PRELIMINARY RESULTS OF A PHASE 1 STUDY OF SEA-CD40, GEMCITABINE, NAB-PACLITAXEL, AND PEMBROLIZUMAB IN PATIENTS WITH METASTATIC PANCREATIC DUCTAL ADENOCARCINOMA (PDAC)

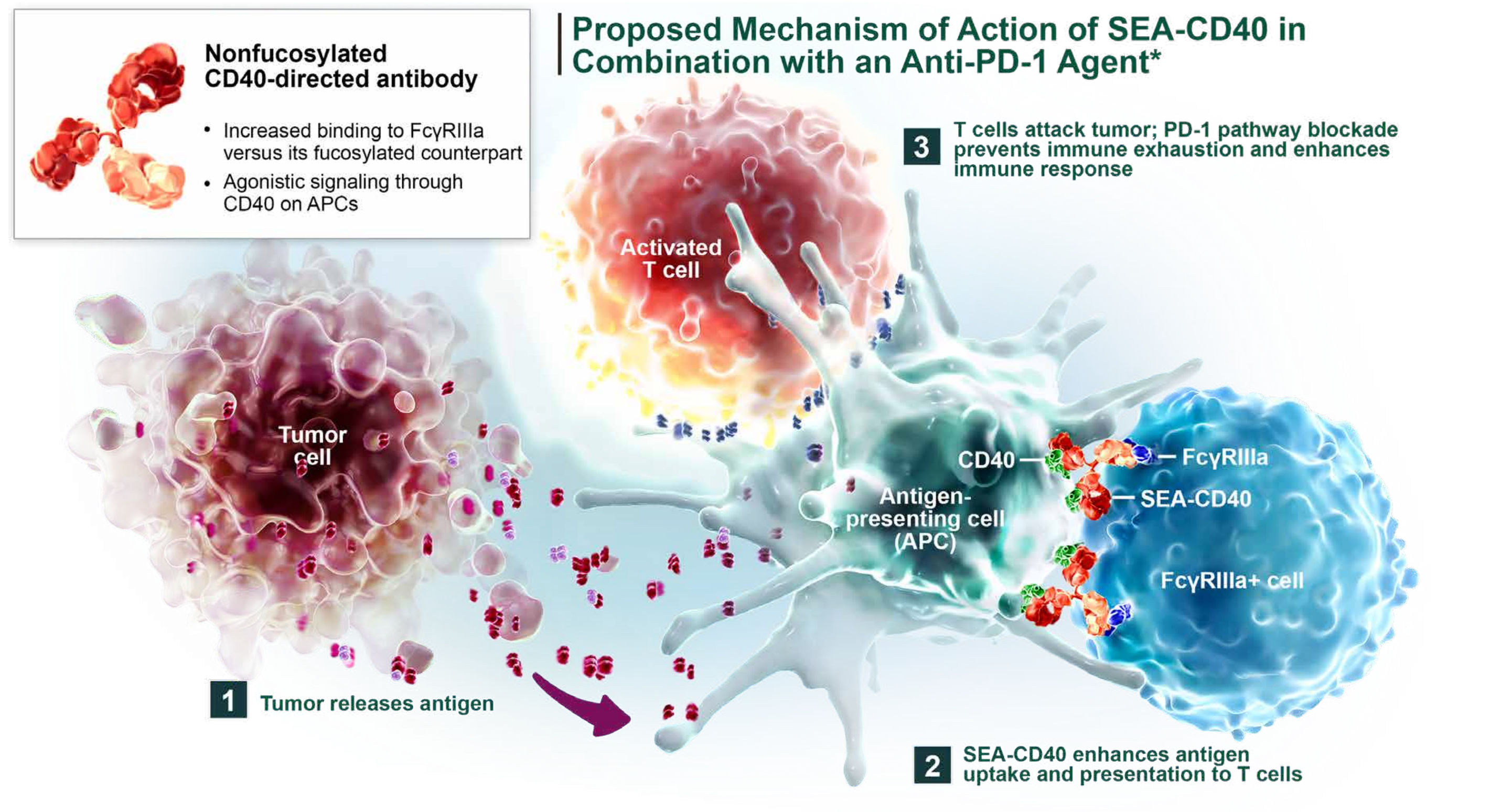
David Lawrence Bajor[1], Martin Gutierrez[2], Gina M. Vaccaro[3], Ashiq Masood[4], Ursa Brown-Glaberman[5], Juneko E. Grilley-Olson[6], Hedy L. Kindler[7], Mark Zalupski[8], Elisabeth I. Heath[9], Sarina Anne Piha-Paul[10], Peigen Zhou[11], Hailing Lu[11], Sahar Ansari[11], Jonathan Hayman[11, 12], Michael W. Schmitt[11], Andrew L. Coveler[12]

[1]Case Western Reserve University/University Hospitals Cleveland Medical Center, Cleveland, OH; [2]Hackensack University Medical Center, Hackensack, NJ; [3]Providence Cancer Institute, Portland, OR; [4]Rush University Medical Center, Chicago, IL; [5]University of New Mexico Comprehensive Cancer Center, Albuquerque, NM; [6]University of North Carolina Lineberger Comprehensive Cancer Center/University of North Carolina Chapel Hill, Chapel Hill, NC; [7]University of Chicago Medical Center, Chicago, IL; [8]University of Michigan, Ann Arbor, MI; [9]Karmanos Cancer Institute, Detroit, MI; [10]University of Texas MD Anderson Cancer Center, Houston, TX; [11]Seagen Inc, Bothell, WA; [12]Seattle Cancer Care Alliance/University of Washington, Seattle, WA

Background

- Patients with metastatic PDAC often are treated with gemcitabine and nab-paclitaxel; however, survival is limited, and more effective regimens are needed[1]
- SEA-CD40 is an investigational, receptor-agonistic, nonfucosylated, humanized IgG1 monoclonal antibody directed to CD40, which is expressed on antigen-presenting cells[2]
- SEA-CD40 binds with increased affinity to FcγRIIIa resulting in enhanced effector function and CD40 agonism, allowing amplification of immune stimulation and antitumor activity[3]
- In preclinical models, the combination of SEA-CD40 and chemotherapy resulted in significant antitumor activity, which was further enhanced with anti-PD1 treatment[3]
- SGNS40-001 is assessing SEA-CD40 as monotherapy and in combination with other agents. Study Part L is assessing SEA-CD40 in combination with gemcitabine, nab-paclitaxel, and pembrolizumab in a PDAC cohort[4,5]

SEA-CD40 Proposed Mechanism of Action


Nonfucosylated CD40-directed antibody
Increased binding to FcγRIIIa versus its fucosylated counterpart
Agonistic signaling through CD40 on APCs
Proposed Mechanism of Action of SEA-CD40 in Combination with an Anti-PD-1 Agent*
3 T cells attack tumor; PD-1 pathway blockade prevents immune exhaustion and enhances immune response
Activated T cell
Tumor cell
CD40
FcγRIIIa
SEA-CD40
Antigen-presenting cell (APC)
FcγRIIIa+ cell
1 Tumor releases antigen
2 SEA-CD40 enhances antigen uptake and presentation to T cells

***SEA-CD40 is an investigational agent, and its safety and efficacy have not been established.**

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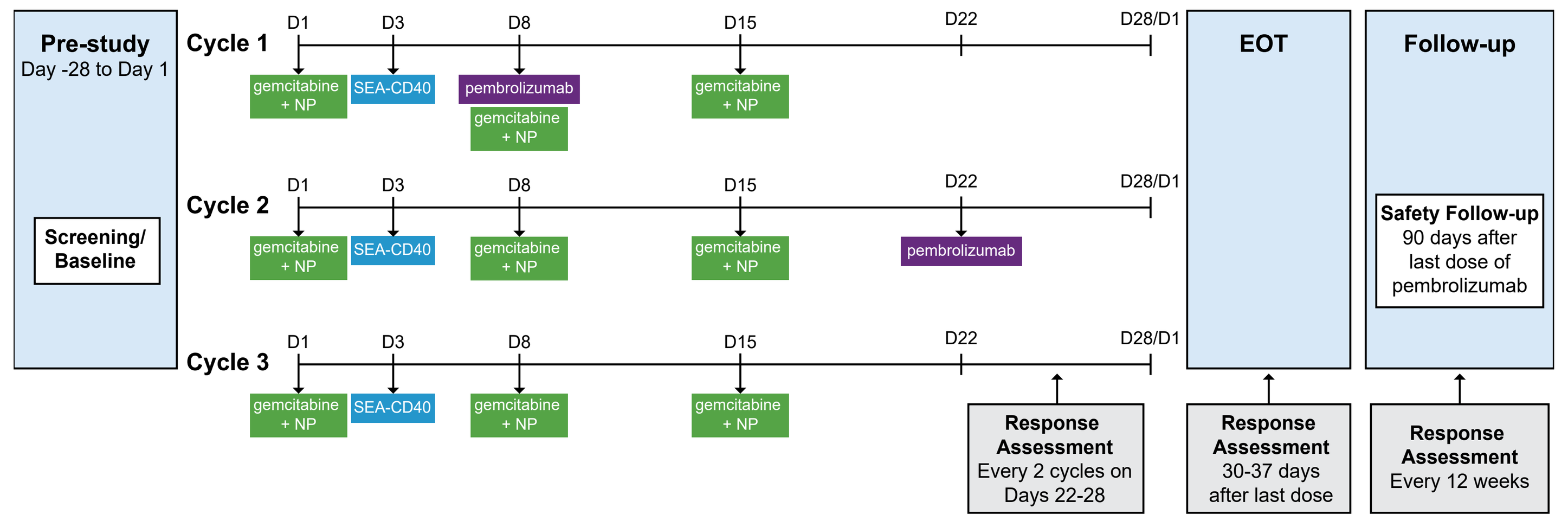
Study Design


Pre-study
Day -28 to Day 1
Screening/ Baseline
Cycle 1
Cycle 2
Cycle 3
D1
D3
D8
D15
D22
D28/D1
gemcitabine + NP
SEA-CD40
pembrolizumab
EOT
Follow-up
Safety Follow-up
90 days after last dose of pembrolizumab
Response Assessment
Every 2 cycles on Days 22-28
Response Assessment
30-37 days after last dose
Response Assessment
Every 12 weeks

- In this ongoing phase 1 study (NCT02376699), Cohort L[a] was to enroll approximately 60 efficacy-evaluable patients, including approximately 40 patients in the dose-finding cohort (20 patients at each dose level) and an additional 20 patients in the dose-expansion cohort at the recommended phase 2 dose[b]
- Key Eligibility Criteria
  - Must have histologically or cytologically confirmed metastatic PDAC not amenable to curative therapy for which patients did not receive previous systemic therapy in the metastatic setting
  - Previous adjuvant or neoadjuvant therapy for non-metastatic PDAC allowed if fully completed >4 months before study treatment
- Endpoints
  - Efficacy: confirmed ORR per RECIST by investigator (primary); ORR per iRECIST by investigator, DCR, DOR, PFS, OS (secondary)
  - Safety: AEs, laboratory abnormalities, DLTs (secondary)
  - PK parameter estimates and ATAs (secondary)

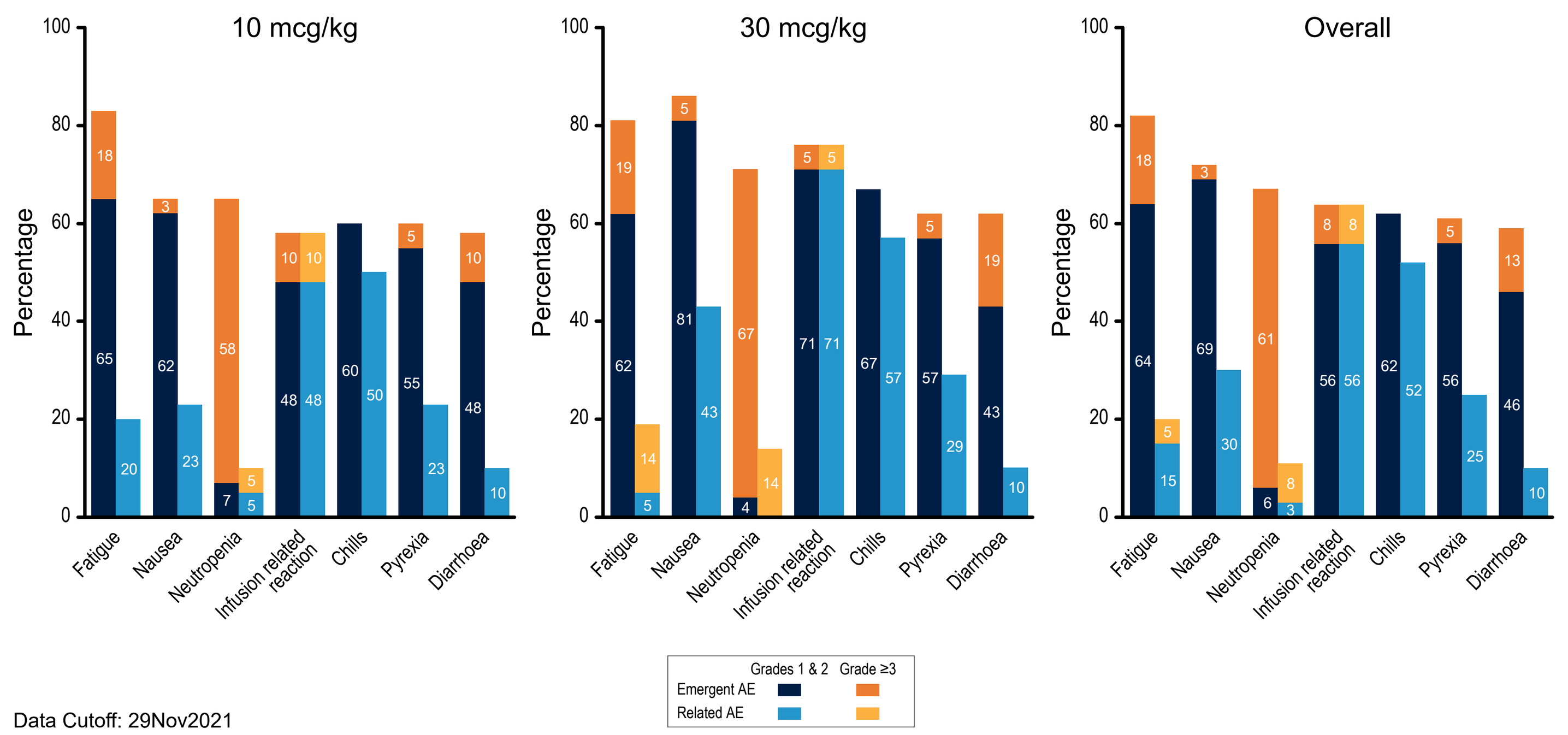
a Patients must be ≥18 years; have an ECOG status ≤1; adequate renal, hepatic, and hematologic function; and measurable disease per RECIST v1.1 criteria.
b Study drug administration (IV): SEA-CD40 10 or 30 mcg/kg on Day 3 every 28 days; Gemcitabine 1000 mg/m² on Days 1, 8, and 15 every 28 days; Nab-paclitaxel 125 mg/m² on Days 1, 8, and 15 every 28 days; Pembrolizumab 400 mg every 42 days starting on Day 8 of Cycle 1. Continued treatment permitted in patients with ongoing clinical benefit. Pembrolizumab to discontinue after ~2 years (18 pembrolizumab treatments).

Demographics and Characteristics at Baseline

Characteristic	10 mcg/kg N=40	30 mcg/kg N=21	Total N=61
Age, median years (range)	66.0 (40–80)	65.0 (41–76)	66.0 (40–80)
Sex, n (%)			
Male	18 (45)	11 (52)	29 (48)
Female	22 (55)	10 (48)	32 (52)
ECOG Performance Status, n (%)			
0	24 (60)	8 (38)	32 (52)
1	16 (40)	13 (62)	29 (48)
Liver Lesion, n (%)			
Yes	24 (60)	16 (76)	40 (66)
No	16 (40)	5 (24)	21 (34)
Received Radiation Therapy, n (%)			
Yes	7 (18)	3 (14)	10 (16)
No	33 (83)	18 (86)	51 (84)
Received Surgery, n (%)			
Yes	9 (23)	5 (24)	14 (23)
No	31 (78)	16 (76)	47 (77)
Received Systemic Therapy, n (%)			
Yes	10 (25)	6 (29)	16 (26)
No	30 (75)	15 (71)	45 (74)

Data Cutoff: 29Nov2021

Overall AEs and AEs Related to Treatment



Data Cutoff: 29Nov2021

- IRRs were the most common AEs considered related to SEA-CD40 and were generally ≤ Grade 2
  - All patients received mandatory pre-medication with H1+H2 antihistamines, acetaminophen, ibuprofen, and anti-emetic of investigator's choice, as well as a controlled infusion rate
- There was a trend toward better tolerability at 10 mcg/kg
- AEs leading to treatment discontinuation:
  - SEA-CD40 10 mcg/kg: immune-mediated lung disease, n=2 (5% of treatment group); septic shock, n=1 (3%)
  - SEA-CD40 30 mcg/kg: colitis, n=1 (5%); portal vein thrombosis, n=1 (5%)

Abbreviations

AE: adverse event; APC: antigen-presenting cell; ATA: antitherapeutic antibody; C: cycle; CI: confidence interval; D: day; DCR: disease control rate; DLT: dose limiting toxicities; DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; EOT: end of treatment; FcγRIII: a receptor on macrophages, natural killer cells, and neutrophils; IgG: Immunoglobulin G; iRECIST: immune Response Evaluation Criteria in Solid Tumours; IRR: immune-related response; mcg: microgram; mg: milligram; NE: not evaluable; NK: natural killer (cell); NP: nab-paclitaxel; ORR: objective response rate; PD-1: programmed cell death protein 1; PDAC: pancreatic ductal adenocarcinoma; PD: progressive disease; PFS: progression-free survival; PK: pharmacokinetic; PR: partial response; OS: overall survival; RECIST: Response Evaluation Criteria in Solid Tumours; SD: stable disease; Treg: T regulatory cells

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1. Von Hoff DD, et al. N Engl J Med 2013; 369: 1691-703.
2. Vonderheide RH. Clin Cancer Res 2007; 13(4): 1083-8.
3. Neff-LaFord H, et al. Abstract 5535; Virtual Meeting II of the American Association for Cancer Research; June 22-24, 2020.
4. Bajor DL, et al. Poster (Abstract TPS451); American Society of Clinical Oncology Gastrointestinal Cancers Symposium Virtual Congress; January 15–17, 2021.
5. Grilley-Olson JE, et al. Poster (Abstract 3093); American Society of Oncology 2018, Chicago, IL, June 1–5, 2018.

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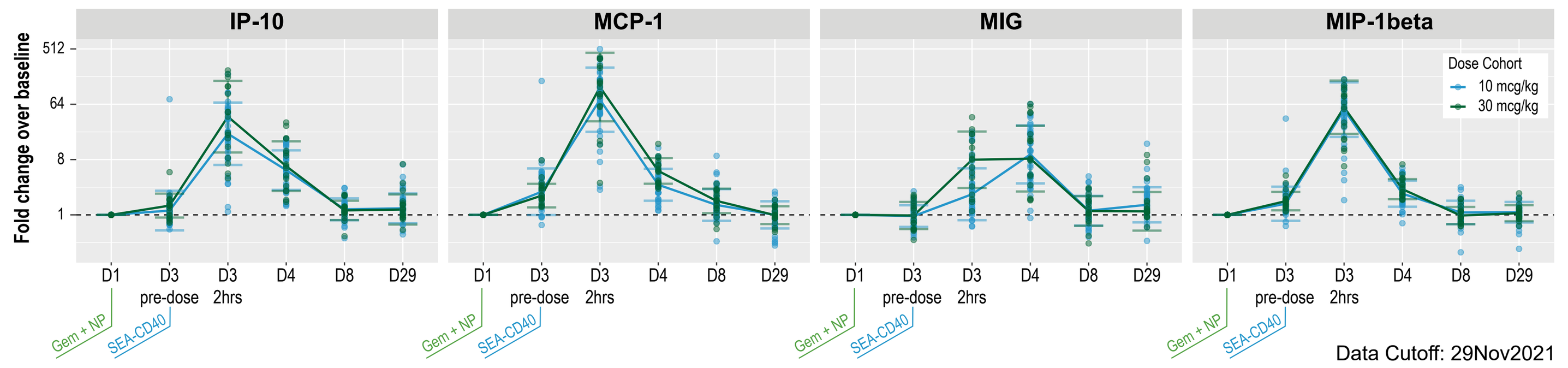
Transient Increase in Circulating Cytokines and Chemokines in Peripheral Blood Associated With Immune Activation and Trafficking After Treatment

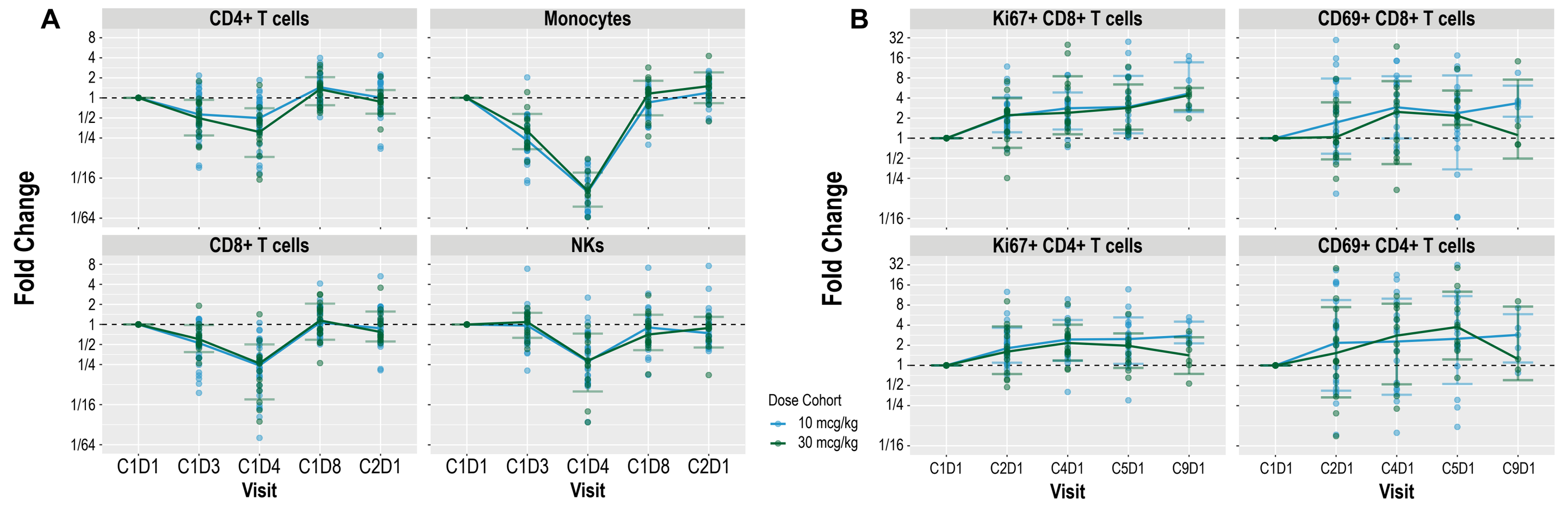


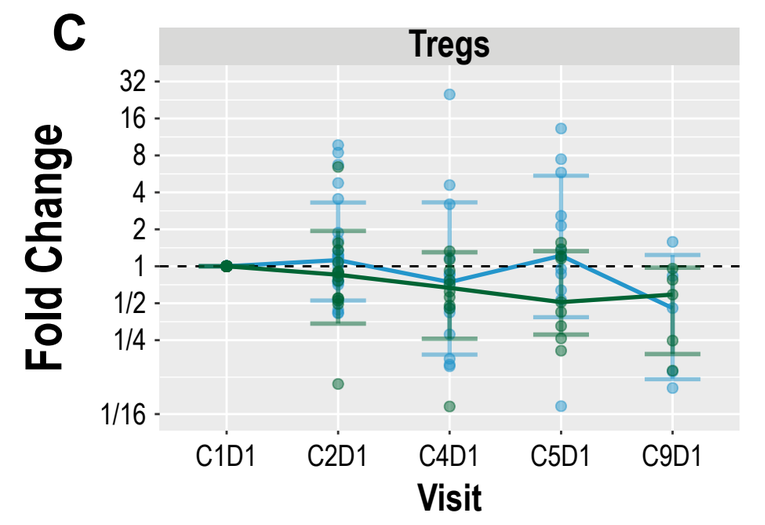
Data Cutoff: 29Nov2021

Fold of change over baseline (C1D1-pre) for each cytokine is shown. One dot represents one patient. A connecting line represents a group median. Error bars represent median±SD. Corrected P-value <0.001 between peak induction and baseline. IP-10 (CXCL10): interferon gamma-induced protein 10; MCP: monocyte chemoattractant protein-1; MIG (CXCL9): monokine induced by interferon-gamma; MIP-1beta: macrophage inflammatory protein-1 beta.

- Patients had transient increases in circulating cytokines and chemokines associated with immune activation and trafficking, as well as increases in markers of activation on peripheral NK cells and T cells
- Similar cytokine induction was observed after SEA-CD40 monotherapy, 4 hours after SEA-CD40 infusion (data not shown)

Changes in Immune Subsets in Peripheral Blood After Treatment Indicates Immune Activation and No Induction of Tregs





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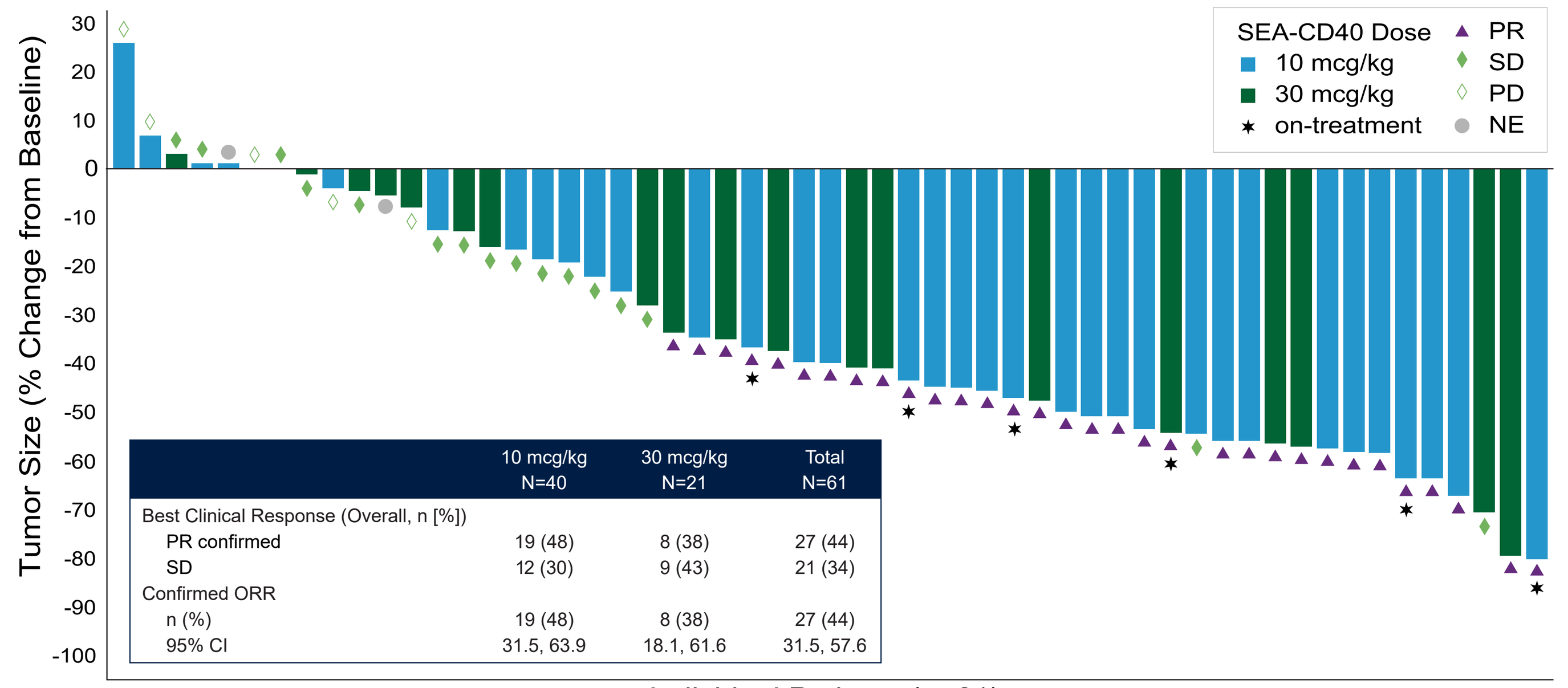
(A) Transient decrease in circulating monocytes, NK, and CD4+ and CD8+ T cells at 24 hour after SEA-CD40 infusion (corrected p-value <0.05). Fold of change over baseline (C1D1) is shown for all parameters. One dot represents one patient. A connecting line represents a group median. Error bars represent median±SD.

(B) Increased expression of activation (CD69) and proliferation (Ki67) markers on circulating CD4+ and CD8+ T cells (corrected p-value <0.05).

(C) No significant change in circulating Treg levels after SEA-CD40. Tregs are defined as CD4+CD25+CD127low/- cells (p-value >0.10).

- There was no difference in activation markers of peripheral immune subsets observed between the two dose levels

Best Percent Change in Tumor Size From Baseline per RECIST v1.1 and Objective Response Rate

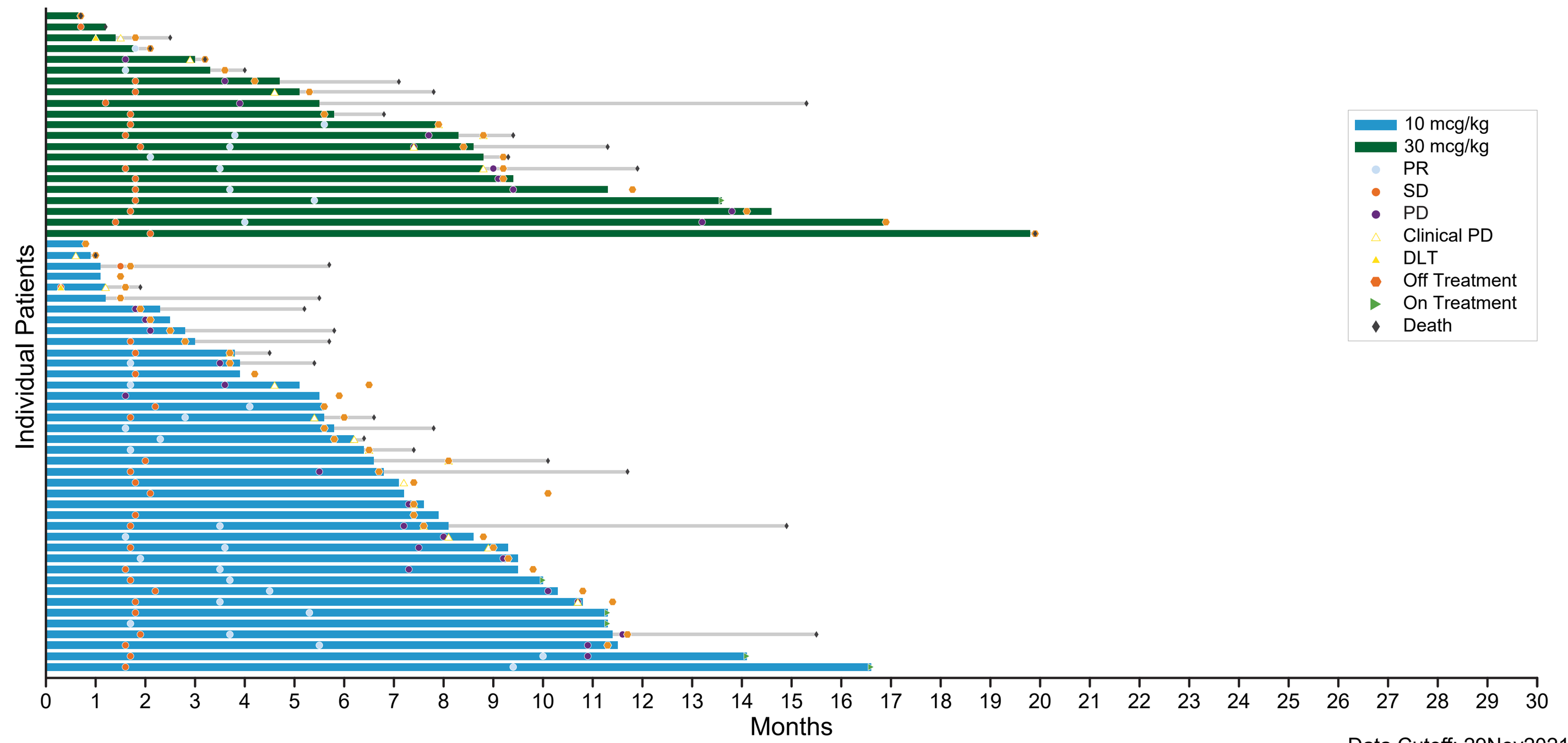


	10 mcg/kg N=40	30 mcg/kg N=21	Total N=61
Best Clinical Response (Overall, n [%])			
PR confirmed	19 (48)	8 (38)	27 (44)
SD	12 (30)	9 (43)	21 (34)
Confirmed ORR			
n (%)	19 (48)	8 (38)	27 (44)
95% CI	31.5, 63.9	18.1, 61.6	31.5, 57.6

Data Cutoff: 29Nov2021

- There were comparable response rates observed at both dose levels

Duration of Treatment



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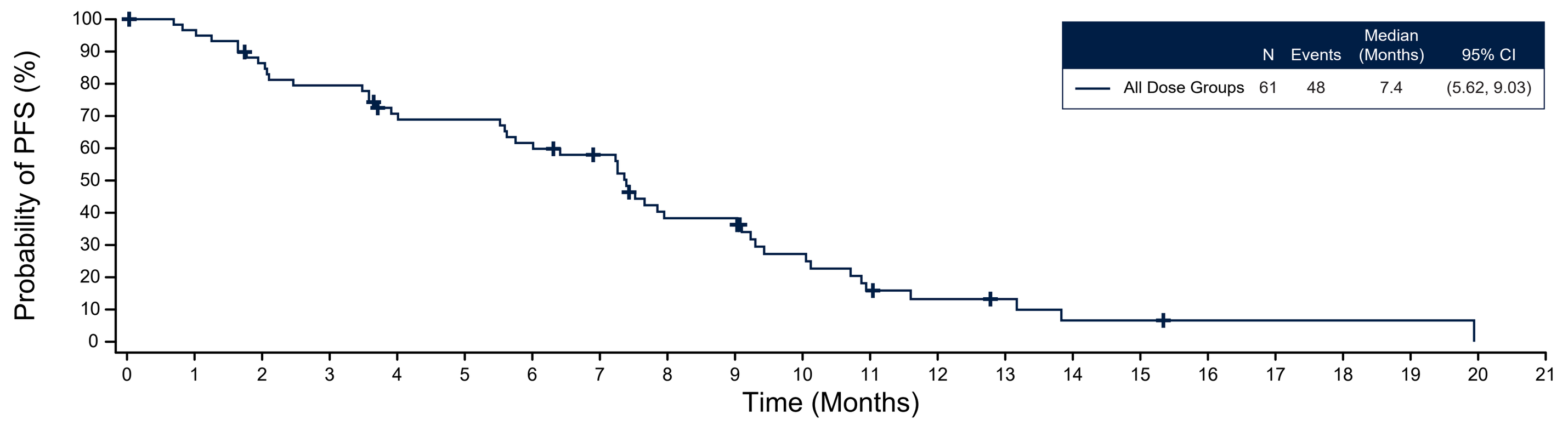
Progression-Free Survival

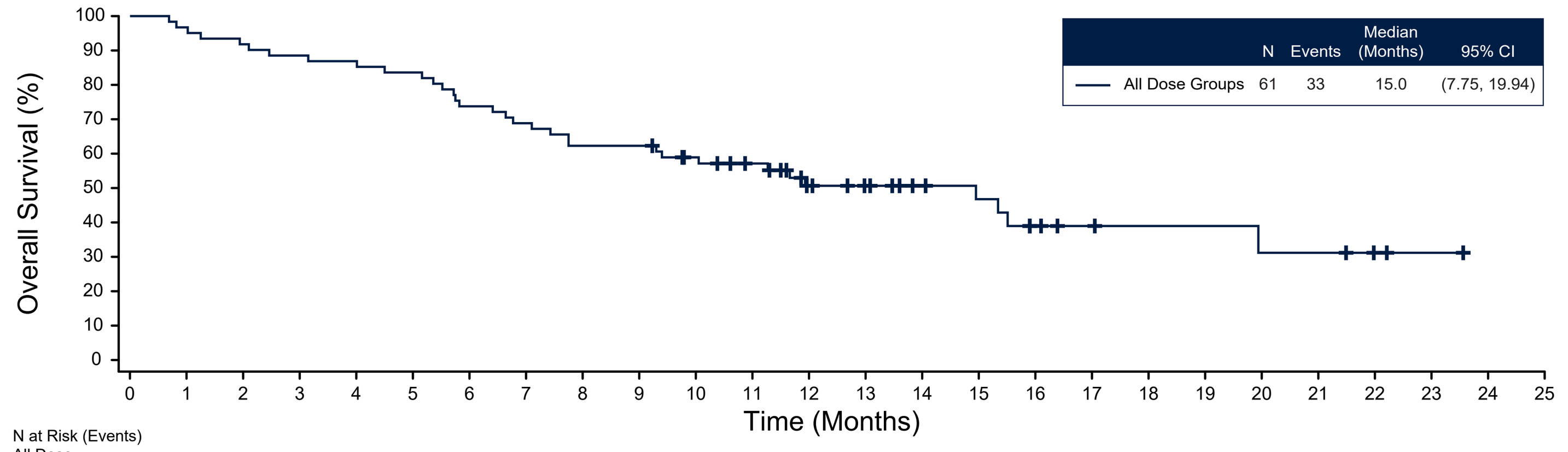


N at Risk (Events)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
All Dose Groups	61(0)	57(2)	50(8)	46(12)	39(17)	38(18)	34(22)	30(24)	19(34)	19(34)	12(39)	7(44)	5(45)	4(45)	2(47)	2(47)	1(47)	1(47)	1(47)	1(47)	0(48)

Median follow-up (months): 10 mcg/kg, 6.6 (range: 0–15.3); 30 mcg/kg, 7.4 (0.7–19.9); total, 6.9 (0–19.9)

Data Cutoff: 29Nov2021

Overall Survival



N at Risk (Events)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
All Dose Groups	61(0)	59(2)	56(5)	54(7)	53(8)	51(10)	45(16)	42(19)	38(23)	38(23)	33(25)	29(26)	21(29)	18(29)	14(29)	12(30)	8(32)	6(32)	5(32)	5(32)	4(33)	4(33)	2(33)	1(33)	0(33)

Median follow-up (months): 10 mcg/kg, 10.7 (range: 0.8–22.2); 30 mcg/kg, 9.4 (0.7–23.6), total: 10.6 (0.7–23.6)

Data Cutoff: 29Nov2021

Conclusions

- SEA-CD40 is an investigational, nonfucosylated, CD40-receptor agonist that potently activates the innate immune system
- Preliminary results demonstrate that SEA-CD40 in combination with gemcitabine, nab-paclitaxel, and pembrolizumab has a tolerable safety profile
- Evidence of immune activation in this study was consistent with the proposed SEA-CD40 mechanism of action
- 10 mcg/kg SEA-CD40 was selected as the recommended phase 2 dose for further development, including an ongoing phase 2 basket trial in lung cancer and melanoma
- Antitumor activity appears encouraging compared to historical chemotherapy outcomes, but additional survival follow-up is needed to determine if there is a plateau in the curve
- This chemoimmunotherapy regimen may warrant further evaluation in a randomized setting

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