DATA SUPPLEMENT

Phase 1 Dose-Escalation Study of SEA-CD40, a Nonfucosylated CD40 Agonist, in Advanced Solid Tumors and Lymphomas

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SUPPLEMENTARY TABLES AND FIGURES

Table S1: Treatment-emergent adverse events reported in ≥15% of patients in any treatment group

Preferred Term Severity	0.6 µg/kg (N=1) n (%)	3 µg/kg (N=1) n (%)	10 µg/kg (N=7) n (%)	30 µg/kg (N=24) n (%)	45 µg/kg (N=9) n (%)	60 µg/kg (N=13) n (%)	30 µg/kg[a] (N=12) n (%)	Total (N=67) n (%)
Any event	1 (100)	1 (100)	7 (100)	24 (100)	9 (100)	13 (100)	11 (92)	66 (99)
Grade 1	0	0	0	0	1 (11)	0	0	1 (1)
Grade 2	0	0	2 (29)	8 (33)	1 (11)	2 (15)	4 (33)	17 (25)
Grade 3	1 (100)	1 (100)	2 (29)	11 (46)	5 (56)	9 (69)	3 (25)	32 (48)
Grade 4	0	0	2 (29)	3 (13)	2 (22)	1 (8)	1 (8)	9 (13)
Grade 5	0	0	1 (14)	2 (8)	0	1 (8)	3 (25)	7 (10)
Infusion related reaction	0	0	6 (86)	20 (83)	8 (89)	7 (54)	6 (50)	47 (70)
Grade 1	0	0	1 (14)	4 (17)	2 (22)	1 (8)	3 (25)	11 (16)
Grade 2	0	0	4 (57)	15 (63)	4 (44)	3 (23)	3 (25)	29 (43)
Grade 3	0	0	1 (14)	1 (4)	2 (22)	3 (23)	0	7 (10)
Chills	0	0	5 (71)	16 (67)	6 (67)	7 (54)	6 (50)	40 (60)
Grade 1	0	0	2 (29)	7 (29)	2 (22)	2 (15)	3 (25)	16 (24)
Grade 2	0	0	3 (43)	8 (33)	4 (44)	5 (38)	3 (25)	23 (34)
Grade 3	0	0	0	1 (4)	0	0	0	1 (1)
Nausea	0	0	6 (86)	16 (67)	5 (56)	7 (54)	5 (42)	39 (58)

Preferred Term Severity	0.6 µg/kg (N=1) n (%)	3 µg/kg (N=1) n (%)	10 µg/kg (N=7) n (%)	30 µg/kg (N=24) n (%)	45 µg/kg (N=9) n (%)	60 µg/kg (N=13) n (%)	30 µg/kg[a] (N=12) n (%)	Total (N=67) n (%)
Grade 1	0	0	1 (14)	10 (42)	3 (33)	3 (23)	3 (25)	20 (30)
Grade 2	0	0	5 (71)	6 (25)	2 (22)	4 (31)	2 (17)	19 (28)
Fatigue	1 (100)	1 (100)	3 (43)	14 (58)	4 (44)	5 (38)	7 (58)	35 (52)
Grade 1	1 (100)	0	2 (29)	2 (8)	1 (11)	1 (8)	4 (33)	11 (16)
Grade 2	0	1 (100)	1 (14)	10 (42)	3 (33)	3 (23)	2 (17)	20 (30)
Grade 3	0	0	0	2 (8)	0	1 (8)	1 (8)	4 (6)
Vomiting	0	0	4 (57)	11 (46)	2 (22)	5 (38)	4 (33)	26 (39)
Grade 1	0	0	2 (29)	10 (42)	1 (11)	1 (8)	3 (25)	17 (25)
Grade 2	0	0	2 (29)	1 (4)	1 (11)	2 (15)	1 (8)	7 (10)
Grade 3	0	0	0	0	0	2 (15)	0	2 (3)
Anaemia	0	0	2 (29)	8 (33)	3 (33)	6 (46)	4 (33)	23 (34)
Grade 1	0	0	1 (14)	0	0	0	2 (17)	3 (4)
Grade 2	0	0	0	3 (13)	2 (22)	1 (8)	1 (8)	7 (10)
Grade 3	0	0	1 (14)	5 (21)	1 (11)	5 (38)	1 (8)	13 (19)
Hypotension	0	0	1 (14)	6 (25)	6 (67)	4 (31)	4 (33)	21 (31)
Grade 1	0	0	0	1 (4)	0	1 (8)	0	2 (3)
Grade 2	0	0	1 (14)	2 (8)	5 (56)	1 (8)	4 (33)	13 (19)
Grade 3	0	0	0	3 (13)	1 (11)	1 (8)	0	5 (7)

Preferred Term Severity	0.6 µg/kg (N=1) n (%)	3 µg/kg (N=1) n (%)	10 µg/kg (N=7) n (%)	30 µg/kg (N=24) n (%)	45 µg/kg (N=9) n (%)	60 µg/kg (N=13) n (%)	30 µg/kg[a] (N=12) n (%)	Total (N=67) n (%)
Grade 4	0	0	0	0	0	1 (8)	0	1 (1)
Dyspnoea	0	0	2 (29)	9 (38)	1 (11)	4 (31)	4 (33)	20 (30)
Grade 1	0	0	1 (14)	2 (8)	0	1 (8)	0	4 (6)
Grade 2	0	0	1 (14)	6 (25)	1 (11)	1 (8)	3 (25)	12 (18)
Grade 3	0	0	0	1 (4)	0	2 (15)	1 (8)	4 (6)
Headache	0	0	3 (43)	9 (38)	2 (22)	2 (15)	3 (25)	19 (28)
Grade 1	0	0	3 (43)	5 (21)	1 (11)	2 (15)	2 (17)	13 (19)
Grade 2	0	0	0	3 (13)	1 (11)	0	1 (8)	5 (7)
Grade 3	0	0	0	1 (4)	0	0	0	1 (1)
Constipation	1 (100)	0	2 (29)	5 (21)	2 (22)	2 (15)	4 (33)	16 (24)
Grade 1	1 (100)	0	1 (14)	5 (21)	1 (11)	1 (8)	2 (17)	11 (16)
Grade 2	0	0	1 (14)	0	0	1 (8)	2 (17)	4 (6)
Grade 3	0	0	0	0	1 (11)	0	0	1 (1)
Pyrexia	0	0	0	5 (21)	3 (33)	5 (38)	3 (25)	16 (24)
Grade 1	0	0	0	4 (17)	3 (33)	3 (23)	0	10 (15)
Grade 2	0	0	0	1 (4)	0	2 (15)	3 (25)	6 (9)
Back pain	0	0	1 (14)	2 (8)	2 (22)	6 (46)	4 (33)	15 (22)

Preferred Term Severity	0.6 µg/kg (N=1) n (%)	3 µg/kg (N=1) n (%)	10 µg/kg (N=7) n (%)	30 µg/kg (N=24) n (%)	45 µg/kg (N=9) n (%)	60 µg/kg (N=13) n (%)	30 µg/kg[a] (N=12) n (%)	Total (N=67) n (%)
Grade 1	0	0	0	1 (4)	2 (22)	2 (15)	3 (25)	8 (12)
Grade 2	0	0	0	0	0	4 (31)	1 (8)	5 (7)
Grade 3	0	0	1 (14)	1 (4)	0	0	0	2 (3)
Oedema peripheral	0	0	2 (29)	6 (25)	3 (33)	2 (15)	2 (17)	15 (22)
Grade 1	0	0	1 (14)	3 (13)	3 (33)	2 (15)	0	9 (13)
Grade 2	0	0	1 (14)	2 (8)	0	0	1 (8)	4 (6)
Grade 3	0	0	0	1 (4)	0	0	1 (8)	2 (3)
Tachycardia	0	0	3 (43)	5 (21)	3 (33)	2 (15)	1 (8)	14 (21)
Grade 1	0	0	3 (43)	3 (13)	2 (22)	1 (8)	1 (8)	10 (15)
Grade 2	0	0	0	2 (8)	1 (11)	0	0	3 (4)
Grade 3	0	0	0	0	0	1 (8)	0	1 (1)
Abdominal pain	0	0	2 (29)	3 (13)	1 (11)	3 (23)	4 (33)	13 (19)
Grade 1	0	0	0	0	0	2 (15)	2 (17)	4 (6)
Grade 2	0	0	1 (14)	2 (8)	1 (11)	0	2 (17)	6 (9)
Grade 3	0	0	1 (14)	1 (4)	0	1 (8)	0	3 (4)
Decreased appetite	0	0	0	4 (17)	2 (22)	2 (15)	5 (42)	13 (19)
Grade 1	0	0	0	1 (4)	2 (22)	1 (8)	3 (25)	7 (10)
Grade 2	0	0	0	3 (13)	0	1 (8)	2 (17)	6 (9)

Preferred Term Severity	0.6 μg/kg (N=1) n (%)	3 μg/kg (N=1) n (%)	10 μg/kg (N=7) n (%)	30 μg/kg (N=24) n (%)	45 μg/kg (N=9) n (%)	60 μg/kg (N=13) n (%)	30 μg/kg[a] (N=12) n (%)	Total (N=67) n (%)
Cough	0	0	1 (14)	3 (13)	1 (11)	4 (31)	2 (17)	11 (16)
Grade 1	0	0	1 (14)	1 (4)	1 (11)	3 (23)	1 (8)	7 (10)
Grade 2	0	0	0	2 (8)	0	0	1 (8)	3 (4)
Grade 3	0	0	0	0	0	1 (8)	0	1 (1)
Dizziness	1 (100)	0	2 (29)	1 (4)	2 (22)	1 (8)	3 (25)	10 (15)
Grade 1	1 (100)	0	2 (29)	1 (4)	1 (11)	1 (8)	2 (17)	8 (12)
Grade 2	0	0	0	0	1 (11)	0	0	1 (1)
Grade 3	0	0	0	0	0	0	1 (8)	1 (1)
Wheezing	1 (100)	0	0	3 (13)	1 (11)	4 (31)	1 (8)	10 (15)
Grade 1	1 (100)	0	0	2 (8)	1 (11)	0	1 (8)	5 (7)
Grade 2	0	0	0	1 (4)	0	3 (23)	0	4 (6)
Grade 3	0	0	0	0	0	1 (8)	0	1 (1)

[a]Intensified dosing (Days 1 and 8 in Cycles 1 and 2, with Day 1 only in subsequent cycles)
Preferred terms from MedDRA v17.1

Supplementary Table S2: IHR-related adverse events in patients with solid tumors (Part A) and lymphomas (Part C)

Preferred Term Severity	0.6 µg/kg (N=1) n (%)	3 µg/kg (N=1) n (%)	10 µg/kg (N=7) n (%)	30 µg/kg (N=24) n (%)	45 µg/kg (N=9) n (%)	60 µg/kg (N=13) n (%)	30 µg/kg[a] (N=12) n (%)	Total (N=67) n (%)
Any event	0	0	6 (86)	21 (88)	8 (89)	7 (54)	7 (58)	49 (73)
Grade 1	0	0	1 (14)	3 (13)	2 (22)	1 (8)	3 (25)	10 (15)
Grade 2	0	0	4 (57)	15 (63)	4 (44)	3 (23)	4 (33)	30 (45)
Grade 3	0	0	1 (14)	3 (13)	2 (22)	2 (15)	0	8 (12)
Grade 4	0	0	0	0	0	1 (8)	0	1 (1)
Infusion related reaction	0	0	6 (86)	20 (83)	8 (89)	7 (54)	6 (50)	47 (70)
Grade 1	0	0	1 (14)	4 (17)	2 (22)	1 (8)	3 (25)	11 (16)
Grade 2	0	0	4 (57)	15 (63)	4 (44)	3 (23)	3 (25)	29 (43)
Grade 3	0	0	1 (14)	1 (4)	2 (22)	3 (23)	0	7 (10)
Anaphylactic reaction	0	0	0	1 (4)	0	1 (8)	0	2 (3)
Grade 3	0	0	0	1 (4)	0	0	0	1 (1)
Grade 4	0	0	0	0	0	1 (8)	0	1 (1)
Cytokine release syndrome	0	0	0	2 (8)	0	0	0	2 (3)
Grade 2	0	0	0	1 (4)	0	0	0	1 (1)

Preferred Term Severity	0.6 μg/kg (N=1) n (%)	3 μg/kg (N=1) n (%)	10 μg/kg (N=7) n (%)	30 μg/kg (N=24) n (%)	45 μg/kg (N=9) n (%)	60 μg/kg (N=13) n (%)	30 μg/kg[a] (N=12) n (%)	Total (N=67) n (%)
Grade 3	0	0	0	1 (4)	0	0	0	1 (1)
Hypersensitivity	0	0	0	1 (4)	0	0	1 (8)	2 (3)
Grade 1	0	0	0	1 (4)	0	0	0	1 (1)
Grade 2	0	0	0	0	0	0	1 (8)	1 (1)

[a]Intensified dosing (Days 1 and 8 in Cycles 1 and 2, with Day 1 only in subsequent cycles)
Preferred terms from MedDRA v17.1

Supplementary Table S3. SEA-CD40 DLTs in patients with solid tumors (Part A)

Preferred term Severity	30 mg/kg (N=2) n	45 mg/kg (N=2) n	60 mg/kg (N=2) n
Infusion related reaction/infusion reaction Grade 3	1	2	1
Anaphylactic reaction/anaphylaxis Grade 4	0	0	1
Cytokine release syndrome/cytokine release Grade 3	1	0	0

Supplementary Table S4. SEA-CD40 PK parameter summaries for dose escalation cohorts in patients with solid tumors (Part A) and lymphomas (Part C)

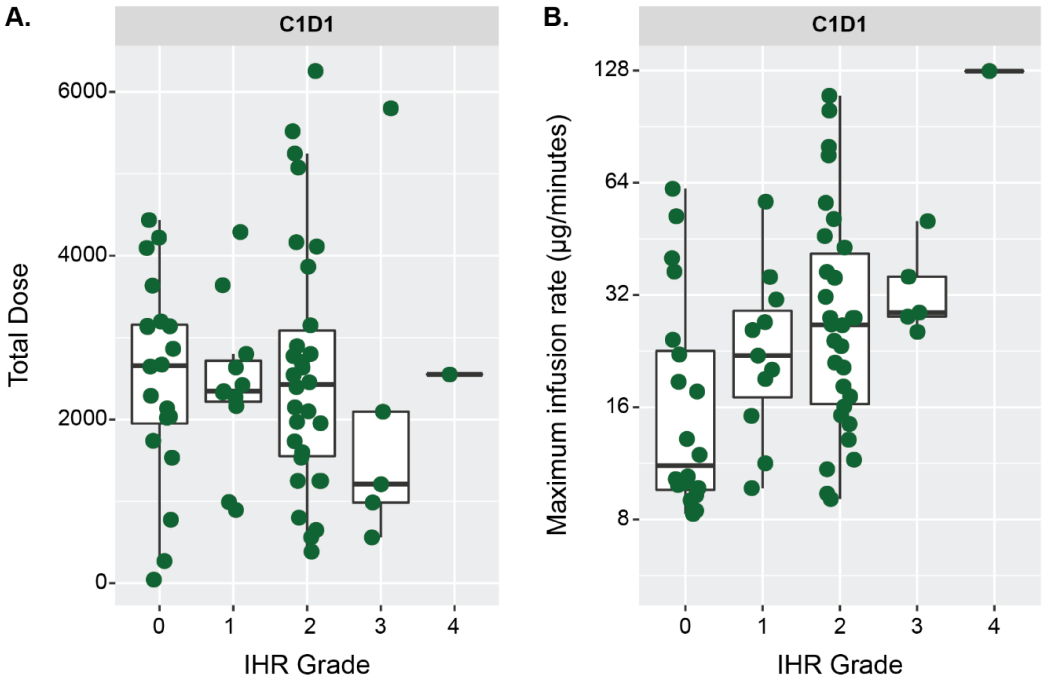
			Part A				Part C			
			Dose (µg/kg)				Dose (µg/kg)			
			10	30	45	60	10	30	45	60
Cycle	Parameter	Statistic[a]								
1	$AUC_{0\text{-last}}$ (hr*ng/mL)	N	4	15	3	9	3	3	2	2
		Median	23.9	99.1	252	335	5.61	36.4	177	457
		(Min, Max)	(5.43, 36.3)	(8.02, 435)	(152, 356)	(101, 1260)	(4.64, 6.45)	(13.1, 69.3)	(79.6, 275)	(253, 662)
		GM (CV%)	18 (100%)	81.7 (180%)	239 (45%)	352 (86%)	5.52 (17%)	32.1 (100%)	148 (110%)	409 (77%)
	C_{max} (ng/mL)	N	4	14	2	8	3	2	1	1
		Median	6.79	12.5	14.4	22	2.8	6.73	11.6	22.4
		(Min, Max)	(1.61, 16.4)	(2.62, 126)	(13.9, 14.9)	(7.04, 225)	(1.27, 4.24)	(5.97, 7.49)	n.a.	n.a.
		GM (CV%)	5.82 (130%)	13.5 (140%)	14.4 (4.9%)	25.7 (150%)	2.47 (67%)	6.69 (16%)	11.6 (n.e.)	22.4 (n.e.)
	$t_{½}$ (day)	N	0	4	1	5	0	0	1	1
		Median	n.e.	4.02	10.4	3.58	n.e.	n.e.	4.05	2.53
		(Min, Max)	n.e.	(3.3, 5.04)	n.a.	(2.28, 4.9)	n.e.	n.e.	n.a.	n.a.
		GM (CV%)	n.e.	4.03 (22%)	10.4 (n.e.)	3.31 (31%)	n.e.	n.e.	4.05 (n.e.)	2.53 (n.e.)
2	$AUC_{0\text{-last}}$ (hr*ng/mL)	N	3	13	3	7	2	1	2	1
		Median	4.89	138	281	720	10.8	53.1	297	862

			Part A				Part C			
			Dose (µg/kg)				Dose (µg/kg)			
			10	30	45	60	10	30	45	60
		(Min, Max)	(0.305, 11.4)	(5.42, 333)	(110, 518)	(128, 1520)	(9.73, 11.9)	n.a.	(225, 368)	n.a.
		GM (CV%)	2.57 (590%)	83.7 (250%)	252 (92%)	543 (97%)	10.7 (14%)	53.1 (n.e.)	288 (36%)	862 (n.e.)
	C_{max} (ng/mL)	N	3	13	2	7	2	1	2	1
		Median	2.83	14.4	14.7	29.7	14.2	7.68	15.7	20.1
		(Min, Max)	(1.46, 5.97)	(2.12, 113)	(10.2, 19.2)	(16.6, 236)	(9.51, 18.8)	n.a.	(14.3, 17)	n.a.
		GM (CV%)	2.91 (80%)	13.4 (160%)	14 (47%)	41.1 (120%)	13.4 (51%)	7.68 (n.e.)	15.6 (12%)	20.1 (n.e.)
	$t_{½}$ (day)	N	0	4	2	6	0	0	1	n.e.
		Median	n.e.	3.84	6.12	5.05	n.e.	n.e.	6.24	n.e.
		(Min, Max)	n.e.	(0.909, 5.54)	(3.87, 8.38)	(3.49, 6.96)	n.e.	n.e.	n.a.	n.e.
		GM (CV%)	n.e.	2.93 (95%)	5.69 (59%)	4.8 (28%)	n.e.	n.e.	6.24 (n.e)	n.e.
4	$AUC_{0\text{-last}}$ (hr*ng/mL)	N	3	10	3	3	1	1	2	1
		Median	22.4	130	77.3	628	6.08	74.8	377	1000
		(Min, Max)	(2.96, 37.7)	(52.6, 237)	(63.4, 210)	(365, 855)	n.a.	n.a.	(232, 522)	n.a.
		GM (CV%)	13.6 (230%)	122 (53%)	101 (71%)	581 (45%)	6.08 (n.e.)	74.8 (n.e.)	348 (63%)	1000 (n.e.)
	C_{max} (ng/mL)	N	3	10	3	3	1	1	2	1
		Median	4.35	20.1	12.6	27.5	3.48	4.21	22.2	37.1
		(Min, Max)	(1.23, 5.17)	(3.74, 71.6)	(7.25, 15.9)	(3.1, 58.8)	n.a.	n.a.	(9.85, 34.6)	n.a.

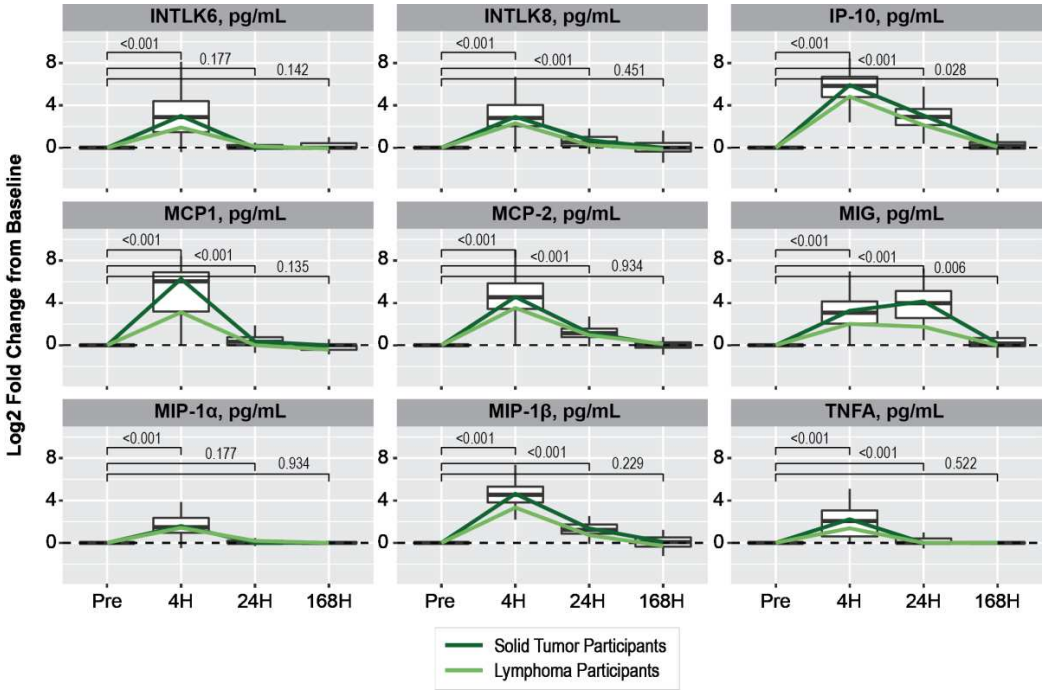
			Part A				Part C			
			Dose (µg/kg)				Dose (µg/kg)			
			10	30	45	60	10	30	45	60
		GM (CV%)	3.02 (92%)	17.6 (130%)	11.3 (42%)	17.1 (310%)	3.48 (n.e)	4.21 (n.e.)	18.5 (110%)	37.1 (n.e.)
	$t_{½}$ (day)	N	0	2	1	2	0	n.e.	1	1
		Median	n.e.	6.5	1.4	8.05	n.e.	n.e.	4.57	3.44
		(Min, Max)	n.e.	(3.74, 9.27)	n.a.	(3.58, 12.5)	n.e.	n.e.	n.a.	n.a.
		GM (CV%)	n.e.	5.89 (71%)	1.4 (n.e.)	6.7 (110%)	n.e.	n.e.	4.57 (n.e.)	3.44 (n.e.)

$AUC_{0\text{-last}}$=average area under the concentration-time curve from time zero to time of last measurable concentration; GM=geometric mean; C_{max}=maximum concentration; CV=coefficient variable; n.a.=not applicable; n.e.=not estimable; PK=pharmacokinetics; $t_{½}$=half life

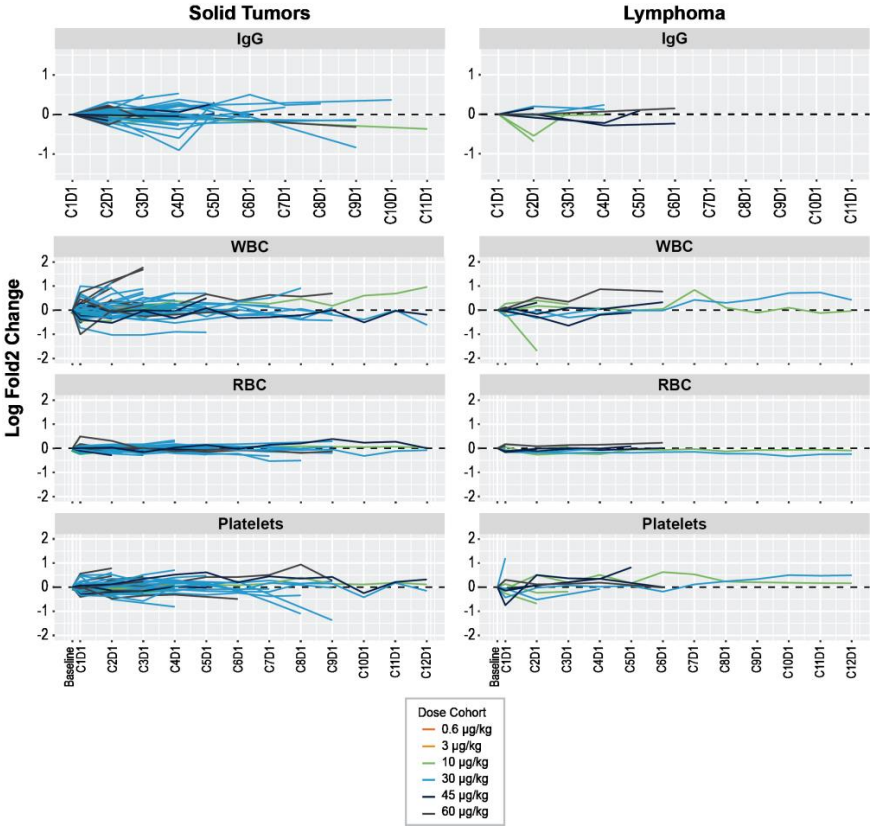
[a]Patients for whom the SEA-CD40 infusion was stopped early due to an adverse event (full dose not received) were not included in PK parameter statistics. If a full dose was received within 24 hours after interruption, $AUC_{0\text{-last}}$ and $t_{½}$ but not C_{max} were included in PK parameter statistics.



Supplementary Figure S1: Impact of total dose (A) and infusion rate (B) on observed infusion reactions within 24 hours after first dose. Analysis of infusion reactions occurring after the first dose was performed to control for effects of potential confounding factors, such as pre-dose medications used after Cycle 1. Patients who did not have any infusion reactions were classified as grade 0 (20 patients). There was no association between the infusion reaction grade and the administered dose (A. Spearman correlation: 0.08, P=0.48). There was a significant association between infusion reaction grade and infusion rate (B. Spearman correlation: 0.42; P=0.0004).



Supplementary Figure S2: Dynamics of plasma cytokine changes after SEA-CD40 infusion. Major cytokine changes were generally observed 4 hours after dosing, and levels of plasma cytokines return to baseline 24-168 hours after infusion. Two patients from the lowest dose cohorts of 0.6 and 3 μg/kg, considered pharmacodynamically inactive, were excluded from the analysis. Data are from Cycle 1. INTLK6, interleukin 6; INTLK8, interleukin 8; IP-10, interferon-γ-inducible protein-10; MCP1, monocyte chemoattractant protein-1; MIP-1α, macrophase inflammatory protein-1α; MIP-1β, macrophase inflammatory protein-1β; TNFA, tumor necrosis factor alpha.



Supplementary Figure S3: Changes over time in immunoglobulin, WBC, RBCs, and platelets. Each line represents a single patient and line color represents the dose group. Changes relative to baseline in serum IgG levels and WBC, RBC, and platelet counts in peripheral blood are plotted separately for solid tumor and lymphoma patients. IgG, immunoglobulin G; RBC, red blood cell; WBC, white blood cell