Peripheral Pharmacodynamic Effects of Ociperlimab in Combination With Tislelizumab in Patients With Advanced Solid Tumors: AdvanTIG-105 Phase 1 Dose-Escalation Study

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Conclusions

Pharmacodynamic assessments in the AdvanTIG-105 dose-escalation study demonstrated reduced total Treg frequency at higher doses and downregulation of TIGIT on Treg, CD4+, and CD8+ T cells in peripheral blood following multiple ociperlimab doses. Total CD4+ and CD8+ T-cell frequencies were unaffected within the first cycle of ociperlimab and tislelizumab dosing.

Induced cytokine release of IL12/23p40, CCL4, and CXCL10 at C1D8 and IFNγ and TNFα at C2D1 suggest enhanced proinflammatory effects of myeloid cells and enhanced immune response upon ociperlimab monotherapy and in combination with tislelizumab.

The pharmacodynamic observations support the potential mechanism of action of ociperlimab as an Fc-competent anti-TIGIT monoclonal antibody.

BACKGROUND

- T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domain (TIGIT) is a co-inhibitory, immune checkpoint receptor that is upregulated on T cells and natural killer cells in multiple solid tumors, which can inhibit anticancer immune responses
- Ociperlimab (BGB-A1217) is a novel, humanized monoclonal antibody that binds to TIGIT with high affinity and specificity, and has demonstrated competent binding with C1q and all Fcγ receptors while inducing antibody-dependent cellular cytotoxicity
- AdvanTIG-105 is a phase 1 study of ociperlimab in combination with tislelizumab, an anti-PD-1 antibody, in patients with advanced solid tumors. The safety, pharmacokinetics, and preliminary antitumor activity results in the AdvanTIG-105 dose-escalation study were reported at ASCO 2021. The preliminary efficacy of a PD-L1-positive non-small cell lung cancer cohort in the dose-expansion study was presented at WCLC 2022
- Here we report the pharmacodynamic biomarker data derived from human peripheral blood in the AdvanTIG-105 dose-escalation study

METHODS

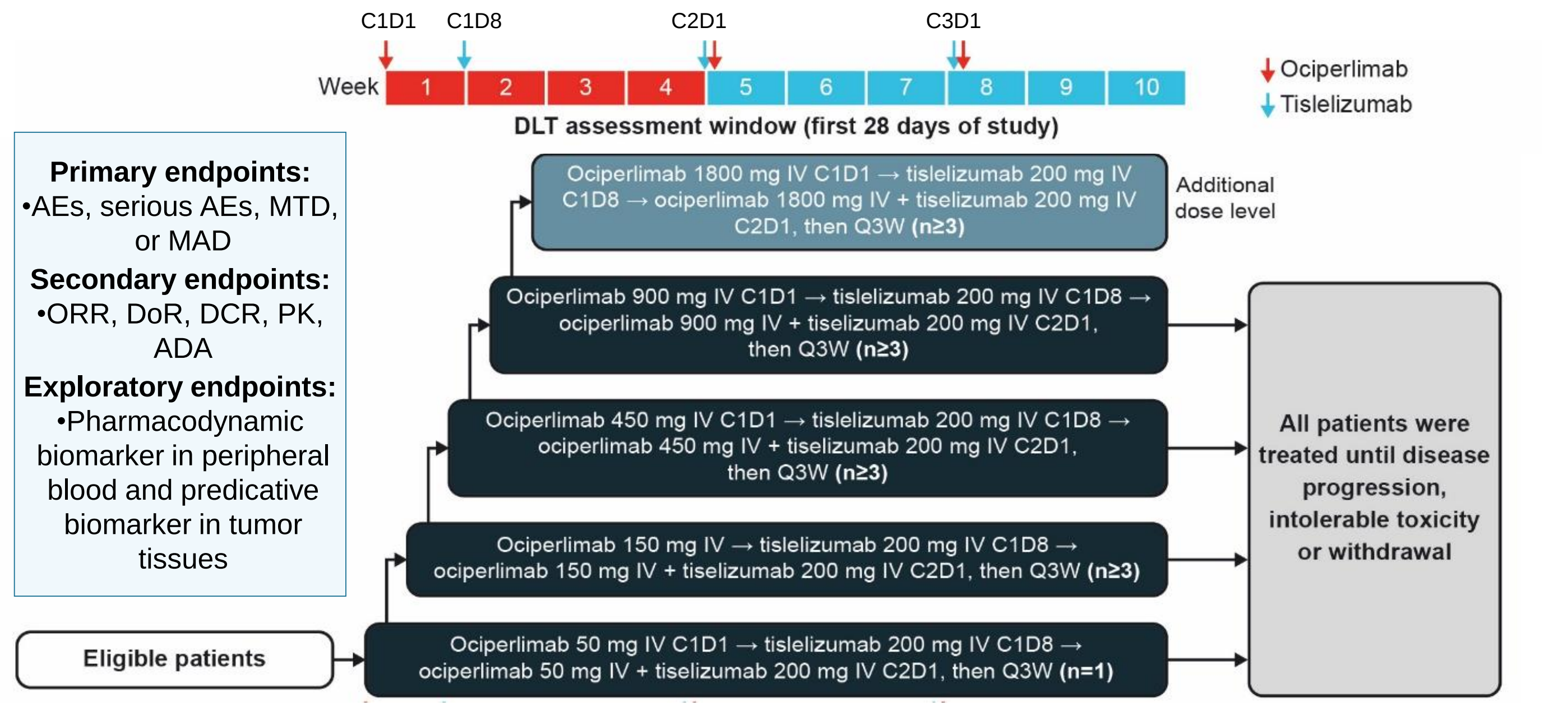
Study Design and Patients

- A phase 1 dose-escalation study was conducted in 32 patients with advanced, metastatic, unresectable solid tumors for which standard therapy was ineffective, intolerable, or unavailable (clinicaltrials.gov: NCT04047862; **Figure 1**)

Pharmacodynamic Assessments

- Peripheral blood samples were collected at specified timepoints and analyzed by flow cytometry to monitor changes in total and TIGIT-expressing immune cell subsets including Tregs, CD8+, and CD4+ T cells, before and after treatment
- Data from 450-, 900-, and 1800-mg cohorts were analyzed for trend change in total and TIGIT+ Treg, CD8+, and CD4+ T cells after dosing
- Plasma samples were tested using Meso Scale Discovery V-plex panels to assess the cytokine/chemokine release upon treatment
- *P* values comparing cytokine induction at C1D8 and C2D1 with baseline were descriptive

Figure 1. AdvanTIG-105 Dose-Escalation Study Design



DLT assessment window (first 28 days of study)

Primary endpoints:
•AEs, serious AEs, MTD, or MAD
Secondary endpoints:
•ORR, DoR, DCR, PK, ADA
Exploratory endpoints:
•Pharmacodynamic biomarker in peripheral blood and predicative biomarker in tumor tissues

Eligible patients

Ociperlimab 50 mg IV C1D1 → tislelizumab 200 mg IV C1D8 → ociperlimab 50 mg IV + tiselizumab 200 mg IV C2D1, then Q3W **(n=1)**

Ociperlimab 150 mg IV → tislelizumab 200 mg IV C1D8 → ociperlimab 150 mg IV + tiselizumab 200 mg IV C2D1, then Q3W **(n≥3)**

Ociperlimab 450 mg IV C1D1 → tislelizumab 200 mg IV C1D8 → ociperlimab 450 mg IV + tiselizumab 200 mg IV C2D1, then Q3W **(n≥3)**

Ociperlimab 900 mg IV C1D1 → tislelizumab 200 mg IV C1D8 → ociperlimab 900 mg IV + tiselizumab 200 mg IV C2D1, then Q3W **(n≥3)**

Ociperlimab 1800 mg IV C1D1 → tislelizumab 200 mg IV C1D8 → ociperlimab 1800 mg IV + tiselizumab 200 mg IV C2D1, then Q3W **(n≥3)**

Additional dose level

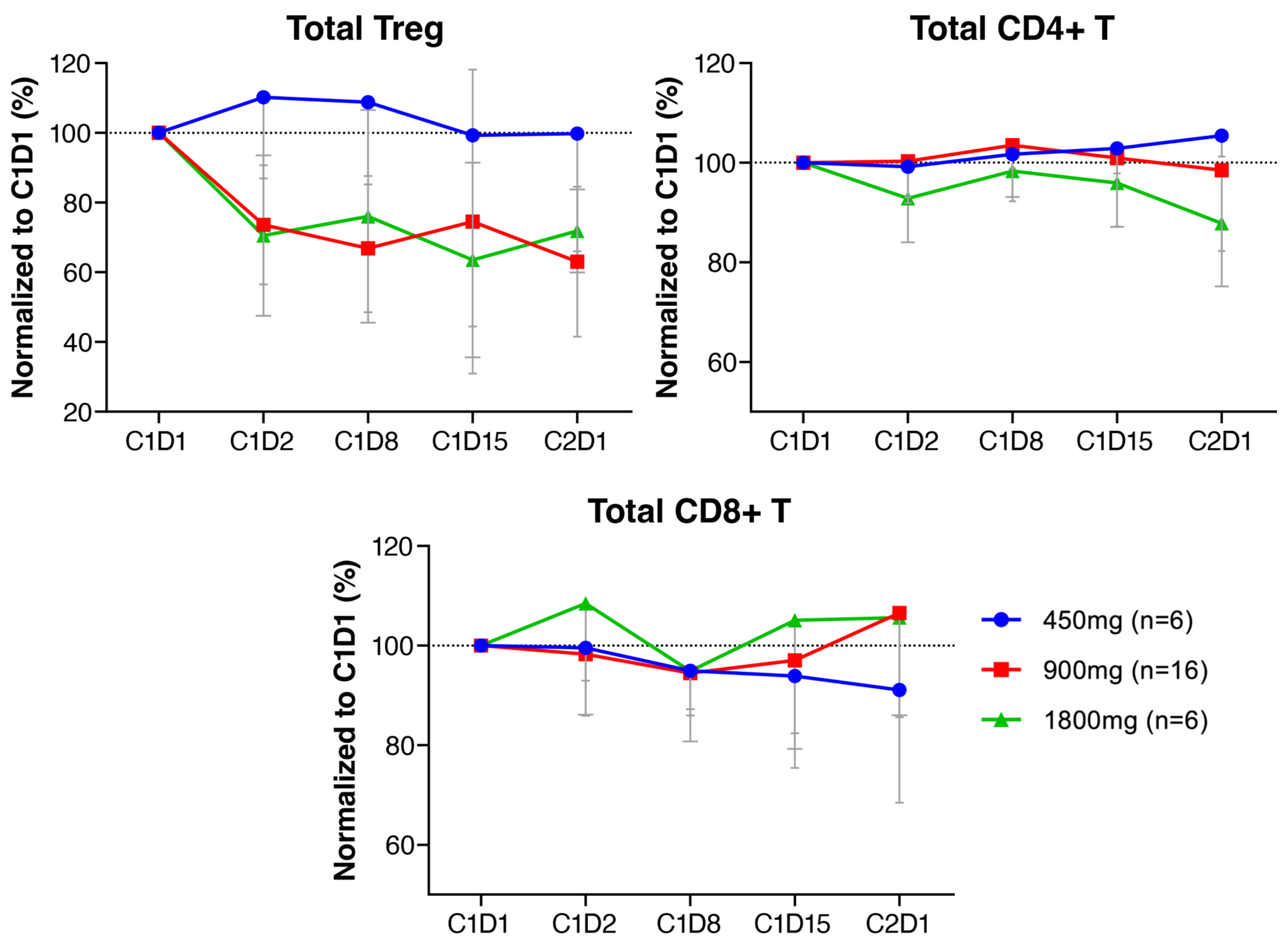
All patients were treated until disease progression, intolerable toxicity or withdrawal

Abbreviations: ADA, antidrug antibody; AEs, adverse events; C, cycle; D, day; DCR, disease control rate; DLT, dose-limiting toxicity; DoR, duration of response; IV, intravenous; MAD, multiple ascending dose; MTD, maximum tolerated dose; ORR, objective response rate; PK, pharmacokinetics; Q3W, every 3 weeks.

RESULTS

- Total Treg frequency decreased over time following a higher dose (900 mg and 1800 mg), but not at a lower dose (450 mg) of ociperlimab (**Figure 2**)
- No differences in total CD4+ and CD8+ T-cell populations were found across doses

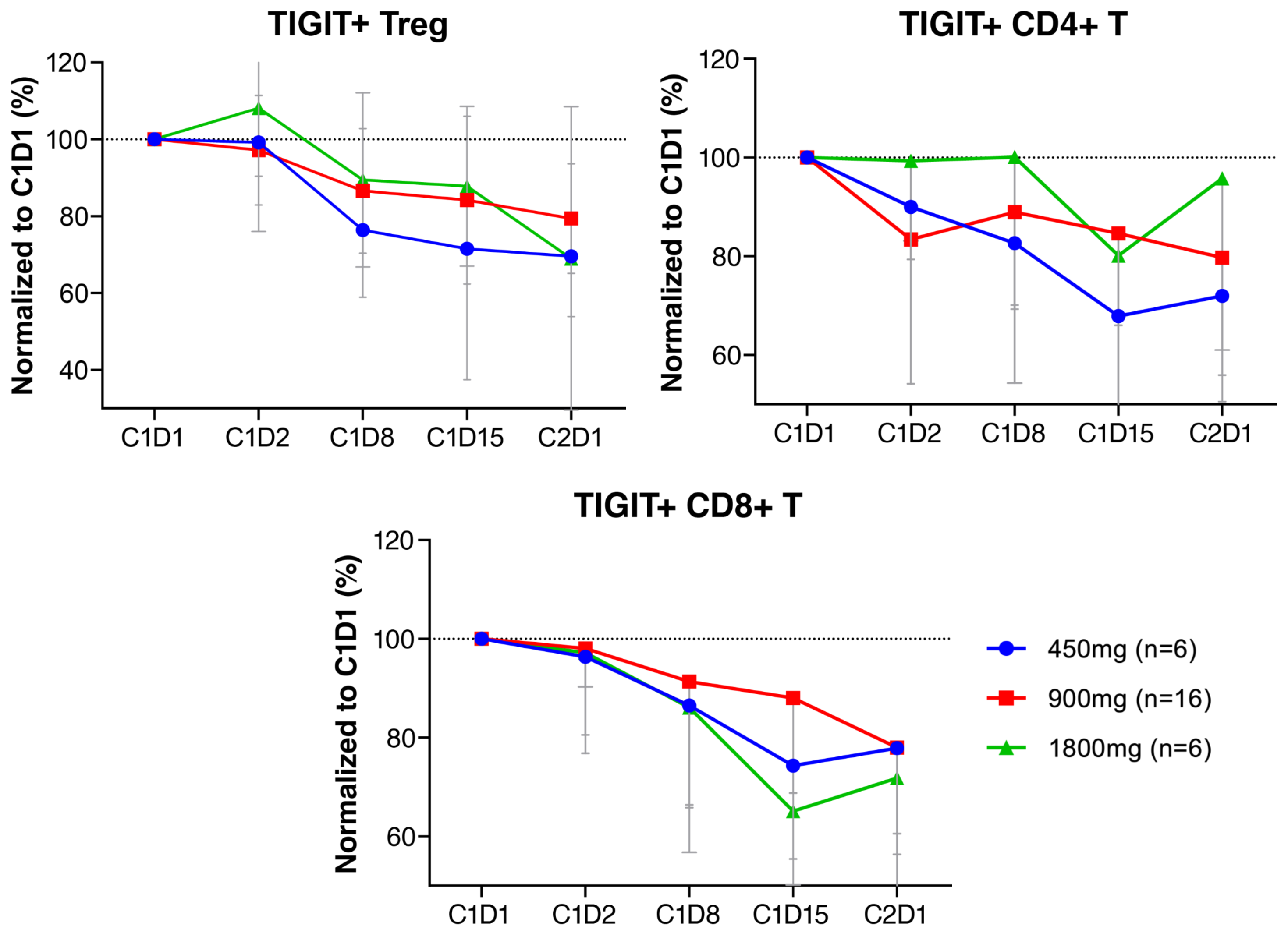
Figure 2. Treg Frequency Was Reduced Following Ociperlimab Treatment at Higher Doses



Normalized to baseline. Mean and SD are shown.
Abbreviations: C, cycle; D, day.

- TIGIT downregulation was observed on blood Treg, CD8+, and CD4+ T cells at C1D8 after ociperlimab monotherapy with multiple doses (**Figure 3**)
- The reduced TIGIT expression was sustained within the first treatment cycle

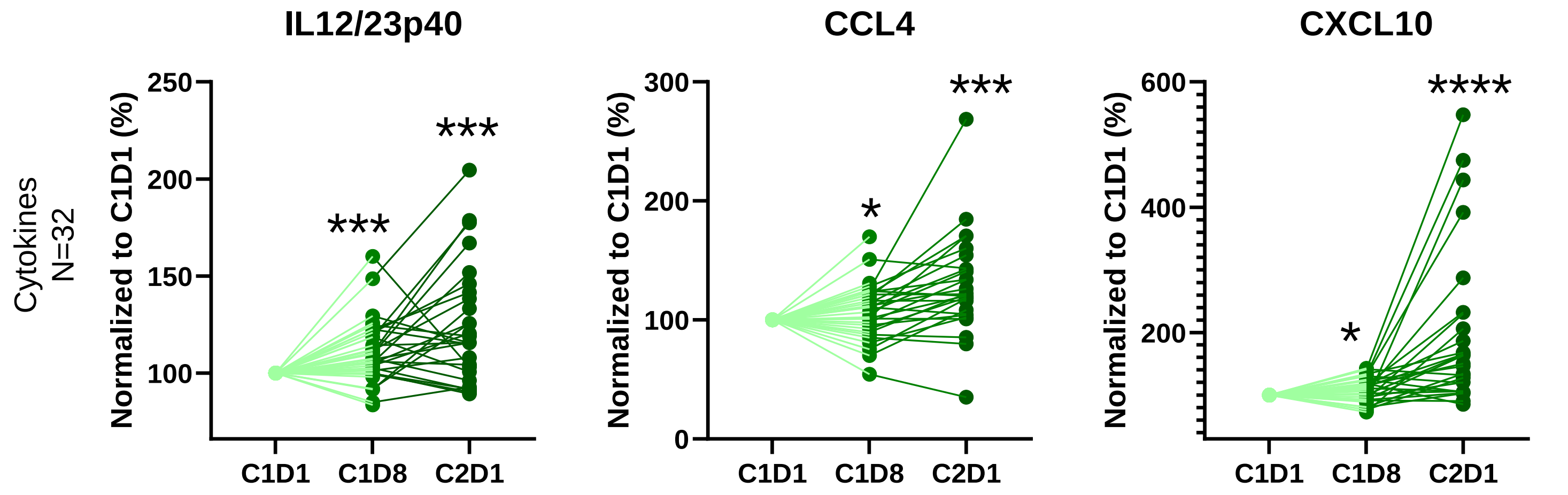
Figure 3. TIGIT Was Downregulated in Blood Treg, CD8+, and CD4+ T Cells After Dosing



Normalized to baseline. Mean and SD are shown.
Abbreviations: C, cycle; D, day.

- Proinflammatory cytokines/chemokines, IL12/23p40, CCL4, and CXCL10, primarily derived from myeloid cells, were enhanced at C1D8 after ociperlimab treatment and in C2D1 after combination with tislelizumab (**Figure 4**)

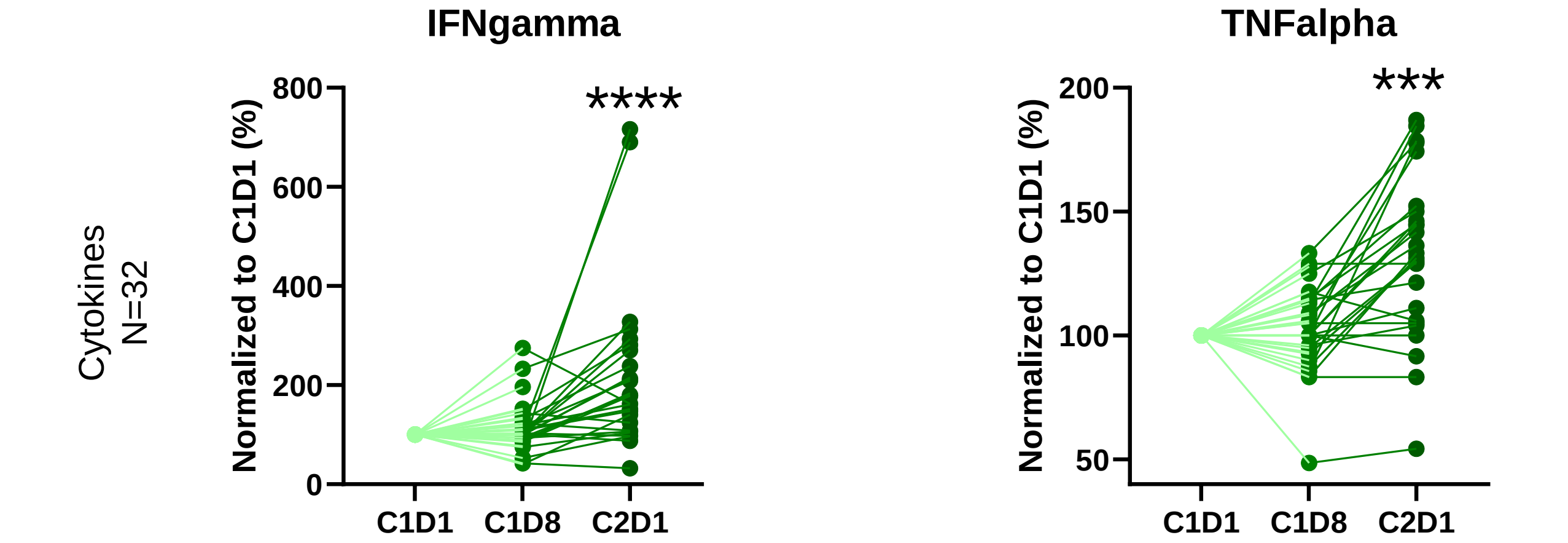
Figure 4. Proinflammatory Cytokines/Chemokines Were Induced at C1D8 After Ociperlimab Treatment



Assessment of differences in medians for cytokines between two groups was done by paired Wilcoxon Ranked-Sum test. (*$P<0.05$, **$P<0.01$, ***$P<0.001$, ****$P<0.0001$).
Abbreviations: C, cycle; D, day.

- IFNγ and TNFα release in plasma was significantly induced at C2D1 but not at C1D8
- The enhanced IFNγ and TNFα release indicate enhanced effector function of immune cells after ociperlimab/tislelizumab combination treatment (**Figure 5**)

Figure 5. Enhanced IFNγ/TNFα Release Was Observed at C2D1 After Ociperlimab/Tislelizumab Treatment



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Abbreviations: C, cycle; D, day.

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Disclosures

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