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Phase 1 dose-escalation study of SEA-CD40: a non-fucosylated CD40 agonist, in advanced solid tumors and lymphomas

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ABSTRACT

Background SEA-CD40 is an investigational, non-fucosylated, humanized monoclonal IgG_1 antibody that activates CD40, an immune-activating tumor necrosis factor receptor superfamily member. SEA-CD40 exhibits enhanced binding to activating FcγRIIIa, possibly enabling greater immune stimulation than other CD40 agonists. A first-in-human phase 1 trial was conducted to examine safety, pharmacokinetics, and pharmacodynamics of SEA-CD40 monotherapy in patients with advanced solid tumors and lymphoma.

Methods SEA-CD40 was administered intravenously to patients with solid tumors or lymphoma in 21-day cycles with standard 3+3 dose escalation at 0.6, 3, 10, 30, 45, and 60 µg/kg. An intensified dosing regimen was also studied. The primary objectives of the study were to evaluate the safety and tolerability and identify the maximum tolerated dose of SEA-CD40. Secondary objectives included evaluation of the pharmacokinetic parameters, antitherapeutic antibodies, pharmacodynamic effects and biomarker response, and antitumor activity.

Results A total of 67 patients received SEA-CD40 including 56 patients with solid tumors and 11 patients with lymphoma. A manageable safety profile was observed, with predominant adverse events of infusion/hypersensitivity reactions (IHRs) reported in 73% of patients. IHRs were primarily ≤grade 2 with an incidence associated with infusion rate. To mitigate IHRs, a standardized infusion approach was implemented with routine premedication and a slowed infusion rate. SEA-CD40 infusion resulted in potent immune activation, illustrated by dose dependent cytokine induction with associated activation and trafficking of innate and adaptive immune cells. Results suggested that doses of 10–30 µg/kg may result in optimal immune activation. SEA-CD40 monotherapy exhibited evidence of antitumor activity, with a partial response in a patient with basal cell carcinoma and a complete response in a patient with follicular lymphoma.

Conclusions SEA-CD40 was tolerable as monotherapy and induced potent dose dependent immune cell activation and trafficking consistent with immune activation. Evidence of monotherapy antitumor activity was observed in patients with solid tumors and lymphoma. Further evaluation of SEA-CD40 is warranted, potentially as a component of a combination regimen.

Trial registration number NCT02376699.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ CD40 is a key regulator of immune response and is expressed on nearly all B-cell lymphomas and some solid tumors. Antibodies targeting CD40 have shown potential antitumor activity via immune activation and targeted cell killing. SEA-CD40 may have improved immune stimulation and antitumor activity, compared to other CD40 agonists, due to higher binding affinity to activating receptor FcγRIIIa.

WHAT THIS STUDY ADDS

⇒ SEA-CD40 is a sugar-engineered non-fucosylated antibody that demonstrated a manageable safety profile, potent immune activation, and antitumor activity, including a complete response in a patient with follicular lymphoma.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The favorable safety profile, antitumor activity, and immunostimulatory properties of SEA-CD40 monotherapy as observed in this study, suggest that pairing SEA-CD40 with chemotherapy or additional antibody-drug conjugates could have the potential to improve outcomes across multiple cancer types.

INTRODUCTION

CD40 is a member of the tumor necrosis factor receptor superfamily and a key regulator of immune response via expression on antigen-presenting cells (APCs), including dendritic cells, monocytes, and B cells.[1 2] CD40 is additionally expressed on some solid tumors and nearly all B-cell lymphomas.[3–8] Agonistic antibodies targeting CD40 have the potential for antitumor therapeutic benefit via inducing innate immune activation that can support generation of antigen-specific antitumor T cell responses. Additionally, direct CD40 targeting could induce antibody-mediated target cell killing of CD40+ cancer cells.[2]

SEA-CD40 is an investigational, agonistic, nonfucosylated humanized IgG1 monoclonal antibody derived from the normally fucosylated CD40 monoclonal antibody, dacetuzumab,[9 10] which was originally developed for treatment of B-lineage malignancies.[11] Nonfucosylated antibodies have the potential for enhanced activity via increased binding to activating receptor FcγRIIIa (CD16).[12] SEA-CD40 binds FcγRIIIa with higher affinity than dacetuzumab[9 10] and can promote clustering and agonism of Fc receptors, which may lead to a more robust activation signal in effector cells. Concomitant binding of SEA-CD40 to both CD40 and FcγRIIIa induces potent CD40 agonistic signaling, APC activation, and immune stimulation.[9 10] Furthermore, CD40 agonism on APCs upregulates chemokines and cytokine production and costimulatory receptors, leading to enhanced tumor antigen presentation to T cells[1] and upregulates costimulatory receptors on innate immune cells in a manner that promotes the conversion of naïve CD8+T cells into antigen-experienced memory CD8+T cells.[13] CD40 signaling induced robust antitumor immune responses in multiple preclinical models, both alone and in combination with checkpoint blockade antibodies.[10 14–16] In preclinical studies, the enhanced effector function of SEA-CD40 conferred greater immune stimulation and antitumor activity relative to other CD40-directed therapies,[17 18] thus supporting the rationale for this study.

Here, we report the results of this phase 1, open-label, multipart, dose-escalation study to evaluate safety and tolerability and identify the maximum tolerated dose (MTD) of SEA-CD40 in patients with advanced solid malignancies or lymphomas, and determine SEA-CD40 pharmacokinetics (PK), effect on pharmacodynamic (PD) biomarkers, and antitumor activity of SEA-CD40. The study was conducted with additional parts to examine combinations of SEA-CD40 with other antitumor therapies. This report pertains to SEA-CD40 monotherapy dose escalation in solid tumors (study part A) and lymphomas (study part C).

MATERIALS AND METHODS

Study design and treatment

Between February 24, 2015 and April 26, 2018, 56 patients with solid tumors and 11 patients with lymphoma were enrolled in parts A and C, respectively, at 13 clinical sites in the USA.

Table 1 SEA-CD40 intravenous monotherapy dose levels and number of patients

	Dose every 3 weeks (day 1 μg/kg)	Solid tumors (n)	Lymphomas (n)
Single-patient cohorts	0.6	1	0
	3	1	0
Standard 3+3 dose escalation cohorts	10	4	3
	30	21	3
	45	6	3
	60	11	2
	30*	12	0
	Total	56	11

*Intensified dosing (days 1 and 8 in cycles 1 and 2, with day 1 only in subsequent cycles).

SEA-CD40 was administered intravenously in 21-day cycles (day 1 of each cycle; every 3 weeks) with standard 3+3 dose escalation. Due to the agonistic properties of the molecule and potential for cytokine release syndrome, a minimum anticipated biological effect level (MABEL) approach was used for starting dose calculation. The MABEL dose was based on the most sensitive endpoint, EC20 for TNFα in a human whole blood cytokine release assay (0.6 μg/kg). The predicted first anticipated active dose (10 μg/kg), based on the estimated potential for SEA-CD40 to induce 90%, 60%, and 30% maximal upregulation of MHC class I, CD86, and MHC class II, respectively, was leveraged for the dose escalation strategy. It is standardly recommended that there are less than three dose escalations to get to the anticipated active dose, so 0.6 μg/kg was proposed as a conservative starting dose followed by 3 μg/kg, then 10 μg/kg (predicted first anticipated active dose) with half-log escalations (30 μg/kg, 100 μg/kg, etc) thereafter. Intermediate dose levels could be evaluated based on SEA-CD40's clinical profile. The dose levels assessed on trial were 0.6, 3, 10, 30, 45, and 60 μg/kg on day 1.

An intensified dosing regimen was also examined, consisting of 30 μg/kg dosed on day 1 and day 8 of the first two cycles, with only one dose of SEA-CD40 administered on day 1 in subsequent cycles. The number of patients for each dose is shown in table 1.

Eligibility

Eligible patients were ≥18 years of age with histologically confirmed advanced malignancy (solid tumors or lymphomas), measurable disease, and Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. Patients with solid tumors had metastatic or unresectable tumors with relapsed, refractory, or progressive disease after ≥1 prior systemic therapy, with no further standard treatment options available, and measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) V.1.1. Patients with lymphoma had classical Hodgkin lymphoma, diffuse large B-cell lymphoma (DLBCL), or indolent lymphoma (including follicular lymphoma) with relapsed, refractory or progressive disease defined as ≥2 prior systemic therapies for patients with classical Hodgkin's lymphoma who were not candidates for, failed or were deemed ineligible for autologous stem cell therapy (SCT); ≥1 prior systemic therapy and prior intensive salvage therapy (defined as combination chemotherapy±autologous SCT) for patients with DLBCL unless they refused or were deemed ineligible; and ≥1 prior chemoimmunotherapy regimen that included an anti-CD20 monoclonal antibody for patients with indolent lymphoma with no other more appropriate treatment options available.

Measurable disease for solid tumors was defined as ≥1 tumor lesion ≥10 mm in the longest diameter or a lymph node ≥15 mm in short-axis measurement assessed by computed tomography (CT) scan (RECIST V.1.1). Lesions situated in a previously irradiated area were considered measurable if progression was demonstrated. Measurable disease for lymphomas was defined as fluorodeoxyglucose-avid disease by positron emission tomography (PET) and measurable disease of ≥15 mm in the greatest transverse diameter by CT, as assessed locally by the site.

Safety assessments

Safety monitoring included ongoing assessment of adverse events (AEs) and dose-limiting toxicities (DLT)s from study day 1 (during and postdose) through the end-of-treatment visit or 30 days after the last dose of study treatment. All patients with ≥1 dose of any treatment were included in the safety assessment. AEs were summarized using the Medical Dictionary for Regulatory Activities and severity was graded according to National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) V.4.03. DLTs were defined and graded according to CTCAE V.4.03. The MTD was defined as the highest dose with >30% of patients in the dose escalation cohort at that dose level experiencing a DLT.

Pharmacokinetic assessments

Plasma samples for intensive PK testing were collected in cycles 1, 2, and 4 in the dose escalation cohorts. Predose samples were collected in cycles 3, 5, and subsequent dosing cycles at times specified per protocol. SEA-CD40 plasma concentrations were analyzed via a validated liquid chromatography-mass spectroscopy/mass spectroscopy assay, with the lowest level of quantitation concentration of 0.5 ng/mL. Incidence of antidrug antibodies (ADAs) were measured using a validated immunoassay. PK parameter estimates for SEA-CD40 dosed as monotherapy were available for 41 patients with solid tumor malignancies (Part A) and for 10 patients with lymphoma (part C). Noncompartmental analysis was performed using Phoenix WinNonlin V.8.2 (Certara USA, Princeton, New Jersey, USA) to determine PK parameters for each patient.

Plasma concentration-time profiles and dose proportionality analyses were performed using GraphPad Prism version V.8.0 (GraphPad Software, San Diego, California, USA).

Pharmacodynamic assessments

Heparinized whole blood samples from a subset of patients treated with SEA-CD40 30 µg/kg (25 patients with solid tumors and 3 patients with lymphoma) were collected predose, end of infusion, and approximately 4, 24, 72, and 168 hours postinfusion, and tested by flow cytometry by Flowmetric (Doylestown, Pennsylvania, USA). After red blood cell (RBC) lysis, samples were stained with cocktails of antibodies and LIVE/DEAD fixable red reagent (Thermo Fisher Scientific, Waltham, Massachusetts, USA), then fixed and permeabilized with Fix/Perm kit (eBioscience, Thermo Fisher Scientific). Samples subsequently underwent intracellular staining and fixation, followed with data acquisition on the LSRFortessa flow cytometry platform (BD Biosciences, Franklin Lakes, New Jersey, USA). Data were analyzed with FlowJo software. For immunophenotyping, cytotoxic T lymphocytes were classified as CD45+/CD3+/CD8+; helper T lymphocytes as CD45+/CD3+/CD4+; NK cells as CD45+/CD3−/CD56+/CD16+; and monocytes as CD45+/CD3−/CD14+. Immune cell activation was determined by measuring expression of the cell surface markers CD69, HLA-DR, and CD54.

Complete blood counts including enumeration of T, B, and NK cells in peripheral blood were performed at clinical sites per institutional standards. Immunoglobulin levels were quantified in serum per institutional standards.

Plasma cytokines and chemokines were analyzed using a Luminex platform at Myriad/Rules Based Medicine (Austin, Texas, USA). Plasma samples were obtained predose, and at approximately 4, 24, and 168 hours postinfusion.

Analysis of CD40 expression

Tumor biopsies were obtained prior to initiating study treatment. If the investigator deemed a tumor inaccessible or inappropriate for biopsy, an archived tumor biopsy within the previous 12 months could be used.

CD40 expression on tumor cells was evaluated by Mosaic Laboratories (Lake Forest, California, USA) on formalin-fixed paraffin embedded tumor samples, using anti-CD40 monoclonal antibody (Sigma Aldrich, Saint-Louis, Missouri, USA). The percentage of tumor cells with CD40 expression was estimated by central pathologist review. Samples with ≥1% tumor cells with detectable CD40 expression at any intensity were considered positive for tumor expression of CD40. The principal SEA-CD40 mechanism of action is hypothesized to be via CD40 agonism on immune cells, so tumor expression of CD40 was not anticipated to be the primary driver of efficacy.

Efficacy assessments

Efficacy in solid tumors was assessed by CT imaging every four cycles (12 weeks), with response assessment using RECIST V.1.1. Efficacy in lymphomas was assessed by diagnostic PET-CT imaging at cycle 2, cycle 4, and every four cycles (12 weeks) thereafter, with response assessment using Lugano classification. Efficacy was assessed in all patients receiving ≥1 dose of study drug who underwent ≥1 postbaseline response assessment or discontinued from the study. Progression-free survival was defined as the time from enrollment to the first documentation of progressive disease or to death due to any cause.

Statistical analysis

As a dose escalation study, there was no formal hypothesis testing. The standard 3+3 design was used to identify the MTD. Descriptive statistics were used to summarize demographics, baseline characteristics, safety, PK, and preliminary antitumor activity by study part and dose group. The analysis set of all treated patients included all patients who received ≥1 dose of SEA-CD40. The DLT-evaluable analysis set included all treated patients who either experienced a DLT or were followed for the full DLT-evaluation period. The efficacy-evaluable analysis set included all treated patients who had a baseline disease assessment and ≥1 evaluable postbaseline disease assessment, had clinical progression per investigator judgment, or discontinued from the study.

RESULTS

Patients

This analysis includes data as of September 17, 2019 cutoff. Enrollment by dose level between 0.6 and 60 µg/kg is shown in table 1. Baseline demographic and disease characteristics are shown in table 2. Gender distribution and median age were similar in both tumor groups. Most patients had ECOG performance status 1. The most common solid tumors were carcinomas of the head and neck, bladder, breast, and kidney. Among lymphomas, most were DLBCL (n=6; 54%), Hodgkin lymphoma (n=3; 27%), and follicular lymphoma (n=2; 18%).

Table 2 Demographics and baseline characteristics

	Solid tumors (N=56)	Lymphomas (N=11)
Median age, years (range)	61 (26–81)	62 (49–86)
Sex, male/female (%)	28/28 (50/50)	6/5 (55/45)
Race, n (%)		
White	44 (79)	9 (82)
African American	5 (9)	0
Asian	2 (4)	0
American Indian or Alaska Native	1 (2)	0
Other	3 (5)	0
Unknown	1 (2)	2 (18)
Baseline ECOG status*, n (%)		
0	17 (30)	3 (27)
1	39 (70)	8 (73)
Prior systemic therapies, n (%)		
1	6 (11)	0
2	10 (18)	2 (18)
3	11 (20)	0
≥4	29 (52)	9 (82)
Types of solid tumors, n (%)		
Head and neck squamous cell carcinoma	7 (13)	—
Bladder carcinoma	5 (9)	—
Breast carcinoma	5 (9)	—
Renal cell carcinoma	5 (9)	—
Esophageal carcinoma	4 (7)	—
Melanoma	4 (7)	—
Non-small cell lung carcinoma	3 (5)	—
Pancreatic carcinoma	3 (5)	—
Cholangiocarcinoma	2 (4)	—
Gastric carcinoma	2 (4)	—
Prostate carcinoma	2 (4)	—
Other†	14 (25)	—
Types of lymphomas, n (%)		
DLBCL	—	6 (55)
Hodgkin lymphoma‡	—	3 (27)
Follicular lymphoma	—	2 (18)

*Values for ECOG performance status range from 0 to 5, with higher scores indicating greater disability.
†Other includes anal squamous cell carcinoma, basal cell carcinoma, colon carcinoma, endometrial, gallbladder, gastroesophageal junction adenocarcinoma, gastroesophageal junction adenocarcinoma (gastric area), lacrimal adenoid cystic carcinoma, mesothelioma, ovarian carcinoma, rhabdomyosarcoma of the head and neck, soft tissue sarcoma, squamous cell cervical carcinoma, thyroid cancer.
‡Hodgkin lymphoma subtypes included mixed cellularity classical Hodgkin lymphoma (cHL) and nodular sclerosis cHL.
DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group.

Safety

Treatment-emergent AEs occurring in ≥15% of patients are summarized by dose cohort and grade in online supplemental table S1. Most events were ≤grade 3, and the most frequently reported (≥50%) were infusion-related reactions, chills, nausea, and fatigue. There were seven patients who died during the safety reporting period (defined as the period following the first dose of study treatment until 30 days after the last dose of study treatment). None of the deaths were considered related to SEA-CD40. Six of the deaths were considered related to disease progression, and one death was attributed to aspiration pneumonia. There were two patients with grade 4 AEs considered related to SEA-CD40. One patient with history of coronary artery disease developed grade 4 acute myocardial infarction within 1 day of receiving the fourth dose of SEA-CD40. Per the investigator, causality was impossible to determine but was assessed as related based on the temporal nature and the possibility that there may have been an acute inflammatory response to SEA-CD40. Additionally, one patient at the highest dose level evaluated (60 µg/kg) experienced grade 4 infusion/hypersensitivity reactions (IHRs) (considered anaphylaxis) with associated grade 4 hypotension.

IHRs were defined as events recorded with the NCI CTCAE terms of 'cytokine release syndrome,' 'infusion related reaction', 'hypersensitivity', or 'anaphylactic reaction'. IHRs in part A and C were reported in 49 patients (73%), including 8 with grade 3 and 1 with grade 4 IHRs (online supplemental table S2). IHRs persisted despite implementation of premedication with H1 and H2 histamine receptor blockers, acetaminophen, ibuprofen, and anti-emetic of choice. Steroid premedication with hydrocortisone was additionally trialed in three patients treated with 60 µg/kg SEA-CD40 but did not prevent IHRs, and thus was not implemented in additional patients. Correlative analyses revealed no association between IHR grade after the first infusion and the administered dose (online supplemental table S2A). However, there was a significant association between IHR grade and SEA-CD40 infusion rate. The only reported grade 4 IHR was associated with the fastest infusion rate (128 µg/min) performed (online supplemental table S2B). As a result, a standardized slow infusion approach was implemented after February 2018. The approach used an initial infusion rate limited to 10 µg/min, with a maximum infusion rate of up to 20 µg/min in subsequent cycles. Based on safety monitoring committee (SMC) recommendations, the slow infusion approach was used in conjunction with the empirical premedication regimen noted above in all subsequent patients.

Patients were treated with doses of SEA-CD40 ranging between 0.6 and 60 µg/kg. During 3+3 dose escalation, the SMC considered doses of 0.6, 3, 10, and 30 µg/kg tolerable with no DLTs reported. Further dose assessment included a total of 24 patients dosed at 30 µg/kg. While two of these patients exhibited IHRs that were considered to meet DLT criteria outside of 3+3 dose escalation, the SMC considered the dose of 30 µg/kg tolerable, therefore allowing higher doses to be examined. A dose of 60 µg/kg was assessed but was initially considered intolerable due to IHR DLTs; an intermediate dose of 45 µg/kg was subsequently assessed but was also initially considered intolerable due to IHR DLTs. The protocol was amended to allow higher dose levels to be reassessed if IHR management could be improved with mitigating measures (eg, reduced infusion rates). After a maximum infusion rate of ≤20 µg/kg was implemented, doses of 45 and 60 µg/kg were reassessed. Both dose levels were deemed tolerable with this reduced infusion approach, with no DLTs reported. DLTs are summarized in online supplemental table S3.

Pharmacokinetics

PK was analyzed in patients who received SEA-CD40 at doses of 10, 30, 45, or 60 µg/kg by intravenous infusion of variable duration (3–613 min). The arithmetic mean (SD) SEA-CD40 serum concentration vs time profiles for 10–60 µg/kg SEA-CD40 monotherapy are shown in figure 1. At the lowest SEA-CD40 dose levels tested (0.6 and 3 µg/kg, part A), most serum concentrations were below the lower limit of quantitation (0.500 ng/mL) which precluded estimation of PK parameters. Estimated PK parameter summaries for the other dose levels are shown in online supplemental table S4.

Average area under the concentration-time curve from time zero to time of last measurable concentration ($AUC_{0\text{-last}}$) values were greater than dose proportional below 30 µg/kg, approximately dose proportional from 30 to 60 µg/kg in the solid tumor dose escalation cohort, and greater than dose proportional from 10 to 60 µg/kg in the lymphoma dose escalation cohort. Intravenous infusion rates and lengths in cycles 1, 2, and 4 were highly variable; therefore, dose proportionality was not assessed using C_{max}. The SEA-CD40 C_{max} was attained at the end of the infusion, after which serum concentrations decreased rapidly over time in a multiexponential fashion.

Median terminal half-life ($t_{1/2}$) estimations for SEA-CD40 in the solid tumor dose escalation cohort were 4.0 (n=4), 10.4 (n=1), and 3.6 (n=5) days after administration of 30, 45, or 60 µg/kg, respectively (cycle 1) (online supplemental table S4). In all cohorts, most patients did not have detectable SEA-CD40 by predose of the subsequent cycle. The median and geometric mean exposures were higher in the solid tumor cohort compared with the lymphoma cohort from 10 to 45 µg/kg doses, although given the low patient numbers in the lymphoma cohort, this observation should be interpreted with caution. SEA-CD40 exposures were of similar magnitudes after cycles 1, 2, and 4, suggesting that SEA-CD40 did not accumulate upon repeat dosing (figure 1, online supplemental table S4). Dose intensification resulted in similar serum concentration profiles, with no evidence of accumulation upon repeat dosing.

Postdose ADAs were positively detected in a total of 4 of 51 (8%) evaluated patients (all part A) with only 1 patient that developed ADAs before cycle 6. Due to low incidence of ADAs, there were not enough data to characterize any direct impacts of ADAs on SEA-CD40 PK.

Pharmacodynamics

SEA-CD40 infusion resulted in dose-dependent increases in peripheral cytokines associated with immune activation and trafficking, specifically interferon-γ-inducible protein-10 (IP-10), monocyte chemoattractant protein-1, monokine induced by interferon-γ (MIG), and macrophage inflammatory protein-1b (MIP-1b) (figure 2A and online supplemental figure S2). Cytokine changes were predominantly observed between 4 and 24 hours postdose (depending on the cytokine), and cytokine levels typically normalized to predose levels within 24–168 hours postdose. Changes from baseline in plasma cytokine concentrations were minimal in patients dosed at 0.6 and 3 µg/kg, with consistent cytokine increases detected at doses

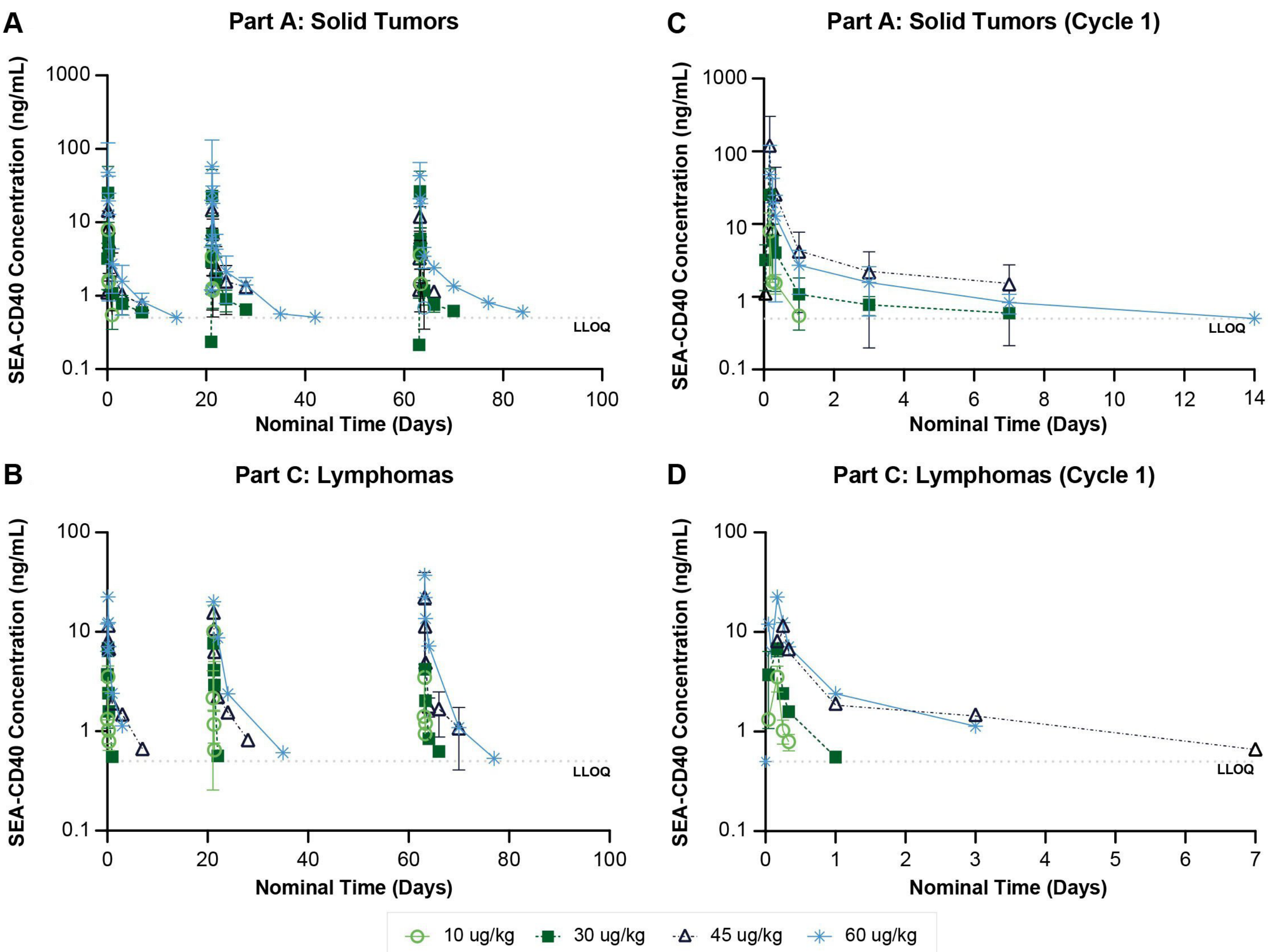

Figure 1 SEA-CD40 plasma concentration versus time profiles for SEA-CD40 following intravenous administration every 3 weeks in patients with solid tumor malignancies and lymphomas. Arithmetic means are shown, with error bars depicting SD. (A) SEA-CD40 concentrations in patients with solid tumors in part A; (B) SEA-CD40 concentrations in patients with lymphomas in part C; (C) SEA-CD40 concentrations in patients with solid tumors after cycle 1 in part A; (D) SEA-CD40 concentrations in patients with lymphomas after cycle 1 in part C. LLOQ; lower limit of quantitation.

≥10 µg/kg. The highest cytokine response was observed in patients dosed at 30 µg/kg. The cytokine response appeared to plateau or potentially decrease at doses above 30 µg/kg (figure 2A).

Changes in immune cell populations and immune activation after SEA-CD40 infusion were assessed by flow cytometry in peripheral blood collected from patients infused with 30 µg/kg SEA-CD40. Consistent with the reproducible induction of cytokines linked to SEA-CD40-induced immune activation and trafficking, flow cytometry revealed rapid decreases in T cells (CD4+ and CD8+), NK cells, and monocytes in the first 4 hours postinfusion (figure 2B). Normalization of T cells after 24 hours and NK cells and monocytes after 72 hours (figure 2B) was also observed, consistent with transient immune cell margination induced by SEA-CD40. Coincident to rapid migration of T and NK cells, increased activation marked by increased CD69 expression on both CD4+ and CD8+ T cells, and increased HLA-DR expression on NK cells were observed during the first 24 hours postinfusion for T cells, and up to 72 hours postinfusion for NK cells. Dose intensification did not provide any obvious benefit in terms of immune activation (data not shown).

Treatment with SEA-CD40 was also associated with cumulative, dose-dependent depletion of B cells (figure 2C). However, immunoglobulin levels (online supplemental figure S2) were not decreased. White blood cells, RBC, and platelets appeared stable over time (online supplemental figure S3).

Clinical activity

Among 44 patients with solid tumors, 6 exhibited reductions in tumor burden from baseline (figure 3A). There was one partial response in a patient with metastatic basal cell carcinoma, and five patients (gastroesophageal junction adenocarcinoma, basal cell carcinoma, anal squamous cell carcinoma, head and neck squamous cell carcinoma, and mesothelioma) exhibited prolonged

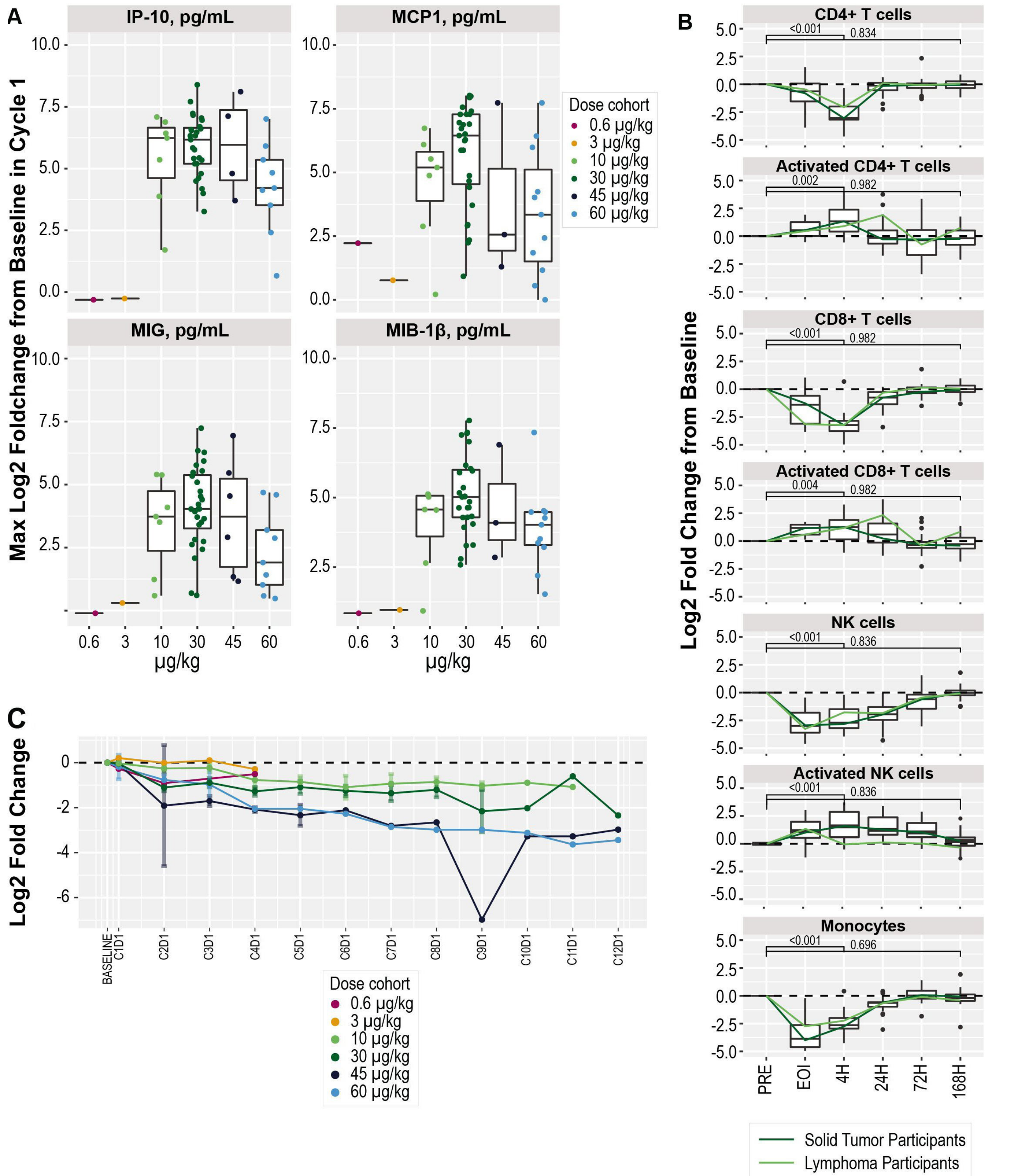

Figure 2 Pharmacodynamic changes observed after SEA-CD40 infusion. (A) Changes in selected cytokines are shown after infusion, with the fold change relative to predose shown by the vertical axis. Samples were collected in cycle 1, 4 hours after infusion for IP-10, MCP1, and MIP-1b, and 24 hours after infusion for MIG. The timepoints are selected based on highest changes observed over time for each marker. Changes were significant only for 30 vs 60 μg/kg. (IP-10 (p=0.03, fdr=0.105); MCP1 (p=0.017, fdr=0.102); MIG (p=0.012, fdr=0.102); MIB-1b (p=0.035, fdr=0.105)). P values are from t test. (B) Changes in immune cells assessed by flow cytometry in patients with solid tumors and lymphoma infused with 30 μg/kg SEA-CD40. The vertical axis depicts fold change from baseline. P values are from paired t test comparing preinfusion with 4 and 168 hours. Activated CD8+T cells determined by CD69+ and activated NK cells determined by HLA-DR+. (C) Relative changes in absolute B cell counts in patients with solid tumors assessed by flow cytometry. Each line represents the median of changes per dose cohort and error bars show the SE from the median. MCP1, monocyte chemoattractant protein-1; MIG, monokine induced by interferon-γ; MIP-1b, macrophage inflammatory protein-1b; PRE, predose; EOI, end of infusion.

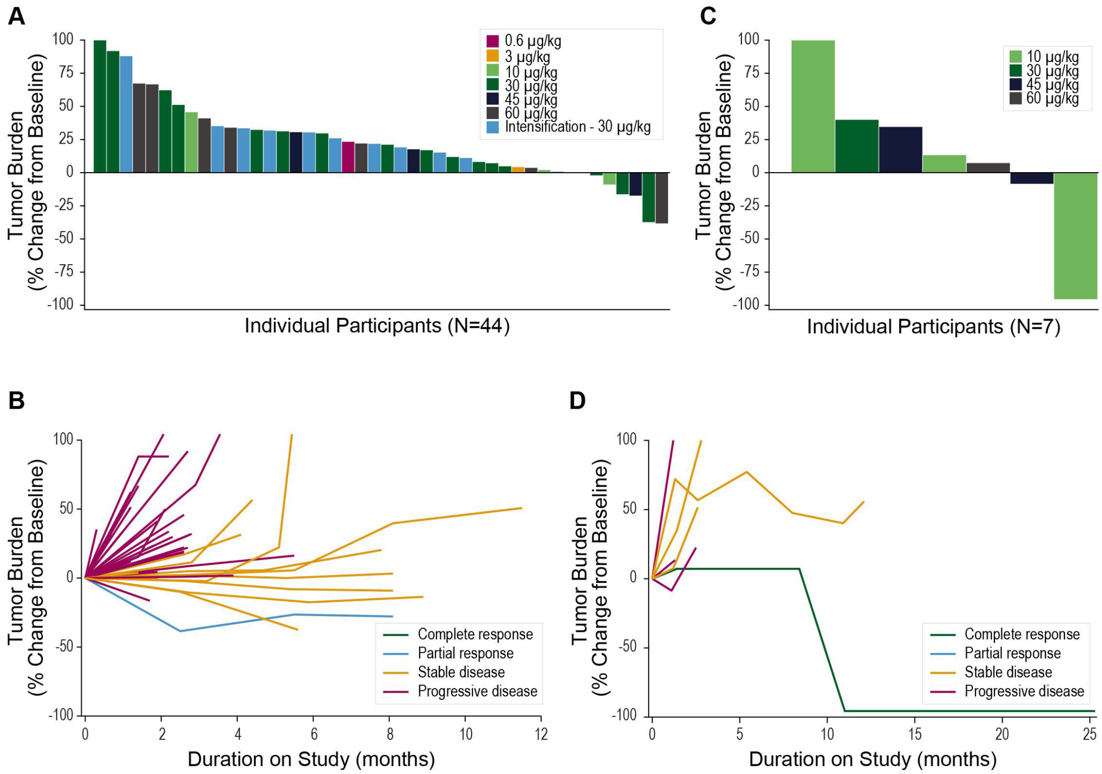

Figure 3 Tumor burden change from baseline in solid tumor patients (A, B) and lymphoma patients (C, D). In A, C, color indicates dose level as denoted in the inset. In B, D, color (inset) denotes tumor response by RECIST criteria for patients with solid tumors and Lugano criteria for patients with lymphoma. RECIST, Response Evaluation Criteria in Solid Tumors.

stable disease of approximately 6 months or greater (figure 3B).

Among seven patients with lymphomas, there was one durable complete response and three patients (two with Hodgkin's lymphoma (nodular sclerosis) and one with B-cell non-Hodgkin's lymphoma (germinal center B-cell-like DLBCL)) with stable disease, with one demonstrating prolonged SD >6 months (figure 3C–D). Four patients with DLBCL were not efficacy evaluable, due to rapid disease progression prior to response assessment. The complete response occurred in a patient with follicular lymphoma who had received seven prior lines of therapy. The patient maintained complete response after >2 years on study treatment, and discontinued study treatment following a grade 3 IHR in cycle 38.

We assessed CD40 expression on neoplastic cells by immunohistochemistry to determine whether CD40 expression on tumor cells correlates with antitumor response. CD40 expression was detectable on neoplastic cells in 16 of 43 (37%) evaluable patients based on an expression cut-off of 1% of cells. There was no clear correlation between CD40 expression and reduction in tumor burden (p=0.545, analysis of variance test). We did not analyze for a correlation between CD40 expression and antitumor response in lymphomas due to nearly ubiquitous CD40 expression in B cell lymphomas.[19 20]

DISCUSSION

In this phase 1 dose escalation study of SEA-CD40 in patients with solid tumors and lymphomas, SEA-CD40 exhibited an acceptable safety profile, potent PD activity, and evidence of disease control that suggest the potential for clinical benefit. The predominant AEs observed with SEA-CD40 were IHRs, which were generally grades 1–2 and were consistent with immune activation from SEA-CD40. IHR severity was correlated with infusion rate, and thus a standardized infusion approach with a slow infusion rate (maximum rate of 20 µg/min) and routine premedication was implemented for future development. This infusion rate remains feasible for outpatient administration while improving tolerability.

SEA-CD40 exhibited rapid PK clearance without evidence of accumulation, consistent with binding to immune cells. Rapid and potent immune activation by SEA-CD40 is supported by the finding of T cell activation and APC, NK, and T cell transient reduction with a rapid recovery consistent with trafficking within hours of infusion, as predicted by its expected mechanism of action.[9 10] Cytokines associated with immune activation and trafficking were observed to increase with SEA-CD40 dosing, with a greater extent of cytokine induction for doses ≥10 µg/kg relative to lower doses. The highest median cytokine induction was observed at 30 µg/kg. The cytokine response appeared to plateau or potentially decrease at doses above 30 µg/kg, suggesting that doses 10–30 µg/kg may result in optimal immune activation.

Transient decrease in monocytes, T cells and NK cells in peripheral blood were reproducibly observed in concert with cytokine changes and were associated with upregulation of markers of T and NK cell activation (CD69, HLA-DR, CD54), which may be consistent with trafficking of effector cells out of the circulation following activation. SEA-CD40 induced dose-dependent B-cell depletion that deepened over multiple cycles in patients dosed at 10 µg/kg and higher, with no evidence of persistent depletion of circulating immunoglobulin levels. The magnitude of B cell depletion was more pronounced for doses above 30 µg/kg, again supporting prioritization of doses between 10 and 30 µg/kg for further development.

SEA-CD40 exhibited cytokine induction and innate immune cell activation at doses ≥10 µg/kg, a dose level ~10 to 100-fold lower than clinical doses for other CD40 agonists.[21–23] The highly potent immune activation of SEA-CD40 is attributed to the non-fucosylation of the anti-CD40 antibody.[9 10 24] The SEA-CD40 non-fucosylated backbone enhances innate immune cell activation in two complementary ways: (1) by facilitating the clustering and agonism of CD40, and (2) by driving a positive activating signal through FcγRIIIa expressed on immune effector cells (eg, NK and myeloid cells). In contrast, other CD40 antibodies in clinical development can agonize CD40, but either engage both activating FcγRIIIa and inhibitory FcγRIIIa receptors (sotigalimab) or unable to engage Fc receptors on myeloid cells (selicrelumab).[17 18] These molecules are not able to drive the additional positive signal to the myeloid cells. For example, in vitro, SEA-CD40 uniquely drives release of immune activating cytokines when combined with chemotherapy to drive antigen release. In contrast, other CD40 agonists that were assessed amplify immune suppressive cytokines,[17 18] such that immune activation may be less favorable than that with SEA-CD40. Prior trials have assessed CD40 agonists as both monotherapy and in combination with additional therapies,[1 13 21 23] and SEA-CD40 has potential for enhanced activity in these settings based on its favorable PD properties.

Reductions in tumor burden from baseline (figure 3A) were observed in patients with solid tumors. One partial response was observed, and five other patients exhibited prolonged stable disease (figure 3B). There was one durable complete response in a patient with follicular lymphoma and one durable stable disease in a patient with Hodgkin's lymphoma (figure 3C,D).

These data for the dose escalation of this first-in-human study provide evidence of immune activation consistent with the proposed mechanism of action and suggest doses of 10–30 µg/kg SEA-CD40 are appropriate for further investigation. A separate cohort of this phase 1 study has thus investigated 10–30 µg/kg SEA-CD40 in combination with chemotherapy and pembrolizumab in patients with metastatic pancreatic ductal adenocarcinoma.[25] SEA-CD40 is being assessed in additional tumor types in an ongoing phase 2 basket trial at a dose of 10 µg/kg (NCT02376699).

Conclusions

SEA-CD40 was adequately tolerated in patients with advanced solid tumors and lymphoma, with a predominant toxicity of IHRs that are generally grades 1–2 and may be mitigated with a slowed infusion rate. Evidence of monotherapy antitumor activity and robust PD activity was observed in both solid tumor and lymphoma patients. The potent immunostimulatory properties of SEA-CD40 observed in this study suggest it may be a promising partner for combination therapy. While SEA-CD40 exhibited evidence of antitumor activity as monotherapy, pairing SEA-CD40 with chemotherapy or antibody–drug conjugates could provide additional clinical benefit, as antigen release would be coupled with stimulation of antigen uptake and presentation. In addition, combination with PD-1 blockade could enable sustained immune activation. SEA-CD40 combination regimens are being evaluated in ongoing cohorts[25] (NCT02376699) and have the potential to improve outcomes across multiple types of cancer.

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Data availability statement Data are available on reasonable request. De-identified patient-level trial data that underlie the results reported in this publication will be made available on a case-by-case basis to researchers who provide a methodologically sound proposal. Additional documentation may also be made available. Data availability will begin after approval of the qualified request and end 30 days after receipt of datasets. All requests can be submitted to CTDR@seagen.com and will be reviewed by an internal review committee. Please note that the data sharing policy of this clinical study's sponsor, Seagen Inc., requires all requests for clinical trial data be reviewed to determine the qualification of the specific request. This policy is available at https://www.seagen.com/healthcare-professionals/clinical-data-requests and is aligned with BIO's Principles on Clinical Trial Data Sharing (available at https://www.bio.org/blogs/principles-clinical-trial-data-sharing-reaffirm-commitment).

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