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

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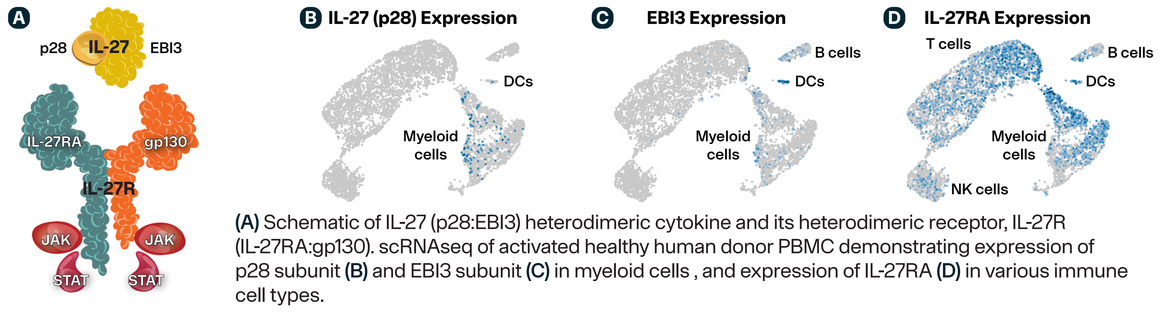
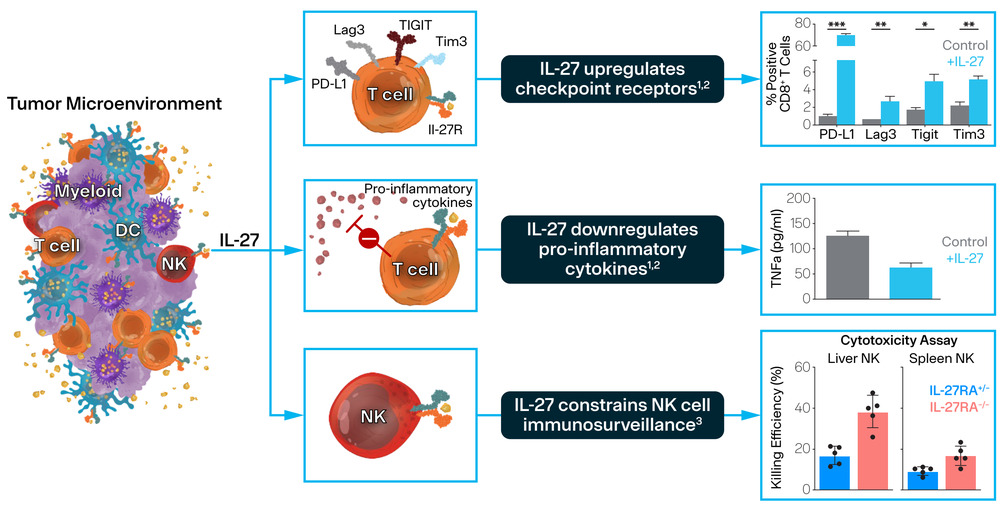
Background

- 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, that 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 that 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.



(A) Schematic of IL-27 (p28:EBI3) heterodimeric cytokine and its heterodimeric receptor, IL-27R (IL-27RA:gp130). scRNAseq of activated healthy human donor PBMC demonstrating expression of p28 subunit **(B)** and EBI3 subunit **(C)** in myeloid cells , and expression of IL-27RA **(D)** in various immune cell types.

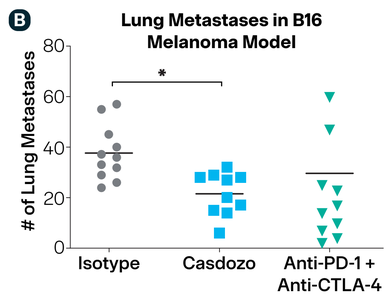
IL-27 Suppresses Antitumor Immunity in the Tumor Microenvironment



Treatment with Anti-IL-27 Antibody Results in Antitumor Activity in Lung and Liver in Mouse Tumor Models

(A)

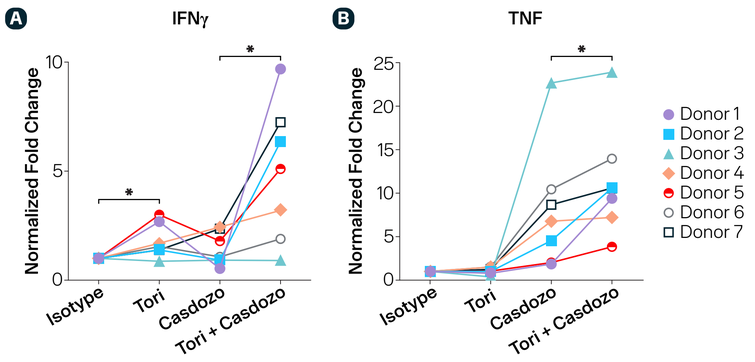
In Vivo Study	Tumor Location	Antitumor Activity (anti-IL-27 mAb)
Multiple subcutaneous syngeneic tumor models	Subcutaneous	No activity or acceleration of tumor growth
B16 lung metastasis model	Subcutaneous	No activity
	Lung	Antitumor activity
RCC orthotopic model, with lung metastasis	Kidney	No activity
	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. **(B)** 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). Lungs were collected on Day 18 and metastases calculated by quantitative image analysis. **(C)** CHS-381 (high-affinity anti-IL-27 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

Human PBMC from healthy donors 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.



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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

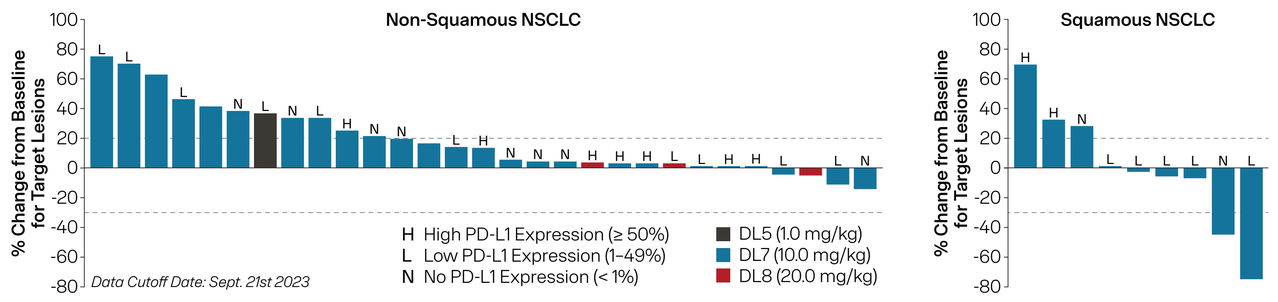
Study Overview: 10 mg/kg Q3W Casdozo Across 6 Cohorts

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

Clinical Data Summary:

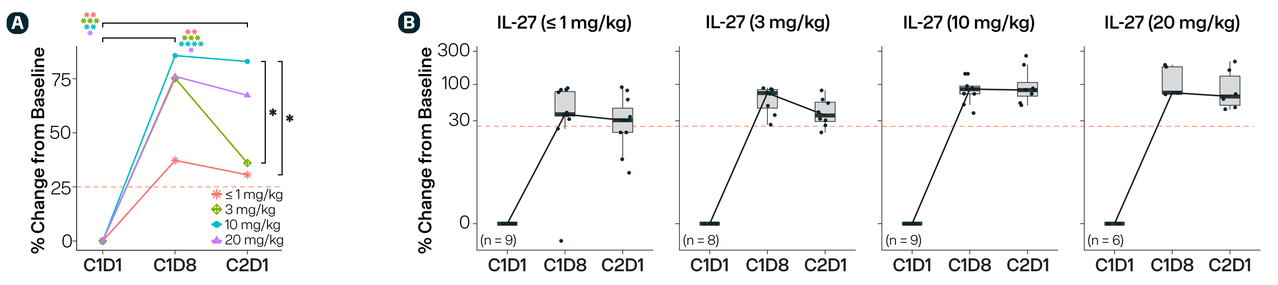
Safety	• Acceptable, no DLTs
Efficacy	• PRs: 1 ccRCC (casdozo), 1 NSCLC (casdozo), 1 HCC (casdozo/pembro)
Biomarkers	• Pharmacodynamic: complete IL-27 signaling inhibition • PoM: NK & T cell activation

Casdozokitug Single Agent Clinical Activity Observed in NSCLC



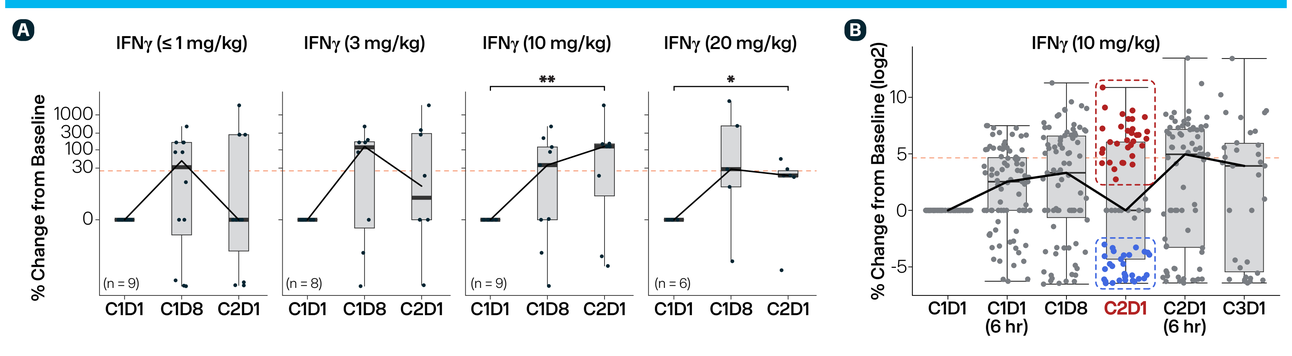
- 2 confirmed PRs in PD-L1 negative or low, squamous NSCLC; 1 durable disease stabilization in adenocarcinoma; all 3 previously treated with anti-PD-(L)1 antibodies.
- Antitumor activity (PR) also observed in RCC (monotherapy) and HCC (combination with pembro).
- Quantitation of IL-27 expression by IHC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

Casdozokitug Treatment Increases Circulating IL-27 Levels in the Blood



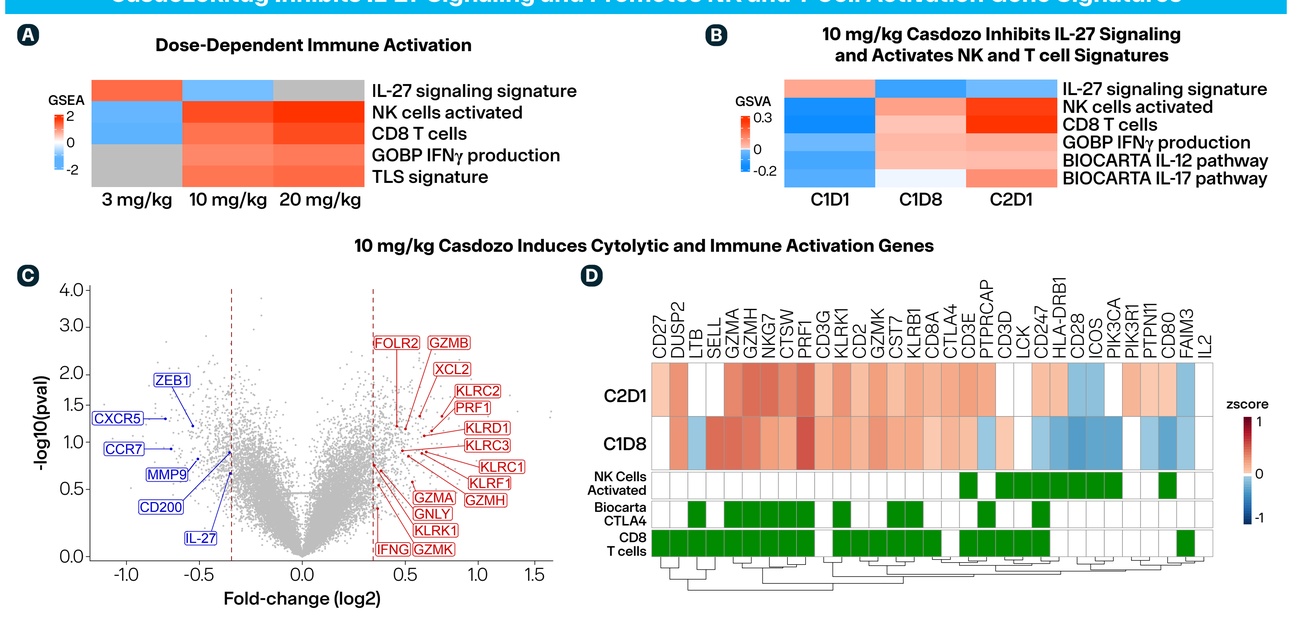
Casdozo administration increases circulating IL-27 in a dose-dependent manner, consistent with the antibody binding to its target and preventing cytokine clearance. Serum samples from monotherapy dose escalation patients were collected and analyzed by MSD assay. **(A)** Median IL-27 % change vs baseline (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. Patient serum samples collected from monotherapy dose escalation and expansion cohorts were analyzed by MSD assay. **(A)** IFNγ % change at C1D8 and C2D1 vs baseline (C1D1) in casdozo dose escalation cohorts at indicated doses. Statistical analysis by paired ks-tests. **(B)** IFNγ % change at indicated time points vs baseline from patients enrolled in monotherapy dose escalation and dose expansion at 10 mg/kg (n = 68 at baseline). Casdozo induced IFNγ through 1 dosing cycle (C2D1) in a subset of patients. The dashed horizontal lines indicate a 25% increase from baseline.

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[4-6] and GSEA-derived NES values with corresponding exploratory p-values < 0.3 were plotted. Gene sets failing the p-value threshold are colored gray. **(B)** Casdozo administration of 10 mg/kg promotes immune activation through full dosing cycle. GSVA analysis of individual PBMC RNAseq samples were performed at the timepoints indicated. **(C)** Select genes upregulated (red) or downregulated (blue) at C1D8 vs baseline (FC ≥ 1.25) after 10 mg/kg casdozo administration. **(D)** Heat map (right): select pathway genes at C2D1 and C1D8 vs baseline (C1D1). Paired PBMC samples from patients receiving 3 mg/kg (n=2), 10 mg/kg (n=11) and 20 mg/kg (n=4) were analyzed.

Conclusions

- IL-27 suppresses antitumor immune responses in the TME.
- Anti-IL-27 Ab-mediated blockade of IL-27 results in significant antitumor activity in lung and liver of tumor-bearing mice.
- Casdozokitug has demonstrated antitumor activity as monotherapy and in combination with a PD-1 inhibitor, with favorable safety profile in multiple solid tumors (treatment-refractory NSCLC and ccRCC patients; confirmed PR 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 is observed in first-line HCC (NCT05359861). > 60% of patients demonstrated tumor shrinkage on initial scans, with 38% ORR to date in response-evaluable set (n = 28): 3 CRs, 8 PRs (1 unconfirmed PR).[7]
- Clinical studies evaluating casdozokitug in combination with toripalimab are ongoing in NSCLC patients (NCT04374877) and planned as triplet therapy (casdozokitug/toripalimab/bevacizumab) in first-line HCC patients.

Abbreviations: Ab = antibody; adeno = adenocarcinoma; C*x*D*y* = Cycle *x* Day *y*; CR = confirmed response; DC = dendritic cell; DLT = dose-limiting toxicity; EBI3 = Epstein-Barr virus-induced gene 3; GOBP = gene ontology biological process; GSEA = gene signature expression analysis; GSVA = gene set variation analysis; HCC = hepatocellular carcinoma; IHC = immunohistochemistry; IFNγ = interferon gamma; *n*L = *n*° line of treatment; MSD = Meso Scale Discovery; NASH = non alcoholic steatohepatitis; NES = normalized enrichment score; NSCLC = non-small cell lung cancer; PBMC = peripheral blood mononuclear cells; PD-1 = programmed death-1 immunoglobulin superfamily member; ORR = objective response rate; pembro = pembrolizumab; PR = partial response; Q*n*W = every *n* weeks; RCC = renal cell carcinoma; SCC = squamous cell carcinoma; scRNAseq = single-cell RNA sequencing; SEM = standard error of the mean; TAM = tumor associated macrophages; TLS = tertiary lymphoid structures; TMA = tumor microarray; TME = tumor microenvironment; 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)** Genesets from Gene GOBP, an internally determined IL-27 signature: Surface IL-27, *J Immunother Cancer* 2021;9(Suppl 2):A1-A1054. **5)** TLS signature: Meylan et al, *Immunity* 2022. **6)** Custom genesets derived from the LM22 matrix comprised of gene coefficients from sorted immune cell sub-types: Chen et al, *Methods Mol Biol* 2018. **7)** 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.