CHS-114, an Anti-CCR8 Cytolytic Monoclonal Antibody Demonstrates Selective Intratumoral Treg Depletion and Favorable Immune Remodeling in Participants With Advanced Solid Tumors

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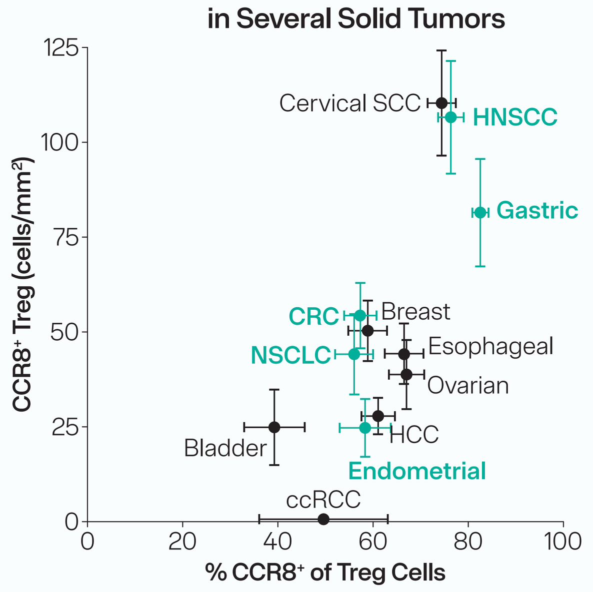
INTRODUCTION

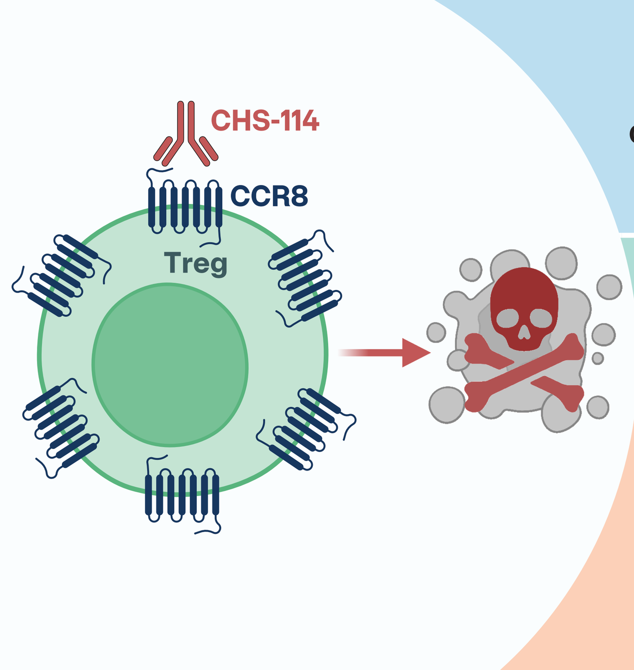
- Intratumoral regulatory T cells (itTregs) are associated with resistance to cancer therapy, including programmed cell death protein 1 (PD-1) inhibitors.
- C-C motif chemokine receptor 8 (CCR8) is a G-protein-coupled receptor that is preferentially expressed on highly immunosuppressive tumor-infiltrating Tregs.[1,2]
- Selective depletion of CCR8⁺ itTregs aims to improve cancer therapy and avoid autoimmunity associated with broad Treg depletion.[3,4]
- CCR8⁺ itTregs are prevalent in a broad range of solid tumors including head and neck squamous cell carcinoma (HNSCC), gastric cancer (GC), and colorectal cancer (CRC).
- CHS-114 is a selective, cytolytic anti-CCR8 monoclonal antibody with enhanced effector function (afucosylated) and no off-target binding.[5]
- CHS-114 has the potential to overcome immune suppression within the tumor microenvironment (TME) by eliminating the suppressive Treg cells and recruiting effector T cells, turning cold tumors to hot, and enhancing antitumor immunity when combined with other immuno-oncology agents such as the anti-PD-1 antibody toripalimab.[6]
- An ongoing Phase 1 (NCT05635643), single-agent and toripalimab (tori) combination dose escalation/expansion study is evaluating CHS-114 in advanced solid tumors including HNSCC. Additionally, a study evaluating CHS-114 in upper gastrointestinal cancers (GC, gastroesophageal junction [GEJ], esophageal adenocarcinoma [EAC]), esophageal squamous cell carcinoma (ESCC), and CRC (NCT06657144) recently began enrolling study participants (NCT06657144).
- CHS-114 has demonstrated an acceptable safety profile to date and antitumor activity in HNSCC.

CCR8⁺ Tregs Are Enriched in Several Solid Tumors



Density (y-axis) and frequency (x-axis) of CCR8⁺ Tregs (of total Tregs) in tumor microarrays from 12 types of solid tumors evaluated using a multiplex immunofluorescence (mIF) assay. Tumor types in which clinical benefit has been observed with anti-CCR8 antibodies (CHS-114-101 study or competitor trials) are **bolded in green**. For evaluating CCR8⁺ Tregs, CCR8 and FOXP3 staining was performed.

CHS-114 Is a Selective, Cytolytic Anti-CCR8 Monoclonal Antibody



Antibody Characteristics
- High affinity to CCR8 (K_D = 502 pm)
- Effector function enhanced: afucosylated for potent ADCC and ADCP activity*
- Highly selective with no off-target binding**
- Targeted therapy: "Bind and Kill" via CCR8 to deplete intratumoral Tregs

Non-Clinical Studies
- Robust CCR8⁺ Treg depletion in in vitro and in vivo studies[5]
- Tumor growth inhibition in hCCR8 knock-in murine model[5]
- Disease linkage: high CCR8⁺ Treg density observed in a majority of solid tumors

Clinical Studies
- CCR8⁺ Tregs are associated with poor prognosis and cancer therapy resistance (including PD-1 inhibitors [PD-1i]).
- Partial response in 4L PD-1 refractory HNSCC in combination with toripalimab[7]
- No dose-limiting toxicities (DLTs) during dose escalation with monotherapy or in combination treatment with toripalimab
- Robust Treg depletion and increased CD8⁺ T cells in the TME (on-treatment) as monotherapy and in combination with toripalimab

*ADCC = antibody-dependent cellular cytotoxicity; ADCP = antibody-dependent cellular phagocytosis. **Off-target binding was evaluated on a retrogenix screen against ~5500 extracellular/secreted proteins. Illustration created with BioRender.com.

METHODS

- This is a Phase 1, first-in-human, open-label single-agent and combination dose trial to evaluate CHS-114 in patients with advanced solid tumors and HNSCC (NCT05635643).
- Here we present updated interim clinical biomarker data from the HNSCC expansion cohort for CHS-114 monotherapy (Arm 1b) and the toripalimab combination (Arm 2) study; enrollment for Arm 3 is ongoing.

Complete — **Arm 1a: Monotherapy Dose Escalation**
BOIN design
2L+ solid tumors
Evaluated 7 dose levels
DL1; n = 1
DL2-7; n = 3 or 4
Clinical cutoff date: 24 Jan 2025

Complete — **Arm 1b: Monotherapy Dose Expansion / Biopsy Cohort**
BOIN design
2L+ HNSCC
CHS-114 DL-A
CHS-114 DL-B
*paired biopsy cohort

Complete — **Arm 2: Combination Therapy Dose Escalation**
3+3 design
2L+ HNSCC
CHS-114 DL-A + toripalimab 240 mg Q3W
CHS-114 DL-B + toripalimab 240 mg Q3W

Ongoing — **Arm 3: Combination Therapy Dose Optimization**
2L HNSCC
R in 1:1
N = 20 → Arm 3a: CHS-114 DL-A + toripalimab 240 mg Q3W
N = 20 → Arm 3b: CHS-114 DL-B + toripalimab 240 mg Q3W
(one arm may be expanded up to N = 40)
→ **Phase 2**

- 20 heavily pre-treated participants
- No DLTs reported up to dose level (DL) 7 (1200 mg)
- Stable disease observed in NSCLC, OC, PDAC, EC (~ 1 yr), and CRC
- Disease control rate: 47%
- Pharmacologically active doses identified based on safety and immune biomarkers (≥ DL5)

- 20 evaluable HNSCC participants (13 monotherapy, 7 in combination)
- Acceptable safety profile and no DLTs with and without toripalimab
- Intratumoral biomarker data (Arm1b): Robust CCR8 Treg cell depletion and increase in CD8 T cell numbers
- 1 partial response in CHS-114/toripalimab combo (4L; PD-1i refractory)

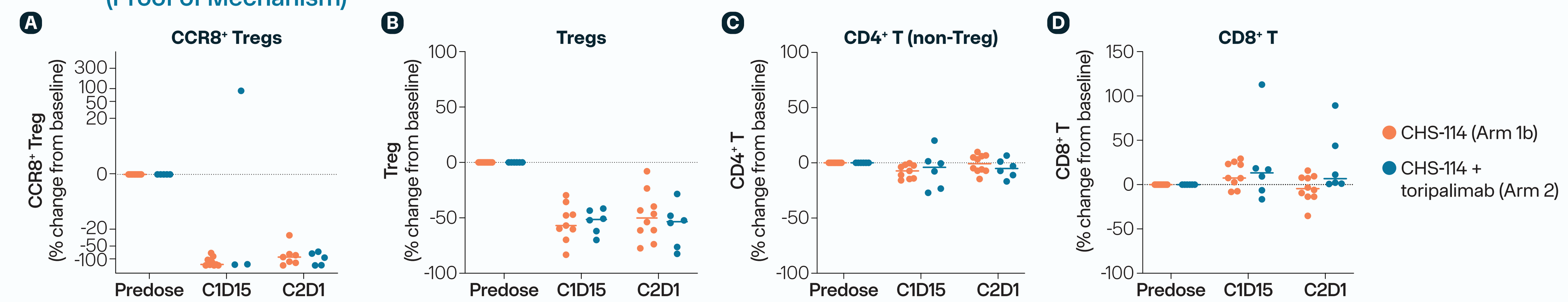
Additional Platform Study
- Upper gastrointestinal tumors (GC, GEJ, EAC), ESCC, and CRC (NCT06657144)
- Toripalimab and other combinations

RESULTS

CHS-114-Mediated Robust and Selective Peripheral CCR8⁺ Treg Depletion in HNSCC Participants Treated With and Without Toripalimab

Robust Target Depletion (Proof of Mechanism)

CHS-114 Spares Non-CCR8⁺ Tregs, CD4⁺ T, and CD8⁺ T Cells (Proof of Selectivity)

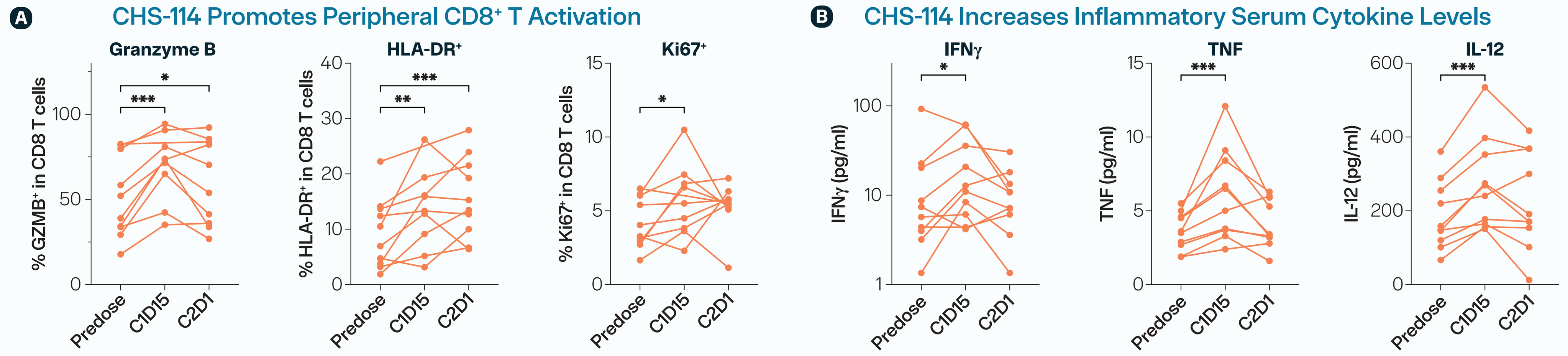


CCR8⁺ Tregs and other immune cells in PBMCs of HNSCC participants were evaluated by Cytek flow cytometry at indicated time points in CHS-114-101 monotherapy dose expansion and toripalimab combination dose escalation cohorts. **(A)** Robust CCR8⁺ Treg depletion in the periphery was observed through Cycle 1. CHS-114 treatment with and without toripalimab led to a decrease in the subset of Tregs, while preserving broader Treg **(B)**, non-Treg CD4⁺ **(C)**, and CD8⁺ **(D)** T cell populations, confirming the specificity of CHS-114 for CCR8⁺ Tregs. Tregs: CD127^{lo} CD25^{hi} within CD3⁺ CD4⁺ T cells; non-Treg CD4 and CD8⁺ T: CD56⁻ FOXP3⁻ CD3⁺. n = 10 (CHS-114) and n = 6 (CHS-114 + toripalimab) at baseline.

CHS-114 Administration Promotes Peripheral Immune Activation in HNSCC Participants

A CHS-114 Promotes Peripheral CD8⁺ T Activation

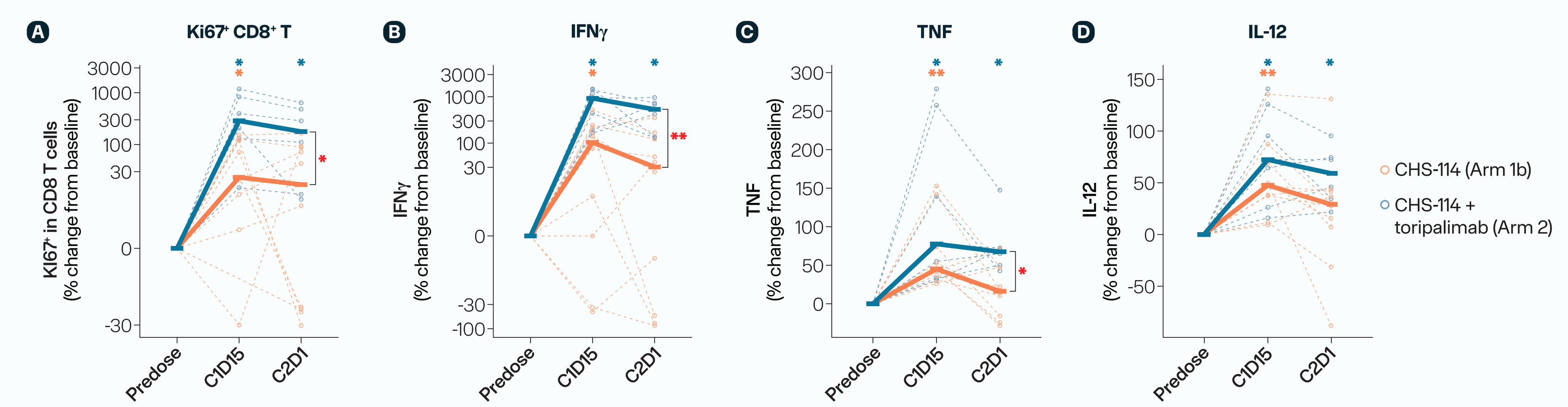
B CHS-114 Increases Inflammatory Serum Cytokine Levels



Immune profiling of PBMC using Cytek flow cytometry **(A)** and serum cytokine analysis by MSD **(B)** at indicated time points for participants enrolled in CHS-114-101 HNSCC monotherapy dose expansion. **(A)** Increases in CD8⁺ T cell cytotoxicity (granzyme B [GZMB]), activation (HLA-DR), and proliferation (Ki67) compared with pretreatment levels were observed. **(B)** Increases in serum inflammatory and Th1 cytokines (IFNγ, TNF, IL-12) were also observed. The data are consistent with CHS-114 promoting peripheral immune activation in HNSCC participants. Participants with longitudinal samples are plotted (C1D1 [predose], C1D15, and C2D1); n = 10 at baseline. Statistical tests: Mixed-effect analysis (A) and paired t-test (B).

Synergistic Activity of CHS-114 and Toripalimab on Peripheral Immune Activation in HNSCC Participants

CHS-114-Mediated Peripheral Immune Activation Is Further Augmented by Toripalimab



Ki67⁺ CD8⁺ T	C1D15	C2D1
CHS-114	23%	25%
CHS-114 + tori	302%	198%

IFNγ	C1D15	C2D1
CHS-114	108%	31%
CHS-114 + tori	922%	549%

TNF	C1D15	C2D1
CHS-114	45%	16%
CHS-114 + tori	78%	68%

IL-12	C1D15	C2D1
CHS-114	48%	29%
CHS-114 + tori	72%	59%

Immune profiling of PBMC using Cytek flow cytometry **(A)** and serum cytokine analysis by MSD **(B, C, D)** at indicated time points for participants enrolled in CHS-114-101 HNSCC monotherapy dose expansion (orange) or toripalimab (tori) combination dose escalation cohorts (blue). CHS-114 with toripalimab mediated a robust increase in **(A)** CD8⁺ T cell proliferation (Ki67) and **(B-D)** Th1 inflammatory cytokines that was sustained through the dosing cycle. The data support the combination of CHS-114 with toripalimab to enhance immune responses (orange vs blue). Participants with longitudinal samples are plotted (C1D1 [predose], C1D15, and C2D1); thick solid lines (median values); thin dashed lines (individual participants). Asterisks (orange [CHS-114]; blue: [CHS-114 + tori]) denote significant percent changes from C1D1 (one-sample Wilcoxon). Red asterisks denote significant differences between arms at C2D1 (Wilcoxon test). Tables show median percent change from baseline (n = 10 for CHS-114 and n = 6 for CHS-114 + tori at baseline).

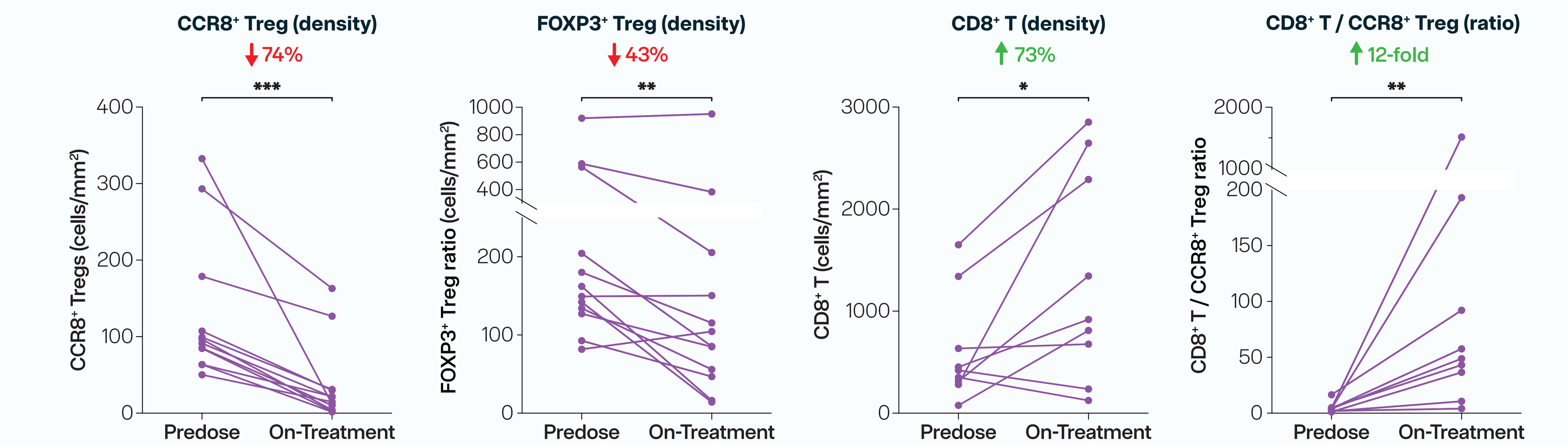
Abbreviations: 2L/4L = second/fourth line; BOIN = Bayesian optimal interval design; C1D1 = Cycle 1 Day 1, predose; C1D15 = Cycle 1 Day 15; C2D1 = Cycle 2 Day 1, predose; CCR8 = chemokine receptor 8; ccRCC = clear cell renal cell carcinoma; CRC = colorectal cancer; DL = dose level; DLT = dose-limiting toxicity; EC = endometrial cancer; GC = gastric cancer; HCC = hepatic cell carcinoma; HNSCC = head and neck squamous cell carcinoma; itTreg = intratumoral regulatory T cell; mIF = multiplex immunofluorescence; MSD = Meso Scale Discovery; NSCLC = non-small cell lung cancer; OC ovarian cancer; PBMC = peripheral blood mononuclear cells; PD-1 = programmed cell death protein 1; PD-1i = PD-1 inhibitor; PDAC = pancreatic ductal adenocarcinoma; Q3W = every 3 weeks; SCC = squamous cell carcinoma; TME = tumor micro-environment; tori = toripalimab; TNF = tumor necrosis factor; Treg = regulatory T cell.

References: 1) De Simone et al. *Immunity* 2016;45(5):1135-47. 2) Plitas et al. *Immunity* 2016;45(5):1122-34. 3) Kidani Y, et al. *Proc Natl Acad Sci USA* 2022;119(7):e2114282119. 4) Haruna M, et al. *Sci Rep* 2022;12(1):5377. 5) Wang X, et al. *J Immunother Cancer* 2024;12(Suppl 2): A1–A1683. 6) Rajasekaran N, et al. *Int J Radiat Oncol Biol Phys* 2024;118(5):e89. 7) Worden F et al. *Cancer Res* 2025;85 (8_Supplement_2): CT038.

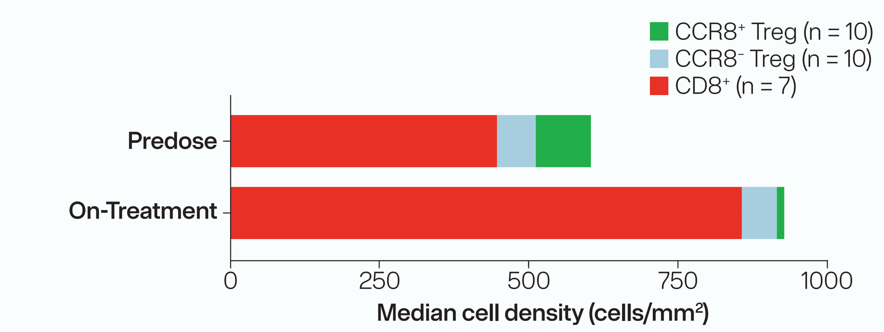
Statistics: * = p < 0.05; ** = p < 0.01; *** = p < 0.001; **** = p < 0.0001; when not shown, comparisons are not statistically significant.

CHS-114 Treatment Depletes CCR8⁺ itTregs and Increases CD8⁺ T Cells in HNSCC Tumors — Turns Tumors "Hot"

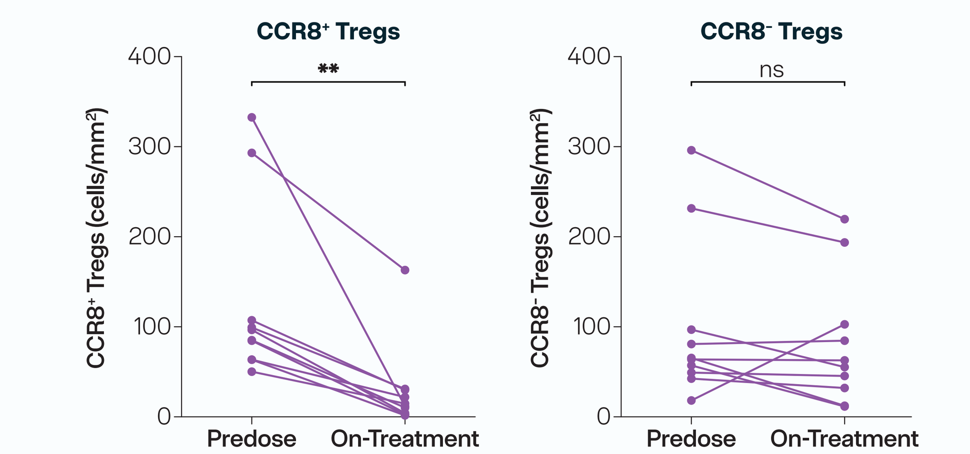
A CHS-114 Treatment Remodels the Tumor Microenvironment (TME)



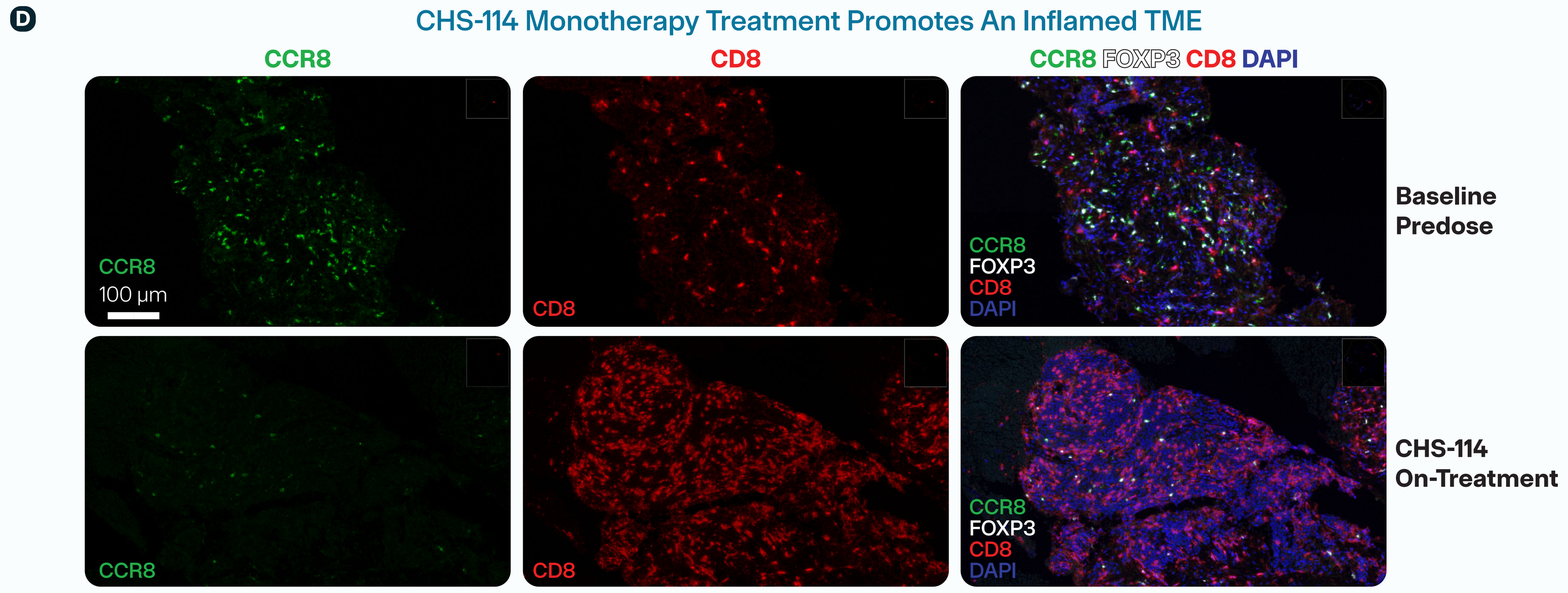
B Remodeled TME Following CHS-114 Treatment



C CHS-114 selectively depletes CCR8⁺ Tregs in the TME



D CHS-114 Monotherapy Treatment Promotes An Inflamed TME



A validated mIF assay was performed on predose and on-treatment (post-Cycle 2 dosing) tumor tissue samples from HNSCC participants in the CHS-114-101 monotherapy dose expansion (n = 10) and toripalimab combination dose escalation studies (n = 2). **(A)** Density of CCR8⁺ Tregs (CCR8⁺ FOXP3⁺ CD8⁻; n = 12), FOXP3⁺ Tregs (FOXP3⁺ CD8⁻; n = 12), and CD8⁺ T cells (CD8⁺ CCR8⁻ FOXP3⁻; n = 9) and fold change of ratio of CD8⁺ cells to CCR8⁺ Tregs (n = 9) are depicted. **(B)** Median cell density of indicated cell populations is shown predose and on CHS-114 monotherapy treatment. **(C)** Comparing density of CCR8⁺ (pos) and CCR8⁻ (neg) Tregs within the TME predose and on CHS-114 monotherapy treatment (n = 10). CHS-114-mediated depletion of CCR8⁺ Tregs, but not CCR8⁻ Treg cells, in the TME, confirming CHS-114 specificity within the TME. **(D)** Representative images from the mIF assay show that CHS-114 remodeled the TME in favor of antitumor immunity by increasing the ratio of CD8⁺ T cells (cytotoxic T lymphocytes) to CCR8⁺ Tregs, confirming the mechanism of action.

CONCLUSIONS

- CHS-114 mediated robust and selective depletion of peripheral CCR8⁺ Tregs, accompanied by immune activation in HNSCC study participants. These findings further support the two doses selected for the dose expansion studies.
- CHS-114-mediated immune activation is significantly enhanced and sustained with toripalimab in HNSCC study participants.
- In on-treatment tumor biopsies, CHS-114 depleted CCR8⁺ Tregs and increased CD8⁺ T cells in the TME, indicating favorable TME remodeling and establishing proof of mechanism.
- To date, CHS-114 with and without toripalimab has a manageable safety profile and promising early antitumor activity (with toripalimab) in patients with HNSCC.
- Taken together, these data support further evaluation of CHS-114 in combination with other drugs, including toripalimab; a 2L PD-1i-experienced HNSCC CHS-114 study with toripalimab dose optimization is ongoing to support recommended Phase 2 dose selection and to evaluate whether CCR8⁺ Tregs are the primary mechanism of PD-1i resistance in HNSCC.