Phase 1 study of anti-CCR8 antibody CHS-114 with and without anti-PD-1 antibody toripalimab in patients with advanced solid tumors

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Abstract Presentation #CT038

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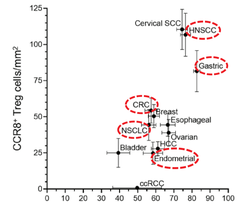
BACKGROUND

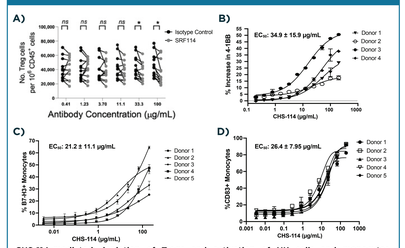
- C-C motif chemokine receptor 8 (CCR8) is a G-protein coupled receptor that is highly expressed on tumor-infiltrating T regulatory cells (Tregs)[1]
- Intratumoral CCR8+ Tregs are highly immunosuppressive, enriched in the tumor microenvironment (TME) and frequently associated with a lack of response to immunotherapy, therefore selective depletion of intratumoral Tregs is an attractive immunotherapy strategy[2]
- Strong scientific rationale for targeting CCR8 in head and neck squamous cell carcinoma (HNSCC) and other solid tumors:
  - CCR8+ Tregs are most abundant in HNSCC, cervical squamous cell carcinoma (SCC), and gastric cancer, and broadly expressed in several solid tumors, including colorectal cancer (CRC) and lung cancer
  - Radiation and PD-1 blockade on Tregs are known to increase Tregs, supporting the use of anti-CCR8 with anti-PD-1 agents
- CHS-114 is a selective, cytolytic anti-CCR8 monoclonal antibody (mAb) with no off-target binding[3]
- CHS-114 has the potential to overcome Treg-mediated immune suppression within the TME by recruiting T cells, turning cold tumors to hot, and enhancing antitumor immunity when combined with other immuno-oncology (IO) agents such as the anti-PD-1 antibody, toripalimab[4]

CCR8+ Tregs in Solid Tumors



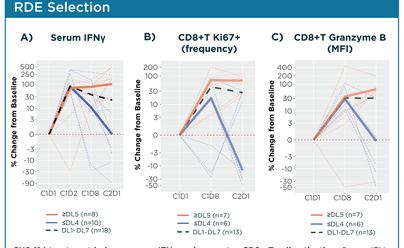
Density (y-axis) vs frequency (x-axis) of CCR8+ Tregs (of total FOXP3+ Tregs) in tumor microarrays from 12 types of solid tumors evaluated by an mIF assay. Tumor types in which clinical benefit has been observed with anti-CCR8 antibodies (CHS-114-101 study or competitor trials) are highlighted (red circles). For evaluating CCR8+ Tregs, CCR8 and FOXP3 staining was performed.

In Vitro Pharmacology Informs CHS-114 Target Trough Levels in Human Clinical Studies



CHS-114–mediated depletion of Tregs and activation of NK cells and monocytes. A) PBMCs were treated with increasing concentrations of CHS-114 or isotype control at 37°C for 16 hours. The number of Tregs (CD4+ FOXP3+) per million of CD45+ cells was determined by flow cytometry. **B)** PBMCs were treated with increasing concentrations of CHS-114 or isotype control at 37°C for 16 hours. The frequency of NK cells expressing 4-1BB was determined by flow cytometry. The percent increase in frequency of 4-1BB (normalized to isotype control) was calculated. EC_{50} values of CHS-114 were calculated based on 4-1BB induction on NK cells. **C-D)** PBMCs were treated with increasing concentrations of CHS-114 at 37°C for 16 hours. The frequency of B7-H3 and CD83 expressing monocytes was determined by flow cytometry. EC_{50} values of CHS-114 were calculated based on B7-H3 frequency **(C)** and CD83 frequency on monocytes **(D)**. **Based on the above, in vitro pharmacology data target trough levels for the expected pharmacological activity in participants treated with CHS-114 in clinical trials were defined.**

CHS-114–Mediated Peripheral Immune Activation During Dose Escalation Supports Biologically Active Dose and RDE Selection



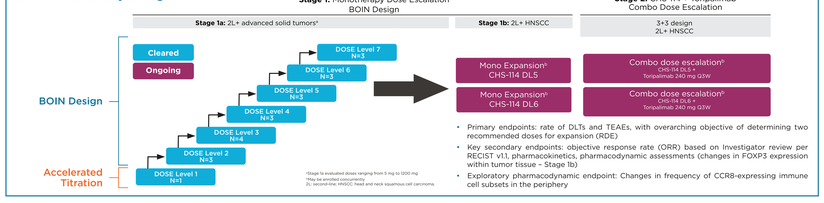
CHS-114 treatment induces serum IFNγ and promotes CD8+ T cell activation: Serum IFNγ by MSD analysis **(A)**; and immune profiling: CD8+ T cell proliferation **(Ki67, B)** and cytotoxicity **(GZMB, C)** in PBMC samples were measured by Cytek FACS assay at indicated time points. An increase in IFNγ and CD8+ T cell activation (Ki67, GZMB) compared to pre-treatment levels was observed through one dosing cycle for participants enrolled in CHS-114-101 monotherapy dose escalation and HNSCC dose expansion (only select participants from HNSCC dose expansion). Furthermore, **IFNγ induction and CD8+ T cell activation was sustained at DL5 and higher doses supportive of a pharmacologically and biologically active dose.** Participants with longitudinal samples are plotted (C1D1 and C2D1); N's based on number of participants at baseline. Thick solid and dashed lines represent median values for groups defined in the legend; thin dashed lines represent individual participants. MFI: mean fluorescent intensity; GZMB: Granzyme B

- A Phase 1, first-in-human (FIH), open-label single-agent and combination dose trial was initiated to evaluate CHS-114 in patients with advanced solid tumors and HNSCC. During monotherapy dose escalation (Stage 1a):[5]
  - CHS-114 demonstrated an acceptable safety profile in heavily pre-treated patients with advanced solid tumors, with no DLTs reported to date and generally low-grade treatment-emergent adverse events (TEAEs)
  - There were no complete or partial responses, but 47.4% of patients had stable disease (SD); one patient with SD >12 months remains on study
  - Pharmacokinetic (PK) exposure increased with dose, was approximately dose proportional, and the elimination appeared linear with a half-life of about 10 days (range 9-17 days)
  - Depletion of peripheral CCR8+ Tregs was observed (>85% in the periphery) and depletion was maintained over the dosing interval, establishing proof of mechanism; CHS-114 did not deplete non-CCR8+ Tregs and effector CD4 T cells (proof of specificity)
- Two doses were selected for dose optimization based on safety, peripheral CCR8+ Treg depletion, PK and biomarker data

METHODS

- A Phase 1, FIH, open-label single-agent and combination dose trial to evaluate CHS-114 in patients with advanced solid tumors and HNSCC (NCT05635643)
- Here we report CHS-114 monotherapy and combination results in the HNSCC patients enrolled in the trial as of the January 24, 2025, data cutoff date

SRF114-101 Study Design



- Primary endpoints: rate of DLTs and TEAEs, with overarching objective of determining two recommended doses for expansion (RDE)
- Key secondary endpoints: objective response rate (ORR) based on Investigator review per RECIST v1.1; pharmacokinetics, pharmacodynamic assessments (changes in FOXP3 expression within tumor tissue – Stage 1b)
- Exploratory pharmacodynamic endpoint: Changes in frequency of CCR8-expressing immune cell subsets in the periphery

RESULTS

HNSCC Demographics & Baseline Characteristics

	CHS-114 Monotherapy (n=14)	CHS-114 + Toripalimab (n=7)
Age, median years (range)	67 (42, 88)	67 (49, 79)
Gender, n (%)		
Female	3 (21.4)	2 (28.6)
Male	11 (78.6)	5 (71.4)
Race, n (%)		
American Indian or Alaska Native	0	0
Asian	0	0
Black or African American	2 (14.3)	0
Native Hawaiian or Other Pacific Islander	0	0
White	12 (85.7)	7 (100.0)
Unknown	0	0
Other	0	0
Not Reported	0	0
ECOG, n (%)		
0	4 (28.6)	5 (71.4)
1	10 (71.4)	2 (28.6)
Median time since initial diagnosis, months (range)	25.5 (11, 184)	21 (15, 84)
Lines of prior systemic therapy, n (%)		
0	1 (7.1)	0
1-2	7 (50.0)	5 (71.4)
3-4	5 (35.7)	2 (28.6)
≥5	1 (7.1)	0
PD-L1 expression[a], n (%)		
Positive	13 (92.9)	7 (100.0)
Negative	1 (7.1)	0
Not Done	0	0

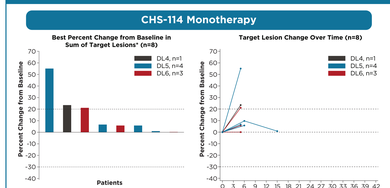
[a]Patients with HNSCC from stage 1a (n=2) and stage 1b (n=12)
[a]PD-L1 expression measured by combined positive score (CPS) or tumor proportion score (TPS)

Safety Summary in HNSCC

AE Summary	CHS-114 Monotherapy (n=14)	CHS-114 + Toripalimab (n=7)
Treatment-emergent adverse event (TEAE), n (%)	12 (85.7)	7 (100.0)
Treatment-related[a] AE, n (%)	7 (50.0)	7 (100.0)
Grade ≥3 TEAE, n (%)	4 (28.6)	5 (71.4)
Grade ≥3 treatment-related[a] AE, n (%)	1 (7.1)	4 (57.1)
Serious treatment-emergent adverse event (TESAE), n (%)	3 (21.4)	3 (42.9)
Treatment-related[a] SAE, n (%)	0	0
TEAE leading to study drug(s) discontinuation*, n (%)	0	4 (57.1)
Treatment-related[a] AE leading to CHS-114 discontinuation*, n (%)	0	2 (28.6)
TEAE leading to death, n (%)	0	0
Treatment-related[a] AE leading to death, n (%)	0	0

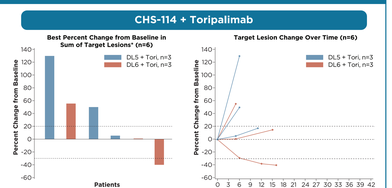
[a]For monotherapy with HNSCC, treatment-related AEs are CHS-114–related AE; For stage 2 subjects, treatment-related AEs are CHS-114 and/or toripalimab related AEs.
*For stage 2 subjects, treatment discontinuation are CHS-114 and/or toripalimab discontinuation.

HNSCC Response Summary – Investigator Assessment per RECIST v1.1



*as of the January 24, 2025, data cutoff date

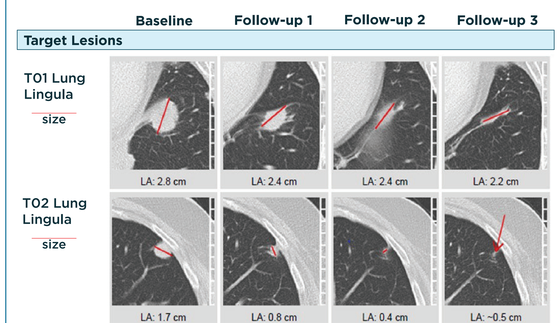
Best Overall Response, n (%)	Response Evaluable DL4 (n=1)	Response Evaluable DL5 (n=5)	Response Evaluable DL6 (n=3)
Partial response (confirmed)	0	0	0
Stable disease	0	2 (40.0)	2 (66.7)
Progressive disease	1 (100.0)	3 (60.0)	1 (33.3)
Not evaluable	0	0	0



*as of the January 24, 2025, data cutoff date

Best Overall Response, n (%)	Response Evaluable DL5 + Tori (n=4)	Response Evaluable DL6 + Tori (n=3)
Partial response (confirmed)	0	1 (33.3)
Stable disease	1 (25.0)	1 (33.3)
Progressive disease	2 (50.0)	1 (33.3)
Not evaluable	1 (25.0)	0

Confirmed Partial Response in Target Lesions



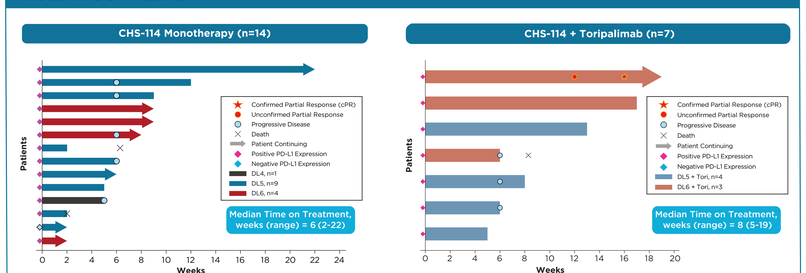
RECIST Assessment:

- Target lesions: **40.0% reduction** in the target lesions at the time of confirmed PR at follow-up 3
- Non-target lesions: 2 out of 4 non-target lesions **disappeared** after 2 treatment cycles
- No new lesions

Responder Demographics:

- Oropharyngeal squamous cell carcinoma (OPSCC)
- P16 positive, PD-L1 CPS 4, and TMB 8 mut/Mb
- Mutations: CDKN2A, EGFR, NOTCH, PIK3CA
- Patient was diagnosed at Stage 4 and refractory to 3 prior lines of systemic therapy including anti-PD-1 (~12 mo from 1L aPD-1 plus chemo)

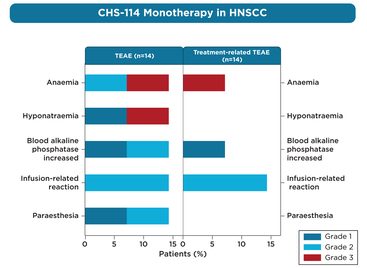
HNSCC Time on Treatment



Time on treatment = days from first dose to end of treatment

CHS-114 TEAEs and Treatment-Related TEAEs

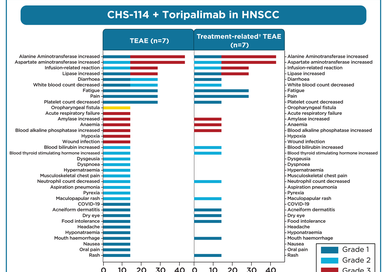
Majority of TEAEs consistent with advanced disease; low rate of high-grade TEAEs



TEAEs and Treatment-Related TEAEs Occurring in ≥ 10% of Patients (n=14)

CHS-114 With Toripalimab TEAEs and Treatment-Related TEAEs

TEAEs consistent with the safety profile of toripalimab



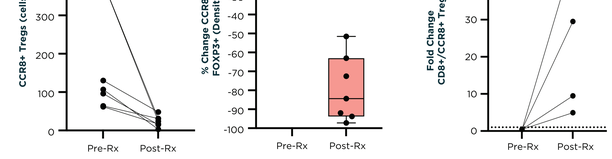
[1]Treatment-related AEs are CHS-114 and/or toripalimab-related AEs.

TEAEs and Treatment-Related TEAEs Occurring in ≥ 10% of Patients (n=7)

CHS-114 Depletes CCR8+ Tregs and Remodels the TME in Favor of Anti-Tumor Immunity

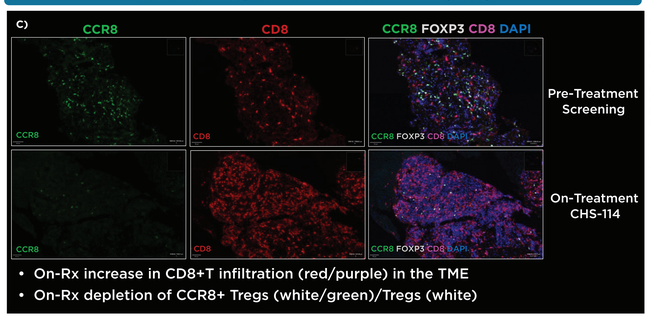
Depletion of Intratumoral CCR8+ Tregs

Increase in Intratumoral CTL/Treg Ratio



CHS-114 treatment remodels the tumor microenvironment (TME): A validated mIF assay was performed on pre- and post- (cycle 2 post-dosing) treatment (Rx) fresh biopsy samples from HNSCC patients in the CHS-114-101 monotherapy dose expansion studies (DL4, DL5). **(A, left)** CCR8+ Tregs (CCR8+ FOXP3+) density and **(A, right)** percent change of density from baseline. **(B)** Fold change of ratio of CD8+ cells (CD8+ CCR8- (FOXP3-) to CCR8+ Tregs (CCR8+ FOXP3+ CD8-). N=7 (A); N=4 (B). Statistical analysis: Wilcoxon paired test (A, N=7); unpaired t-test (B, N=4); *P* value: * ≤ 0.05.

CHS-114 Monotherapy Treatment Promotes an Inflamed TME (HNSCC)



- On-Rx increase in CD8+T infiltration (red/purple) in the TME
- On-Rx depletion of CCR8+ Tregs (white/green)/Tregs (white)

CHS-114 treatment remodels the TME: (C) Representative images from the mIF assay are presented. CHS-114 mediated robust depletion of CCR8+ Tregs in the TME confirming the proof of concept. Furthermore, **CHS-114 remodeled the TME in favor of anti-tumor immunity by increasing the CTL (cytotoxic T lymphocyte; CD8+T) to CCR8+ Treg ratio confirming the mechanism of action.**

CONCLUSIONS

- Two doses were selected for dose optimization based on safety, peripheral CCR8+ Treg depletion, PK and biomarker data; these two doses are supported by the observed immune activation in blood and CCR8+ Treg depletion in tumor
- CHS-114 with and without toripalimab had a manageable safety profile in HNSCC patients
- CHS-114 with toripalimab had promising antitumor activity in HNSCC that warrants continued exploration
- 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
  - CHS-114 administration leads to a substantial increase in CD8+ T cells in the TME providing a strong rationale for combining with other drugs such as T cell engagers and bispecifics
- All together, these data support further evaluation of CHS-114 in combination with other drugs including toripalimab; a second-line (2L) HNSCC CHS-114 with toripalimab dose optimization study is ongoing

REFERENCES: **1.** Kidani Y, et al. *Proc Natl Acad Sci USA*. 2022;119(7):e2114282119. **2.** Haruna M, et al. *Sci Rep*. 2022;12(1):5377. **3.** Wang X, et al. *J Immunother Cancer*. 2024;12(Suppl 2):A1–A1683. **4.** Rajasekaran N, et al. *Int J Radiat Oncol Biol Phys*. 2024;118(5):e89. **5.** Patnaik A, et al. *J Clin Oncol*. 2024;42(suppl 16):2664.

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