# Casdozokitug, a novel IL-27 inhibitor, in combination with PD-(L)1 and VEGF blockade in hepatocellular carcinoma: Results from the CADILYZE™ Phase 2 study

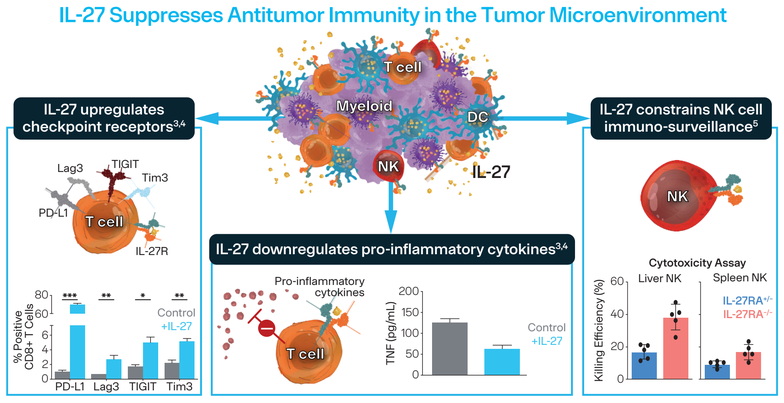

**Xiao Wang[1], Narendiran Rajasekaran[1], Stephen Lam Chan[2], Kun-Ming Rau[3], Amit Mahipal[4], Eric Cheung[5], Thomas Yau[6], Junaid Arshad[7], Chih-Hung Hsu[8], Erica Tsang[9], Su Pin Choo[10], Min-Hee Ryu[11], Koho Iizuka[1], Hong Tang[1], Jeyarama Ananta[1], Sruthi Ravindranathan[1], Anne Uyei[1], Theresa LaVallee[1], Rosh Dias[1], Varun N. Kapoor[1], George Lau[12], Daneng Li[13]**

[1]Coherus Oncology, Redwood City, CA, USA; [2]State Key Laboratory of Translational Oncology, Department of Clinical Oncology, The Chinese University of Hong Kong, Hong Kong, China; [3]E-Da Cancer Hospital, Kaohsiung City, Taiwan; [4]University Hospitals Seidman Cancer Center, Cleveland, OH, USA; [5]Cancer and Blood Specialty Clinic, Los Alamitos, CA, USA; [6]The University of Hong Kong, Hong Kong, China; [7]University of Arizona Cancer Center, Tucson, AZ, USA; [8]National Taiwan University Hospital, Taipei City, Taiwan; [9]The Princess Margaret Cancer Centre, Toronto, ON, Canada; [10]Curie Oncology, National Cancer Centre, Singapore; [11]University of Ulsan College of Medicine - Asan Medical Center (AMC), Seoul, South Korea; [12]Humanity and Health Clinical Trial Centre, Hong Kong, China; [13]City of Hope Comprehensive Cancer Center, Duarte, CA, USA.

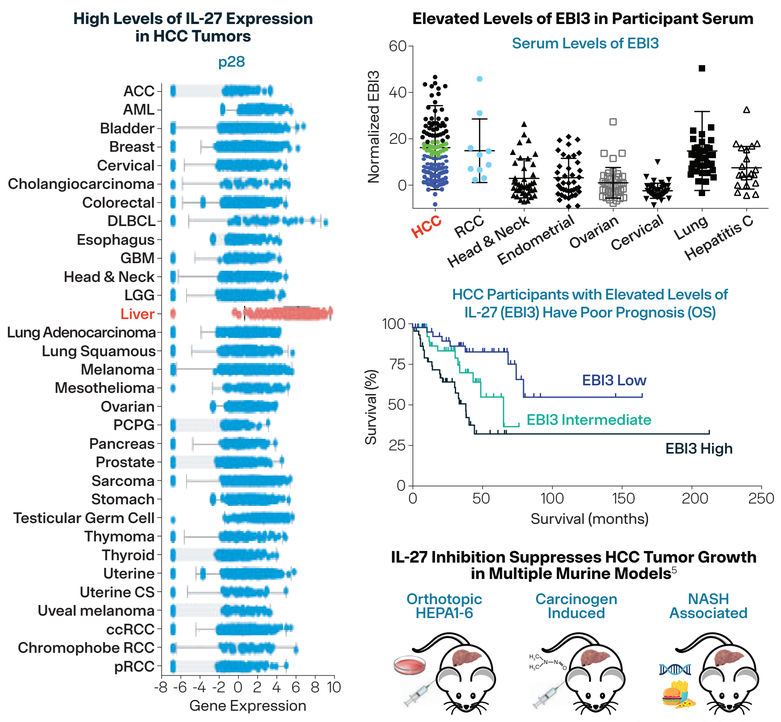

## Background

- Casdozokitug (CHS-388) is a first-in-class human monoclonal antibody that binds with high affinity to the IL-27 p28 subunit, thereby blocking IL-27/IL-27R signaling and reversing IL-27–mediated immune suppression
- IL-27, a heterodimeric cytokine composed of EBI3 and p28 subunits, is highly expressed by tumor-associated macrophages (TAMs) across multiple cancers, including hepatocellular carcinoma (HCC); elevated circulating IL-27 levels are associated with an increased risk of HCC
- Preclinically, inhibiting IL-27 signaling resulted in antitumor activity across multiple in vivo models of hepatocarcinogenesis, showing a requirement for enhanced NK cell–mediated cytotoxicity
- In the Phase 1 study (NCT04374877), casdozokitug demonstrated a favorable safety profile, antitumor activity (PR), and enhanced immune activity as a single agent and in combination with PD-1 inhibitors in NSCLC, RCC, and HCC[1]
- Here we report from the CADILYZE™ 201 Phase 2 study (NCT05359861), casdozokitug in combination with atezolizumab/bevacizumab demonstrated a manageable safety profile and a CR rate of 17.9% in unresectable 1L metastatic HCC, with responders exhibiting increased NK cell activity and early serum IFN-γ increases[2]
- The clinical study schema and biomarker plan for the ongoing CADILYZE™ 202 study (NCT06679985) that compare the casdozokitug/toripalimab (PD-1 monoclonal antibody)/bevacizumab triplet to toripalimab/bevacizumab in 1L participants with unresectable, locally advanced, or metastatic HCC are also presented

### IL-27 Suppresses Antitumor Immunity in the Tumor Microenvironment




### Rationale for Blocking IL-27 in Hepatocellular Carcinoma




### Phase 1 Dose Escalation and Dose Expansion Study of Casdozokitug in Solid Tumors

**Dose Escalation Completed**

Monotherapy dose escalation (q4w) in participants 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 squamous NSCLC
***Biomarkers*** Pharmacodynamics: complete IL-27 signaling inhibition, NK & T cell activation

**Dose Expansion Completed**

10 mg/kg q4w casdozokitug (q3w in the pembrolizumab combination)
6 Cohorts across 3 indications: NSCLC, HCC, and RCC

***Clinical Data Summary:***
***Safety*** Acceptable, no DLTs
***Efficacy*** **PRs:** 1 ccRCC (casdozokitug), 1 squamous NSCLC (casdozokitug), 1 HCC (casdozokitug/pembrolizumab)
***Biomarkers*** Pharmacodynamics: complete IL-27 signaling inhibition, NK & T cell activation




**Casdozokitug Monotherapy Demonstrated Enhanced Immune Activity in Advanced Solid Tumors, Including HCC**

(A) Serum samples (n = 12) collected at C1D1 (baseline), C1D8, and C2D1 in participants with advanced solid tumors treated with casdozokitug monotherapy at 10 mg/kg and 20 mg/kg in the dose escalation arm and tested for IFN-γ, IL-12, and TNF with Meso Scale Discovery (MSD) platform. Statistical test: one-sample Wilcoxon test.

## CADILYZE™ 201: Clinical Study Design and Response Outcomes

### CADILYZE™ 201: A Phase 2 Trial Evaluating the Efficacy and Safety of Casdozokitug in Combination with Atezolizumab/Bevacizumab in Participants with 1L Advanced or Metastatic HCC

**Open-Label (N = 30)**
1L unresectable/metastatic HCC
aPD-(L)1 naïve
≥1 measurable lesion
BCLC B or C
Child-Pugh A
ECOG PS 0-1
Controlled HBV or cured HCV

→ Atezolizumab 1200 mg + Bevacizumab 15 mg/kg + Casdozokitug 10 mg/kg — IV q3w →

**Primary endpoint:** Safety
**Key secondary endpoints:** PFS*, ORR*, DCR

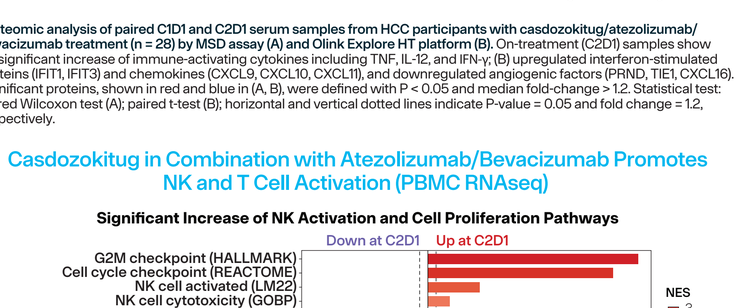
*RECIST v1.1 (primary) and mRECIST (secondary)

| Best overall response (RECIST v1.1), n (%) | Response evaluable (n = 28)* |
|---|---|
| Overall response rate (ORR) | 11 (39.3) |
| Complete response (CR) | 5 (17.9) |
| Partial response (PR) | 6 (21.4) |
| Stable disease (SD)† | 8 (28.6) |
| Progressive disease (PD) | 9 (32.1) |

*The number of participants analyzed for efficacy (RECIST n = 28) is lower than the number of participants analyzed for safety (N = 30) due to no post-baseline scan being obtained; †SD includes 1 participant with an unconfirmed PR.

Casdozokitug in combination with atezolizumab/bevacizumab demonstrated:
- Clinical response irrespective of viral status (eg, HBV, HCV, none)
- A CR rate of 17.9%, which is higher than the 8% or 3% CR rate reported in prior Phase 3 studies in HCC (IMbrave150[6] and HIMALAYA[7]), respectively
- The combination had an acceptable safety profile, with AEs consistent with the known profiles of the individual agents and no new safety signals observed

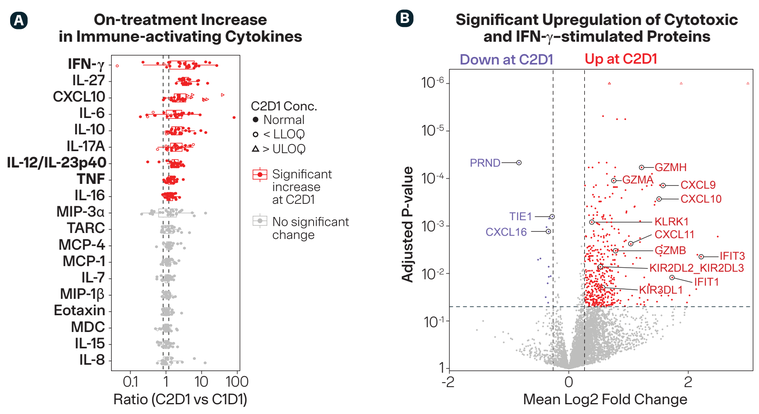
### Casdozokitug in Combination with Atezolizumab and Bevacizumab (SOC) in HCC Demonstrated Improved Antitumor Activity, Including Depth of Response (CR Rate)




Horizontal dashed lines indicate +20% and –30% change from baseline. Responses are reflective of individual target lesion response. Clinical data cut: November 10, 2025.

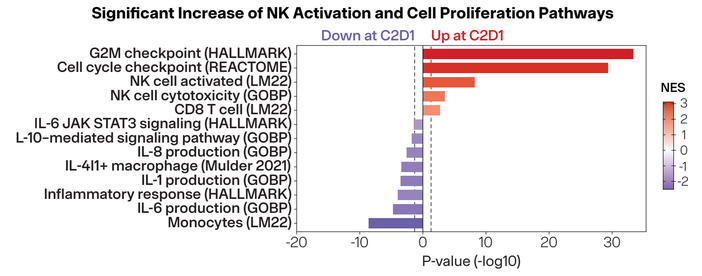
## CADILYZE™ 201: Pharmacodynamic Activity of Casdozokitug/Atezolizumab/Bevacizumab

### Casdozokitug in Combination with Atezolizumab/Bevacizumab Promotes Robust Peripheral Immune Activation in HCC (Serum Protein)




**Proteomic analysis of paired C1D1 and C2D1 serum samples from HCC participants with casdozokitug/atezolizumab/bevacizumab treatment (n = 28) by MSD assay (A) and Olink Explore HT platform (B).** On-treatment (C2D1) samples show (A) significant increase of immune-activating cytokines including TNF, IL-12, and IFN-γ; (B) upregulated interferon-stimulated proteins (IFIT1, IFIT3) and chemokines (CXCL9, CXCL10, CXCL11), and downregulated angiogenic factors (PRND, TIE1, CXCL16). Significant proteins, shown in red and blue in (A, B), were defined with P < 0.05 and median fold-change > 1.2. Statistical test: paired Wilcoxon test (A); paired t-test (B); horizontal and vertical dotted lines indicate P-value = 0.05 and fold change = 1.2, respectively.

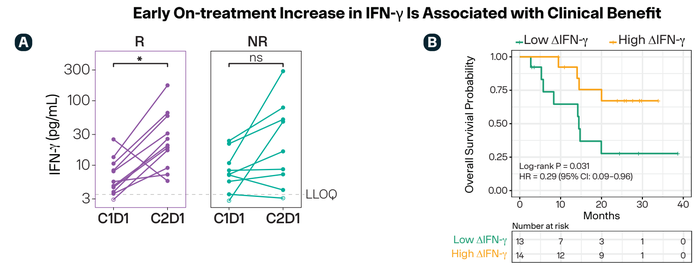
### Casdozokitug in Combination with Atezolizumab/Bevacizumab Promotes NK and T Cell Activation (PBMC RNAseq)



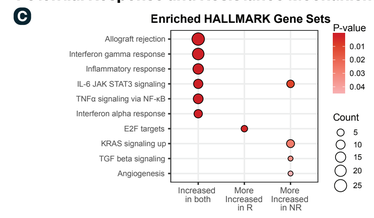

**Bulk RNAseq of paired PBMC samples at C1D1 and C2D1 from HCC participants with casdozokitug/atezolizumab/bevacizumab treatment (n = 21).** Gene set enrichment analysis (GSEA) comparing C2D1 vs C1D1 (n = 21) shows significant upregulation of NK / T activation and cell proliferation, and downregulation of inflammatory and myeloid-associated gene sets. Vertical dotted lines indicate a P-value = 0.05.

## CADILYZE™ 201: Biomarkers Associated with Clinical Response

**Early On-treatment Increase in IFN-γ Is Associated with Clinical Benefit**

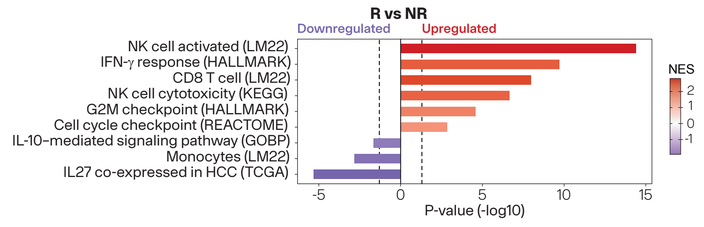



**Distinct On-treatment Proteomic Signatures Reveal Potential Response and Resistance Mechanisms**



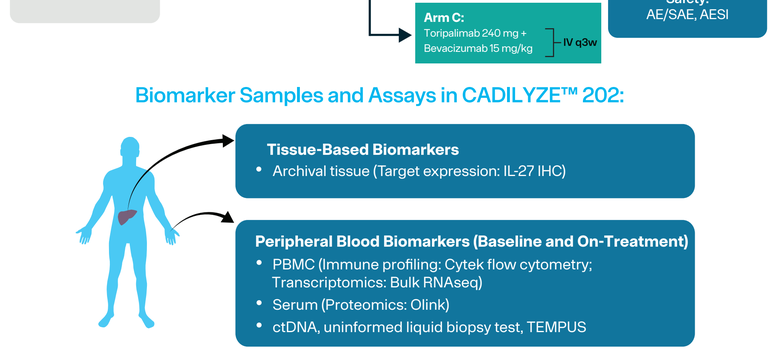

**Response-associated on-treatment changes in circulating protein biomarkers.** (A) Significant increase in circulating IFN-γ at C2D1 compared with baseline in responders (R; CR/PR, n = 11) but not in non-responders (NR; PD, n = 9). (B) On-treatment increase of IFN-γ is associated with longer OS. Kaplan-Meier survival curves compare OS between participants stratified by the median on-treatment change of IFN-γ. The P-value was calculated using the log-rank test (n = 27; includes response-evaluable participants with cytokine data available). (C) HALLMARK gene sets enriched in sets of proteins using hypergeometric test. R-specific proteins were enriched in HALLMARK_E2F_TARGETS (proliferation). NR-specific proteins were enriched in IL-6/JAK/STAT3, TGF-β signaling, and angiogenesis, consistent with HCC resistance.

### Stronger Peripheral T and NK Cell Activation Signatures in Responders (PBMC RNAseq)




**On-treatment transcriptomic changes (C2D1 compared with pre-treatment, C1D1) correlate with clinical response.** Pre-ranked GSEA on R vs NR (n = 7 per group) in C2D1-C1D1 differences in PBMCs. R compared to NR, show a clear enrichment of pro-inflammatory/antitumorigenic pathways (including NK cell activation, IFN-γ response, CD8 T-cell cytotoxicity, and cell cycle) and suppression of signatures associated with monocyte and IL-10, as well as IL-27 co-expression genes (HCC-TCGA). Vertical dotted lines indicate a P-value = 0.05. Statistical test: Limma for differential analysis of genes, fgsea for gene set enrichment analysis.

## CADILYZE™ 201: Preliminary Association of Higher Level of IL-27+ Tumor-Associated Macrophages in Archival Tissue Samples with Clinical Response (CR/PR)




| Participant | #1 | #2 | #3 | #4 | #5 | #6 | #7 |
|---|---|---|---|---|---|---|---|
| Site | Liver | Liver | Liver | Liver | Liver | Liver | LN Met |
| Viral status | Neg | HBV | HBV | HCV | Neg | Neg | HBV |
| IL-27 score | 1.5 | 2 | 1 | 0 | 0 | 0.5 | 1 |

Resection
Biopsy
Partial/complete response
Stable disease
Progressive disease

(A) Immunohistochemical staining for IL-27 was performed on archival resection and biopsy samples using an independently validated assay using polyclonal IL-27 antibody AF2526. (B) Samples were scored blindly based on semi-quantitative scoring system (0-3+) evaluating the abundance of IL-27+ tumor-associated macrophages (TAMs).

## CADILYZE™ 202: Randomized Phase 2 Study Evaluating Inhibition of IL-27, PD-1, and VEGF

### CADILYZE™ 202: A Phase 2 Trial Evaluating the Efficacy and Safety of Casdozokitug in Combination with Toripalimab/Bevacizumab in Participants with 1L Advanced or Metastatic HCC

**Participant Population:**
- 1L unresectable / metastatic HCC
- ≥1 measurable lesion
- Not suitable for surgical or local therapy
- Child-Pugh A
- ECOG PS score: 0 or 1
- Controlled HBV or cured HCV

**Stratification Factors:**
- Geographic region: Asia, excluding Japan, vs the rest of the world
- Macrovascular invasion or extrahepatic spread of disease (presence vs absence)

N = 75 → R in 1:1:1

- **Arm A:** Toripalimab 240 mg + Bevacizumab 15 mg/kg + Casdozokitug dose level A — IV q3w
- **Arm B:** Toripalimab 240 mg + Bevacizumab 15 mg/kg + Casdozokitug dose level B — IV q3w
- **Arm C:** Toripalimab 240 mg + Bevacizumab 15 mg/kg — IV q3w

**Primary endpoint:** ORR
**Key secondary endpoints:** DoR, PFS
**Secondary endpoints:** OS, DCR
**Safety:** AE/SAE, AESI

### Biomarker Samples and Assays in CADILYZE™ 202:



**Tissue-Based Biomarkers**
- Archival tissue (Target expression: IL-27 IHC)

**Peripheral Blood Biomarkers (Baseline and On-Treatment)**
- PBMC (Immune profiling: Cytek flow cytometry; Transcriptomics: Bulk RNAseq)
- Serum (Proteomics: Olink)
- ctDNA, uninformed liquid biopsy test, TEMPUS

## Conclusions

- IL-27 is highly expressed in HCC, and preclinical and early clinical studies show that inhibition of IL-27 promotes antitumor activity
- CADILYZE 201™ study reveals that casdozokitug in combination with SOC treatment of 1L HCC participants results in immune activation, and NK cell activation and IFN-γ increases associate with better clinical benefit
- CADILYZE 202™ is a randomized Phase 2 study evaluating toripalimab in combination with bevacizumab with and without casdozokitug with clinical data maturing
- Future analysis will evaluate molecular response and radiographic tumor measurements as well as PFS

**Abbreviations**: 1L = first line; ACC = adrenocortical carcinoma; AE = adverse event; AESI = adverse event of special interest; AML = acute myeloid leukemia; BCLC = Barcelona Clinic Liver Cancer; CR = complete response; CxDy = Cycle x Day y; DC = dendritic cell; DCR = disease control rate; DLBCL = diffuse large B-cell lymphoma; DLTs = dose-limiting toxicities; DoR = duration of response; EBI3 = Epstein-Barr virus–induced gene 3/IL-27B subunit; ECOG PS = Eastern Cooperative Oncology Group Performance Status; GSEA = gene set enrichment analysis; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; IFN-γ = interferon gamma; IHC = immunohistochemistry; IL = interleukin; IV = intravenous; LLOQ = lower limit of quantification; mRECIST = modified Response Evaluation Criteria in Solid Tumors; MSD = Meso Scale Discovery; NES = normalized enrichment score; NK = natural killer; NR = non-responder; NSCLC = non-small cell lung cancer; ORR = overall response rate; OS = overall survival; p28 = IL-27A subunit; PBMC = peripheral blood mononuclear cell; PD = progressive disease; PD-(L)1 = programmed death (ligand)-1; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; qxw = every x weeks; R = responder; RCC = renal cell carcinoma; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SAE = serious adverse event; SD = stable disease; SOC = standard of care; TAMs = tumor-associated macrophages; TGF = transforming growth factor; TNF = tumor necrosis factor; ULOQ = upper limit of quantification; VEGF = vascular endothelial growth factor. **Statistics**: * = P < 0.05; ** = P < 0.01; *** = P < 0.001; ns = not significant.


**References**: (1) Li, et al. *J Clin Oncol*. 2025;43:TPS4217. (2) Rajasekaran, et al. *Cytokines*. 2025;poster PB-020. (3) Chihara, et al. *Nature*. 2018;558:454-459. (4) DeLong, et al. *Immunohorizons*. 2019;3:13-25. (5) Aghayev, et al. *Cancer Discov*. 2022;12:1960-1983. (6) Finn, et al. *N Engl J Med*. 2020;382:1894-1905. (7) Abou-Alfa, et al. *NEJM Evid*. 2022;1(8):EVIDoa2100070.



**Acknowledgments**: The authors would like to thank the participants and their families, caregivers, and investigators involved in this study. Medical writing, editorial assistance, and poster production support were provided by The Phillips Group Oncology Communications, Inc., funded by Coherus Oncology, Inc.



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