Poster #
LB365

Results from a phase 1 study of botensilimab and balstilimab in treatment refractory hepatocellular carcinoma

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BACKGROUND

- Botensilimab (BOT) is an Fc-enhanced, multifunctional anti-CTLA-4 antibody with differentiated mechanisms of action, designed to extend therapy to cold or poorly immunogenic solid tumors including hepatocellular carcinoma (HCC; **Figure 1**)[1]
- BOT alone, or when combined with balstilimab (BAL; anti-PD-1 antibody), has previously demonstrated durable responses across nine different treatment-refractory tumors including microsatellite stable metastatic colorectal cancer, relapsed/refractory sarcomas, and platinum refractory/resistant ovarian cancer[2-4]
- Effective therapy options for patients with HCC who progress on or after first-line immunotherapy (I-O) are limited[5-7]
- We sought to determine whether BOT/BAL could confer responses patients with HCC who progressed on or after prior I-O
- To our knowledge, this is the first report of a prospective cohort of patients with HCC treated with combined anti-CTLA-4/anti-PD-1 (BOT/BAL) therapy after first line I-O-based therapy

Botensilimab Mechanism of Action

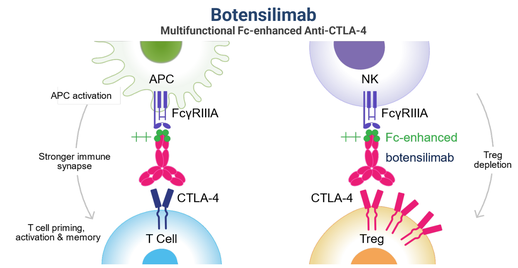

Figure 1. A novel innate and adaptive immune activator. BOT promotes enhanced T cell priming and expansion, T cell activation and memory formation, activation of antigen presenting cells, and reduction of intratumoral regulatory T cells, while improving safety through a reduction in complement-mediated toxicities.[1] To drive durability of tumor response, BOT is combined with BAL, which has activity comparable to commercially available PD-1 inhibitors[8,9]

C-800-01 Study Design: HCC Cohort (N=19)

NCT0386027: First-in-human trial of **BOT ± BAL** in patients with advanced cancer[10]

Key Eligibility

- Patients with HCC who progressed on or after prior I-O
- No encephalopathy or recent paracentesis[a]
- Hepatitis B/C allowed, if controlled[a]

BOT/BAL Treatment *(up to 2 years)*

BOT [Fc-enhanced CTLA-4] 1 or 2 mg/kg Q6W + BAL [PD-1] 3 mg/kg Q2W

Combination therapy

Week: 0 2 4 6 8 10 12

Study Endpoints

- Efficacy: ORR, DCR, DOR, PFS, OS
- Safety: AEs

Patient Population

- *Safety Analysis Population* – **19** patients with HCC treated with 1 or 2 mg/kg BOT Q6W plus 3 mg/kg BAL Q2W
  - *Efficacy Evaluable Population* – **18** of these patients with ≥1 post-baseline 6-week imaging scan

[a]Criteria added with a protocol amendment.

References 1. Chand D, et al. *Cancer Discov.* 2024;14:2407-2429. 2. Bullock AJ, et al. *Nat Med.* 2024;30:2558-2567. 3. Wilky BA, et al. *J Clin Oncol.* 2024; 0:JCO-24-02524. 4. Bockorny B, et al. *Gynecol Oncol.* 2023; 176:S35-S36. 5. Chan SL, et al. *J Hepatol.* 2024; 81:258-264. 6. El-Khoueiry AB, et al. *J Clin Oncol.* 2024;42:4007-4007. 7. Yoo C, et al. *J Clin Oncol.* 2024; 42:477-477. 8. O'Malley, et al. *Gynecol Oncol.* 2021; 163:274-280. 9. O'Malley, et al. *J Clin Oncol.* 2021; 40:762-771. 10. https://clinicaltrials.gov/ct2/show/NCT03860272.

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RESULTS

Baseline Characteristics

	Overall N=19
Median age, years (range)	67 (39–82)
Sex, n (%)	
Male	15 (79%)
Female	4 (21%)
ECOG PS, n (%)	
0	10 (53%)
1	9 (47%)
Prior lines of therapy, n (%)	
Median (range)	2 (1–7)
≥3	5 (26%)
Prior therapies, n (%)	
Anti-PD-(L)1	19 (100%)
Prior tyrosine kinase inhibitors	12 (63%)
Prior atezolizumab/bevacizumab	11 (58%)

	Overall N=19
Botensilimab dose, n (%)	
1 mg/kg BOT + BAL	9 (47%)
2 mg/kg BOT + BAL	10 (53%)
AFP at baseline, n/N (%)	
Median (range)	293.1 (0.7–91,989)
<200 ng/mL	8/17 (47%)
>400 ng/mL	9/17 (53%)
ALBI score, n (%)	
1	10 (53%)
2	9 (47%)
Hepatitis status, n (%)	
Hepatitis B positive	8 (42%)
Hepatitis C positive	4 (21%)
Extrahepatic metastases, n (%)	13 (68%)

Table 1. Baseline demographics and patient characteristics in the safety analysis population (N=19). Median follow-up was 11.4 months (range, 1.5–34.3). Data cutoff: December 5, 2024.

Efficacy

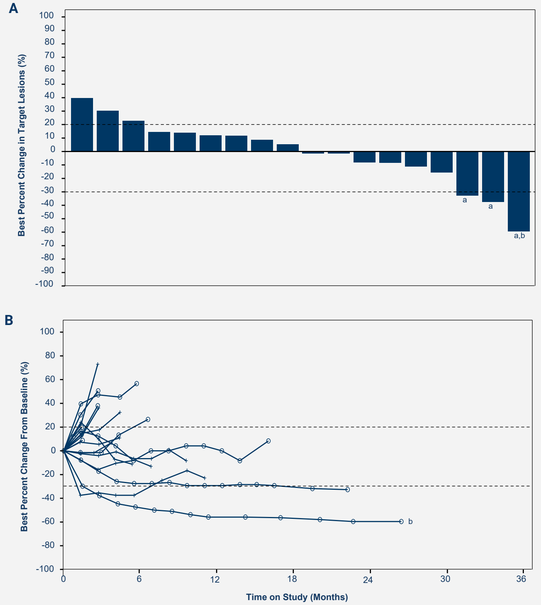

Figure 2. Clinical efficacy in efficacy-evaluable patients with HCC (n=18). (A) Best overall response and (B) response over time. [a]A RECIST 1.1-confirmed CR or PR. [b]Patient with a 'functional' CR including normalization of AFP; only residual lesion is a PET-negative hepatic cyst.

	Efficacy Evaluable n=18[a]
ORR, n (%) 95% CI	3 (17%) 4–41
BOR, n (%)	
PR[b]	3 (17%)
SD	10 (56%)
PD	5 (28%)
DCR, n (%)[c] 95% CI	13 (72%) 47–90
CBR, n (%)[d] 95% CI	9 (50%)[c] 26–74
Median DOR, months (95% CI)	NR (9.8–NR)
Median PFS, months (95% CI)	4.4 (1.4–6.9)
Median OS, months (95% CI)	12.3 (8.4–21.4)

Table 2. Clinical efficacy and outcomes in efficacy-evaluable patients with HCC (n=18). [a]One patient was not evaluable for efficacy as they expired before their first post-baseline 6-week imaging scan. [b]All three responders received prior atezolizumab/bevacizumab; one also received lenvatinib; another also received sorafenib and a MER/AXL-targeted therapy (clinical trial). [c]DCR was defined as a CR, PR, or SD ≥6 weeks (1 scan). [d]CBR was defined as a CR, PR, or SD ≥18 weeks (3 scans). Five patients had SD ≥24 weeks, including one patient with SD=66 weeks.

Abbreviations AE, adverse event; AFP, alpha fetoprotein; ALBI, albumin-bilirubin; APC, antigen presenting cell; AXL, AXL receptor tyrosine kinase; BAL, balstilimab; BOR, best overall response; BOT, botensilimab; CBR, clinical benefit rate; CR, complete response; CTLA-4, cytotoxic T-lymphocyte associated protein 4; DCR, disease control rate (CR, PR, or SD ≥6 weeks); DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; Fc, fragment crystallizable; FcγR, fragment crystallizable gamma receptor; HCC, hepatocellular carcinoma; I-O, immunotherapy; ITT, intention-to-treat; mCRC, metastatic colorectal cancer; MER, MER receptor tyrosine kinase; MSS, microsatellite stable; NE, not evaluable; NK, natural killer; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression free survival; PD, progressive disease; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PET, positron emission tomography; PR, partial response; PS, performance status; QD(W, every X weeks; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; TRAE, treatment-related adverse event; Treg, regulatory T cell

Survival

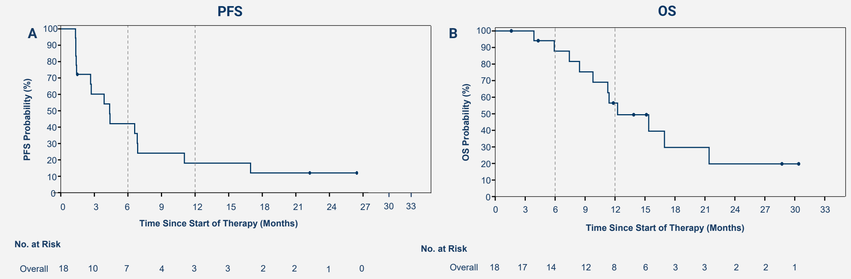

Figure 2. Clinical outcomes in efficacy-evaluable patients with HCC (n=18).

Safety

	Overall N=19	
	Any Grade	Grade 3
Any immune-mediated TRAE, n (%)[a]	13 (68%)	7 (37%)
Diarrhea/colitis	7 (37%)	3 (16%)
Hepatitis	4 (21%)	3 (16%)
Skin adverse reactions	4 (21%)	1 (5%)
Constitutional	3 (16%)	0 (0%)
Adrenal Insufficiency	2 (11%)	1 (5%)
Hypothyroidism	2 (11%)	0 (0%)
Myocarditis/pericarditis	1 (5%)	1 (5%)
Myositis/rhabdomyolysis	1 (5%)	1 (5%)
Pituitary dysfunction	1 (5%)	1 (5%)
Thyroiditis	1 (5%)	1 (5%)

- No new safety signals
- Safety in HCC consistent across tumor types in study
- No treatment-related deaths

Table 3. Immune-mediated TRAEs in the safety analysis population (N=19). Immune-mediated TRAEs were defined as related to treatment, treated with steroids (of any dose) and/or other immunosuppressants, or as events requiring hormone replacement. Twelve patients (63%) received systemic steroids and/or TNF-α inhibitors, while 3 (16%) received hormone replacement for an immune-mediated AE.

CONCLUSIONS

- BOT/BAL demonstrated durable responses and prolonged SD in patients with treatment-refractory HCC (with a median of two prior lines of therapy and progressed on or after I-O), including patients who received prior atezolizumab/bevacizumab
- The DCR and survival data provide early evidence of antitumor activity in the setting of prior I-O-based therapy
- The safety profile was manageable and consistent with other disease cohorts treated with BOT/BAL
- This cohort is limited by the small sample size and the high percentage of patients with ALBI 2 liver disease who have a poorer prognosis
- These results support further investigation of BOT/BAL in HCC in future randomized studies

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