City of Hope®

Multidisciplinary Approaches to Cancer Symposium

Next Generation Therapies in HCC

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Disclosures

- Consultant for AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Coherus, Eisai, Exelixis, Genentech, Transthera, Trisalus, & Merus; and Grant Research Support from AstraZeneca

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This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.

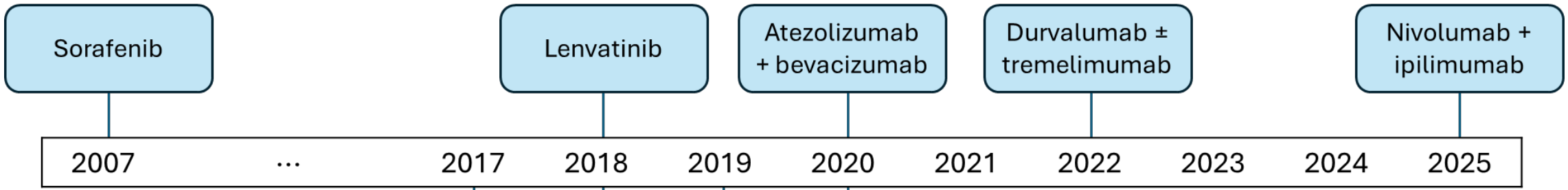
Introduction: Primary Liver Cancer

- Sixth-leading cancer diagnosis; third-leading cause of cancer-related deaths worldwide[1]
- Hepatocellular carcinoma (HCC) comprises up to 90% of liver cancers[1, 2]
- 5-year survival rates for primary liver cancer:[3]
    - All stages: 21.6%
    - Metastatic/unresectable disease: 3.3%
- Up to 70% of HCC patients have unresectable disease at time of diagnosis[4]
    - Typically limited to **systemic treatments**[2, 4–7]

1. Bray et al. *CA Cancer J Clin* 2024 2. Llovet et al. *Nat Rev Dis Primers* 2021 3. https://seer.cancer.gov/statfacts/html/livibd.html
4. Gholam et al. *Cancers* 2019 5. Li et al. *Cancers (Basel)* 2019 6. Sonbol et al. *JAMA Oncol* 2020 7. Vogel et al. *Lancet* 2022

HCC Systemic Treatment Landscape

First-Line Treatments

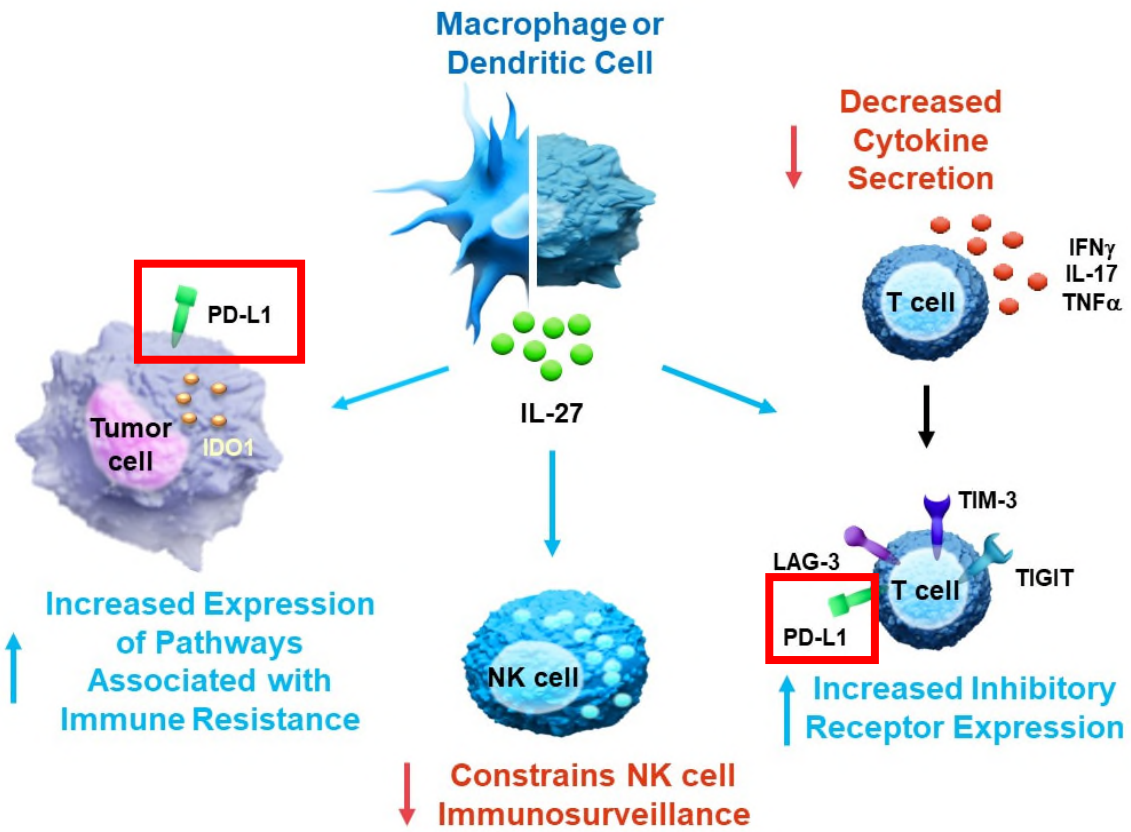


Second-Line and Beyond Treatments

- Regorafenib
- Pembrolizumab[1]
- Ramucirumab
- Nivolumab + ipilimumab[2]
- Cabozantinib

1. Accelerated FDA approval has not been removed
2. Accelerated FDA approval

IL-27: Potential Target for HCC Treatment

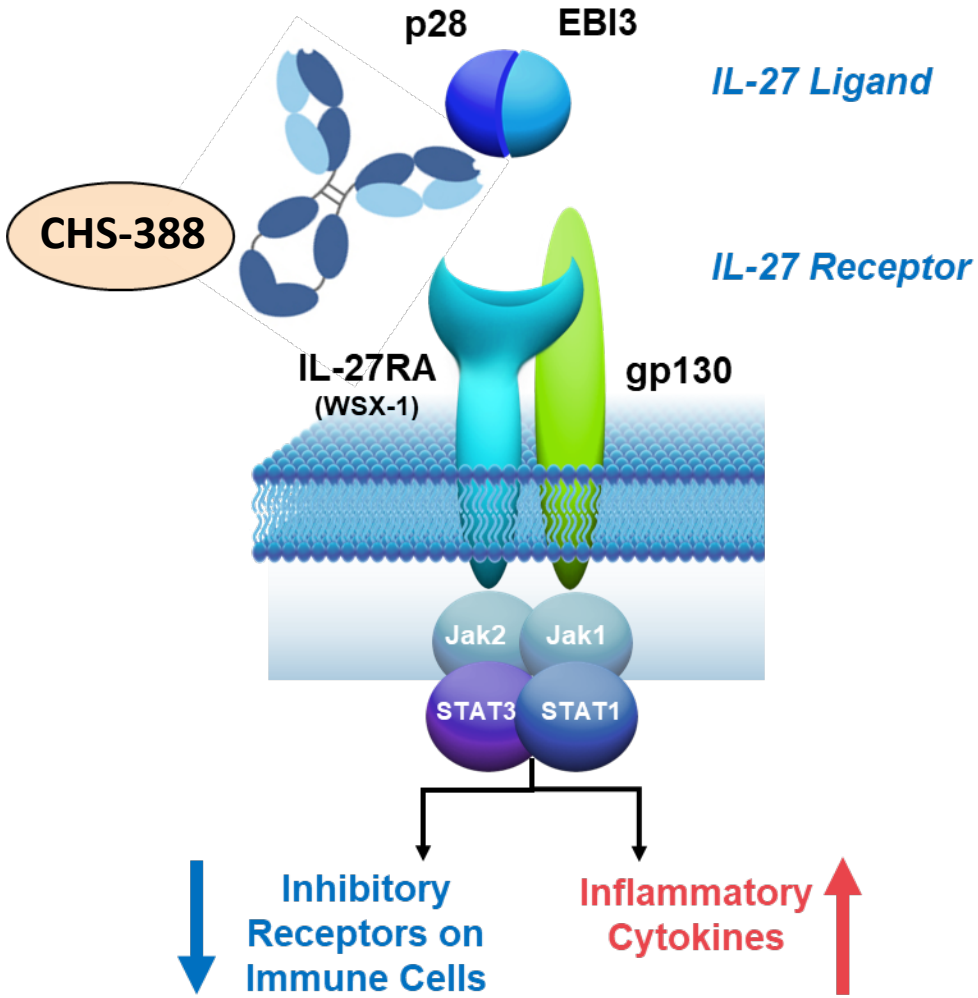


- Immunoregulatory cytokine[1]
  - Inhibits antitumor immune response[2, 3]
  - Increases immune resistance[2, 3]
  - Upregulates PD-L1 expression on tumor cells and T cells[4–6]
  - **Promotes HCC development in murine models[7]**

Image, 1. Naing et al. *J Clin Oncol* 2022 (2501) 2. Villarino et al. *Immunity* 2003 3. DeLong et al. *Immunohorizons* 2019
4. Carbotti et al. *Oncotarget* 2015 5. Chihara et al. *Nature* 2018 6. Golan et al. *J ImmunoTher Cancer* 2022 7. Aghayev et al. *Cancer Discov* 2022

Casdozokitug (CHS-388): IL-27 Antagonist

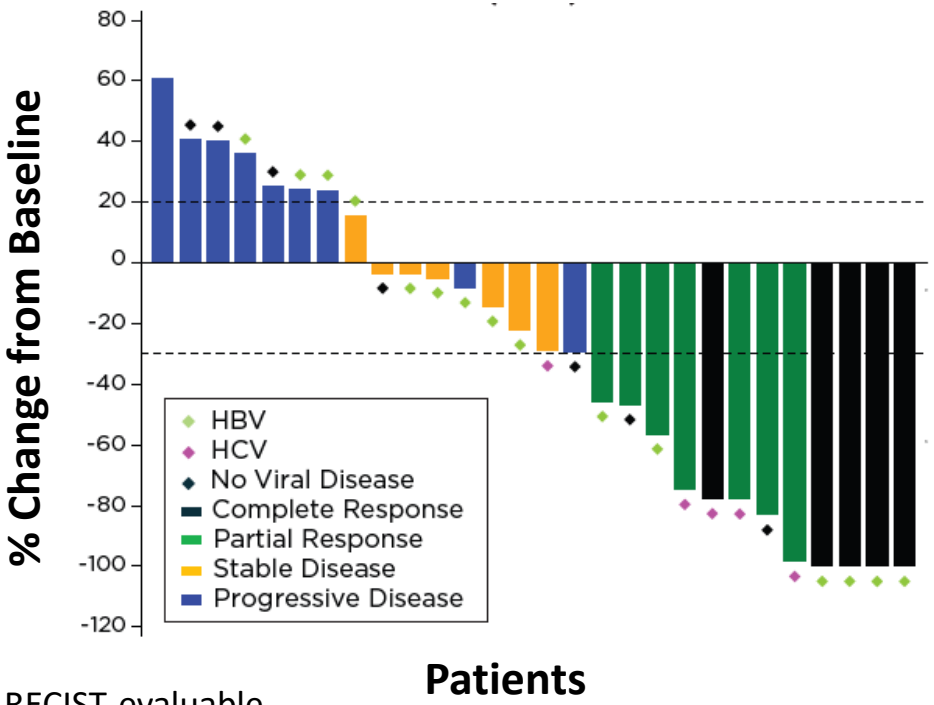
- First-in-class anti-IL-27 antibody
  - Targets p28 subunit
- Inhibits downstream Jak/STAT signaling
- Induces increases in serum IFN-ɣ and NK cell gene activation in cancer patients
  - **Suggests reversal of IL-27–mediated immune suppression**



Naing et al. *J Clin Oncol* 2022 (2501)
Li et al. *J Clin Oncol* 2024 (470)

Targeting IL-27: Casdozokitug + Atezolizumab + Bevacizumab

Best Percent Change from Baseline in Sum of Target Lesions (n=28)



RECIST-evaluable

	RECIST 1.1 (n=29)	mRECIST (n=28)
Median PFS, months (95% CI)	8.1 (1.9–13.6)	--
Median OS, months (95% CI)	19.9 (14.2–NR)	--
ORR, n (%)	11 (37.9)	12 (42.9)
DCR, n (%)	19 (65.5)	19 (67.9)
Best Overall Response, n (%)		
Complete Response	5 (17.2)	5 (17.9)
Partial Response (confirmed)	6 (20.7)	7 (25.0)
Stable Disease*	8 (27.6)	7 (25.0)
Progressive Disease	9 (31.0)	8 (28.6)
Not Evaluable	1 (3.4)	1 (3.6)

* Includes 1 patient with an unconfirmed PR at the time of data cutoff

A Randomized Phase 2 Study of Casdozokitug in Combination with Toripalimab Plus Bevacizumab in Patients With Unresectable and/or Locally Advanced or Metastatic Hepatocellular Carcinoma (NCT06679985)

Eligibility Criteria

- Unresectable/metastatic HCC
- Not amenable to curative therapy
- ≥1 measurable lesion per RECIST v1.1
- Child-Pugh A
- ECOG PS 0 or 1

x Prior systemic therapy for HCC
x Previously received anti-IL-27 antibody or targeted therapy
x Fibrolamellar or sarcomatoid HCC or mixed cholangiocarcinoma/HCC
x Uncontrolled HBV and/or uncured HCV

Toripalimab 240 mg + Bevacizumab 15 mg/kg + Casdozokitug 700 mg IV Q3W (n=24)

Toripalimab 240 mg + Bevacizumab 15 mg/kg + Casdozokitug 1400 mg IV Q3W (n=24)

Toripalimab 240 mg + Bevacizumab 15 mg/kg IV Q3W (n=24)

Treatment up to 2 years or until disease progression or intolerable toxicity

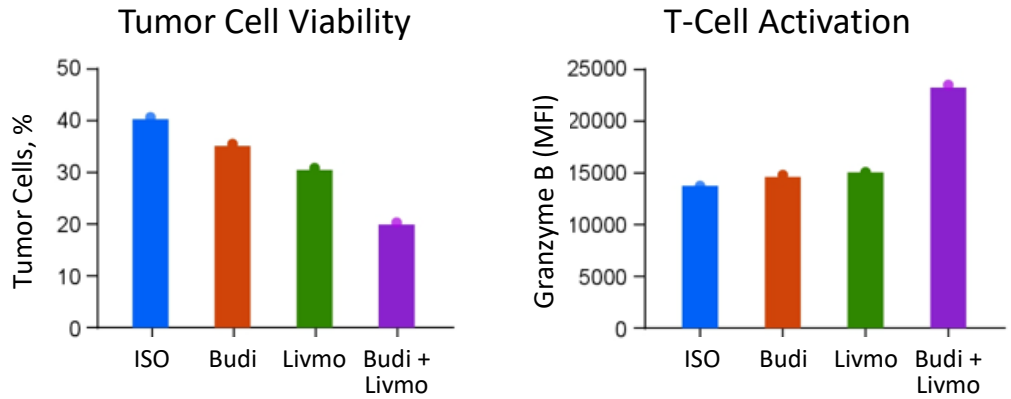
Primary endpoint
- Objective response rate

Secondary endpoints
- Duration of response
- Progression-free survival
- Overall survival
- Disease control rate
- Safety

Stratification factors
- Region (Asia [excluding Japan] vs rest of world)
- Macrovascular invasion or extrahepatic spread of disease (presence vs absence)

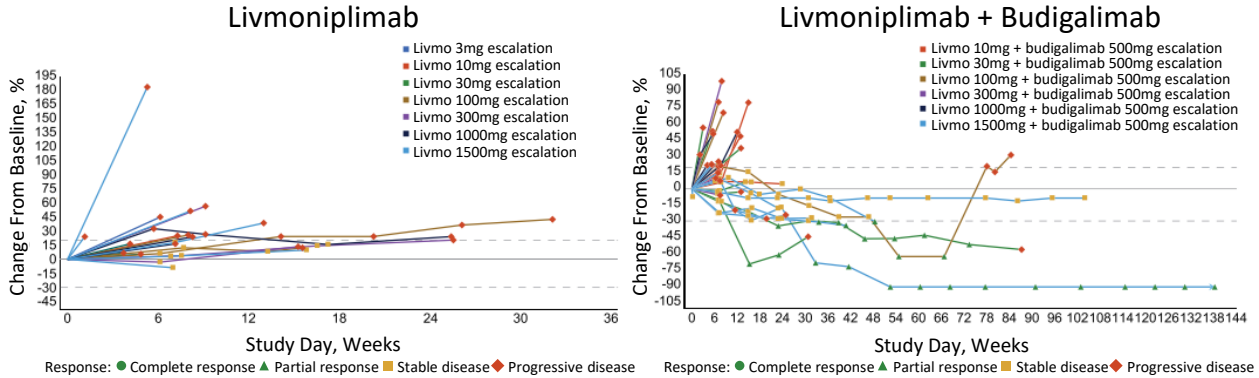
Targeting TGF-β: Livmoniplimab + Budigalimab

- Livmoniplimab + budigalimab (anti-PD-1) enhanced tumor cell killing and T-cell activity in tumor explants[1]
- Phase 1 study of livmoniplimab + budigalimab in patients with advanced solid tumors[2, 3]
  - Included 12 patients with advanced HCC who progressed on ≥1 systemic therapy (PD-1/L1 inhibitors not permitted)[2]
  - Response rate: 42% (5 of 12 patients; n=4 per RECIST 1.1; n=5 per iRECIST)



ISO, isotype antibody; MFI, mean/median fluorescence intensity.

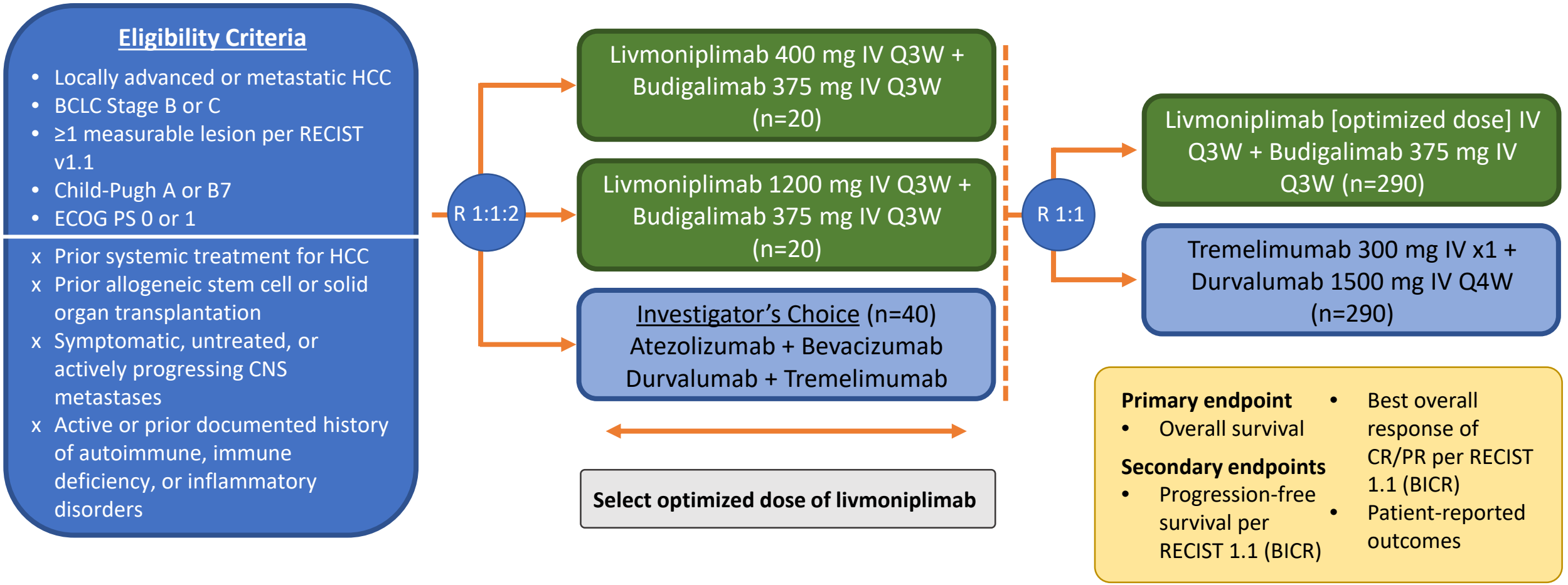
Percent change in target lesion sum diameter measurements from baseline in response-evaluable population



Response-evaluable population = received at least 1 dose of study drug and have either had at least 1 post-dose tumor assessment or discontinued treatment due to AE, PD, or death.

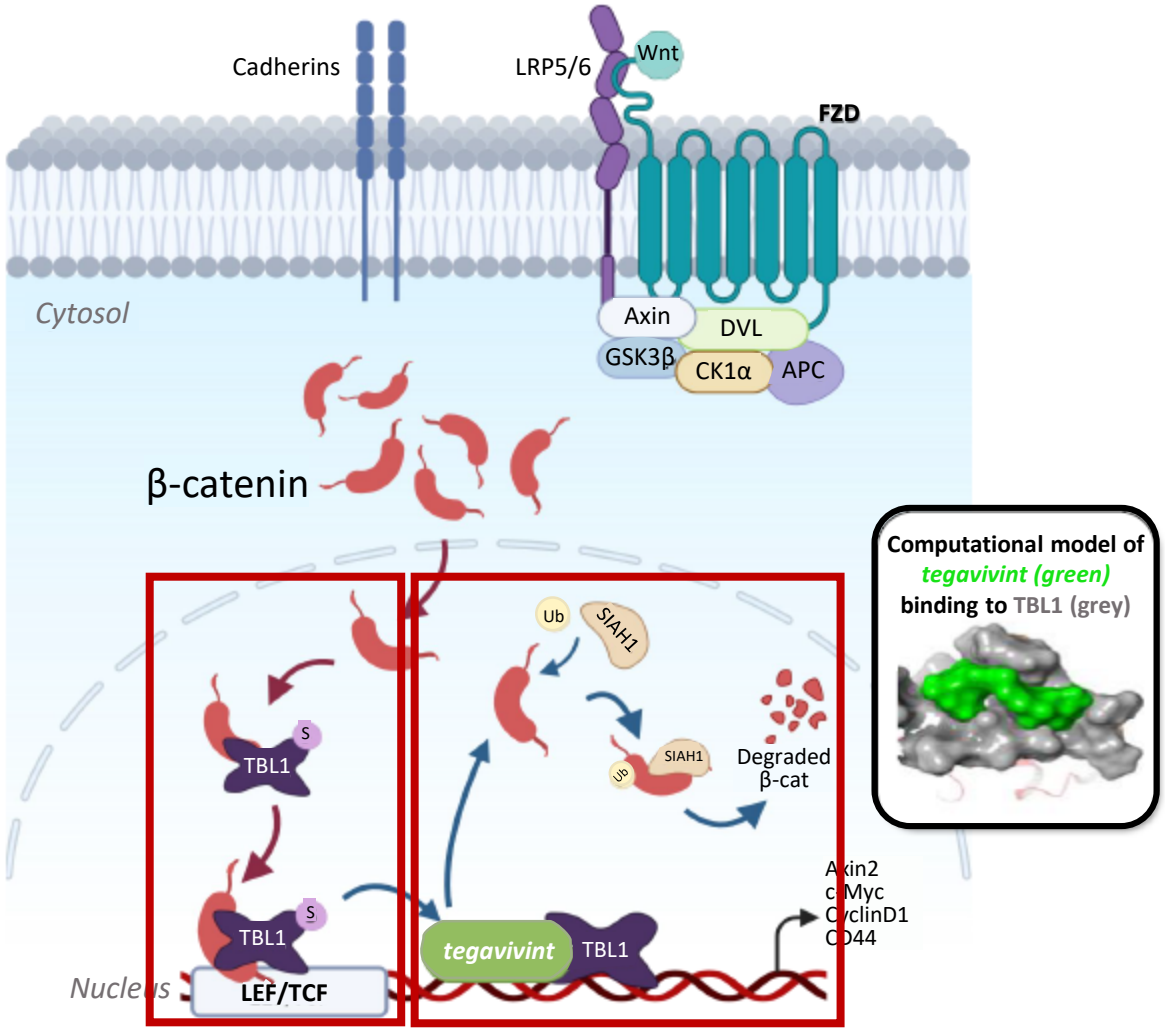
1. Dandamudi et al. *J Clin Oncol* 2024 (2594) 2. Tolcher et al. *J ImmunoTher Cancer* 2022 (770) 3. Shimizu et al. *Front Oncol* 2024

LIVIGNO-2: A Phase 2/3, Randomized Study to Evaluate the Dose Optimization, Safety, and Efficacy of Livmoniplimab in Combination with Budigalimab in Subjects with Locally Advanced or Metastatic Hepatocellular Carcinoma Who Have Not Previously Received Systemic Treatment (NCT06109272)



TBL1 (Wnt/β-catenin): Potential Target for HCC Treatment

- Up to 50% of HCC cases have Wnt/β-catenin activating mutations
  - Increases oncogene transcription[1]
- Transducin beta-like protein 1 (TBL1) prevents nuclear β-catenin degradation[2]
- **Blocking TBL1 allows nuclear β-catenin degradation → reduces oncogene expression[3, 4]**



1. Khalaf et al. *J Hepatocell Carcinoma* 2018 2. Kuang et al. *Dig Dis* 2016
3. Li et al. *J Clin Oncol* 2024 (TPS4192) 4, Image. Li et al. *Ann Oncol* 2025 (176P)

A Phase 1/2 Exploratory Study of the TBL1 Inhibitor Tegavivint (BC2059) in Patients With Advanced Hepatocellular Carcinoma (NCT05797805)

Eligibility Criteria

- Unresectable/metastatic HCC
- Progression, intolerance, or contraindication to at least 1 line of systemic therapy for advanced HCC
- *APC*, *AXIN1*, or *CTNNB1* mutation
- Child-Pugh A or ≤7 B
- ECOG PS 0 or 1

x Fibrolamellar or sarcomatoid HCC or mixed cholangiocarcinoma/HCC
x Hepatic encephalopathy
x Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality
x CNS metastases

Dose Level 4
Tegavivint 8 mg/kg IV weekly

Dose Level 3
Tegavivint 6.5 mg/kg IV weekly

Dose Level 2
Tegavivint 5 mg/kg IV weekly

Dose Level 1
Tegavivint 3 mg/kg IV weekly

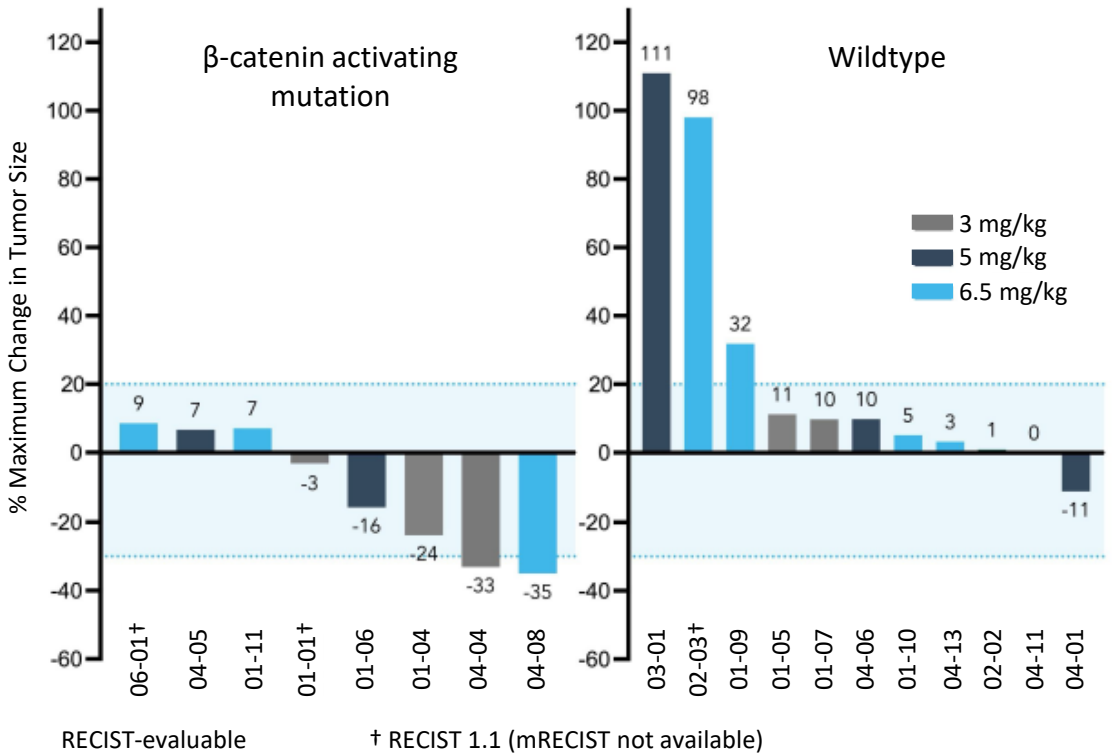
RP2D

Monotherapy Dose Expansion

Li et al. *J Clin Oncol* 2024 (TPS4192)

Targeting TBL1 (Wnt/β-catenin): Tegavivint

Maximum Change in Tumor Size (mRECIST) (n=19)



RECIST-evaluable

† RECIST 1.1 (mRECIST not available)

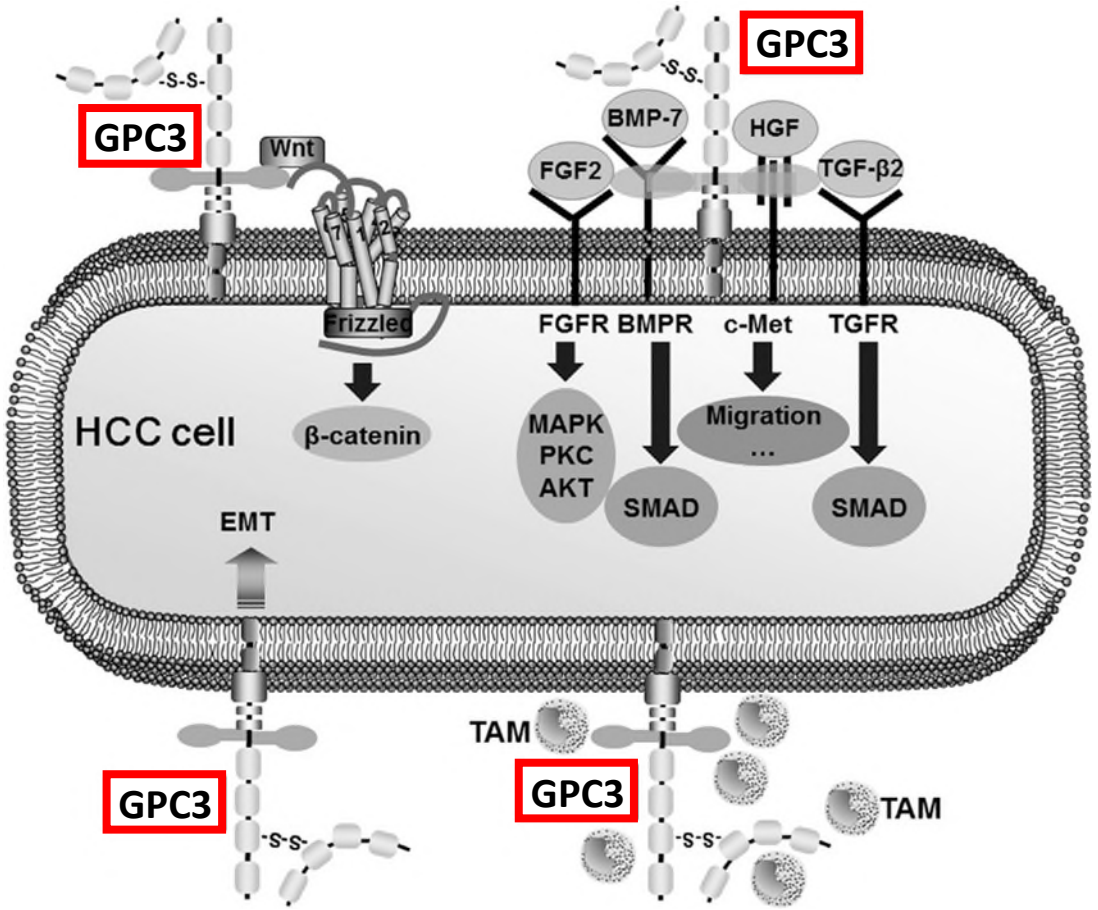
Best Response, n (%)	β-catenin mutant (n=12)	Wildtype (n=12)
Partial Response	2 (17)	0
Stable Disease	5 (42)	5 (42)
Progressive Disease	1 (8)	6 (50)
Not Evaluable	4 (33)	1 (8)
ORR (evaluable patients)	2 of 8 (25)	0 of 11
DCR (evaluable patients)	7 of 8 (88)	5 of 11 (45)

- 50% of patients with β-catenin activating mutations had disease control >6 months
- No grade 4 or 5 TRAEs

Li et al. *Ann Oncol* 2025 (176P)

GPC3: Potential Target for HCC Treatment

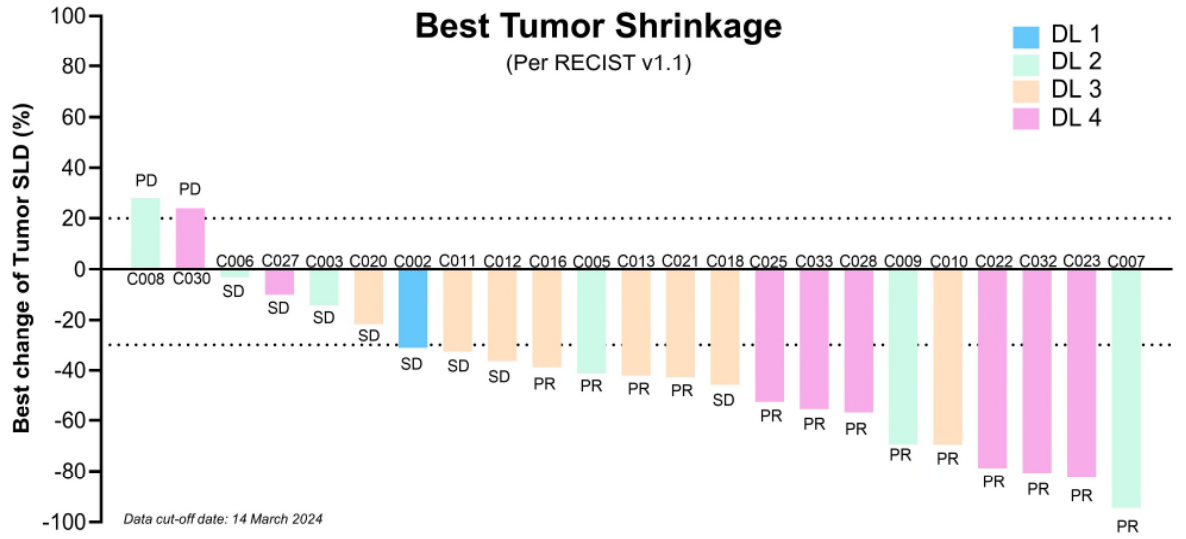
- Glypican 3: proteoglycan membrane protein[1]
  - Plays key role in fetal development[2]
  - Not expressed in normal adult liver tissue[3]
- Overexpressed in various tumors, including HCC[3, 4]
  - Promotes disease progression[1, 2, 4]
- **High GPC3 expression associated with poor prognosis in HCC[3, 5]**
  - Shorter DFS, shorter OS[3]
  - Reduced treatment effect for combination atezolizumab/bevacizumab vs sorafenib[5]

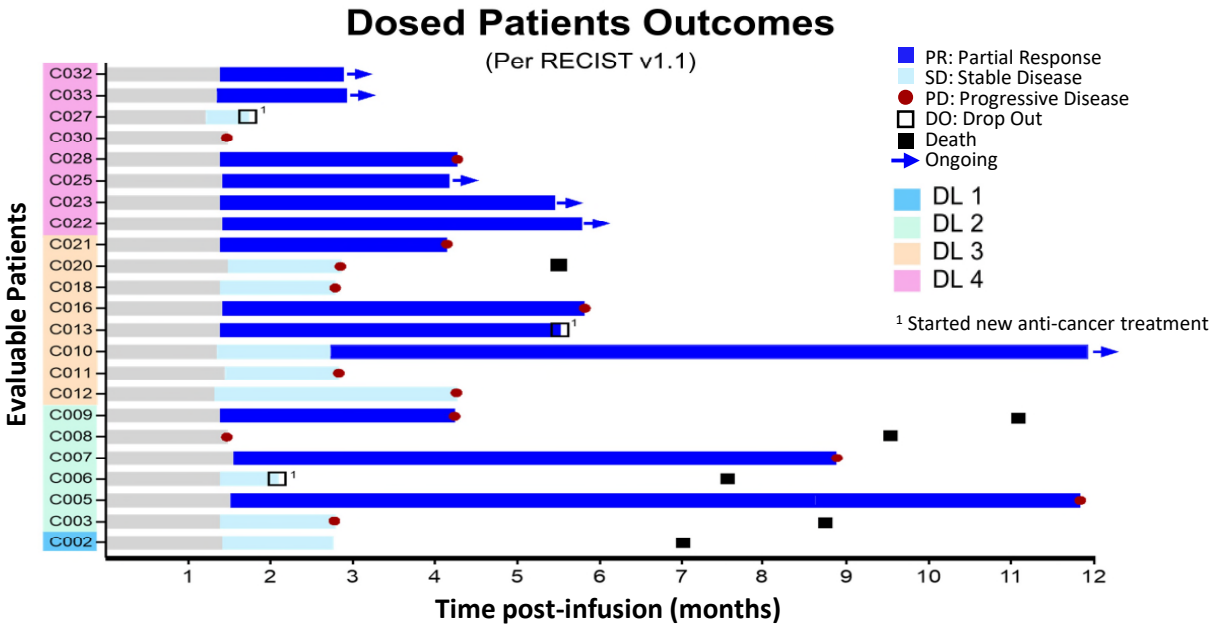


Image, 1. Zhou et al. *Med Res Rev* 2018 2. Filmus. *Glycobiology* 2001 3. Wu et al. *J Hepatocell Carcinoma* 2016 4. Nishida and Kataoka. *Cancers (Basel)* 2018 5. Zhu et al. *Nat Med* 2022

Targeting GPC3: CAR-T Cells

- GPC3 CAR-T cells armored with dominant negative TGF-β receptor II (TGFβRIIDN)
- ORR: 56.5% (13 partial responses)
  - ORR for DL4: 75.0% (6 partial responses)
  - DCR: 91.3%
- Median target lesion reduction: 42.2%
- Median duration of response: 7.36 months
  - 5 of 10 evaluated patients had durable response at 6 months
- Median OS not reached





Zhang et al. *J Clin Oncol* 2024 (4019)

A Phase 1/2 Open-Label Study to Evaluate the Safety, Cellular Kinetics, and Efficacy of AZD5851, a Chimeric Antigen Receptor T-Cell (CAR-T) Therapy directed against GPC3 in Adult Participants with Advanced/Recurrent Hepatocellular Carcinoma (NCT06084884)

Eligibility Criteria

- Unresectable/metastatic HCC
- Progression, intolerance, or contraindication to at least 1 line of systemic therapy for advanced HCC
- BCLC Stage C or Stage B not amenable to curative-intent treatment
- ≥1 measurable lesion per RECIST v1.1
- GPC3-positive tumor
- Child-Pugh A
- ECOG PS 0 or 1

- x Mixed cholangiocarcinoma/HCC
- x Prior treatment with any CAR-T cell therapy or GPC3-directed therapy
- x Hepatic encephalopathy
- x CNS metastases

Part A: Phase 1, Dose Escalation
GPC3-Positive, ≥2nd Line HCC

Dose Level 2
N=3–6 evaluable

- Dose Level 2 Backfill
- Up to ~N=22

Dose Level 1
N=3–6 Evaluable

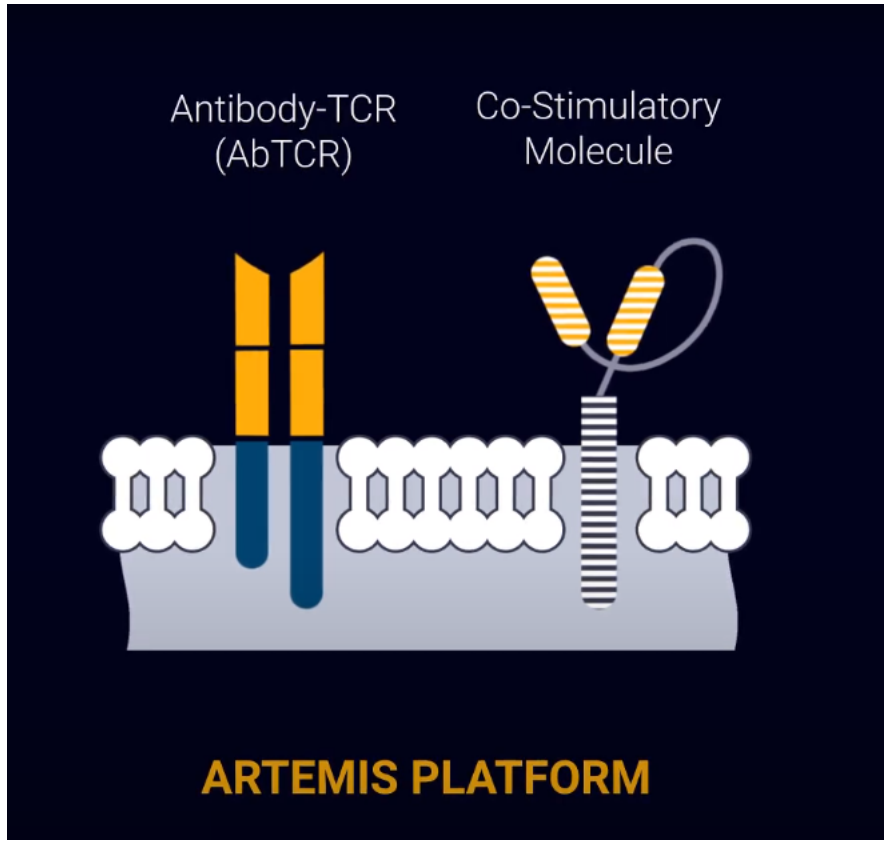
- Dose Level 1 Backfill
- Up to ~N=22

Recommended Dose for Expansion

Part B: Phase 2, Dose Expansion
GPC3-Positive, ≥2nd Line HCC

Dose Level X Expansion
N=50

Targeting GPC3: ARTEMIS® Cell Receptor Platform



- ARTEMIS: Antibody Redirected T Cells with Endogenous Modular Immune Signaling
- Antibody-T-Cell receptor (AbTCR) combined with co-stimulatory molecule
- Optimizes a patient's T cells to identify, bind to, and destroy cancer cells
- Preclinical *in vitro* and *in vivo* murine data suggest ARTEMIS®-modified T cells are effective at killing tumor cells[1]

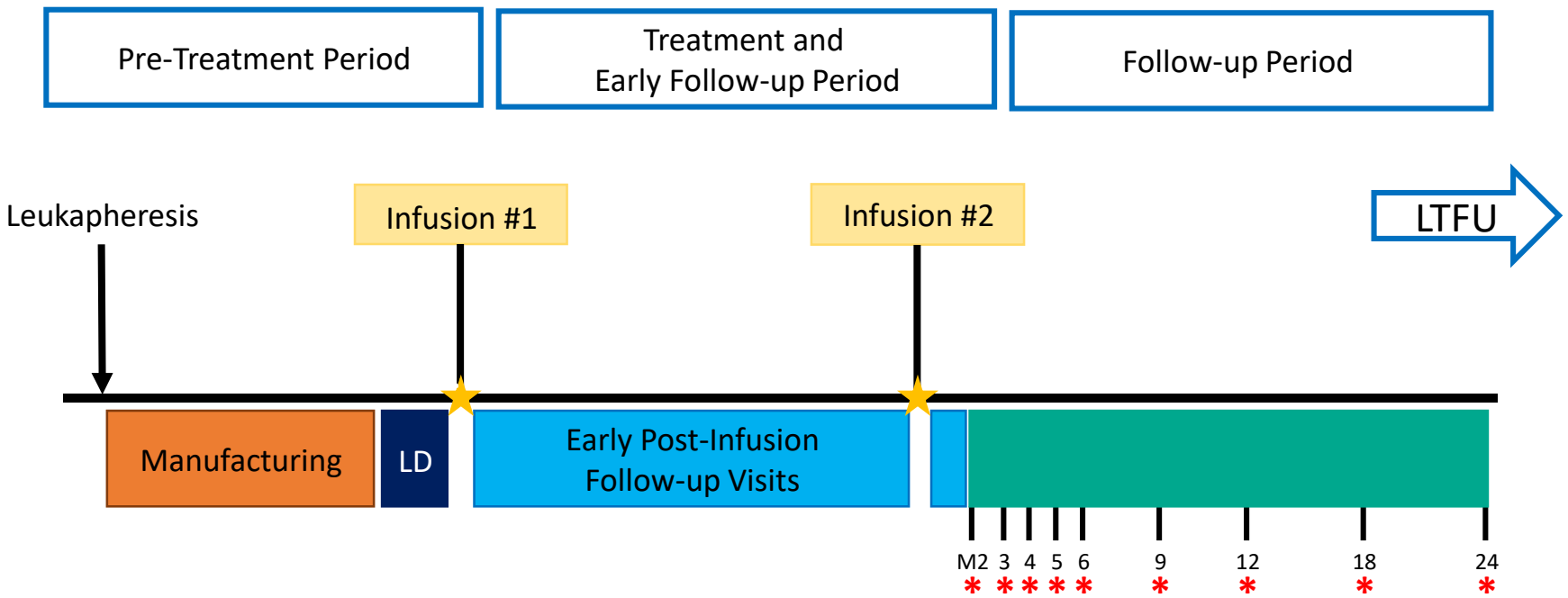
1. Xu et al. *Cell Discovery* 2018

An Open-Label, Dose Escalation, Multicenter Phase 1/2 Clinical Trial of ECT204 T-cell Therapy in Adults with Advanced Hepatocellular Carcinoma (ARYA-3) (NCT04864054)

Eligibility Criteria

- Unresectable, recurrent, and/or metastatic HCC
- Progression, intolerance, or contraindication to at least 2 lines of systemic therapy for advanced HCC
- GPC3-positive tumor by IHC
- Child-Pugh A6 or better
- Karnofsky PS ≥70

- x HCC involving >50% of the liver
- x Prior treatment with any GPC3-directed therapy
- x Active autoimmune disease requiring systemic immunosuppressive therapy
- x Compromised circulation in main portal vein, hepatic vein, or vena cava



* Tumor response assessment

LD, lymphodepletion; LTFU, long-term follow-up; M, month

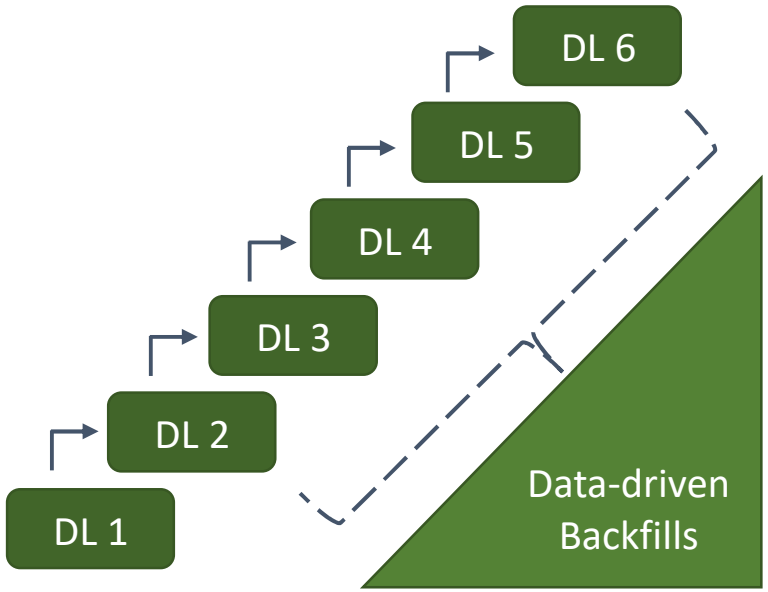
A Phase I First-in-Human Study Evaluating Safety, Pharmacokinetics, and Efficacy of ABBV-324 in Adults with Hepatocellular Carcinoma or Squamous Cell Non-Small Cell Lung Cancer (NCT06858813)

Eligibility Criteria

- Locally advanced or metastatic and/or unresectable HCC
- Failure of at least 1 line of systemic therapy for advanced HCC*
- Measurable disease per RECIST v1.1
- Child-Pugh A
- ECOG PS 0 or 1

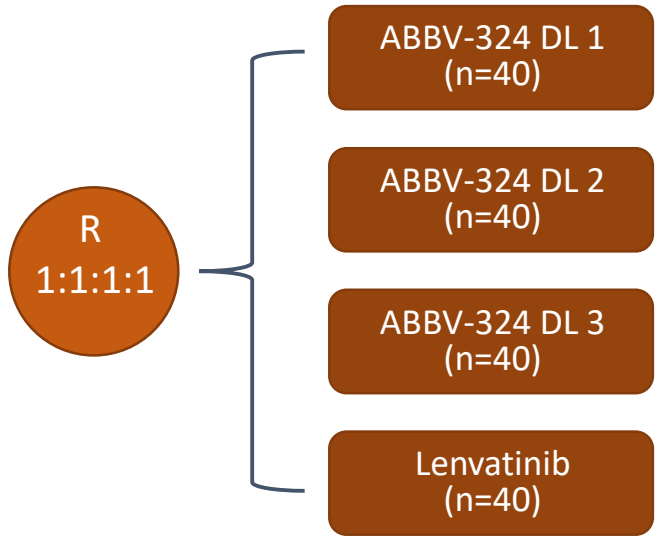
x Fibrolamellar, sarcomatoid HCC, or mixed cholangiocarcinoma/HCC
x Coinfection with HBV and HCV
x Untreated brain or meningeal metastases
x History of clinically significant, intercurrent lung-specific illnesses
x Clinically significant congestive heart failure, ischemic cardiovascular event, cardiac arrythmia, pericardial effusion, or pericarditis within 6 months

Part 1: Monotherapy Escalation (N=72)
MTD/Preliminary efficacy



Approximately 36 subjects will be enrolled in dose escalation and up to 36 subjects may be enrolled as backfills

Part 2: 2L+ HCC Monotherapy Dose Optimization (N=160)



ABBV-324 dose levels will be determined based on data collected in Part 1 dose escalation

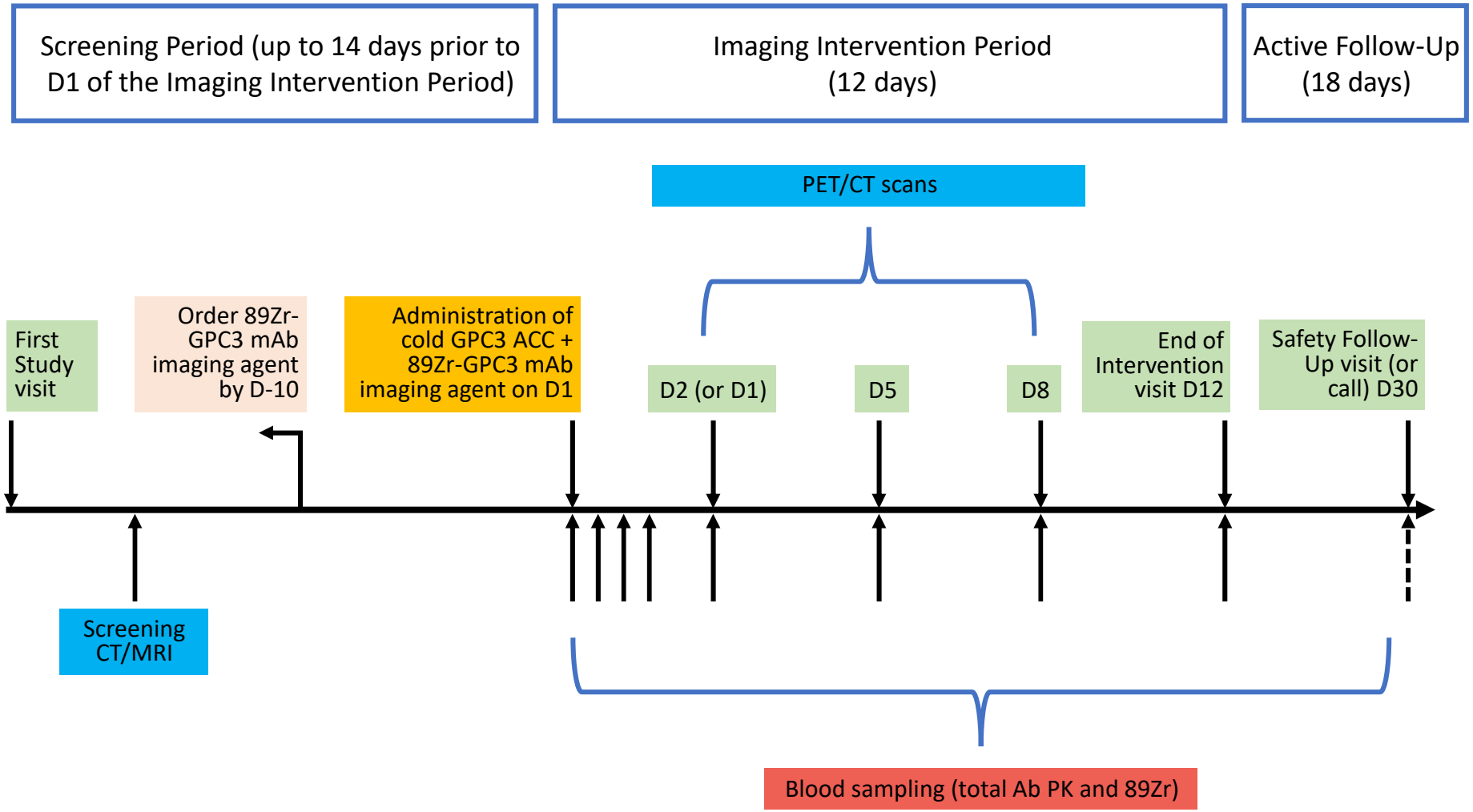
* Part 2: Failure of at least 1 prior systemic treatment consisting of an immune CPI-containing regimen for HCC including, but not limited to, atezolizumab in combination with bevacizumab or tremelimumab in conversation with durvalumab. Note: Patients who have received prior lenvatinib will not be eligible for Part 2.

An open-label phase 1 imaging study to evaluate the biodistribution, dosimetry, safety and pharmacokinetics of BAY 3630942, a 89Zr-labeled monoclonal antibody, with a pre-infusion of BAY 3547922, a monoclonal antibody-chelator conjugate, in patients with hepatocellular carcinoma (NCT06345001)

Eligibility Criteria

- Histologically confirmed HCC or non-invasive diagnosis of HCC according to AASLD criteria
- Child-Pugh A or B7
- ECOG PS 0 or 1

x Prior or ongoing GPC3-targeted therapy
x Uncontrolled hypertension despite optimal medical management
x Impaired cardiac function or clinically significant cardiac disease
x Unstable angina or new-onset angina in last 3 months
x Pleural effusion/ascites causing respiratory compromise (≥Grade 2 dyspnea)
x Current hepatic encephalopathy
x Dual HBV and HCV infection



Conclusions

- The systemic treatment landscape for advanced HCC continues to rapidly evolve
- Novel targets may improve outcomes as monotherapy or when combined with existing treatment regimens/targets
- Cellular/targeted therapies (CAR-T cells, T cell receptors, ADCs) may offer other treatment modalities
- **Optimization of care for this vulnerable patient population is an ongoing process**

Thank you

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