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Case report of fatal immune-mediated myocarditis following treatment with davoceticept (ALPN-202), a PD-L1-dependent CD28 costimulator and dual PD-L1/CTLA-4 checkpoint inhibitor, in combination with pembrolizumab

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ABSTRACT

Engagement of programmed death-1 (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) can interfere with the CD28 signaling requisite for T-cell activation. While immune checkpoint inhibitors (ICIs) can relieve this suppression, they are unable to drive CD28 costimulation that may mechanistically contribute to ICI resistance. Thus, CD28 costimulation in the context of checkpoint inhibition may activate immunosuppressed T-cells in the tumor microenvironment. Davoceticept (ALPN-202) is an Fc fusion of a CD80 variant immunoglobulin domain (vIgD) designed to mediate PD-L1-dependent CD28 costimulation while inhibiting the PD-L1 and CTLA-4 checkpoints. PD-L1-restriction of davoceticept's CD28 costimulatory activity may minimize systemic T-cell activation and avoid untoward systemic toxicities. At the same time, preclinical studies have suggested that treatment with davoceticept during PD-1 inhibition may enhance antitumor activity by upregulating PD-L1, potentially synergizing with davoceticept's PD-L1-dependent costimulatory mechanism. This report details two cases of fatal cardiac events following treatment with davoceticept in combination with pembrolizumab (anti-PD-1) in the phase 1 study, NEON-2. Both events occurred in females in their 60s; one with choroidal melanoma and prior immunotherapy, the other with ICI-naïve microsatellite stable colorectal cancer. The clinical courses were fulminant with symptom onset at 2 weeks, followed by rapid decline. Cardiac autopsy from one patient confirmed immune-related myocarditis, and immunosequencing revealed expansion of a single T-cell clone that was not present in the pretreatment tumor. These cases highlight the importance of understanding risk factors that may contribute to immune-related myocarditis and other severe immune-related adverse events when CD28 agonism is targeted in the context of checkpoint inhibition.Trial registration number: NEON-2 (NCT04920383).

INTRODUCTION

Immune checkpoint inhibitors (ICIs) targeting programmed death-1 (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) can activate antitumor T-cells; however, this immune activation can sometimes lead to immune dysregulation and result in serious or fatal immune-related adverse events (irAEs). Approximately 20% of patients receiving anti-PD-1 monotherapy, 30% receiving anti-CTLA-4 monotherapy, and 55% receiving the combination (combo) will experience serious irAEs including dermatitis, colitis, hypophysitis, hepatitis, pneumonitis, nephritis, and myocarditis.[1] Immune-related myocarditis is rare with an incidence between 0.04% and 1.14% but with a mortality rate of up to 50%.[2–7]

METHODS

NEON-2 (NCT04920383) was a multicenter, open-label phase 1 dose escalation trial to study the safety and efficacy of davoceticept in combination with pembrolizumab (anti-PD-1 mAb) that enrolled a total of 29 patients. The NEON-2 protocol is available in online supplemental file 1. The results of NEON-1 (NCT04186637), the single-agent dose escalation of davoceticept, along with NEON-2, are detailed in the accompanying manuscript by Davar *et al*. Plasma cytokine levels were measured by multiplexed immunoassay (Myriad RBM; Austin, Texas, USA). Postmortem gross and microscopic evaluation of cardiac and pretreatment tumor

tissue from case 2 was performed at Emory University (Atlanta, Georgia, USA), and immunohistochemistry for PD-L1 with the 22C3 antibody was conducted at PhenoPath (Seattle, Washington, USA). Adaptive immunosequencing of the CDR3 regions of human T-cell receptor (TCR)β chains was performed (Adaptive Biotechnologies, Seattle, Washington, USA).[8–10]

RESULTS AND DISCUSSION

Case 1

A patient in her early 60s with a history of choroidal melanoma metastatic to the liver, previously treated with ipilimumab (anti-CTLA-4 mAb) and nivolumab (anti-PD-1 mAb) for 10 weeks followed by nivolumab maintenance for an additional 7 weeks, was assigned to a dose regimen of davoceticept 0.3 mg/kg intravenously every 3 weeks and pembrolizumab 400 mg intravenously every 6 weeks. At screening, she had non-specific anterior T wave changes on ECG that were considered clinically insignificant, and normal creatine kinase (CK) 52 U/L (normal range (NR) 20–175). Thyroid-stimulating hormone (TSH) and free T4 were 82.98 mIU/L (NR 0.5–4.8) and 2.83 pmol/L (NR=12–22), respectively, prompting initiation of levothyroxine. The patient received one dose of intravenous davoceticept (0.3 mg/kg)+pembrolizumab (400 mg). 13 days after treatment, she presented with fatigue, body aches, nausea, dehydration, hypotension (blood pressure, BP 88/60), and tachycardia (pulse 108 beats per minute, bpm). Workup suggested cardiogenic shock with N-terminal pro-brain natriuretic peptide (BNP) 6489.9 pmol/L (NR 42.4–7627), troponin T 2.389 µg/L (NR<0.014), and lactic acid 4.0 mmol/L (NR 0.0–2.0). TSH and free T4 were 74 mIU/L (NR 0.3–5.00) and 3.87 pmol/L (NR 7.74–20.64), respectively. ECG showed a new right bundle branch block (BBB) and faint ST elevation in aVR while an echocardiogram demonstrated an ejection fraction (EF) of 27% and basal hypokinesia. Mild pericardial effusion and portal vein thrombosis extending to inferior vena cava were noted on CT. She was started on intravenous heparin and levothyroxine dose was increased, she was transferred to the intensive care unit, started on pressors (epinephrine, dobutamine), steroids (methylprednisolone 1 g/day), and empiric antibiotics (vancomycin, cefepime). Infectious workup including SARS-CoV2 was negative. Despite some initial improvement in EF while on pressors, she developed encephalopathy, deteriorating further and ultimately expired 4 days later, 17 days after treatment with davoceticept and pembrolizumab. Autopsy was not performed due to pandemic-related restrictions; the cause of death was assessed as cardiogenic shock with probable immune-related myocarditis.

Case 2

A patient in her early 60s with ICI-naïve microsatellite stable metastatic colorectal adenocarcinoma, and a history of non-ST elevation myocardial infarction, pulmonary embolism on oral anticoagulation, and type 2 diabetes mellitus, was assigned to a dose regimen of davoceticept 0.1 mg/kg intravenously every 3 weeks and pembrolizumab 400 mg intravenously every 6 weeks. Screening and baseline cardiac testing demonstrated occasional premature ventricular contractions, and moderate ST depression by ECG, considered clinically insignificant and EF 60% by echocardiogram. Screening laboratory values were CK 66 U/L (NR 30–223 U/L), troponin-I 0.006 µg/L (NR 0.003–0.014) BNP 97 ng/L (NR<99), creatinine 97.26 µmol/L (NR 53.05–106.08), all within NR. Baseline TSH and free T4 were within normal limits. The patient received a single dose of intravenous davoceticept (0.1 mg/kg) and pembrolizumab (400 mg). BNP was asymptomatically elevated to 176 ng/L on day 1 but returned to normal levels (59 ng/L) by day 8. On day 13, she presented to clinic reporting fatigue, nausea, and left arm pain for 2–3 days. She was hypotensive (BP 78/61), and ECG showed new junctional tachycardia and atrial fibrillation, later evolving to a new left BBB, bigeminy, prolonged QTc, bizarre wide QRS complexes, and tachycardia. She had elevated creatinine 194.5 µmol/L, CK 18 733 U/L, BNP 225 ng/L, troponin-I>25 µg/L, and TSH 5.93 mIU/L (NR 0.45–5.33). Intravenous amiodarone was initiated. Echocardiogram showed severe septal hypokinesis concerning for myocardial infarction. Repeat troponin-I and BNP were >25 µg/L and 210 ng/L, respectively. Cardiac catheterization demonstrated 40%–50% distal left main coronary artery stenosis, 70%–80% left circumflex artery ostial stenosis, subtotal AV groove circumflex disease with dampening, non-obstructive diffuse left anterior descending artery disease, and overall EF 40%–50%; and an ostial right coronary artery drug-eluting stent was placed. Amiodarone was discontinued and pressors were started for hypotension. For presumptive immune-mediated myocarditis (IMC), she was started on high dose corticosteroids (1 mg/kg methylprednisolone) and mycophenolate mofetil (1 g two times per day). However, given a poor prognosis, she elected not to further escalate care and passed away that same day, 15 days after administration of davoceticept and pembrolizumab. Cardiac autopsy demonstrated IMC with lymphocytic infiltration and patchy macrophage inflammation, as evidenced by CD68 staining (figure 1A–D). PD-L1 expression was also observed in the cardiac tissue, with 75% of these cells staining positive (the majority of which had a scoring of 3+, reflective of high PD-L1 expression) (figure 1E).

DISCUSSION

Both cases detailed here occurred in female patients in their early 60s, who presented with constitutional symptoms, including fatigue and nausea, approximately 2 weeks following their first and only doses of davoceticept and pembrolizumab. Clinical presentation was associated with dramatic elevations in troponin and analytes correlating with severe outcomes in IMC in the published literature.[11] These findings aligned with earlier reports that IMC is more common in females, that fatal

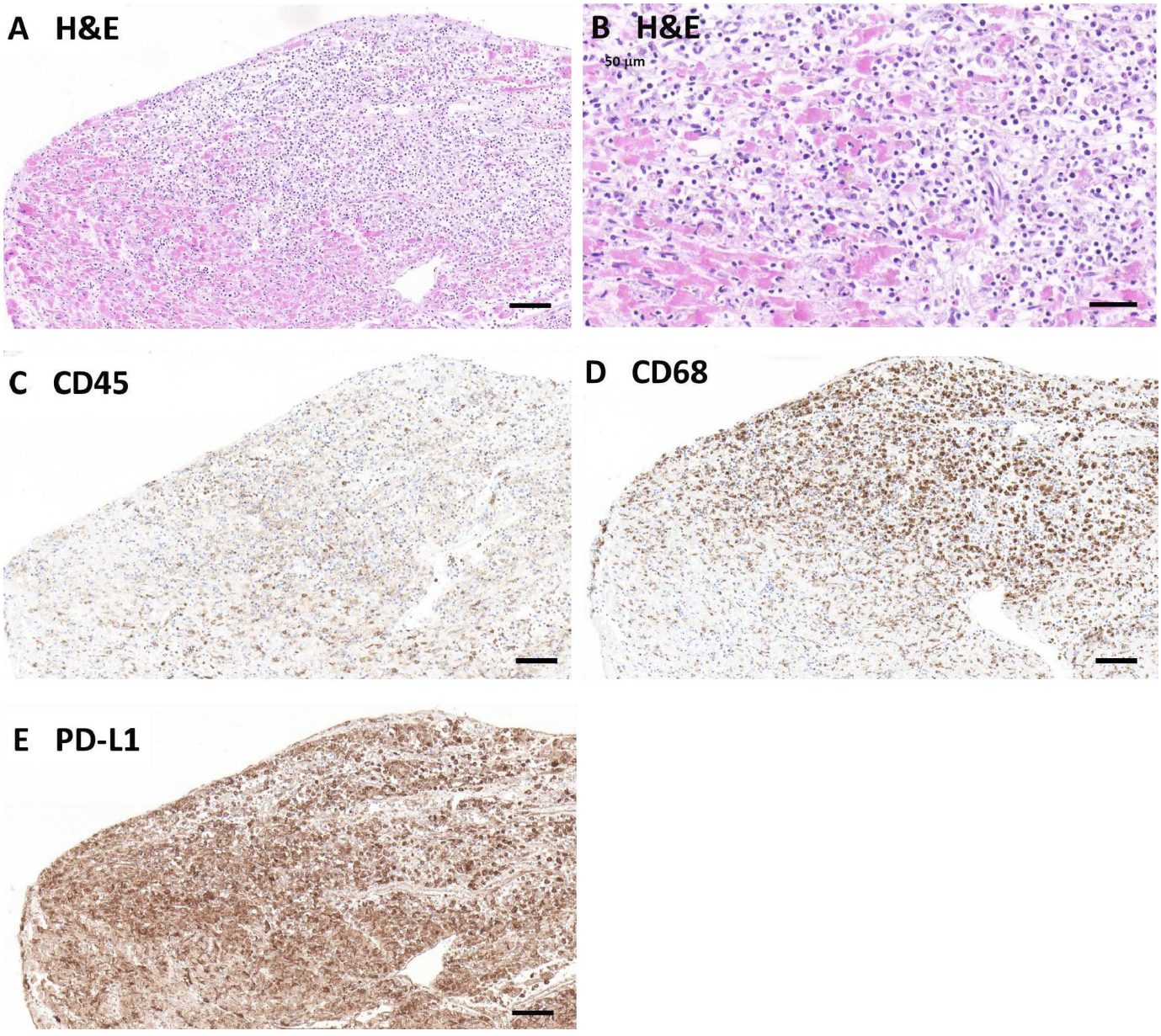
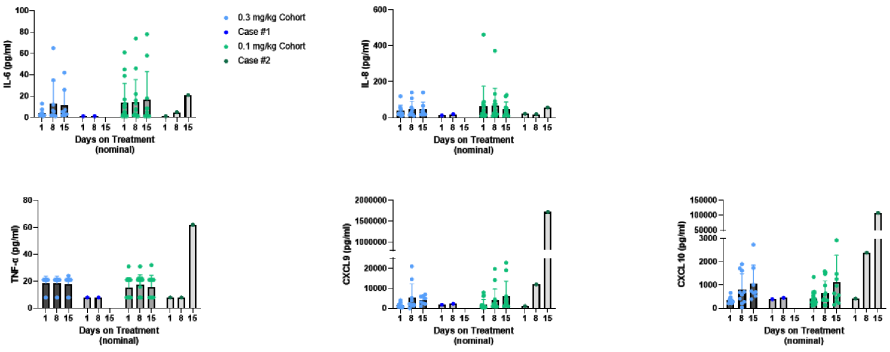


Figure 1 Autopsy findings of immune-mediated myocarditis in case 2. Cardiac tissue from the left ventricle was assessed for inflammation using H&E staining (A–B), CD45 (C), CD68 (D), as well as by IHC for PD-L1 expression using the 22C3 antibody (E). Scale bar shown is 100 µm in all panels except B where it is 50 µm. H&E revealed severe lymphocytic myocarditis with patchy infiltration of macrophages. IHC revealed that 75% of these cells stained positive for PD-L1, the majority of which had a scoring of 3+ (range, 0–3+), reflective of high PD-L1 expression. IHC, immunohistochemistry; PD-L1, programmed death ligand -1.

myocarditis was more common with ICI combination therapy compared with monotherapy, and that fatal irAEs due to combo immunotherapy occur early (around 2 weeks) after treatment initiation.[7 12]

Despite case similarities, there were also notable differences. Case 1 was ICI experienced; case 2 was ICI-naive. Case 2 had a marked increase in interferon γ-inducible chemokines (CXCL9 and CXCL10) in the blood at days 8 and 15, as well as tumor necrosis factor-alpha (TNFα) at day 15 relative to other patients in the study receiving the same doses of study drugs (figure 2A) and was accompanied by a macrophage and lymphocytic infiltrate in the cardiac tissue (figure 1A–D). CXCL9 and CXCL10 are critical to the expansion of intratumoral CD8+T cells in the context of PD-1 blockade.[13] In addition, these chemokines have been implicated in heart failure and myocarditis.[14–16] Interestingly, neither patient displayed increased interleukin (IL)-6 or IL-8, which are cytokines routinely elevated in cytokine release syndrome.[17 18] Immunosequencing analysis of the cardiac and pretreatment tumor tissue from case 2 identified 111 enriched clones, with 106 being exclusive to the cardiac compared with the pretreatment tumor. Of these, one TCR sequence accounted for 12% of the TCR repertoire, suggestive of a

A



B

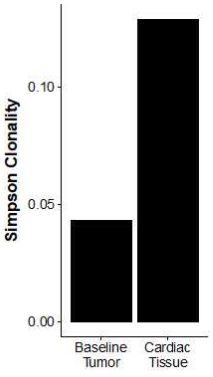
Immunosequencing Summary

Sample	N	T Cells	Clonotypes	T-cell Fraction	Simpson Clonality	Frequency of Most Abundant Clones
Baseline Tumor	1	9,080	5,877	0.079	0.043	0.027
Cardiac Tissue	1	48,263	14,297	0.474	0.129	0.12

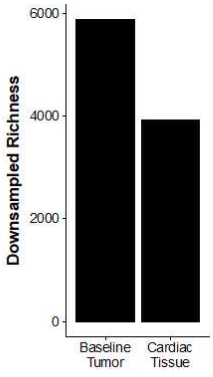
[1]Immunosequencing of the CDR3 regions of human TCRβ chains was performed using the Adaptive Immunosequencing Assay.

[2]Metrics shown here are calculated on productive rearrangements only (in-frame sequences with no stop codon that can produce a functional receptor).

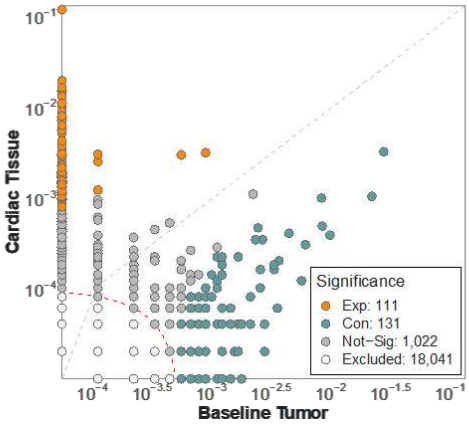
C



D



E



F

Top Clone in Cardiac Tissue Sample

	-Gene	J-Gene	Template Count	Frequency
CASSFSGELFF+TCRBV07-09+TCRBJ02-02	CASSFSGELFF	TCRBV07-09	TCRBJ02-02	5802	0.1202163

Figure 2 Cytokine and clonotypic changes in patients treated with davoceticept+pembrolizumab who developed immune-related myocarditis. (A) Serum cytokine levels shown were assessed in pre-dose blood draws at day 1, day 8 and day 15. Cytokines from cases 1 and 2 are shown in dark blue and dark green solid circles, respectively. Day 1 and day 8 cytokines from other patients in NEON-2 (exclusive of cases 1 and 2) receiving a single dose of davoceticept on a once weekly and every 3 weeks regimen and day 15 cytokine from patients who received a single dose of davoceticept on every 3 weeks regimen are shown in light blue (0.3 mg/kg) and light green solid circles (0.1 mg/kg). (B) Immunosequencing of the TCRβ CDR3 region in the baseline tumor and cardiac tissue samples. The higher clonality (C) and lower richness (D) in the cardiac tissue sample indicates a skewing of the TCR repertoire toward the most abundant clone. To quantify any enrichment of baseline tumor clones in the cardiac tissue sample, we conducted a differential abundance analysis in (E) between the two samples. The orange circles represent the clones enriched in the cardiac tissue, and the teal circles represent the clones enriched in the baseline tumor sample. Furthermore, the orange circles on the y-axis represent cardiac enriched clones only identified in the cardiac sample. Clonal enrichment was calculated according to a binomial distribution framework. In brief, cardiac or baseline tumor enriched clones were identified by a two-sided test of the null hypothesis that the count of one clone will be the same in both the baseline tumor and cardiac tissue samples. The Benjamini-Hochberg procedure was used to control false discovery rate at 0.01. In (F), the table identifies the abundant clone found in the cardiac tissue sample but not in the baseline tumor sample. This abundant clone is found on the y-axis in the top left corner of (E). TCR, T-cell receptor.

single immunodominant clone, rather than broad non-specific expansion. Axelrod *et al* have linked IMC development to the expansion of α-myosin-specific T-cells[19]; however, the BioID of the predominant, cardiac-specific clone from case 2 did not overlap with the V or J gene sequences from clones they described (figure 2B–F).

The reported incidence of IMC is 1%; however, 6.9% (2 of 29) of NEON-2 patients experienced fatal cardiac AEs, one with suspected and one with biopsy-confirmed IMC. Notably, there were no cardiac treatment-related adverse events (TRAE) observed with davoceticept monotherapy.[20] Prominent PD-L1 staining was present in the cardiac tissue of case 2 (figure 1E); however, we cannot conclude if the PD-L1 expression may have precipitated the immune-related myocarditis or may have resulted from cardiac inflammation. It has been suggested that the development of IMC may be related to an expansion of inflammatory macrophages in an IFN-γ and CXCL9/CXCL10-dependent fasion.[15] In this context, checkpoint inhibition in concert with CD28 costimulation may have resulted in IFN-γ-induced immune activation that led to fatal cardiac toxicity.

CONCLUSION

Together, these data suggest that CD28 agonism in the presence of PD-1 inhibition may lead to aberrant or autoreactive T-cell activation resulting in unacceptable toxicities, including fatal immune-related cardiac toxicities.

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Competing interests LC: Consultant: Janssen, AstraZeneca, Pliant Therapeutics, CDR-Life, Actuate TherapeuticsSRC: Research Support (institutional): Alpine Immune SciencesKL: Nothing to disclose. FS: Grants or Contracts: NIH P01 (Deciphering LKB1-associated immunotherapy resistance in lung adenocarcinoma). NL: Support for the present manuscript (institutional): Alpine Immune Sciences; Consulting Fees: SK Life Sciences; Research Funding (institutional): Alexo Therapeutics, Ascentage Pharma, BeiGene, Constellation Pharmaceuticals, Forty Seven, Loxo, Macrogenics, Merck, Pfizer, Regeneron, Apexian Pharmaceuticals, Coordination Therapeutics, Symphogen, CytomX Therapeutics, InhibRx, Incyte, Jounce Therapeutics, Livzon, Northern Biologics, Tesaro, Innovent Biologics, LAM Therapeutics, Ikena, Celgene, Shattuck Labs, Alpine Immune Sciences, Genmab, Odonate, Mersana, Seagen, Alpine Biosciences, Astellas Pharma, Celgene, Helsinn, Therapeutics, Ikena Oncology, Lilly, Sapience Therapeutics, Epizyme, Gilead, Glaxo Smith Kline, Tizona, Servier, Alkermes, KSQ, Repare Therapeutics, Biosplice/Samumed, Sapience Therapeutics, SK Life Sciences, Janssen, Arcus, Artios, BioNTech SE, Alkermes/Mural OncologyAE: Employee of Alpine Immune Sciences; Holds stock options in Alpine Immune Sciences; Support for attending meetings: Alpine Immune Sciences; Patents planned, issued or pending: Tempest Therapeutics, University of CaliforniaHL: Former employee of Alpine Immune Sciences; Holds stock or stock options in Alpine Immune SciencesJS: Employee of Adaptive Biotechnologies; Holds stock in Adaptive Biotechnologies. HT: Support for present manuscript: Biostatistician supporting work on the manuscript; Employee of Alpine Immune Sciences; Holds stock options in Alpine Immune SciencesMJC: Employee of Merck Sharp & Dohme, a subsidiary of Merck & Co., Rahway, New Jersey, USA; Owns stock in Merck & Co. SLP: Employee of Alpine Immune Sciences; Holds stock or stock options in Alpine Immune Sciences. AN: Employee of Alpine Immune Sciences; Holds stock options in Alpine Immune SciencesDD: Support for present manuscript: Alpine Immune Sciences; Grants/Research Support (institutional): Arcus, CellSight Technologies, Immunocore, Merck, Regeneron Pharmaceuticals, Tesaro/GSK. Consulting Fees: ACM Bio, Ascendis Pharma; Clinical Care Options (CCO), Gerson Lehrman Group (GLG), Merck, Medical Learning Group (MLG), Xilio Therapeutics. Payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing or educational events: Castle Biosciences. Patents planned, issued or pending: US Patent 63/124,231, "Compositions and Methods for Treating Cancer", December 11, 2020 US Patent 63/208,719, "Compositions and Methods For Responsiveness to Immune Checkpoint Inhibitors (ICI), Increasing Effectiveness of ICI and Treating Cancer", June 9, 2021.

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