Preliminary results of a phase 1, first-in-human, dose escalation study of the anti-CCR8 cytolytic antibody, CHS-114 (formerly SRF114) in patients with advanced solid tumors

Abstract #2664

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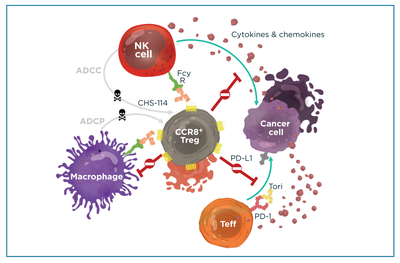
INTRODUCTION

- FOXP3+ regulatory T cells (Tregs) play a crucial role in orchestrating immunosuppression within the TME, and their increased frequency within tumors correlates with poor clinical prognosis
- Past attempts at Treg depletion have lacked selectivity which resulted in autoimmune toxicity
- Chemokine receptor 8 (CCR8) is a G protein-coupled receptor (GPCR) that is highly upregulated by intratumoral Tregs compared to their peripheral counterparts and other immune cell types
- Anti-CCR8 mAb mediated depletion of intratumoral Tregs results in antitumor activity and T cell infiltration in a PD-1 resistant mouse model
- CHS-114 is an afucosylated mAb highly selective for CCR8 with no off-target binding
  - Afucosylation enhances cytolytic activity and promotes killing of intratumoral CCR8+ Tregs



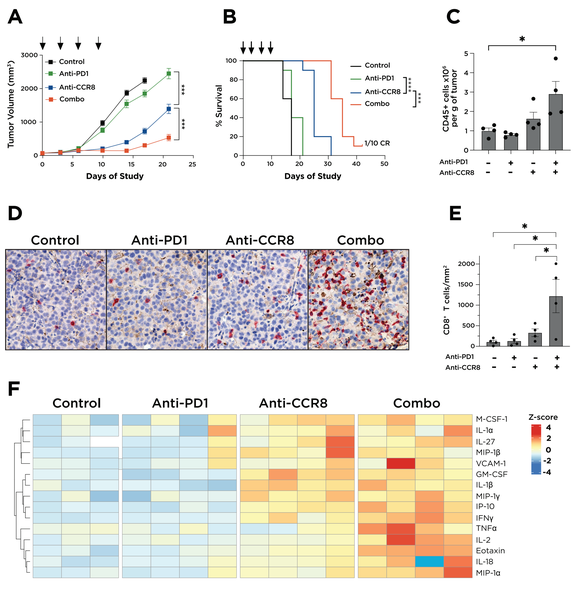
- Other CCR8-targeting mAbs currently in development lack selectivity and exhibit off-target binding
- Minimal non-specific depletion of circulating Tregs mitigates risk of autoimmunity while maintaining efficacy
- CHS-114 has the potential to overcome Treg mediated immune suppression within the TME by recruiting T cells, turning cold tumors to hot, and enhancing antitumor immunity when combined with other IO agents, such as toripalimab
- **A Phase 1, first-in-human (FIH) clinical trial was initiated to evaluate CHS-114 in patients with advanced solid tumors and head and neck squamous cell carcinoma (HNSCC)**

CHS-114 Selectively Binds CCR8, A GPCR Preferentially Expressed on Tumor Resident Treg Cells

Selected Antibodies	Number of Non-CCR8 Targets Identified
CHS-114	**0**
mAb2	1
mAb3	8
mAb4	15
mAb5	20
Comparator Antibodies	**Non-CCR8, "Off Target" Binding**
Comparator 1	ANGPTL7
Comparator 2	J chain
Comparator 3	SEMA4B

GPCRs are challenging antibody targets due to limited surface protein accessibility; as a result GPCR targeted mAbs often show off target binding. A screen of 5,528 proteins using cell microarray technology was performed for CHS-114 and 3 other clinical stage CCR8 mAb (antibodies derived from patent sequences).

CCR8 Cell Depletion Enhances PD-1 Antitumor Immunity and Increases Tumor Infiltrating CD8+ T Cells.



1x10⁵ B16F10 cells were injected to the flank of C57BL/6 mice subcutaneously. Mice were randomized to four groups and dosing with isotype control antibodies, anti-CCR8 (mouse IgG2a, 50 µg/mouse), anti-PD-1 (rat IgG2a, 200 µg/mouse), or combo treatments on day 6 post tumor implantation (n=10/group).

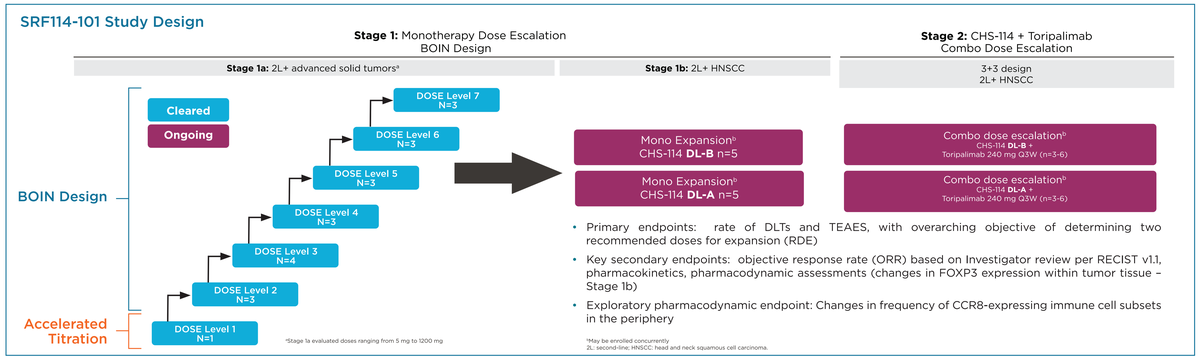
A) Anti-tumor activity (tumor growth inhibition assessment). **B)** Survival curves. **C)** Tumor cytometric analyses and average frequency, respectively, of TILs on Study Day 9. Total number of CD45+ cells per gram of tumor was measured by normalizing the total CD45+ cell count to tumor weight (n=4) **(D)** Representative IHC images of tumor infiltrating CD8+ T cells (red chromogen, Study Day 9). **E)** Quantification of CD8+ T cells using image analysis on digitally scanned slides (n=4). **F)** Production of pro-inflammatory cytokines and chemokines in B16F10 tumors. Cytokines and chemokines were detected by Luminex assay in snap-frozen and lysed tumors Study Day 8 (n=3-4). Statistical analysis was performed using log-rank test **(B)** or one-way ANOVA **(A, C, E)**. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

Reference: Panduro, Marisella, et al. "Depletion of CCR8+ tumor Treg cells with SRF114 or anti-CCR8 therapy promotes robust antitumor activity and reshapes the tumor microenvironment toward a more pro-inflammatory milieu." *Cancer Research* 83.7_Supplement (2023): 5125-5125.

METHODS

- Phase 1, FIH, open-label, single-agent and combination therapy dose escalation (NCT05635643)
- Stage 1 (CHS-114 single-agent dose escalation) employed the Bayesian optimal interval (BOIN) design including accelerated titration and 3+3 run-in
  - Stage 1a enrolled patients with advanced solid tumors who received ≥1 standard treatment
  - Stage 1b, is enrolling an additional 5 patients with advanced/metastatic HNSCC at each of two dose levels (DLs); patients must be willing to undergo pre- and on-treatment biopsies
- Stage 2 (CHS-114 + toripalimab combination dose escalation) is enrolling patients with advanced/metastatic HNSCC and employ a standard 3+3 design
- CHS-114 is administered intravenously (IV) on day 1 of each Q3W cycle; in Stage 2, CHS-114 will be administered in combination with toripalimab 240mg Q3W
- Dose-limiting toxicities (DLTs) were evaluated during Cycle 1 (21 days) using NCI-CTCAE criteria (v5.0 or higher)

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

[b]May be enrolled concurrently
2L: second-line; HNSCC: head and neck squamous cell carcinoma.

RESULTS

Dose Escalation Baseline Characteristics

Demographics n (%)		(n=20)
Age	Median years (Range)	67 (47, 84)
Gender	Female	10 (50)
	Male	10 (50)
Primary Tumor Type	Colorectal	4 (20)
	Endometrial	2 (10)
	Head and Neck Squamous Cell Carcinoma (HNSCC)	2 (10)
	Kidney	1 (5)
	Melanoma	1 (5)
	Non-Small Cell Lung	2 (10)
	Pancreatic	3 (15)
	Other*	5 (25)

Baseline Characteristics n (%)		(n=20)
ECOG PS	0	6 (30)
	1	14 (70)
Median Time Since Initial Diagnosis, Months (range)		47 (11, 257)
Lines of Prior Systemic Therapy	0	0
	1-2	5 (25)
	3-4	6 (30)
	≥5	9 (45)
PD-L1 Expression	Positive	6 (30)
	Negative	5 (25)
	Not Done	9 (45)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; PD-L1, programmed death ligand 1
*Other tumor types include biliary tract (n=1), esthesioneuroblastoma (n=1), ovarian (n=3), and rectal (n=1).

Safety Summary

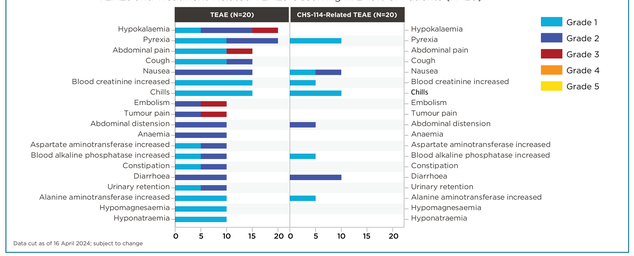
AE Summary	N=20
Treatment emergent adverse event (TEAE), n (%)	19 (95)
CHS-114-related AE, n (%)	8 (40)
Grade ≥3 TEAE, n (%)	7 (35)
Grade ≥3 treatment-related AE, n (%)	0
Serious Treatment Emergent Adverse Event (TESAE), n (%)	6 (30)
Treatment-related SAE, n (%)	1 (5)
TEAE leading to CHS-114 discontinuation, n (%)	1 (5)
Treatment-related AE leading to CHS-114 discontinuation, n (%)	0
TEAE leading to death, n (%)	1 (5)
Treatment-related AE leading to death, n (%)	0

Data cut as of 16 April 2024; subject to change

- No DLTs observed to date, across all dose levels tested
- Treatment-related TEAEs were generally low grade, with the most frequent being diarrhea, nausea, chills and pyrexia, each reported in 2 patients
- 1 patient experienced a treatment-related SAE of Grade 2 colitis

TEAEs and Treatment-Related TEAEs

Majority of TEAEs Consistent With Advanced Disease; Low Rate of High Grade TEAEs



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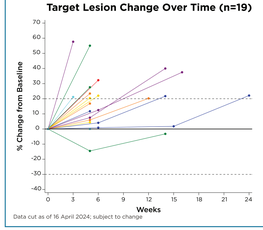
Response Summary based on Investigator Assessment per RECIST v1.1

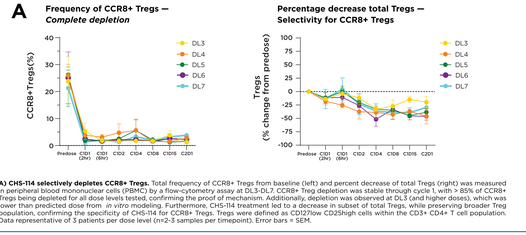


Best overall response, n (%)	Response evaluable (n=19)
Complete response	0
Partial response	0
Stable disease	9 (47.4)
Progressive disease	10 (52.6)

Disease assessments performed every 9 weeks

Data cut as of 16 April 2024; subject to change

Pharmacology: Sustained Peripheral CCR8+ Treg Depletion and Pharmacokinetic Profile



A) CHS-114 selectively depletes CCR8+ Tregs. Total frequency of CCR8+ Tregs from baseline (left) and percent decrease of total Tregs (right) was measured in peripheral blood mononuclear cells (PBMC) by a flow-cytometry assay at DL3-DL7. CCR8+ Treg depletion was stable through cycle 1, with > 85% of CCR8+ Tregs being depleted for all dose levels tested, confirming the proof of mechanism. Additionally, depletion was observed at DL3 (and higher doses), which was lower than predicted dose from *in vitro* modeling. Furthermore, CHS-114 treatment led to a decrease in subset of total Tregs, while preserving broader Treg population, confirming the specificity of CHS-114 for CCR8+ Tregs. Tregs were defined as CD127low CD25high cells within the CD3+ CD4+ T cell population. Data representative of 3 patients per dose level (n=2-3 samples per timepoint). Error bars = SEM.

B) CHS-114 Mean (+SD) serum concentration (Semi-Log) - time profile after single dose of CHS-114 (cycle 1). CHS-114 PK exposure increases with dose. Dose proportionality is observed at all dose levels. PK elimination is linear over all dosing levels with a half-life of approximately 10 days (range: 9-17 days). The PK dataset date was March 28, 2024.

CONCLUSIONS

- CCR8 is a GPCR that shows preferential expression on tumor resident Tregs and has promise as a drug target for selectively targeting immune suppression in the tumor microenvironment
- CHS-114 is a novel afucosylated human IgG1 mAb that selectively and potently targets human CCR8 with no off-target binding and has the potential to overcome Treg immune suppression in the TME by recruiting T cells
- CHS-114 has demonstrated an acceptable safety profile in heavily pre-treated patients with advanced solid tumors, with no DLTs reported to date
- CHS-114 PK exposure increases with dose, is approximately dose proportional, and the elimination appears linear with a half-life of about 10 days (range 9-17 days)
- Depletion of peripheral CCR8+ Tregs was observed and depletion was maintained over the dosing interval, establishing proof of mechanism
- Preliminary results and acceptable safety profile support further evaluation of CHS-114 in combination treatment with the anti-PD-1 antibody, toripalimab, and other IO agents

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