Results from a phase 2 study of triplet blockade of the IL-27, PD-(L)1, and VEGF pathways with casdozokitug (casdozo, CHS-388) in combination with atezolizumab (atezo) and bevacizumab (bev) in patients with unresectable, locally advanced or metastatic hepatocellular carcinoma (uHCC)

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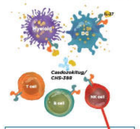
Abstract #470

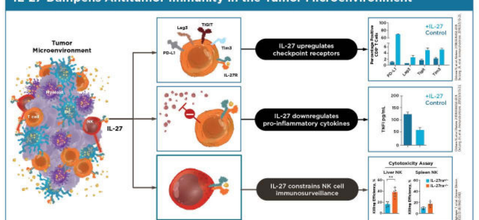
BACKGROUND

- IL-27 is a heterodimeric cytokine expressed by myeloid cells, including macrophages and dendritic cells, which plays a role in modulating immune responses during infection and tumor immune surveillance
- IL-27 regulates the activity of several immune cell types through upregulation of immune suppressive receptors (PD-L1, TIGIT, LAG3) and inhibition of inflammatory cytokines
- **Casdozokitug (or casdozo; CHS-388; formerly SRF388)** (or its mouse surrogate) has shown antitumor activity in several preclinical models of HCC
- IHC evaluation of HCC commercial tissue microarrays revealed that most HCC samples express the target: IL-27+ tumor-associated macrophages (TAMs, internal data)
- Casdozo is the first in class and only clinical-stage IL-27 targeting antibody, which neutralizes IL-27, promotes immune activation and stimulates antitumor response
- A phase 1 study demonstrated a favorable safety profile and antitumor activity alone and in combination with PD-1 blockade in indications known to have high levels of IL-27 pathway activation (NCT04374877)
- Casdozo induces increases in serum IFN-γ and NK cell gene activation in cancer patients, indicating an immune response and reversal of IL-27-mediated immune suppression
- The lead-in phase of the SRF388-201 study evaluated the safety and antitumor activity of this immunoregulatory cytokine antagonist given in combination with atezo and bev in patients with unresectable, locally advanced or metastatic HCC

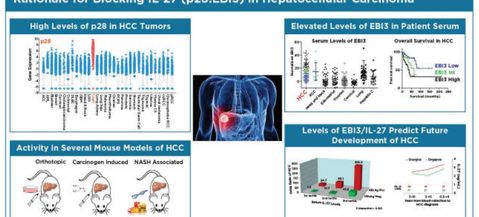
IL-27 Immune Regulatory Cytokine



IL-27 Dampens Antitumor Immunity in the Tumor Microenvironment

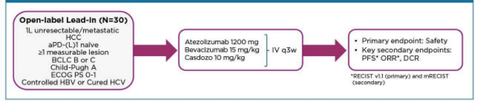


Rationale for Blocking IL-27 (p28:EBI3) in Hepatocellular Carcinoma[1-3]



METHODS

Phase 2 Study Schema of Casdozo/Atezolizumab/Bevacizumab in IO Naïve 1L HCC Patients: SRF388-201



1L, first line; aPD-(L)-1, anti programmed death-ligand 1; BCLC, Barcelona Clinic Liver Cancer; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HBV, hepatitis B virus; HCV, hepatitis C virus; IO, immunotherapy; IV, intravenous; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, overall response rate; PFS, progression-free survival; q3w, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1

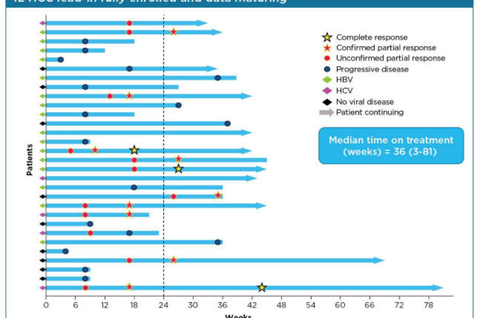
RESULTS

SRF388-201 Baseline Characteristics
1L HCC lead-in

Demographics, n (%)			Lead-in (n=30)
Age	Median years (range)		66 (19, 82)
Gender	Female		7 (23.3)
	Male		23 (76.7)
Race	Asian		20 (66.7)
	Native Hawaiian or Other Pacific Islander		1 (3.3)
	White		7 (23.3)
	Not reported		2 (6.7)
Region		Asia excluding Japan	18 (60.0)
		ROW	12 (40.0)
ECOG		0	7 (23.3)
		1	23 (76.7)

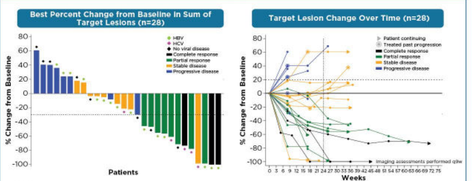
Baseline Characteristics, n (%)			Lead-in (n=30)
Stage	Locally advanced, unresectable		10 (33.3)
	Metastatic		20 (66.7)
Child-Pugh score		A5	27 (90.0)
		A6	3 (10.0)
BCLC stage		B	6 (20.0)
		C	24 (80.0)
Viral status		HBV	16 (53.3)
		HCV	5 (16.7)
		Uninfected	9 (30.0)
Baseline AFP		< 400 ng/mL	16 (53.3)
		≥ 400 ng/mL	14 (46.7)
Macrovascular involvement			7 (23.3)
Varices at study entry			3 (10.0)

SRF388-201 Time on Therapy (n=30)
1L HCC lead-in fully enrolled and data maturing



RESULTS

SRF388-201: Early Activity with Casdozo/Atezo/Bev
11 durable objective responses per RECIST v1.1 including 3 CRs



>60% of patients with tumor shrinkage on initial scans with 38% ORR to date in response evaluable set: 3 CRs, 8* PRs

Best Overall Response (RECIST), n (%)	Response Evaluable (n=29)
Complete response	3 (10.3)
Partial response	8* (27.6)
Stable disease	9** (31.0)
Progressive disease	9 (31.0)

*Includes 1 patient with an unconfirmed PR at the time of data cut-off
**Includes 1 patient with a best response of PR that was not confirmed

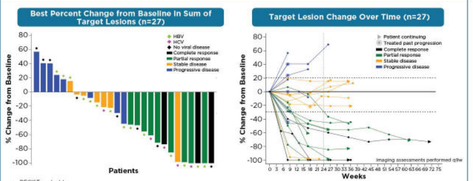
Data cut as of 09 Nov 2023, subject to change

Estimated PFS and DCR in the Response Evaluable Population

	RECIST v1.1 (N=29)	mRECIST (N=28)
Events, n (%)	15 (51.7)	12 (42.9)
Censored, n (%)	14 (48.3)	16 (57.1)
PFS (months)		
Median (95% CI)	8.1 (4.0, -)	NR (2.0, -)
Event-free rate at, %		
6 months (95% CI)	59.5 (38.8, 75.3)	62.1 (40.9, 77.6)
12 months (95% CI)	33.7 (12.1, 57.1)	50.9 (29.0, 69.3)
DCR, n (%)	17 (58.6)	17 (60.7)

CI, confidence interval; DCR, disease control rate; NR, not reached; PFS, progression-free survival

Early mRECIST Activity with Casdozo/Atezo/Bev
12 durable objective responses per mRECIST including 3 CRs



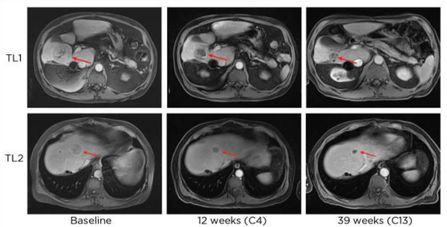
Encouraging early data with 43% ORR by mRECIST criteria

Best Overall Response (mRECIST), n (%)	Response Evaluable (n=28)
Complete response	3 (10.7)
Partial response (confirmed)	9* (32.1)
Stable disease	7** (25.0)
Progressive disease	9 (32.1)

*Includes 1 patient with an unconfirmed PR at the time of data cut-off
**Includes 1 patient with a best response of PR that was not confirmed

Data cut as of 09 Nov 2023, subject to change

Encouraging Evidence of Tumor Response with Casdozo Added to SOC in IL HCC



- 59 yo Hispanic man with cirrhosis, Child-Pugh A, BCLC C, no history of HBV/HCV, stage III unresectable HCC
- Durable PR which occurred at 21 weeks (C7) (-48%)
- Continued shrinkage at 39 weeks (C13) (-56%)
- Patient ongoing at 72 weeks (C24) with continued tumor shrinkage

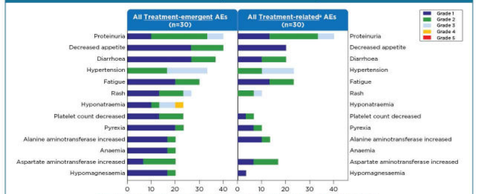
SRF388-201 HCC Lead-in Phase Safety Summary

Per Patient AE Summary	N=30
Treatment emergent adverse event (TEAE), n (%)	30 (100)
Treatment-related AE*, n (%)	27 (90.0)
Grade ≥3 TEAE, n (%)	19 (63.3)
Grade ≥3 treatment-related* AE, n (%)	11 (36.7)
Serious TEAE, n (%)	13 (43.3)
Treatment-related* SAE, n (%)	7 (23.3)
TEAE leading to any study drug discontinuation, n (%)	9 (30.0)
Treatment-related AE leading to any study drug discontinuation, n (%)	6 (20.0)
TEAE leading to CHS-388 discontinuation, n (%)	4 (13.3)
Treatment-related AE leading to CHS-388 discontinuation, n (%)	2 (6.7)
TEAE leading to death, n (%)	3 (10.0)
Treatment-related AE leading to death, n (%)	0

*Related to any treatment in the combination therapy

Data cut as of 09 Nov 2023, subject to change

SRF388-201: Triplet is Well Tolerated
Toxicities consistent with known AE profiles of Atezo/Bev

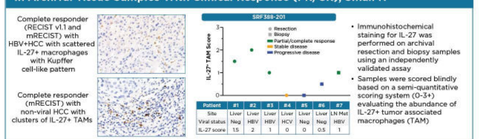


*Related to any treatment in the combination therapy

Data cut as of 09 Nov 2023, subject to change

- Immune-related AEs (irAEs) and bleeding events were infrequent and generally low grade
  - Grade ≥3 treatment-related irAEs included stomatitis, myasthenia gravis and rash, each in 1 patient
  - A treatment-related bleeding event of grade 3 epistaxis occurred in 1 patient

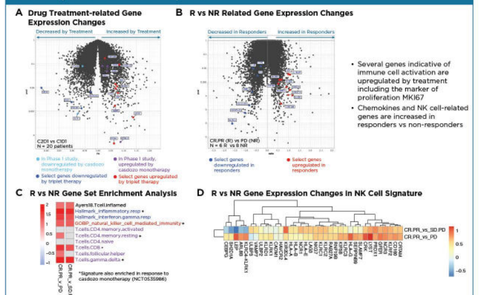
Preliminary Association of Higher Levels of IL-27+ Tumor Associated Macrophages in Archival Tissue Samples With Clinical Response (PR/CR), Small N



Patient	#1	#2	#3	#4	#5	#6
Site	Liver	Liver	Liver	Liver	Liver	LN Met
Viral status	Neg	HBV	HBV	HCV	Neg	Neg	HBV
IL-27 score	15	2	1	0	0.5	1

- Immunohistochemical staining for IL-27 was performed on archival resection and biopsy samples using an independently validated assay
- Samples were scored blindly based on a semi-quantitative scoring system (0-3+) evaluating the abundance of IL-27+ tumor associated macrophages (TAM)

Gene Expression Differences in Treated Patient PBMCs: Pharmacodynamic and Responders vs Non-responders



- Several genes indicative of immune cell activation are upregulated by treatment including the marker of proliferation MKI67
- Chemokines and NK cell-related genes are increased in responders vs non-responders

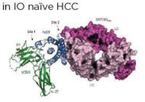
Gene expression analysis of patient PBMCs by bulk RNA-seq comparing C2D1 to C1D1 (pre-treatment).
A) Volcano plot highlighting select genes in response to casdozo/atezo/bev treatment; upregulated (red) or downregulated (blue). A select number of genes that were upregulated (purple) or downregulated (light blue) by casdozo alone from the phase 1 study (NCT04353986) are also highlighted. Paired RNA-Seq sample (on-treatment vs pre-treatment) analysis was used to calculate fold-change (FC, x-axis) and p-value (pval, y-axis). **B)** Volcano plot highlighting select genes that were increased (red) or decreased (blue) by the treatment in R (CR and PR) compared to NR (PD) patients. **C)** Gene set enrichment analysis (GSEA) highlighting signatures that are enriched in R vs NR. Asterix indicates signatures enriched in response to casdozo alone treatment in the phase 1 study.
D) Heatmap of a subset of individual genes within the NK signature highlighting gene expression changes in R vs NR.

CR, complete response; NR, non-responder (PD); PD, progressive disease; PR, partial response; R, responder (PR/CR); SD, stable disease

CONCLUSIONS

Casdozo is a promising novel IO agent with clinical activity in liver cancer that may be associated with IL-27 pathway biomarkers

- IL-27 is an immunoregulatory cytokine that can suppress the antitumor response
- Casdozo is a **first-in-class** immunomodulatory antibody targeting IL-27
- Casdozo has **demonstrated monotherapy and combination antitumor activity** across multiple solid tumor types with a favorable safety profile, and evidence of immune activation
- Triplet blockade of the IL-27, PD-(L)1 and VEGF pathways with casdozo/atezo/bev has an acceptable safety profile to date with promising antitumor activity in IO naïve HCC
  - Encouraging early activity with casdozo/atezo/bev triplet:
    - ORR: 38% per RECIST v1.1 and 43% per mRECIST
    - Response associated with biomarkers of IL-27
- Results support continued evaluation of casdozo with VEGF and PD-(L)1 blockade in HCC
- Study plans in place to evaluate casdozo/toripalimab (anti-PD-1 antibody)/bev for future development



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