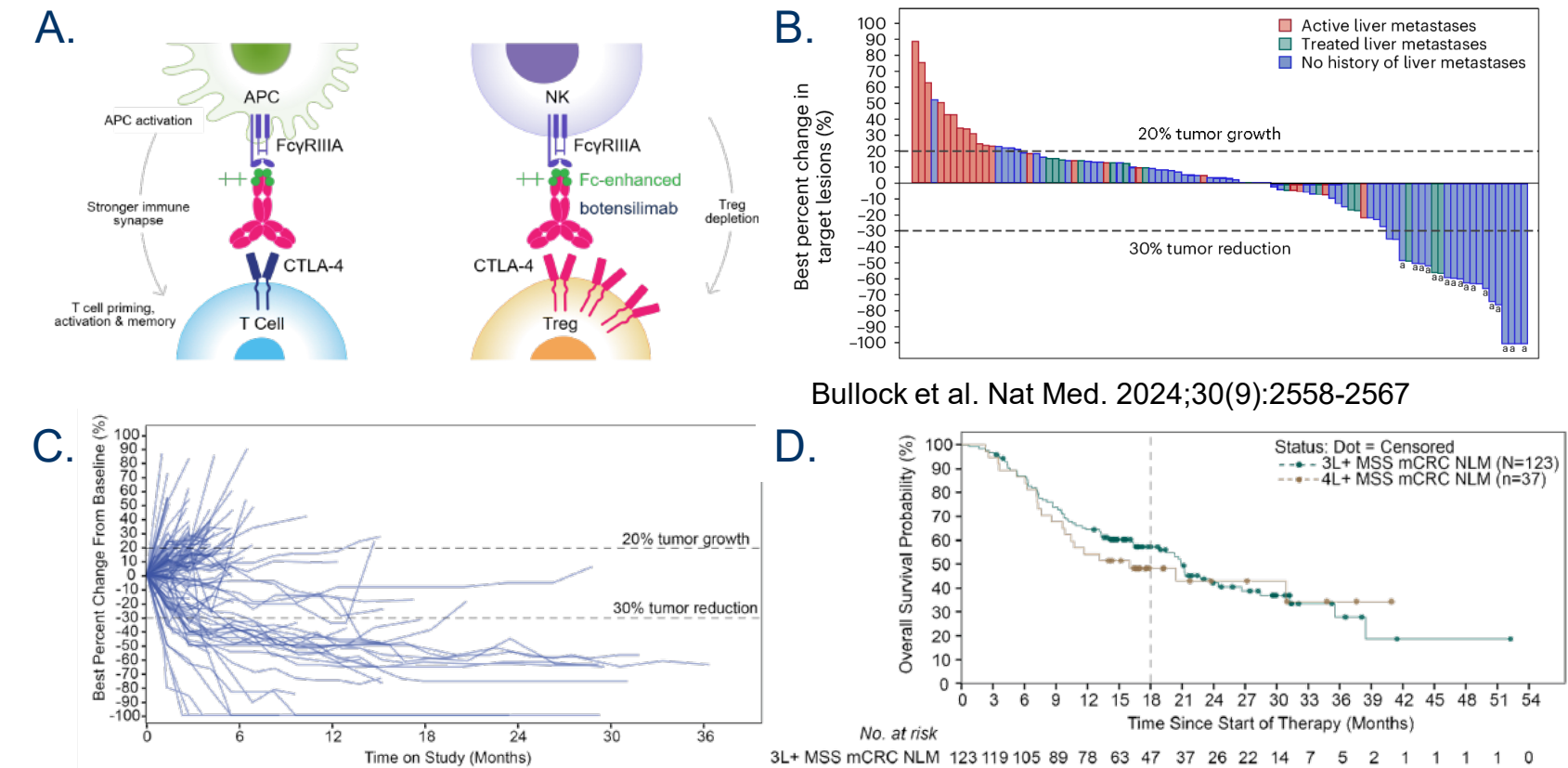


# Preliminary Results of First-line Botensilimab and Balstilimab Optimization in Microsatellite Stable Colorectal Cancer without liver, bone, or brain metastasis (BBOpCo NCT06268015)

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## Background and Rationale

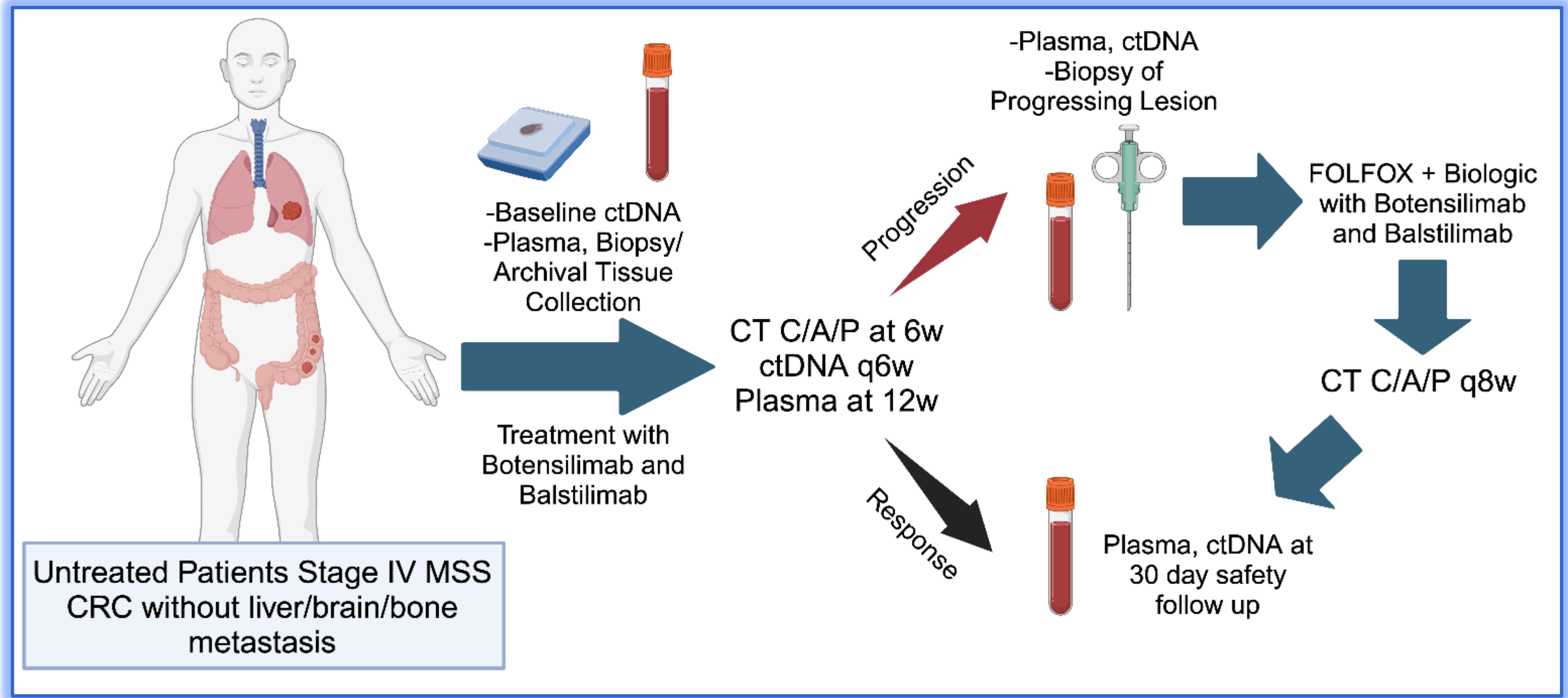
- Microsatellite stable (MSS) colorectal cancer (CRC) has limited response to conventional immune checkpoint blockade (ICB), where the current standard of care (SOC) for first-line (1L) MSS CRC is still chemotherapy with or without anti-vascular endothelial growth factor (VEGF) or anti-epidermal growth factor receptor (EGFR).
- Studies including Checkmate 9X8, AtezoTRIBE, and MODUL in mCRC patients showed that the safety profile of 1L ICB + chemotherapy + bevacizumab identified no new safety signals.
- Given that ICB is generally more tolerable than the current SOC chemotherapy combinations which can have long term side effects, further study of ICB alone is warranted.
- Botensilimab (BOT) is an Fc-enhanced anti-CTLA-4 antibody designed to augment T-cell priming, deplete intratumoral Tregs, and activate antigen-presenting cells to work in "cold" tumors (A) like MSS CRC, where activity was observed in patients without liver metastasis (B).
- A phase 1b study with BOT+ Balstilimab (BAL; an anti-PD-1 antibody) in pretreated patients with MSS CRC achieved a 69% disease control rate (DCR) and 20% ORR in 3L patients without liver metastasis (C), with improved OS versus historical controls in 3L/4L (D). We tested the hypothesis that anatomically selected patients with metastatic MSS CRC would benefit from BOT+BAL in the 1L, potentially negating the need for chemotherapy.



**Other References**  
 Wang, C. et al. Regorafenib and Nivolumab or Pembrolizumab Combination and Circulating Tumor DNA Response Assessment in Refractory Microsatellite Stable Colorectal Cancer. *Oncologist*, 2020, 25(8), p. e1158-e1164.  
 Wang, C. et al. Clinical Response to Immunotherapy Targeting Programmed Cell Death Receptor 1/Programmed Cell Death Ligand 1 in Patients With Treatment-Resistant Microsatellite Stable Colorectal Cancer With and Without Liver Metastases. *JAMA Netw Open*, 2021, 4(8), p. e21184-16.  
 Wang, B. et al. Botensilimab, an Novel Intact/Intact Immune Activator, Plus or Minus Bevacizumab (Bio-P1) in "Cold" and "Hot" Refractory Metastatic Solid Tumors. *Journal for Immunotherapy of Cancer*, 2022, 10, p. A010-A010.  
 Morris, V.K. et al. Treatment of Metastatic Colorectal Cancer. *ASCO Guidelines J Clin Oncol*, 2023, 41(3), p. 678-700.  
 Lee, M.S. et al. Phase II Study of Ipilimumab, Nivolumab, and Panitumumab in Patients With Wild-Type (WT) Microsatellite Stable (MSS) Metastatic Colorectal Cancer (mCRC). *Journal of Clinical Oncology*, 2021, 39(1), p. 1-11.  
 Lenz, H.J. et al. Nivolumab (NIVO) + Fluorouracil/Leucovorin/5-Fluorouracil (5-FU) versus 5-FU/Leucovorin (5-FU) for First-Line (1L) Treatment of Metastatic Colorectal Cancer (mCRC): Phase 3 Results From Checkmate 15B. *Journal of Clinical Oncology*, 2022, 40(4), p. 401-411.  
 Faria, M. et al. Regorafenib, Ipilimumab, and Nivolumab for Patients With Microsatellite Stable Colorectal Cancer and Disease Progression With Prior Chemotherapy: A Phase 3 Randomized Clinical Trial. *JAMA Oncol*, 2023, 9(3), p. 327-334.  
 Traub-Drazatzki, M. et al. First-Line Durvalumab and Tremelimumab with Chemotherapy in RAS-Mutated Metastatic Colorectal Cancer: A Phase 1b/2 Trial. *Nat Med*, 2023, 29(1), p. 2037-2046.  
 Tabernero, J. et al. MODUL, cohort 2: an adaptive, randomized, signal-seeking trial of Ruprosimidine plus bevacizumab with or without atezolizumab maintenance therapy for BRAF/PKR metastatic colorectal cancer. *ESMO Open*, 2023, 7(3), p. 100209.  
 Antonelli, C. et al. Ipilimumab Plus Bevacizumab with or without Atezolizumab in the Treatment of Patients with Metastatic Colorectal Cancer (MAYOR): a multicentre, open-label, randomised, controlled, phase 3 trial. *Lancet Oncol*, 2022, 23(7), p. 874-887.  
 Redouk, N. et al. Incidence and Survival in Synchronous and Metastatic Liver Metastases From Colorectal Cancer. *JAMA Netw Open*, 2022, 5(10), p. e2225558.  
 Yu, J. et al. Liver Metastases Restrains Immunotherapy Efficacy via Macrophage-Mediated T Cell Elimination. *Nat Med*, 2021, 27(1), p. 152-164.  
 Chen, E.X. et al. Liver Metastases and Immune Checkpoint Inhibitor Efficacy in Patients With Refractory Metastatic Colorectal Cancer: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Netw Open*, 2023, 6(7), p. e230504.  
 Alamo, M.B. et al. Combination Durvalumab and Tremelimumab Versus Combination Nivolumab and Ipilimumab for Patients With Advanced BRAF-Mutant Metastatic. *The Oncologist*, 2024, 29(4), p. 412-421.

## Trial Design and Objectives

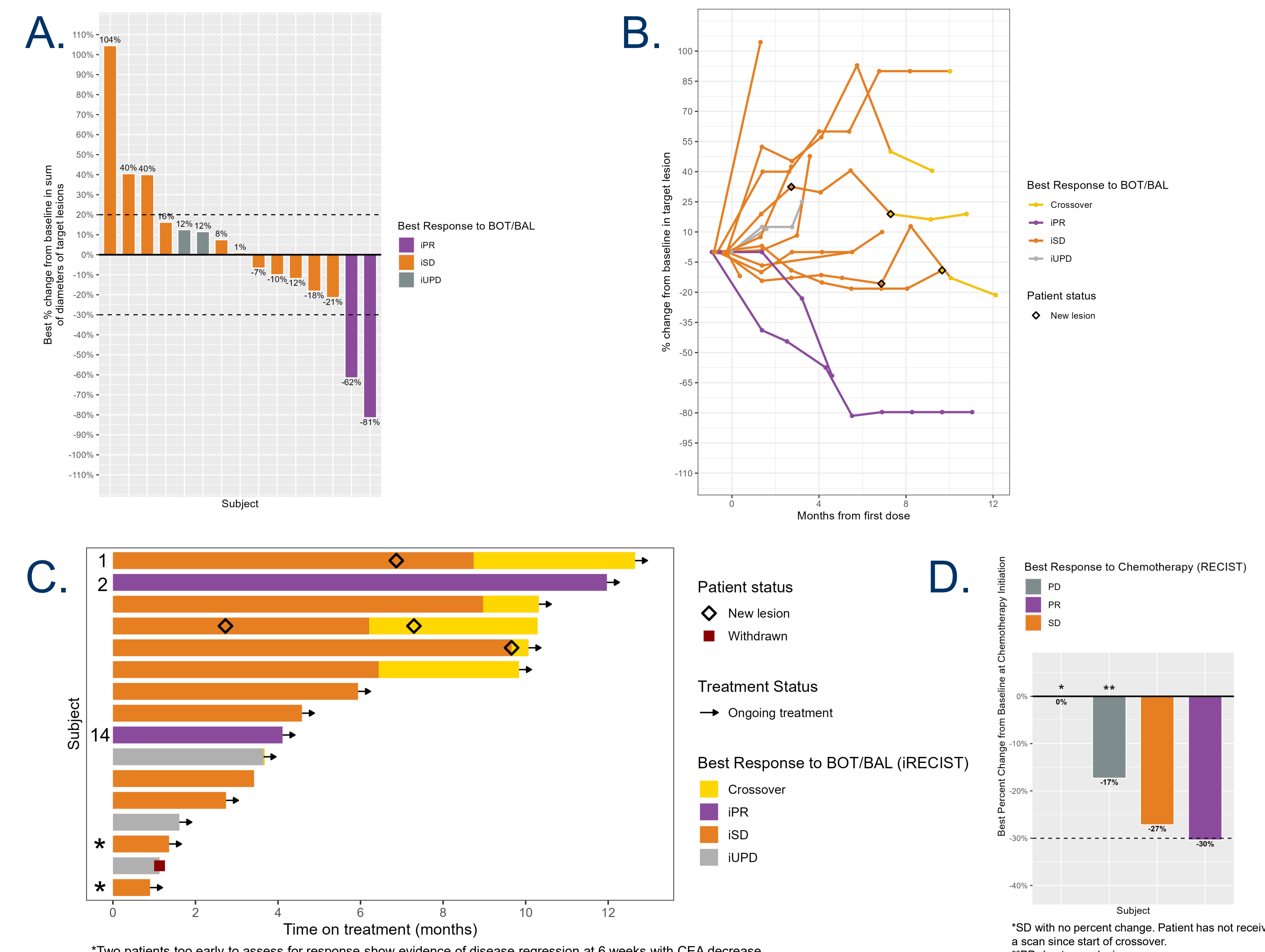
This is a single-arm, interventional, pilot clinical trial. Fifteen evaluable patients with newly diagnosed metastatic and/or unresectable MSS colorectal cancer without liver, bone, or brain metastases have been treated with botensilimab and balstilimab (BOT+BAL). Eligible subjects had not received prior systemic therapy for CRC since diagnosis with metastatic/unresectable disease but could have received adjuvant therapy >6 months. Subjects are treated with BOT (75 mg every 6 weeks, up to 4 doses) and BAL (240 mg every 2 weeks) in 6-week cycles until progression. In the event of progression, mFOLFOX6 and bevacizumab or panitumumab are added to the regimen. Safety testing was done at baseline and is conducted every two weeks while patients are on study drug. Treatment with BOT+BAL, mFOLFOX6, and bevacizumab or panitumumab is continued until radiographic or clinical progression, toxicity, or patient withdrawal. Subjects have a follow-up visit 30 days after the last treatment and will be followed for survival every 12 weeks for up to 2 years.



- Primary Objectives**
- To evaluate the feasibility of administering 1L BOT+BAL alone in MSS CRC without liver, brain, or bone metastasis followed by BOT+BAL in combination with mFOLFOX6 plus bevacizumab or panitumumab as a rescue upon progression.
  - To evaluate the disease control rate (DCR) of 1L BOT+BAL in MSS CRC without liver, brain, or bone metastasis.
  - To confirm the safety and tolerability of botensilimab and balstilimab in the 1L setting.
- Secondary Objectives**
- To describe the overall survival (OS) and progression free survival (PFS) of patients treated with 1L BOT+BAL and during crossover to SOC chemotherapy (PFS2).
  - To determine the best overall response (ORR, iRECIST) of BOT+BAL in patients with MSS CRC without liver, brain, or bone metastasis, and to crossover to SOC chemotherapy (ORR2, RECIST).
- Exploratory Objectives**
- To identify tumor-mediated pathways and immune microenvironment features of resistance to BOT+BAL alone for the development of future biomarkers with a goal of more accurate patient selection.
  - To determine the utility of ctDNA and CEA as dynamic biomarkers of response to immunotherapy in CRC.

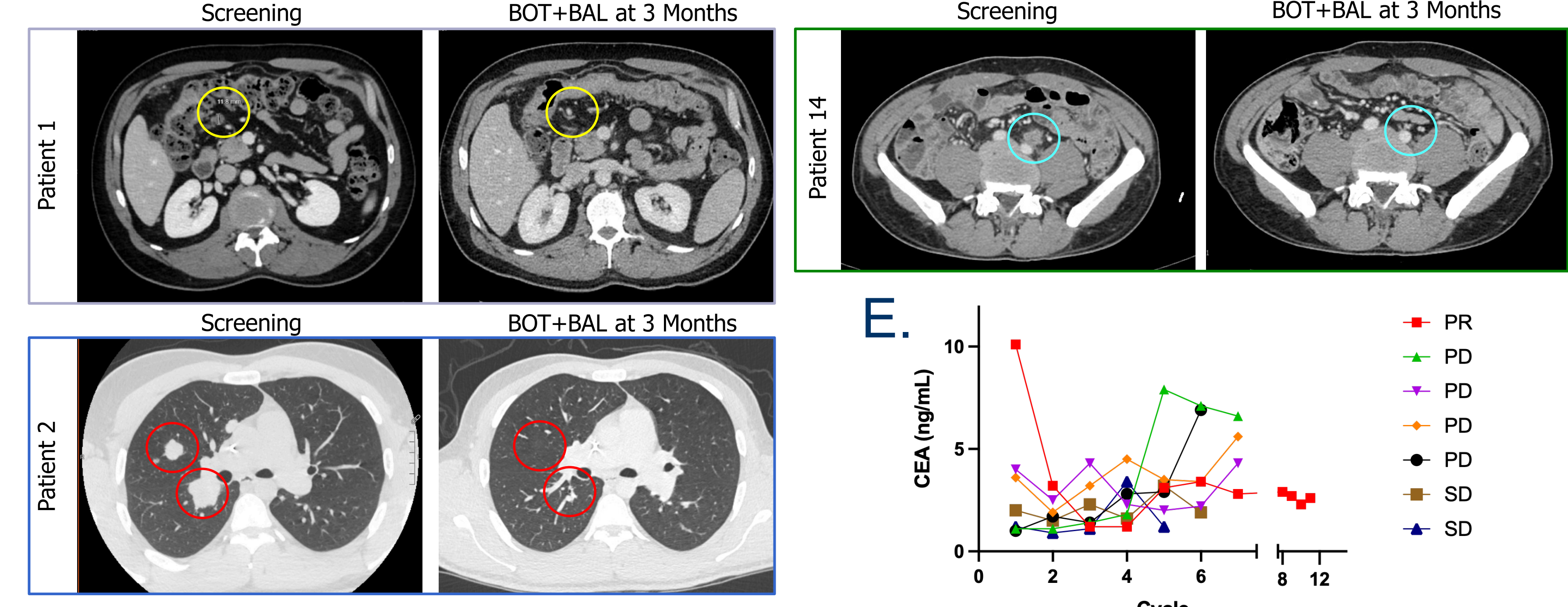
Efficacy-evaluable patients (at least one scan): 15  
 Safety-evaluable patients (at least one dose of BOT+BAL): 16 [One patient withdrew but was assessed for safety]  
 Total Patients Enrolled: 17 [Another patient was a screen fail (SF) and not evaluable for safety or efficacy]

## Preliminary Results



- Data are preliminary; objective response rate will be reported upon protocol-defined data maturity.
- After time of data cut-off (March 31, 2026), additional responses anticipated based on new carcinoembryonic antigen (CEA) levels trends and imaging observations.

**A. Waterfall plot:** Response to BOT+BAL. As of Mar 31, 2026 with a median follow up of 5.1 Months (range 1.3–12.6) and 15 evaluable patients enrolled, there were 2 confirmed iPRs to BOT+BAL alone, one in a patient with lung mets (P12 below) and another with peritoneal metastasis (P14 below), with tissue TMB of 1 and 3 mut/mb respectively, as well as 4 iSD at 24w follow-up (n=8), resulting in a 75% DCR. One patient withdrew. **B. Spider Plot and C. Swimmer's plot** showing durable responses and chemo delay. **D. Waterfall plot:** Response to chemotherapy after crossover. Median freedom from crossover to chemo was 8.7 months (95% CI, 6.4-NE). Of 5 patients crossing over to SOC at a median of 7.6 months (95% CI, 6.2-NE) from BOT+BAL start, 4 were evaluable for response to chemo by RECIST with an 75% DCR. \*1 patient withdrew from the trial and was evaluable for safety but not efficacy



**Representative scans** of a patient with SD but meaningful tumor size reduction who later crossed over (P1) and two confirmed PRs by iRECIST (P12, P14). Corresponding patient numbers in **C. E. CEA dynamics in patients on study >6 months.** CEA decrease preceded radiographic response in P12, red, and aligned with radiographic progression in n=4 patients but was not elevated in others.

## Patient Characteristics and Adverse Events

Characteristic	Median (Q1, Q3)	N = 17
Age (years)	50 (40, 61)	
Sex, n (%)		
Female	6 (35%)	
Male	11 (65%)	
Race, n (%)		
Black or African American	2 (12%)	
Other	2 (12%)	
Not Reported	4 (24%)	
White	11 (65%)	
Ethnicity, n (%)		
Not Hispanic or Latino	13 (76%)	
Not reported	4 (24%)	
BOT+BAL Cycles	Median No. (Q1, Q3)	4 (3, 8)
Sites of Metastasis in evaluable patients, n (%)		
Lungs	6 (43%)	
Lymph nodes	4 (29%)	
Peritoneum	4 (27%)	
Other, primary	1 (7%)	
ECOG PS of safety evaluable patients, n (%)		
0	14 (87%)	
1	2 (13%)	
Mutational Status, n		
KRAS	10	
BRAF V600E	2	
RAS/RAF WT	5	

All patients were confirmed MSS, POLE WT, tissue TMB <10 mut/mb and/or plasma TMB <20 mut/mb

\* 1 patient withdrew but was evaluable for efficacy  
 1 patient was a SF and only characteristics are included

System Organ Class, n (Instance of irAE)	Preferred Term**	Gr1	Gr2
Endocrine disorders, 2	Hypothyroidism	0	2
Gastrointestinal disorders, 17	Abdominal pain	2	1
	Colitis	0	4
	Diarrhea	0	4
	Other	2	0
	Edema limbs	2	0
	Fatigue	4	3
	Fever	3	1
	Other	4	0
	ALT increased	1	2
	AST increased	2	1
	Weight loss	2	0
Metabolism and nutrition disorders, 3	Anorexia	1	2
Musculoskeletal and connective tissue disorders, 5	Arthralgia	0	2
	Other	1	2
Skin and subcutaneous tissue disorders, 11	Rash maculo-papular	1	3
	Other	6	1

**irAE management and Grade 3 Toxicity:**

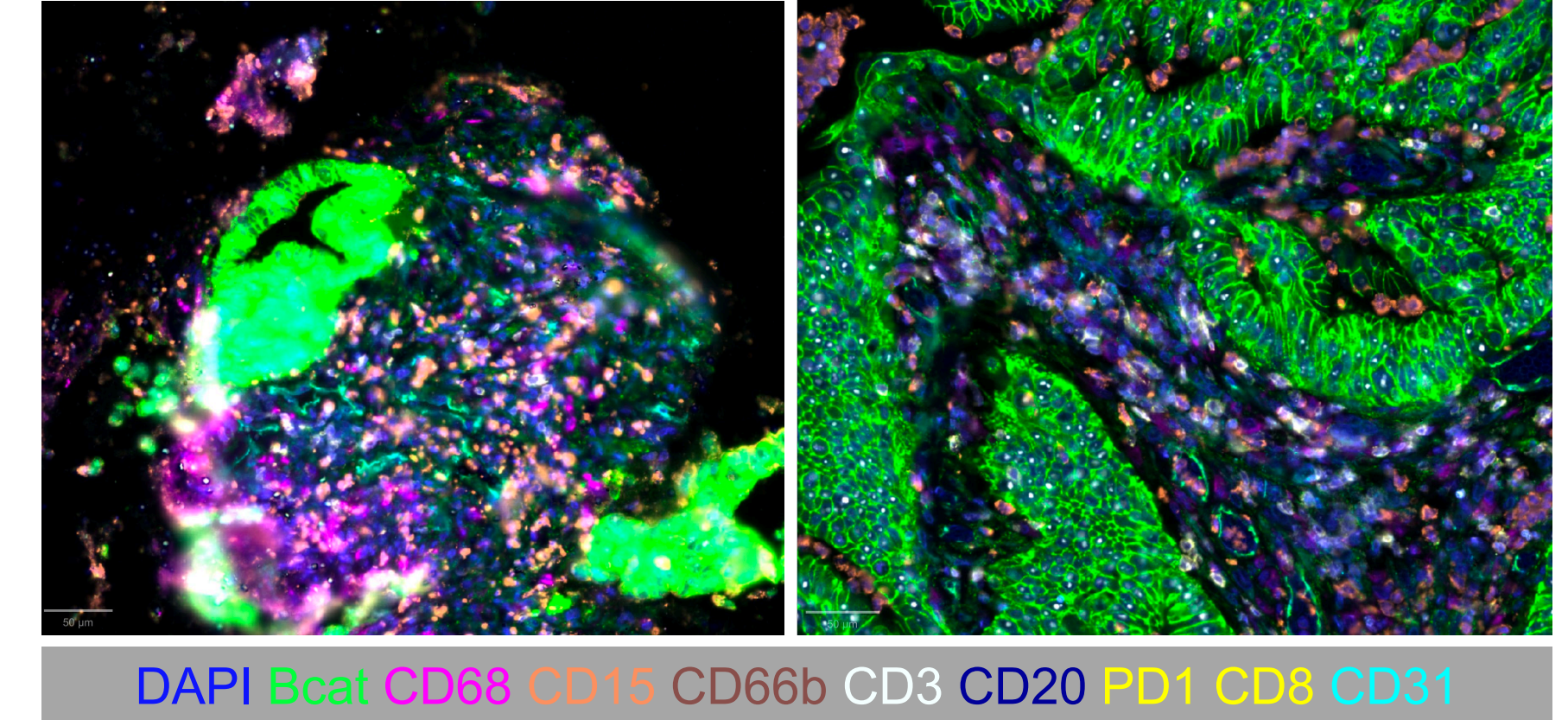
- Grade 3 toxicity was restricted to diarrhea/colitis (3), which we managed with short course prednisone that patients were given to take home before starting therapy, followed by infliximab within 48 hours.
- Early onset symptoms (fever) were managed with naproxen or ibuprofen.
- 3 patients received leflunomide for arthralgia.
- 1 patient was treated with dose interruption and a prednisone taper for presumed hepatitis
- 9 patients were treated with infliximab for Gr2+ colitis; 10 patients were treated with prednisone

\*\*Multiple preferred terms may have occurred in 1 patient during a given event.

## Conclusions and Future Directions

This novel first-line study demonstrates the feasibility of BOT+BAL alone in MSS CRC without liver, bone, or brain metastases and provides early evidence of durable clinical activity in a subset of patients, with the potential to defer cytotoxic chemotherapy in others

- ORR, PFS, and OS are early and updates will be presented in later meetings.
- Together, these findings support further biomarker-informed development of BOT+BAL in the front-line setting via a Phase II study, in patients without liver/bone/brain metastases to justify randomized studies that incorporate endpoints such as time to chemotherapy, ctDNA dynamics, and PFS2 to better capture the full value of early immune intervention.



**Biomarker studies focused on spatial analysis of the tumor microenvironment.** Initial analysis of CODEX multiplex IHC demonstrated higher cDC1s in responders pre-treatment to BOT+BAL (n=2, data not shown), with further review underway of other cells in all baseline samples and on-treatment in cross-over.

- Use of ctDNA to determine response dynamics over time.** CEA utility was limited by patient-to-patient variability, ctDNA analysis may enhance sensitivity in parallel and better capture clinical benefit.
- Future directions will focus on addressing non-response to BOT+BAL and liver metastasis in the first line setting through novel combination strategies.** In part based on exploratory objectives in this study, Duke biobanking and organoids efforts, and work from mouse models in our lab.

## Support

Duke GI Clinical Research Gateway Foundation for Cancer Research  
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