Casdozokitug, a First-in-Class Anti-IL-27 Antagonistic Antibody, Treatment Promotes NK and T Cell Activation and Inflammatory Response in Phase 1 Study of Cancer Patients with Advanced Solid Tumors

Poster 1319

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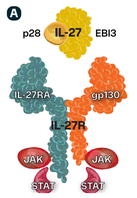
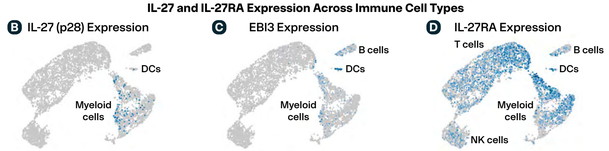
Background

- IL-27 is a heterodimeric member of the IL-12/IL-23 cytokine family comprised of IL-27p28 and EBI3 subunits.
- IL-27 is an immunoregulatory cytokine expressed by myeloid cells, including macrophages and dendritic cells, and dampens T and NK effector function.
- IL-27 is highly expressed by tumor-associated macrophages (TAM) in several cancers, including liver (HCC) and lung (NSCLC), and suppresses antitumor immune responses.
- Casdozokitug (or casdozo; CHS-388; formerly SRF-388) is a first-in-class high-affinity human IgG1 antibody, which neutralizes IL-27, promotes immune activation, and stimulates antitumor response.
- In a Phase 1 study (NCT04374877), casdozokitug demonstrated a favorable safety profile and antitumor activity (PR) as a single agent and in combination with PD-1 blockade in indications known to have high levels of IL-27 pathway activation (NSCLC [n = 2], RCC [n = 1], and HCC [n = 1]).
- Promising antitumor activity and a favorable safety profile were also demonstrated in an ongoing Phase 2 study (NCT05359861) of casdozokitug in combination with atezolizumab and bevacizumab in patients with untreated locally advanced or metastatic HCC.

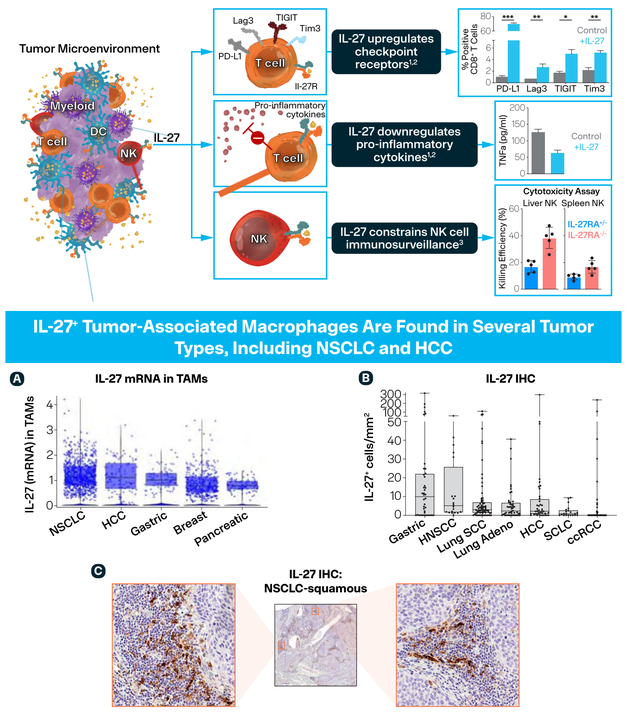


IL-27 and IL-27RA Expression Across Immune Cell Types



(A) Schematic of IL-27 (p28:EBI3) heterodimeric cytokine and its heterodimeric receptor, IL-27R (IL-27RA:gp130) signaling through the JAK:STAT pathway. **(B-D)** scRNAseq of activated healthy human donor PBMC. **(B-C)** IL-27 individual subunits (p28 and EBI3, respectively) expression is mostly restricted to cells of myeloid origin. **(D)** IL-27RA is expressed by immune cells of lymphoid and myeloid lineage.

IL-27 Inhibits T and NK Cell-Driven Antitumor Response in the Tumor Microenvironment



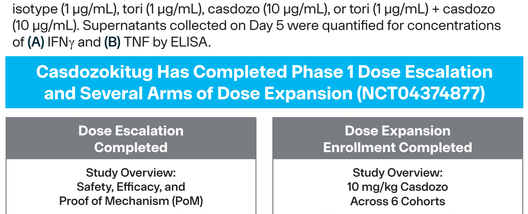
IL-27+ Tumor-Associated Macrophages Are Found in Several Tumor Types, Including NSCLC and HCC

(A) scRNAseq analysis of IL-27 transcripts in TAM from indicated tumor types.[4] **(B)** Density of IL-27+ cells across 7 solid tumors (via IHC of TMA). **(C)** IL-27 IHC on NSCLC-squamous lobectomies. IL-27 expression was observed in cells with TAM-like morphology distributed throughout the lung TME.

Treatment With Anti-IL-27 Antibody Inhibits Tumor Growth in Mouse Models When Tumors Reside in the Lung and Liver

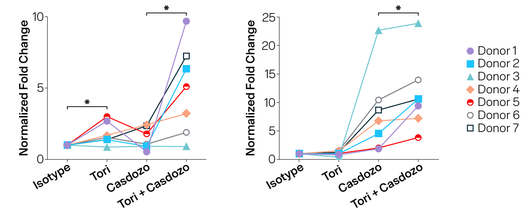
A

In Vivo Study	Tumor Location	Antitumor Activity (Anti-IL-27 mAb)
Multiple subcutaneous syngeneic tumor models	Subcutaneous	No activity or acceleration of tumor growth
B16 lung metastasis model	Subcutaneous	No activity
	Lung	Antitumor activity
RCC orthotopic model, with lung metastasis	Kidney	No activity
	Lung	Anti-metastatic activity
HCC models (carcinogen, NASH, HEPA1-6)	Liver	Antitumor activity



(A) Overview of antitumor activity of IL-27 blockade in mouse tumor models showing tissue-specific activity. **(B)** IL-27 blockade by casdozo treatment inhibits tumor growth in a model of lung metastases. B16F10 cells were injected into C57BL/6 mice that were treated with 50 mg/kg IgG1 or casdozo (Days -7, 0, 7, 14) or with anti-PD-1 + anti-CTLA-4 Ab (Days 0, 4, 7, 11). Lung metastases on Day 18 were quantified via image analysis. **(C)** CHS-381 (high-affinity anti-IL-27 mouse surrogate of CHS-388) inhibits NASH-associated HCC growth. MUP-uPA+ mice received either mouse IgG2a or CHS-381 for the last 15 weeks of 8 months of Western diet feeding. Tumor development was analyzed at 10 months. Average ± SEM tumor load and tumor number of treated mice are shown. Statistics: unpaired Student's t-test (two-tailed).

Casdozokitug in Combination With Toripalimab (Anti-PD-1) Significantly Increases Cytokine Production in Activated PBMC Cultures From Healthy Donors



Casdozo and toripalimab (anti-PD-1 Ab) combination treatment of activated PBMCs results in significantly enhanced immune activation. Fresh healthy human PBMC were activated with 0.25 µg/mL anti-CD3 Ab in the presence of IgG4 isotype (1 µg/mL), tori (1 µg/mL), casdozo (10 µg/mL), or tori (1 µg/mL) + casdozo (10 µg/mL). Supernatants collected on Day 5 were quantified for concentrations of **(A)** IFNγ and **(B)** TNF by ELISA.

Casdozokitug Has Completed Phase 1 Dose Escalation and Several Arms of Dose Expansion (NCT04374877)

Dose Escalation Completed

Study Overview: Safety, Efficacy, and Proof of Mechanism (PoM)

- Monotherapy dose escalation (Q4W) in patients with advanced solid tumors
- 8 dose levels explored

Clinical Data Summary:

PK	Linear and target PK trough levels achieved at 10 mg/kg
Safety	Acceptable, no DLTs
Efficacy	PR at 10 mg/kg in NSCLC
Biomarkers	Pharmacodynamics: complete IL-27 signaling inhibition PoM: NK & T cell activation

Dose Expansion Enrollment Completed

Study Overview: 10 mg/kg Casdozo Across 6 Cohorts

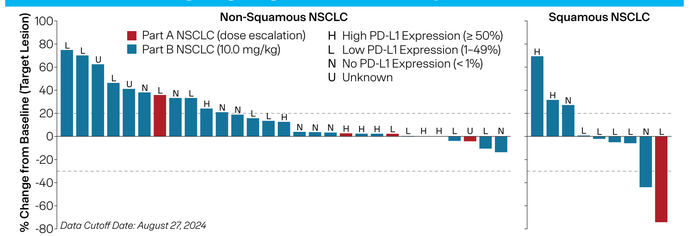
- 2-5L NSCLC monotherapy (n=40)[a]
- 2-4L NSCLC pembro combination (n=6)[b]
- 2-5L RCC monotherapy (n=27)[a]
- 2-5L HCC monotherapy (n=17)[a]
- 2-6L +pembro Pilot (HCC/RCC) (n=10)[b]
- 3-6L +pembro Crossover (HCC/RCC) (n=5)[b]

[a]Q4W [b]Q3W

Clinical Data Summary:

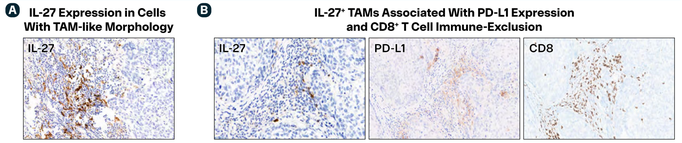
Safety	Acceptable, no DLTs
Efficacy	PRs: 1 ccRCC (casdozo), 1 NSCLC (casdozo), 1 HCC (casdozo/pembro)
Biomarkers	Pharmacodynamic: complete IL-27 signaling inhibition PoM: NK & T cell activation

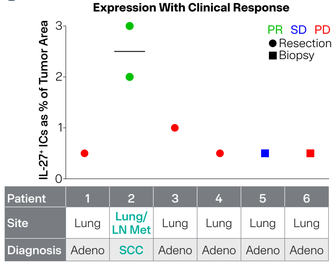
Casdozokitug Single Agent Clinical Activity Observed in NSCLC



- 2 confirmed PRs in PD-L1 negative or low, squamous NSCLC; 1 durable disease stabilization in adenocarcinoma; all 3 previously treated with anti-PD-(L)1 antibodies.
- Antitumor activity (PR) also observed in RCC (monotherapy) and HCC (combination with pembro).
- Quantitation of IL-27 expression by IHC on archival tissue from patient tumors showed a high density of IL-27 expression in patients with PR and stable disease (SD).

IL-27 Expression and Immune Excluded Phenotype Observed in the NSCLC Monotherapy Responder

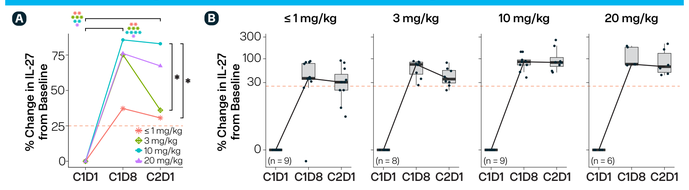




Patient	1	2	3	4	5	6
Site	Lung	Lung/ LN Met	Lung	Lung	Lung	Lung
Diagnosis	Adeno	SCC	Adeno	Adeno	Adeno	Adeno

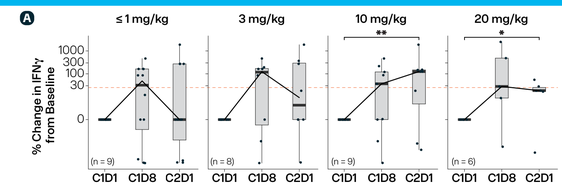
IHC analysis of archival tumor tissue sample from dose escalation NSCLC monotherapy responder (PR). **(A–B)** IHC for IL-27, PD-L1, and CD8 was performed on archival lung resection from a casdozo single-agent responder. The patient's tumor had low PD-L1 expression (CPS 10) and immune excluded phenotype based on CD8 expression. **(C)** IL-27 IHC and quantitation was performed on select patient samples for which archival tissue was available (n = 1 PR, 1 SD, 4 PD).

Casdozokitug Treatment Increases Circulating IL-27 Levels in the Blood

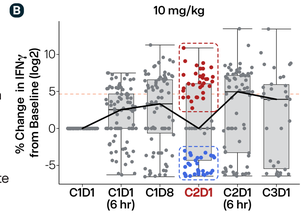


Casdozo administration increases circulating IL-27 in a dose-dependent manner, consistent with the antibody binding to its target and preventing cytokine clearance. Serum samples from monotherapy dose escalation patients were collected and analyzed by MSD assay. **(A)** Median IL-27 % change vs baseline (C1D1) for on-treatment (C1D8 and C2D1) samples. Negative % change median values are reported as zero. **(B)** IL-27 % change from baseline at indicated dose levels and time points. For statistical analysis, paired t-tests were used. The dashed horizontal lines indicate a 25% increase from baseline.

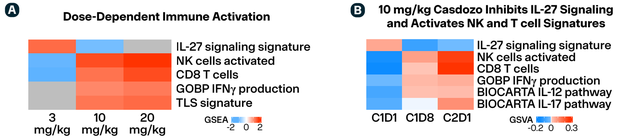
Casdozokitug Treatment Increases Circulating IFNγ Levels in the Blood of Cancer Patients

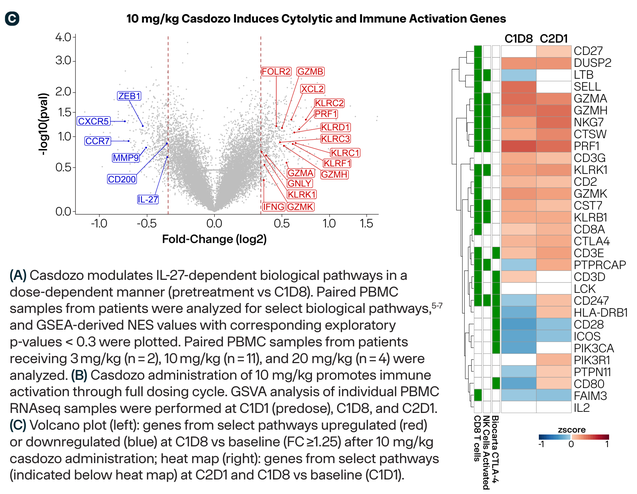


Casdozo administration increases circulating IFNγ, indicative of immune activation and confirming the MOA. IFNγ % change at indicated time points and doses vs baseline in serum of patients enrolled in **(A)** dose escalation cohorts and **(B)** in dose escalation and dose expansion cohorts (n = 68 at baseline), analyzed by MSD assay. Casdozo induced IFNγ through 1 dosing cycle (C2D1) in a subset of patients. The dashed horizontal lines indicate a 25% increase from baseline. Further studies will continue to evaluate if IFNγ increase is associated with clinical benefit.



Casdozokitug Inhibits IL-27 Signaling and Promotes NK and T cell Activation Gene Signatures





(A) Casdozo modulates IL-27-dependent biological pathways in a dose-dependent manner (pretreatment vs C1D8). Paired PBMC samples from patients were analyzed for select biological pathways,[5-7] and GSEA-derived NES values with corresponding exploratory p-values < 0.3 were plotted. Paired PBMC samples from patients receiving 3 mg/kg (n = 2), 10 mg/kg (n = 11), and 20 mg/kg (n = 4) were analyzed. **(B)** Casdozo administration of 10 mg/kg promotes immune activation through full dosing cycle. GSVA analysis of individual PBMC RNAseq samples were performed at C1D1 (predose), C1D8, and C2D1. **(C)** Volcano plot (left): genes from select pathways upregulated (red) or downregulated (blue) at C1D8 vs baseline (FC ≥1.25) after 10 mg/kg casdozo administration; heat map (right): genes from select pathways (indicated below heat map) at C2D1 and C1D8 vs baseline (C1D1).

Conclusions

- IL-27 is an immune cytokine that regulates antitumor immune responses in the TME.
- Casdozokitug is a novel, first-in-class human IgG1 Ab targeting IL-27 subunit alpha (p28) that selectively blocks IL-27 receptor signaling.
- Preclinical evidence shows anti-IL-27 Ab-mediated blockade of IL-27 results in significant antitumor activity in murine models when the tumor is present in lung and liver.
- Casdozokitug has demonstrated monotherapy and PD-1 inhibitor combination antitumor activity with a favorable safety profile in multiple solid tumors (cPR in treatment-refractory NSCLC and ccRCC patients; cPR in HCC patient in combination with pembrolizumab).
- Clinical biomarker data confirmed casdozokitug-mediated pharmacodynamic activity and proof-of-mechanism (immune activation).
- Encouraging clinical activity of casdozokitug in combination with atezolizumab and bevacizumab observed in first-line HCC (NCT05359861). > 60% of patients with tumor shrinkage on initial scans with 38% ORR to date in response evaluable set (n = 28): 3 CRs, 8 PRs (1 unconfirmed PR).[8]
- Clinical studies evaluating casdozokitug in combination with toripalimab are ongoing in NSCLC patients (NCT04374877) and planned as triplet treatment (casdozokitug/toripalimab/bevacizumab) in first-line HCC patients.

Abbreviations: Ab = antibody; adeno = adenocarcinoma; C*x*D*y* = Cycle *x* Day *y*; cPR = confirmed partial responder; ccRCC = clear cell renal cell carcinoma; CR = confirmed response; DC = dendritic cell; DLT = dose-limiting toxicity; EBI3 = Epstein-Barr virus-induced gene 3; ELISA = enzyme linked immunosorbent assay; GOBP = gene ontology biological process; GSEA = gene signature expression analysis; GSVA = gene set variation analysis; HCC = hepatocellular carcinoma; HNSCC = head and neck squamous cell carcinoma; IgG1 = immunoglobulin G class 1; IFNγ = interferon gamma; IHC = immunohistochemistry; IL = interleukin; MOA = mechanism of action; MSD = meso scale discovery; NASH = non-alcoholic steatohepatitis; NES = normalized enrichment score; *n*L = *n*th line of treatment; NSCLC = non-small cell lung cancer; PBMC = peripheral blood mononuclear cells; PD = progressive disease; PD-1 = programmed death-1 immunoglobulin superfamily member; ORR = objective response rate; pembro = pembrolizumab; PK = pharmacokinetics; PoM = proof of mechanism; PR = partial response; *Q#W* = every # weeks; RCC = renal cell carcinoma; SCC = squamous cell carcinoma; scRNAseq = single cell RNA sequencing; SCLC = small cell lung cancer; SD = stable disease; SEM = standard error of the mean; TAM = tumor-associated macrophages; TLS = tertiary lymphoid structures; TMA = tumor microarray; TME = tumor microenvironment; TNF = tumor necrosis factor; tori = toripalimab.

References: 1) Chihara et al, *Nature* 558, 2018 **2)** DeLong et al, *Immunohorizons* 3, 2019. **3)** Aghayev et al, *Cancer Discov*, 12, 2022. **4)** Mulder et al, *Immunity* 54, 2021. **5)** Genesets from Gene GOBP, an internally determined IL-27 signature: Surface IL-27, *J Immunother Cancer* 2021;9(Suppl 2):A1–A1054. **6)** TLS signature: Meylan et al, *Immunity* 2022. **7)** Custom genesets derived from the LM22 matrix comprised of gene coefficients from sorted immune cell sub-types: Chen et al, *Methods Mol Biol* 2018. **8)** Li, D et al. *JCO* 42, 470-470 (2024).

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