)
15 mg/kg, all patients	10	70.0 (34.8-93.3)	NC (NC-NC)	1.88 (1.71-5.43)	NC (NC-NC)	NC (4.28-NC)
15 mg/kg, aggressive[b] NHL	6	50.0 (11.8-88.2)	NC (NC-NC)	1.74 (1.71-1.88)	NC (NC-NC)	13.2 (4.28-NC)
15 mg/kg, indolent[c] NHL	4	100 (NC-NC)	NC (NC-NC)	2.02 (1.71-5.43)	NC (NC-NC)	NC (NC-NC)

[a]One patient with symptoms of disease progression discontinued the study prior to the first response assessment and was not evaluable per the protocol. [b]Aggressive non-Hodgkin lymphoma (NHL) includes diffuse large B-cell lymphoma and mantle cell lymphoma. [c]Indolent NHL includes follicular lymphoma and marginal zone lymphoma. CI: confidence interval; DOR: duration of response; NC: not calculable; ORR: objective response rate; OS: overall survival; PFS: progression-free survival.

study, and in other phase I studies evaluating evorpacept combination therapy in hematologic or solid cancers.[16,24-26] Only one patient discontinued study treatment as a result of an AE (infusion-related reaction during rituximab administration); most AE were mild-to-moderate in severity (most commonly rash and fatigue), and there were no clinically significant patterns of cytopenia or dose-limiting hematologic toxicities. Evorpacept blocks the CD47 myeloid master checkpoint but does not bind the FcγR on macrophages.[10] This absent, but necessary, second signal can be provided by the active Fc domain of rituximab thus sparing normal CD47-expressing cells from CD47-targeted ADCP destruction. In contrast, CD47 blockers with an active Fc domain are often associated with significant off-tumor, on-target toxicities (e.g., anemia and/or thrombocytopenia), due to the ubiquitous expression of CD47 across healthy normal cells leading to CD47-targeted cellular destruction.[8,11,18,27-28] In contrast to evorpacept, the toxicities associated with CD47 blockers with active Fc domains narrow their potential therapeutic window and limit their use in combination with other anti-cancer therapies, particularly those associated with hematologic toxicity.[8,27]

The PK profile of evorpacept has been shown to be similar when administered as a single agent or in combination with trastuzumab or pembrolizumab,[16] and the present study indicates that PK parameters are unaffected when evorpacept is combined with rituximab. In addition, evorpacept 10 or 15 mg/kg in combination with rituximab demonstrated linear PK, which supports previously reported data indicating that steady-state exposure of evorpacept is similar for 20 mg/kg every other week and 40 mg/kg every 4 weeks, and for 30 mg/kg every other week and 60 mg/kg every 4 weeks.[16,25,26,30] The pharmacodynamic analysis indicated complete CD47 target occupancy with evorpacept in peripheral blood cells for both the 10 and 15 mg/kg doses throughout the dosing interval, but with no associated dose-dependent cytopenia, as mentioned earlier. This likely

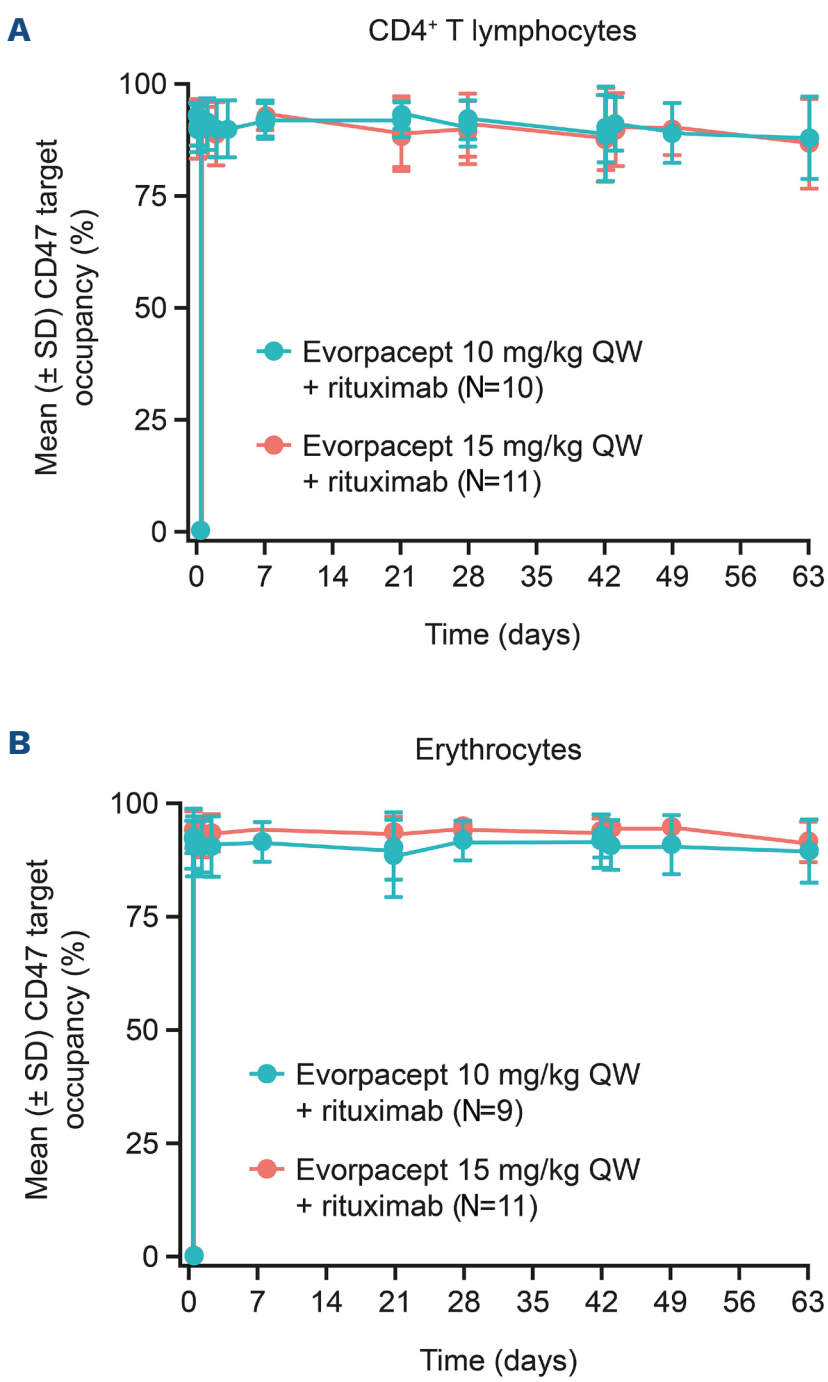

Figure 3. Mean CD47 target occupancy over time. Mean percentages of CD47 target occupancy are shown for each dose of evorpacept (10 and 15 mg/kg). (A) Mean CD47 target occupancy among CD4+ T lymphocytes. (B) Mean CD47 target occupancy among erythrocytes. QW: once weekly; SD: standard deviation.

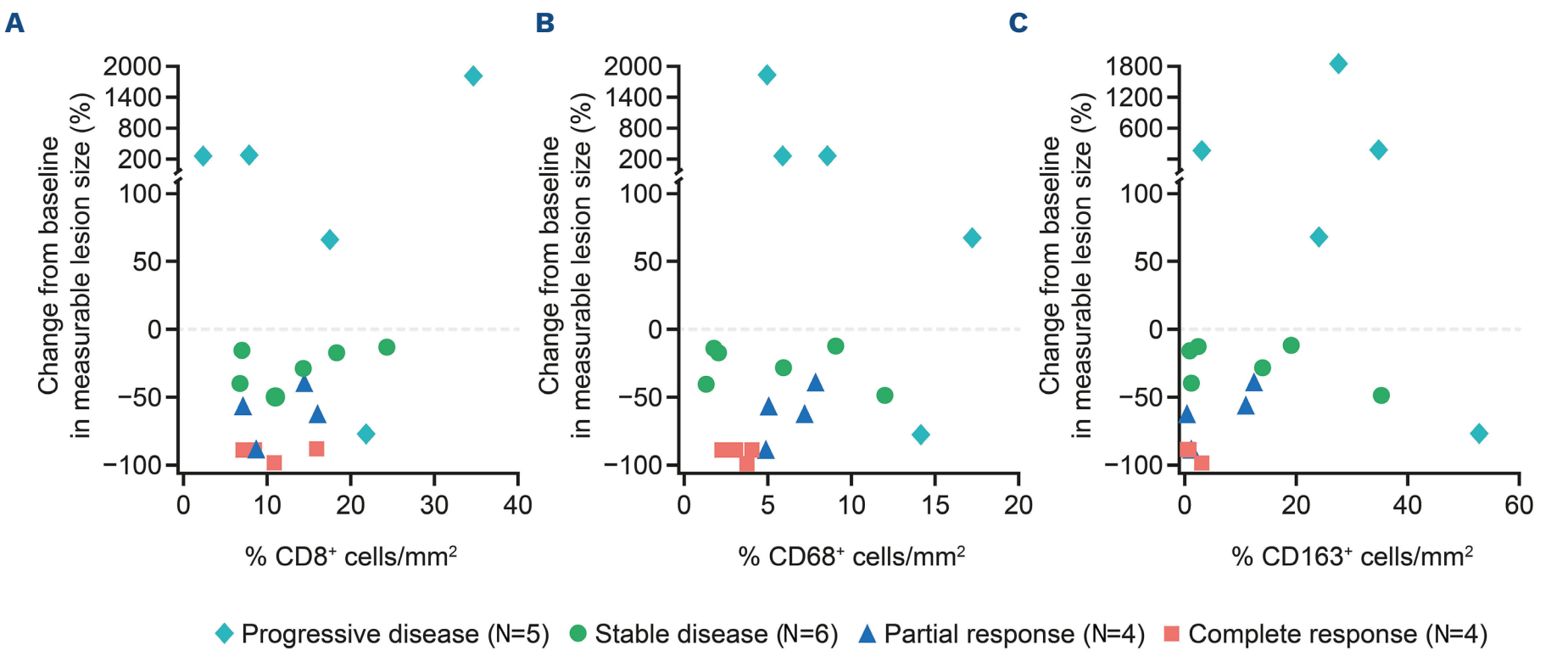

Figure 4. Tumor-infiltrating cell profiles. Baseline data for intratumoral CD8, CD68, and CD163 positivity *versus* tumor response following treatment with evorpacept plus rituximab. Percentages of (A) CD8⁺ cells, (B) CD68⁺ cells, and (C) CD163⁺ cells.

reflects the mechanism of action and distinct molecular design of evorpacept, with its incorporation of an inactive Fc domain.[13-15] The complete CD47 occupancy in peripheral erythrocytes and T lymphocytes with evorpacept 10 or 15 mg/kg once weekly in combination with rituximab is consistent with the previously reported saturation of target-mediated clearance at higher doses (10 mg/kg once weekly and 30 mg/kg once every other week). Preliminary evidence has shown that complete CD47 target occupancy is maintained across the evorpacept dosing interval when higher doses are coupled with a longer dosing interval (e.g., 15 mg/kg once weekly, 30 mg/kg every 2 weeks, and 60 mg/kg once every 4 weeks).[16,25,26,31] The prolonged half-life of evorpacept (up to 30 days at steady state) together with consistent PK in combination regimens, complete target occupancy, and favorable tolerability across a range of dosing schedules support a flexible dosing strategy for evorpacept that enables administration to be scheduled at the same time as combination drugs, for patient and physician convenience.[16,25] Ongoing or planned studies will therefore evaluate evorpacept at doses and schedules ranging from 15 mg/kg once weekly to 60 mg/kg every 4 weeks in various combination regimens and malignancies.[32-35]

Preliminary anti-tumor activity findings were encouraging in this ASPEN-01 study, with evorpacept plus rituximab demonstrating a durable ORR of 50.0% across both indolent and aggressive R/R NHL populations. The ORR of 72.7% in the indolent NHL group compares favorably with ORR reported for rituximab monotherapy (range, 48-57%) in this patient population,[36-38] whereas the CR rate in the aggressive NHL group (9.5%) is lower than reported for regimens currently approved for the treatment of patients with R/R aggressive NHL (range, 25-74%).[39-45] However, the small sample size limits the interpretation of anti-tumor activity with evorpacept, particularly in histologic subtypes, and a larger study is needed. Development of novel treatment options remains an unmet need in patients with aggressive and indolent B-cell NHL, particularly in those with R/R disease whose treatment options are limited and prognosis is poor.[8,46,47] The introduction of CAR T-cell therapies has improved outcomes for some patients with R/R B-cell lymphomas and antibodies have recently been approved for R/R lymphomas in the third- or later-line setting.[48] However, many patients progress on or do not respond to these treatments and are therefore in need of novel therapies.[48] Along with the favorable safety and tolerability profile, the preliminary anti-tumor activity observed in ASPEN-01 supports clinical evaluation of evorpacept plus rituximab in combination with standard-of-care agents for NHL, including lenalidomide, where promising initial activity has been reported.[49,50]

CD68⁺ and CD163⁺ immune cells are established biomarkers for TAM, and previous studies have demonstrated that high levels of CD68⁺ and CD163⁺ cells in tumor tissue (or soluble CD163 in serum) or high expression of *CD68* and *CD163* at diagnosis or relapse are associated with poor outcomes in patients with lymphomas receiving rituximab-based therapy or other regimens.[51-54] Analysis of the ASPEN-01 evorpacept plus rituximab cohort are consistent with these findings, showing that baseline intratumoral CD163⁺ cells moderately correlated with poor response, with a weaker correlation observed for CD68⁺ cells, in patients with R/R NHL.

Limitations of this phase I study, which may be addressed in the phase II setting, include the absence of random-

ization, limited tumor marker assessments, no formal assessment of pseudo progression, and insufficient power of the study to enable definitive conclusions to be drawn regarding clinical activity. Larger cohort sizes would allow for adequately powered comparisons of clinical benefit and pharmacodynamic endpoints, and future studies could consider specific tumor marker assessments, such as cell-free DNA. Additionally, no patient-reported or quality-of-life outcomes were included in the current study.

In conclusion, this analysis from the first-in-human, phase I ASPEN-01 study indicates that evorpacept in combination with rituximab has a tolerable safety profile and promising anti-tumor activity in patients with R/R NHL. Further clinical evaluation of evorpacept in combination with other anti-cancer therapies is ongoing in a range of solid and hematologic malignancies.

Disclosures

TMK has received honoraria from or had an advisory role at Amgen, AstraZeneca, Boryung, Daiichi Sankyo, F. Hoffmann-La Roche Ltd/Genentech, Inc., IMBDx, Inc., Janssen, Novartis, Regeneron, Samsung Bioepis, Sanofi, Takeda, and Yuhan. NJL has received research funding from ALX Oncology, Ascentage, BeiGene, Constellation Pharma, Forty Seven, Alpine, Merck, Pfizer, Regeneron, Apexian, Formation Biologics (Forbius), Symphogen, CytomX, InhibRx, Incyte, Jounce, Livzon, Northern Biologics, Innovent Biologics, Ikena, Odonate, Loxo, Alpine Biosciences, Ikena, Astellas, Celgene, Seagen, Samumed, Sapience Therapeutics, Epizyme, and Mersana; NJL also reports having received personal fees from Innovent Biologics. JS reports consulting fees from AstraZeneca, Bristol Myers Squibb, Genentech/Roche, and Loxo/Lilly, as well as research support for investigator-initiated trials paid to institution from Adaptive Biotechnologies, BeiGene, BostonGene, Genentech/Roche, GlaxoSmithKline, Moderna, Takeda, and TG Therapeutics. MK has received research support/funding from Novartis; has a consulting role at AbbVie, AstraZeneca, Celgene/Bristol Myers Squibb, Adaptive Biotechnologies, ADC Therapeutics, BeiGene, Genentech, ImpactBio, and Syncopation; serves on a speakers' bureau for Seagen; and serves on data monitoring committees for Celgene and Genentech. JFG reports research support from Bristol Myers Squibb, Tesaro, Moderna, Blueprint, Jounce, Array, Merck, Adaptimmune, Novartis, and ALX Oncology; consulting fees from Genentech/Roche, Bristol Myers Squibb, Takeda, Loxo/Lilly, Blueprint, Oncorus, Regeneron, Gilead, Moderna, AstraZeneca, EMD Serono, Pfizer, Novartis, Merck, GlydeBio, and Karyopharm; and payment or honoraria from Pfizer. Further, JFG's spouse has stock and other ownership interests at Ironwood Pharmaceuticals. WM is a recipient of a grant from the NIH and has received research funding from ALX Oncology. PF, SG, AF, HW, JP, and SSR were employed by ALX Oncology at the time of the study and report stock and other ownership interests at ALX Oncology. JP and SSR were on the board of directors at ALX Oncology at the time of the study. JP also reports a leadership or fiduciary role at Tallac Therapeutics. FJ reports a consulting or advisory role at ALX Oncology. HIW reports a consulting role at ALX Oncology, in addition to a leadership role at Tallac Therapeutics. WSK has received research funding from Roche, Johnson & Johnson, Pfizer, Sanofi, Celltrion, Kyowa-Kirin, Dong-A, and Mundipharma.

Contributions

TMK, NJL, MK, JFG, WM, PF, SG, FJ, AF, HIW, JP, and SSR were involved in protocol design. SG, SSR and TMK were responsible for verifying the underlying data. All authors had access to the primary clinical trial data and were involved in data acquisition, data interpretation, and manuscript review/approval.

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Data-sharing statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

1. Willingham SB, Volkmer J-P, Gentles AJ, et al. The CD47-signal regulatory protein alpha (SIRPa) interaction is a therapeutic target for human solid tumors. Proc Natl Acad Sci U S A. 2012;109(17):6662-6667.
2. Oldenborg P-A. CD47: a cell surface glycoprotein which regulates multiple functions of hematopoietic cells in health and disease. ISRN Hematol. 2013;2013:614619.
3. Lu Q, Chen X, Wang S, Lu Y, Yang C, Jiang G. Potential new cancer immunotherapy: anti-CD47-SIRPα antibodies. Onco Targets Ther. 2020;13:9323-9331.
4. Jiang Z, Sun H, Yu J, Tian W, Song Y. Targeting CD47 for cancer immunotherapy. J Hematol Oncol. 2021;14(1):180.
5. Yoshida K, Tsujimoto H, Matsumura K, et al. CD47 is an adverse prognostic factor and a therapeutic target in gastric cancer. Cancer Med. 2015;4(9):1322-1333.
6. Liu J, Wang L, Zhao F, et al. Pre-clinical development of a humanized anti-CD47 antibody with anti-cancer therapeutic potential. PLoS One. 2015;10(9):e0137345.
7. Liu X, Pu Y, Cron K, et al. CD47 blockade triggers T cell-mediated destruction of immunogenic tumors.

Nat Med. 2015;21(10):1209-1215.
8. Advani R, Flinn I, Popplewell L, et al. CD47 blockade by Hu5F9-G4 and rituximab in non-Hodgkin's lymphoma. N Engl J Med. 2018;379(18):1711-1721.
9. Sockolosky JT, Dougan M, Ingram JR, et al. Durable antitumor responses to CD47 blockade require adaptive immune stimulation. Proc Natl Acad Sci U S A. 2016;113(19):E2646–E2654.
10. Petrova PS, Viller NN, Wong M, et al. TTI-621 (SIRPαFc): a CD47-blocking innate immune checkpoint inhibitor with broad antitumor activity and minimal erythrocyte binding. Clin Cancer Res. 2017;23(4):1068-1079.
11. Sikic BI, Lakhani N, Patnaik A, et al. First-in-human, first-in-class phase I trial of the anti-CD47 antibody Hu5F9-G4 in patients with advanced cancers. J Clin Oncol. 2019;37(12):946-953.
12. Zhang W, Huang Q, Xiao W, et al. Advances in anti-tumor treatments targeting the CD47/SIRPα axis. Front Immunol. 2020;11:18.
13. Kauder SE, Kuo TC, Harrabi O, et al. ALX148 blocks CD47 and enhances innate and adaptive antitumor immunity with a favorable safety profile. PLoS One. 2018;13(8):e0201832.
14. Kim TY, Yoon MS, Hustinx H, Sim J, Wong HI, Hyungsuk K. Assessing and mitigating the interference of ALX148, a novel CD47 blocking agent, in pretransfusion compatibility testing. Transfusion. 2020;60(10):2399-2407.
15. Wan H, Chow L, Gainor J, et al. Pharmacodynamic biomarker characterization of ALX148, a CD47 blocker, in combination with established anticancer antibodies in patients with advanced malignancy. Proc Am Soc Clin Oncol. 2020;38(Suppl 15):abstract 3056.
16. Lakhani NJ, Chow LQM, Gainor JF, et al. Evorpacept alone and in combination with pembrolizumab or trastuzumab in patients with advanced solid tumours (ASPEN-01): a first-in-human, open-label, multicentre, phase 1 dose-escalation and dose-expansion study. Lancet Oncol. 2021;22(12):1740-1751.
17. Chao MP, Alizadeh AA, Tang C, et al. Anti-CD47 antibody synergizes with rituximab to promote phagocytosis and eradicate non-Hodgkin lymphoma. Cell. 2010;142(5):699-713.
18. Gilead Sciences, Inc. Press Release, February 07, 2024: Gilead statement on discontinuation of phase 3 ENHANCE-3 study in AML. https://www.gilead.com/news-and-press/company-statements/gilead-statement-on-discontinuation-of-phase-3-enhance-3-study-in-aml. Accessed May 29, 2024.
19. Simon R, Freidlin B, Rubinstein L, Arbuck SG, Collins J, Christian MC. Accelerated titration designs for phase I clinical trials in oncology. J Natl Cancer Inst. 1997;89(15):1138-1147.
20. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059-3068.
21. Del Poeta, Del Principe MI, Buccisano F, et al. Consolidation and maintenance immunotherapy with rituximab improve clinical outcome in patients with B-cell chronic lymphocytic leukemia. Cancer. 2008;112(1):119-128.
22. Byrd JC, Peterson BL, Morrison VA, et al. Randomized phase 2 study of fludarabine with concurrent versus sequential treatment with rituximab in symptomatic, untreated patients with B-cell chronic lymphocytic leukemia: results from Cancer and Leukemia Group B 9712 (CALGB 9712). Blood. 2003;101(1):6-14.
23. National Cancer Institute: Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events (CTCAE). https://evs.nci.nih.gov/ftp1/CTCAE/About.html. Accessed February 14, 2024.
24. Funt SA, Grivas P, Gao X, et al. Evorpacept plus enfortumab vedotin in patients (Pts) with locally advanced or metastatic urothelial carcinoma (la/mUC): phase 1a dose escalation results. J Clin Oncol. 2024;42(Suppl 16):4575.
25. Garcia-Manero G, Erba H, Sanikommu S, et al. Evorpacept (ALX148), a CD47-blocking myeloid checkpoint inhibitor, in combination with azacitidine: a phase 1/2 study in patients with myelodysplastic syndrome (ASPEN-02). Blood. 2021;138(Suppl 1):2601.
26. Garcia-Manero G, Przespolewski A, Abaza Y, et al. Evorpacept (ALX148), a CD47-blocking myeloid checkpoint inhibitor, in combination with azacitidine and venetoclax in patients with acute myeloid leukemia (ASPEN-05): results from phase 1a dose escalation part. Blood. 2022;140(Suppl 1):9046–9047.
27. Ansell SM, Maris MB, Lesokhin AM, et al. Phase I study of the CD47 blocker TTI-621 in patients with relapsed or refractory hematologic malignancies. Clin Cancer Res. 2021;27(8):2190-2199.
28. Sallman DA, Al Malki MM, Asch AS, et al. Magrolimab in combination with azacitidine in patients with higher-risk myelodysplastic syndromes: final results of a phase 1b study. J Clin Oncol. 2023;41(15):2815-2826.
29. Zeidan AM, DeAngelo DJ, Palmer J, et al. Phase 1 study of anti-CD47 monoclonal antibody CC-90002 in patients with relapsed/refractory acute myeloid leukemia and high-risk myelodysplastic syndromes. Ann Hematol. 2022;101(3):557-569.
30. Garcia-Manero G, Scott BL, Kishtagari A, et al. Phase 1 study of azacitidine in combination with evorpacept for higher-risk myelodysplastic syndrome (MDS). Cancer Res. 2024;84(Suppl 7):CT060.
31. Chung HC, Lee K-W, Gainor J, et al. ASPEN-01: A phase 1 study of ALX148, a CD47 blocker, in combination with trastuzumab, ramucirumab and paclitaxel in patients with second-line HER2-positive advanced gastric or gastroesophageal junction cancer. Ann Oncol. 2021;32(Suppl 3):S215-S216.
32. ClinicalTrials.gov. Evorpacept (ALX148) in combination with pembrolizumab in patients with advanced head and neck squamous cell carcinoma (ASPEN-03). ClinicalTrials.gov Identifier: NCT04675294. https://clinicaltrials.gov/ct2/show/NCT04675294. Accessed May 31, 2024.
33. ClinicalTrials.gov. Evorpacept (ALX148) in combination with pembrolizumab and chemotherapy in patients with advanced head and neck squamous cell carcinoma (ASPEN-04). ClinicalTrials.gov Identifier: NCT04675333. https://clinicaltrials.gov/ct2/show/NCT04675333. Accessed May 31, 2024.
34. ClinicalTrials.gov. A study of evorpacept (ALX148) in patients with advanced HER2+ gastric cancer (ASPEN-06). ClinicalTrials.gov Identifier: NCT05002127. https://clinicaltrials.gov/ct2/show/NCT05002127. Accessed May 31, 2024.
35. ClinicalTrials.gov. A study of evorpacept (ALX148) with enfortumab vedotin for subjects with urothelial carcinoma (ASPEN-07). ClinicalTrials.gov Identifier: NCT05524545. https://clinicaltrials.gov/ct2/show/NCT05524545. Accessed May 31, 2024.
36. Piro LD, White CA, Grillo-López AJ, et al. Extended Rituximab (anti-CD20 monoclonal antibody) therapy for relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma. Ann Oncol. 1999;10(6):655-661.
37. McLaughlin P, Grillo-López AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed

indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol. 1998;16(8):2825-2833.
38. Leonard JP, Trneny M, Izutsu K, et al. AUGMENT: a phase III study of lenalidomide plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma. J Clin Oncol. 2019;37(14):1188-1199.
39. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol. 2019;20(1):31-42.
40. Abramson JS, Solomon SR, Arnason J, et al. Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of the phase 3 TRANSFORM study. Blood. 2023;141(14):1675-1684.
41. Dickinson MJ, Carlo-Stella C, Morschhauser F, et al. Glofitamab for relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2022;387(24):2220-2231.
42. Thieblemont C, Phillips T, Ghesquieres H, et al. Epcoritamab, a novel, subcutaneous CD3xCD20 bispecific T-cell-engaging antibody, in relapsed or refractory large B-cell lymphoma: dose expansion in a phase I/II trial. J Clin Oncol. 2023;41(12):2238-2247.
43. Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma. J Clin Oncol. 2020;38(2):155-165.
44. Salles G, Duell J, González Barca E, et al. Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study. Lancet Oncol. 2020;21(7):978-988.
45. Caimi PF, Ai W, Alderuccio JP, Ardeshna KM, et al. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol. 2021;22(6):790-800.
46. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood. 2017;130(16):1800-1808.
47. Thuresson P-O, Vander Velde N, Gupta P, Talbot J. A systematic review of the clinical efficacy of treatments in relapsed or refractory diffuse large B-cell lymphoma. Adv Ther. 2020;37(12):4877-4893.
48. Trabolsi A, Arumov A, Schatz JH. Bispecific antibodies and CAR-T cells: dueling immunotherapies for large B-cell lymphomas. Blood Cancer J. 2024;14(1);27.
49. ClinicalTrials.gov. ALX148, rituximab and lenalidomide for the treatment of indolent and aggressive B-cell non-Hodgkin lymphoma. ClinicalTrials.gov Identifier: NCT05025800. https://clinicaltrials.gov/ct2/show/NCT05025800. Accessed May 31, 2024.
50. Strati P, Feng L, Chihara D, et al. A phase I investigator-initiated trial of evorpacept (ALX148), lenalidomide and rituximab for patients with relapsed or refractory B-cell non-Hodgkin lymphoma. Cancer Res. 2024;84(Suppl 7):CT037.
51. Nikkarinen A, Lokhande L, Amini RM, et al. Soluble CD163 predicts outcome in both chemoimmunotherapy and targeted therapy-treated mantle cell lymphoma. Blood Adv. 2023;7(18):5304-5313.
52. Rodrigues JM, Nikkarinen A, Hollander P, et al. Infiltration of CD163-, PD-L1- and FoxP3-positive cells adversely affects outcome in patients with mantle cell lymphoma independent of established risk factors. Br J Haematol. 2021;193(3):520-531.
53. Le Bris Y, Normand A, Bouard L, et al. Aggressive, early resistant and relapsed mantle cell lymphoma distinct extrinsic microenvironment highlighted by transcriptome analysis. EJHaem. 2022;3(4):1165-1171.
54. Tan KL, Scott DW, Hong F, et al. Tumor-associated macrophages predict inferior outcomes in classic Hodgkin lymphoma: a correlative study from the E2496 Intergroup trial. Blood. 2012;120(16):3280-3287.