Poster #

8P

Botensilimab plus balstilimab in an expanded cohort of 123 patients with metastatic microsatellite stable colorectal cancer and no active liver metastases

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BACKGROUND

- In microsatellite stable metastatic colorectal cancer (MSS mCRC), conventional immunotherapy is largely ineffective, and options remain limited for patients who progress on prior chemotherapy
- Botensilimab (BOT) is an Fc-enhanced, multifunctional anti-CTLA-4 antibody designed to leverage novel mechanisms of action that enhance T cell priming, regulatory T cell depletion, and macrophage and dendritic cell activation to overcome the immunologically "cold" tumor microenvironment in MSS mCRC (Figure 1) while the addition of balstilimab (BAL; anti-PD-1 antibody) sustains the activated immune response[1]
- BOT plus BAL has demonstrated durable clinical responses across multiple treatment-refractory solid tumors including 3L+ MSS mCRC with no active liver metastases (NLM)[2]
- Here we demonstrate durable clinical benefit of BOT/BAL in a larger cohort of patients with 3L+ MSS mCRC NLM, including patients who have exhausted all available standard therapies (4L+), confirming the therapeutic potential of this novel immunotherapy combination in a challenging patient population

Botensilimab Mechanism of Action

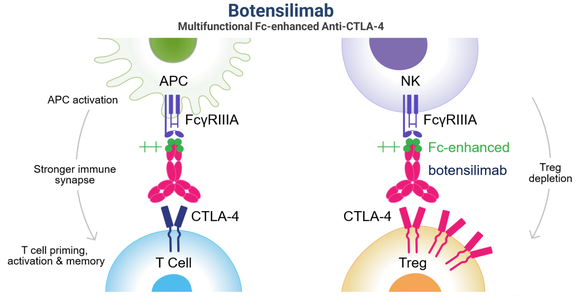


Figure 1. A novel innate and adaptive immune activator supporting superior antitumor immunity. BOT promotes enhanced T cell priming and expansion, T cell activation and memory formation, activation of APCs, and reduction of intratumoral Tregs, while improving safety through a reduction in complement-mediated toxicities associated with conventional CTLA-4 inhibitors.[1]

To drive durability of tumor response, BOT is combined with BAL, which has activity comparable to commercially available PD-1 inhibitors[3,4]

C-800-01 Study Design: MSS mCRC NLM Cohort (N=123)

NCT03860272: First-in-human trial of **BOT ± BAL** in patients with advanced cancer[5]

Key Eligibility

- Relapsed/refractory mCRC
- MSS by local assessment
- Prior I-O allowed

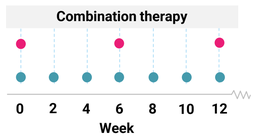
Study Endpoints

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

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



Patient Population

- Data cutoff date: 13-MAR-2025
- *Safety Analysis Population* – **123** patients with **3L+ MSS mCRC NLM** treated with 1 or 2 mg/kg BOT Q6W plus 3 mg/kg BAL Q2W
  - *Late-Line Population* – **37** patients with **4L+ MSS mCRC NLM** who received at least one regimen of regorafenib, trifluridine/tipiracil ± bevacizumab, or fruquintinib

References 1. Chand D, et al. *Cancer Discov*. 2024;14:2407-2429. 2. Bullock AJ, et al. *Nat Med*. 2024;30:2558-2567. 3. O'Malley, et al. *Gynecol Oncol*; 2021; 163:274-280. 4. O'Malley, et al. *J Clin Oncol*; 2021; 40:762-771. 5.https://clinicaltrials.gov/ct2/show/NCT03860272.

RESULTS

Patient Characteristics

	Overall (3L+) N=123	Late-Line (4L+) n=37
Age, median (range)	56 (25–82)	60 (36–81)
Sex, n (%)		
Male	63 (51%)	21 (57%)
Female	60 (49%)	16 (43%)
ECOG PS at baseline, n (%)		
0	56 (46%)	15 (41%)
1	67 (54%)	22 (59%)
Primary Site*		
Colon	81 (66%)	25 (68%)
Rectal	42 (34%)	12 (32%)
Prior lines of therapy, n (%)		
Median (range)	3.0 (1–10)	5.0 (2–10)
≥3	82 (67%)	33 (89%)
Received at least one regimen of regorafenib, trifluridine/tipiracil ± bevacizumab, or fruquintinib	37 (30%)	37 (100%)
Liver Metastases Status, n (%)		
Treated liver metastases	20 (16%)	6 (16%)
No history of liver metastases	103 (84%)	31 (84%)
Other Characteristics, n (%)		
Prior PD-(L)1/CTLA-4, n (%)	18 (15%)	11 (30%)
TMB>13, mut/Mb, n/N (%)	0/52 (%)	0/18 (0%)
RAS mutation, n/N (%)	76/113 (67%)	23/32 (72%)
BRAF mutation, n/N (%)	3/43 (7%)	2/11 (18%)

Clinical Efficacy & Outcomes

	Overall (3L+) N=123	Late-Line (4L+) n=37
ORR, n (%) 95% CI	24 (20%) 13–28	7 (19%) 8–35
BOR, n (%)		
CR	3 (2%)	1 (3%)
PR	21 (17%)	6 (16%)
SD	61 (50%)	19 (51%)
PD	34 (28%)	9 (24%)
NE	4 (3%)	2 (5%)
Median DOR, months (95% CI)	16.6 (5.7–NR)	16.6 (1.9–NR)
DCR at 6 weeks, n (%) 95% CI	85 (69%) 60–77	26 (70%) 53–84
CBR at 24 weeks, n (%)[b] 95% CI	34 (28%) 20–36	10 (27%) 14–44
Median PFS, months (95% CI)	4.0 (2.8–4.1)	4.1 (2.8–6.4)
12-month PFS, % (95% CI)	23% (15–31)	20% (8.5–36.0)
Median OS, months (95% CI)	20.9 (16.2–26.6)	16.2 (9.7–NR)
18-month OS, % (95% CI)	57% (48–66)	48% (31–63)
24-month OS, % (95% CI)	42% (32–52)	43% (25–59)
Median follow-up, months (range)	18.0 (0.7–53.3)	12.0 (2.3–37.1)
Median follow-up (reverse KM), months (95% CI)	25.8 (19.4–31.2)	19.4 (18.5–28.8)

3L+ MSS mCRC NLM (N=123)

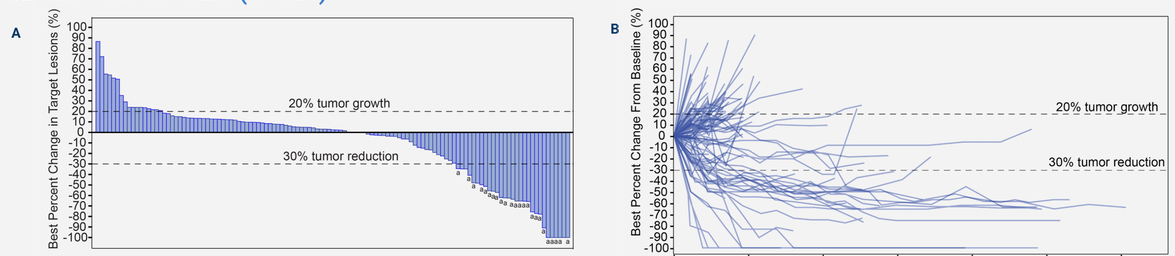


Figure 2. Clinical efficacy. (A) Best overall response and (B) response over time.
[a]A RECIST 1.1-confirmed CR or PR.

Efficacy was similar by dose (N=123):
- 1 mg/kg BOT + BAL ORR: **19%**
- 2 mg/kg BOT + BAL ORR: **20%**

4L+ MSS mCRC NLM (n=37)

Received at least one regimen of regorafenib, trifluridine/tipiracil ± bevacizumab, or fruquintinib

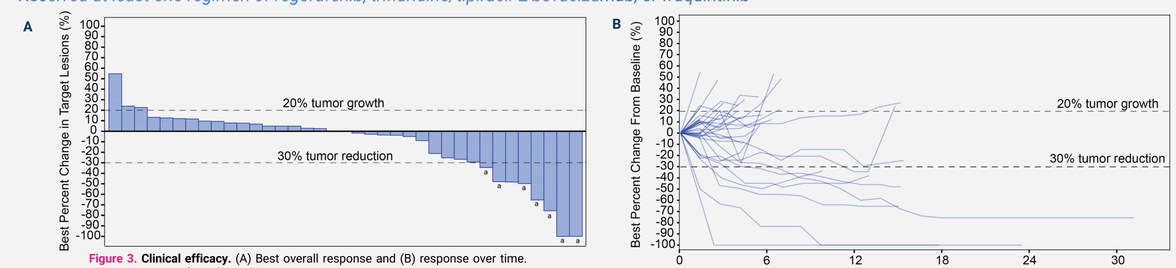
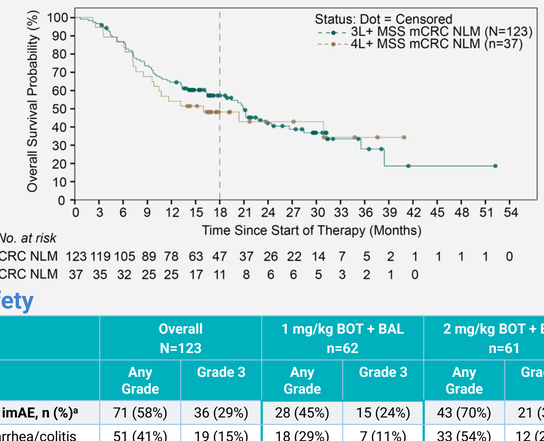


Figure 3. Clinical efficacy. (A) Best overall response and (B) response over time.
[a]A RECIST 1.1-confirmed CR or PR.

Overall Survival



No. at risk

3L+ MSS mCRC NLM	123	119	105	89	78	63	47	37	26	22	14	7	5	2	1	1	1	1	0
4L+ MSS mCRC NLM	37	35	32	25	25	17	11	8	6	6	5	3	2	1	0				

Safety

	Overall N=123		1 mg/kg BOT + BAL n=62		2 mg/kg BOT + BAL n=61	
	Any Grade	Grade 3	Any Grade	Grade 3	Any Grade	Grade 3
Any imAE, n (%)[a]	71 (58%)	36 (29%)	28 (45%)	15 (24%)	43 (70%)	21 (34%)
Diarrhea/colitis	51 (41%)	19 (15%)	18 (29%)	7 (11%)	33 (54%)	12 (20%)[b]
Immune thyroiditis[c]	9 (7%)	0 (0%)	4 (6%)	0 (0%)	5 (8%)	0 (0%)
Pneumonitis	6 (5%)	3 (2%)	1 (2%)	1 (2%)	5 (8%)	2 (3%)
Hepatitis	6 (5%)	3 (2%)	3 (5%)	1 (2%)	3 (5%)	2 (3%)
Adrenal insufficiency	4 (3%)	2 (2%)	2 (3%)	2 (3%)	2 (3%)	0 (0%)
Dermatologic[d]	4 (3%)	1 (1%)	0 (0%)	0 (0%)	4 (7%)	1 (2%)

Table 3. All immune-mediated adverse events in ≥3% of all patients (N=123). [a]imAEs were medically adjudicated. [b]There was only one grade 4 imAE of diarrhea/colitis in the 2 mg/kg BOT dose group (not included in the table). [c]Includes unique patients with hypothyroidism, hyperthyroidism, and thyroiditis. [d]Dermatologic category does not include grade 1 events that were managed with topical steroids only.

- No new safety signals
- GI-related imAEs were the most common and reversible
- Low incidence of visceral toxicities outside the GI tract
- Only one grade 4 imAE across cohort
- No treatment-related deaths (grade 5)

CONCLUSIONS

- Updated data with additional patients and mature follow-up demonstrated remarkable clinical benefit with **deep, durable responses in 3L+ MSS mCRC NLM**
- Similar **remarkable efficacy was observed in late-line patients (4L+)** who have no currently available therapies
- The **safety profile was manageable** with only one grade 4 imAE, no treatment-related deaths, and no new safety signals
- These results form the basis of a **pivotal, global, phase 3 registrational trial** planned to commence by the end of 2025.

Disclosures **BLS**: Consulting or Advisory Role – Agenus; AstraZeneca; Janssen

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Acknowledgments Agenus Inc. funded and is the sponsor of this study. The authors would like to thank the patients and their families for participating in the C-800-01 study, as well as the trial coordinators and investigators for their contributions.

Abbreviations AE, adverse event ; APC, antigen presenting cell; BAL, balstilimab; BOR, best overall response; BOT, botensilimab; BRAF, v-raf murine sarcoma viral oncogene homolog B1; CBR, clinical benefit rate (CR, PR, or SD ≥24 weeks); CR, complete response; CNS, central nervous system; 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; GI, gastrointestinal ; imAE, immune-mediated adverse event; I-O, immuno-oncology; KM, Kaplan-Meier; mCRC, metastatic colorectal cancer; MSS, microsatellite stable; NE, not evaluable; NK, natural killer; NLM, no active liver metastases; 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; PR, partial response; PS, performance status; Q6W, every X weeks; RAS, rat sarcoma virus; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; TMB, tumor mutational burden; Treg, regulatory T cell.