Clinical Features of Long-Term Survivors Treated With Next-Generation Anti–CTLA-4 (Botensilimab) Plus Anti–PD-1 (Balstilimab) in Refractory Microsatellite-Stable Metastatic Colorectal Cancer

Poster 472

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Background

- Survival >18 months remains uncommon in refractory microsatellite-stable metastatic colorectal cancer (MSS mCRC), even in patients with no active liver metastases (NLM)[1-3]
- Given the limited durability of currently available later-line therapies,[1-3] next-generation immune checkpoint inhibitors (ICI) may help address the unmet need in this setting
- Botensilimab (BOT), a multifunctional Fc-enhanced anti–CTLA-4, augments T-cell priming, reduces regulatory T cells, and activates antigen-presenting cells[4]
- BOT ± balstilimab (BAL; anti–PD-1 pharmacologically comparable to approved PD-1 inhibitors) has shown activity in "cold" and ICI-refractory tumors[5-12]
- In a phase 1b cohort (C-800-01 trial) of 123 patients with refractory MSS mCRC NLM, BOT+BAL demonstrated clinically meaningful long-term survival, with a median OS of 21.2 months and a 3-year OS rate of 33%, including an OS curve plateau beyond 2 years[7]

Here, we describe clinical features and efficacy/safety outcomes of long-term survivors (LTS; OS ≥18 months from treatment initiation) within the 123-patient cohort of the C-800-01 trial

C-800-01 Study Design

NCT03860272 (C-800-01): First-in-Human, Phase 1b Trial of BOT±BAL in Patients with Advanced Solid Tumors

Key MSS mCRC NLM Cohort Eligibility

- Relapsed/refractory mCRC NLM
- MSS by local assessment
- Prior ICI allowed
- ECOG PS of 0 or 1

Endpoints

- **Efficacy:** ORR per RECIST 1.1 by investigator, DOR, DCR (CR/PR/SD at ≥6 weeks), CBR (CR/PR/SD at ≥24 weeks), PFS, OS
- **Safety:** imAEs

Analyses

- **Data Cutoff:** December 13, 2025
- **Safety Population (all analyses):** All patients who received ≥1 dose of study drug(s)
  - **Overall Population:** All patients
  - **Long-Term Survivors (LTS; post hoc):** OS ≥18 months from treatment initiation
  - **Short-Term Survivors (STS; post hoc):** OS <18 months from treatment initiation
- Baseline characteristics were compared between LTS and STS using Fisher's exact test

BOT Q6W 1 mg/kg or 2 mg/kg (Fc-enhanced anti–CTLA-4) + **BAL Q2W** 3 mg/kg (anti–PD-1)

Results

Patient Characteristics

Table 1. Demographics and Baseline Disease Characteristics

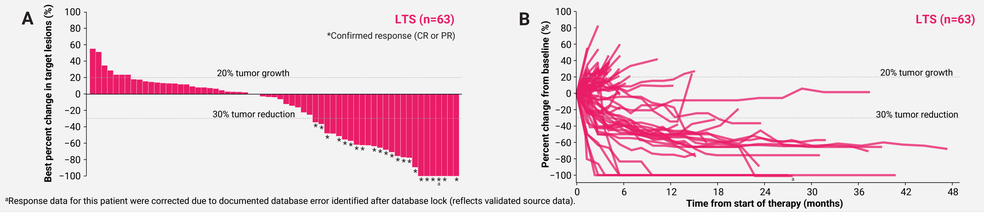
Characteristic		Overall N=123	LTS n=63	STS n=60
Age, years	Median (range)	56 (25–82)	57 (36–82)	56 (25–77)
Sex	Male	63 (51)	34 (54)	29 (48)
ECOG PS	1	67 (54)	30 (48)	37 (62)
Primary site	Colon	81 (66)	40 (63)	41 (68)
	Rectal	42 (34)	23 (37)	19 (32)
Liver metastases status	Treated liver metastases	20 (16)	8 (13)	12 (20)
	No liver metastases	103 (84)	55 (87)	48 (80)
Metastatic disease	≥2 metastatic organ sites	85 (69)	39 (62)	46 (77)
	Lymph node metastases	54 (44)	21 (33)	33 (55)
	Lung metastases	96 (78)	51 (81)	45 (75)
	Peritoneal metastases	48 (39)	23 (37)	25 (42)
	Median time from metastatic disease to 1st dose, months (range)	33.9 (0.2–179.4)	32.3 (5.4–177.3)	37.1 (0.2–179.4)
Prior lines	Median (range)	3 (1–10)	3 (1–9)	4 (1–10)
	≥3 prior lines	82 (67)	35 (56)	47 (78)
	Prior anti–PD-(L)1 or CTLA-4	18 (15)	6 (10)	12 (20)
	≥1 regimen of regorafenib, trifluridine/tipiracil ± bevacizumab, or fruquintinib	37 (30)	15 (24)	22 (37)
Other	MSS/pMMR	123 (100)	63 (100)	60 (100)
	TMB >15, Mut/Mb, n/N (%)[a,b]	0/77 (0)	0/40 (0)	0/37 (0)
	RAS mutation, n/N (%)[b]	76/113 (67)	41/60 (68)	35/53 (66)
	BRAF V600E mutation, n/N (%)[b]	1/60 (2)	0/29 (0)	1/31 (3)
	NLR >3, n/N (%)	76/123 (62)	35/63 (56)	41/60 (68)
	LDH >ULN, n/N (%)	29/119 (24)	12/61 (20)	17/58 (29)
	Albumin <LLN, n/N (%)	10/123 (8)	3/63 (5)	7/60 (12)

n (%) unless otherwise stated.
[a]TMB per tumor-based local clinical test. [b]N represents the number of patients with available data from local clinical test.

- More than half of patients were LTS (51%, 63/123)
- Long-term survival occurred even in heavily pretreated patients, including those previously exposed to immunotherapy
- Most baseline characteristics did not differ significantly (P>0.05) between LTS and STS, including exposure to prior immunotherapy and later-line regimens, ECOG PS, and prognostic biomarkers
- Fewer prior treatment lines were associated with long-term survival, supporting the evaluation of BOT+BAL earlier in the treatment course; LTS were less likely than STS to have received ≥3 prior lines (56% vs 78%; P=0.008)
- The median number of BOT doses was 2 (range, 1–17) in both the overall population and LTS
- The median number of BAL doses was 6 (range, 1–52) and 9 (range, 1–52) in the overall population and LTS, respectively

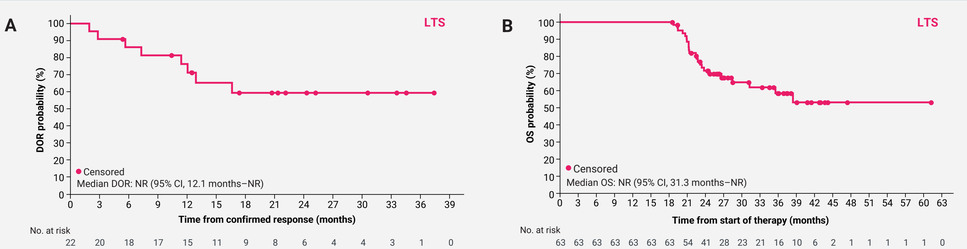
Efficacy in Long-Term Survivors

Figure 1. (A) Best Overall Response and (B) Response Over Time in LTS



[a]Response data for this patient were corrected due to documented database error identified after database lock (reflects validated source data).

Figure 2. (A) Duration of Response and (B) Overall Survival in LTS



- Among LTS, DORs ranged from 1.9 to ≥37.4 months, with 10 responses ongoing at data cutoff
- At last follow-up, 15 of 63 LTS (24%) were alive and off all therapy, of whom 13 (87%) were responders

Table 2. Efficacy Overview

	Overall N=123	LTS n=63
ORR, n (%) | 95% CI	26 (21) | 14–29	22 (35) | 23–48
CR	3 (2)	3 (5)
PR	23 (19)	19 (30)
SD	59 (48)	30 (48)
PD	34 (28)	11 (17)
NE	4 (3)	0
Median DOR, mo (95% CI)	NR (7.3–NR)	NR (12.1–NR)
DCR at ≥6 wks, n (%) | 95% CI	85 (69) | 60–77	52 (83) | 71–91
CBR at ≥24 wks, n (%) | 95% CI	34 (28) | 20–36	30 (48) | 35–61
Median PFS, mo (95% CI)	4.0 (2.8–4.1)	5.5 (4.0–12.5)
18-mo PFS, % (95% CI)	18 (11–26)	32 (20–44)
Median OS, mo (95% CI)	21.2 (16.2–23.8)	NR (31.3–NR)
24-mo OS, % (95% CI)	41 (32–50)	72 (58–81)
30-mo OS, % (95% CI)	37 (28–46)	65 (51–76)
36-mo OS, % (95% CI)	33 (24–43)	59 (43–71)
Follow-up, mo		
Median (range)	20.2 (0.7–62.3)	28.2 (18.7–62.3)
Median reverse KM (95% CI)	34.8 (28.2–38.1)	35.2 (28.5–40.7)

Safety in Long-Term Survivors

Table 3. Treatment-Related Immune-Mediated Adverse Events Occurring in ≥1% of Patients

	Overall N=123		LTS n=63	
n (%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any imAE[a,b]	72 (59)	37 (30)	47 (75)	24 (38)
Gastrointestinal				
Diarrhea/colitis[c]	51 (41)	19 (15)	34 (54)	12 (19)
Hepatitis[d]	6 (5)	3 (2)	5 (8)	3 (5)
Pancreatitis[e]	1 (1)	1 (1)	1 (2)	1 (2)
Enteritis only[e,f]	1 (1)	1 (1)	1 (2)	1 (2)
Endocrine				
Thyroid disorders[g]	9 (7)	0	8 (13)	0
Adrenal insufficiency[h]	4 (3)	2 (2)	1 (2)	1 (2)
Hypophysitis[e]	1 (1)	1 (1)	1 (2)	1 (2)
Pulmonary[i]	6 (5)	3 (2)	2 (3)	0
Dermatologic[j]	4 (3)	1 (1)	2 (3)	1 (2)
Cardiac[k]	2 (2)	2 (2)	2 (3)	2 (3)
Renal[l]	2 (2)	2 (2)	1 (2)	1 (2)
Neurologic[m]	2 (2)	2 (2)	1 (2)	1 (2)
Musculoskeletal				
Myositis[e]	1 (1)	0	1 (2)	0
Polyarthritis[e]	1 (1)	1 (1)	1 (2)	1 (2)

[a]imAEs were medically adjudicated and defined as related to treatment, thought to have an immune mechanism, determined by the investigator to be immune-related, and/or treated with systemic steroids (of any dose) and/or other immunosuppressants or with thyroid replacement hormones. imAEs were identified from a prespecified list of preferred terms. [b]There was only 1 grade 4 imAE (immune-mediated diarrhea/colitis in the BOT 2 mg/kg + BAL group). [c]Diarrhea/colitis (grouped term) included the preferred terms of immune-mediated enterocolitis, colitis, diarrhea, and autoimmune colitis. [d]Hepatitis (grouped term) included the preferred terms of ALT increased, AST increased, immune-mediated hepatitis, and autoimmune hepatitis. [e]Preferred term. [f]Patient was excluded from diarrhea/colitis grouping because they experienced enteritis only (involves the upper gastrointestinal tract). [g]Thyroid disorders (grouped term) included the preferred terms of hypothyroidism, blood TSH increased, hyperthyroidism, immune-mediated hypothyroidism, and thyroiditis. [h]Adrenal insufficiency (grouped term) included the preferred terms of adrenal insufficiency and immune-mediated adrenal insufficiency. [i]Pulmonary (grouped term) included the preferred terms of immune-mediated lung disease and pneumonitis. [j]Dermatologic (grouped term) included the preferred terms of rash maculo-papular and immune-mediated dermatitis. Patients with skin and subcutaneous tissue disorders who received topical steroids only (n=30 in the overall population) were excluded from the imAE analysis. [k]Cardiac (grouped term) included the preferred terms of immune-mediated myocarditis and myocarditis. [l]Renal (grouped term) included the preferred terms of immune-mediated nephritis and tubulointerstitial nephritis. [m]Neurologic (grouped term) included the preferred terms of Bell's palsy and myasthenia gravis.

- imAEs were more frequent among LTS than in the overall population, consistent with prior observations of an association between imAE occurrence and survival with BOT+BAL[11]
- No treatment-related deaths were observed
- Immune-mediated diarrhea/colitis (imDC) resolved in 97% of LTS (n=33/34); median time to resolution from imDC onset was 13 days (IQR, 8–22)
- imDC was successfully managed with early mid-dose oral steroids followed promptly by definitive TNFα therapy with rapid steroid taper[8]

Conclusions

- In this heavily pretreated, refractory MSS mCRC NLM population, **51% of patients survived ≥18 months**
- Among these LTS, **OS plateaued above 50% beyond 3 years**
- In the overall population and LTS, **median DOR was not reached**
- Long-term survival was not confined to patients with favorable prognostic features
- Clinical benefit was accompanied by deep, durable responses, as well as treatment-free intervals among a subset of LTS
- imDC was the most common imAE and was rapidly resolvable with early steroids and definitive TNFα therapy

This represents a previously unreported LTS phenotype in refractory MSS mCRC NLM and supports the differentiated immunologic mechanism of BOT+BAL

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Acknowledgments: Agenus Inc. funded and is the sponsor of this study. We thank the patients and their families for participating in the C-800-01 (NCT03860272) trial, as well as the trial coordinators and investigators.

References: 1. Garcia-Carbonero R, et al. Poster presented at: ESMO 2024. #520P. Barcelona, Spain. **2.** Tabernero J, et al. Poster presented at: ASCO 2024. #3584. Chicago, IL, USA. **3.** Cohen R, et al. *Eur J Cancer*. 2024;207:114160. **4.** Chand D, et al. *Cancer Discov*. 2024;14(12):2407–2429. **5.** O'Malley DM, et al. *Gynecol Oncol*. 2021;163(2):274–280. **6.** O'Malley DM, et al. *J Clin Oncol*. 2022;40(7):762–771. **7.** Schlechter BL, et al. *Clin Cancer Res*. Online August 28, 2026. **8.** Wilky BA, et al. *J Clin Oncol*. 2025;43(11):1358–1368. **9.** Porter R, et al. *J Immunother Cancer*. 2025;13(12):e013222. **10.** El-Khoueiry A, et al. *Liver Cancer*. Online March 30, 2026. **11.** Gordon MS, et al. Oral presentation at: ESMO 2025. #1517MO. Berlin, Germany. **12.** Atkins MB, et al. Poster presented at: ASCO 2026. #259. Chicago, IL, USA.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BAL, balstilimab; BOT, botensilimab; *BRAF*, V-Raf murine sarcoma viral oncogene homolog b; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; CTLA-4, cytotoxic T-lymphocyte associated protein 4; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Fc, fragment crystallizable; ICI, immune checkpoint inhibitor; imAE, immune-mediated adverse event; imDC, immune-mediated diarrhea/colitis; IQR, interquartile range; KM, Kaplan–Meier; LDH, lactate dehydrogenase; LLN, lower limit of normal; LTS, long-term survivor; mCRC, metastatic colorectal cancer; mo, months; MSS, microsatellite-stable; Mut/Mb, mutations per megabase; NE, not evaluable; NLM, no active liver metastases; NLR, neutrophil-to-lymphocyte ratio; No., number; NR, not reached; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-1, programmed cell death protein 1; PD-(L)1, programmed cell death ligand 1; PFS, progression-free survival; pMMR, mismatch repair proficient; PR, partial response; Q2W, every 2 weeks; Q6W, every 6 weeks; *RAS*, rat sarcoma virus; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; STS, short-term survivor; TMB, tumor mutational burden; TNFα, tumor necrosis factor alpha; TSH, thyroid-stimulating hormone; ULN, upper limit of normal; wks, weeks.

Poster presented at the Society for Immunotherapy of Cancer: November 4–8, 2026. Phoenix, AZ, USA.