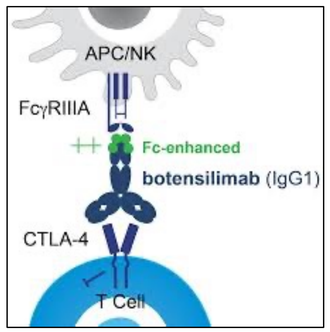
First-line Botensilimab and Balstilimab OPtimization in Microsatellite Stable COlorectal Cancer without liver, bone, or brain metastasis (BBOpCo NCT06268015)

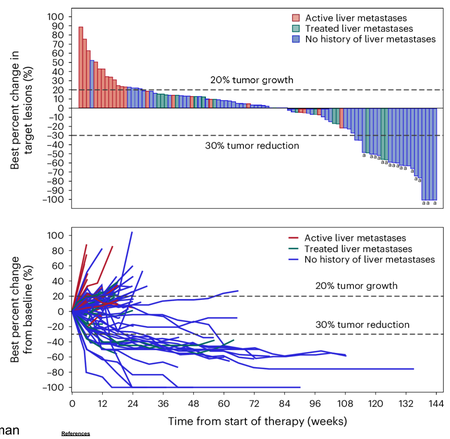
Nicholas DeVito, MD; Gerard Blobe, MD, PhD; Emily Bolch; Kara Bonneau; Tucker Coston, MD; David Hsu, MD, PhD; Niharika Mettu, MD, PhD; Michael Morse, MD; Aman Opneja, MBBS; Lisa Vlastelica, PharmD; Carol Ann Wiggs; John Strickler, MD

Background and Rationale

- Microsatellite stable (MSS) colorectal cancer (CRC) has limited response to conventional immune checkpoint blockade (ICB), though some activity has been observed in patients without liver metastases.
- The current standard of care for first-line MSS CRC is still chemotherapy with or without anti-vascular endothelial growth factor (VEGF) or anti-epidermal growth factor receptor (EGFR).
- Studies such as Checkmate 9X8, AtezoTRIBE, and MODUL studies in mCRC patients showed that the safety profile of first line ICB + chemotherapy + bevacizumab was consistent with previous findings and identified no new safety signals.
- A study of regorafenib, ipilimumab, and nivolumab for patients with MSS CRC without liver metastases showed some clinical activity, although tolerability was a limiting factor. None of these studies met primary endpoints.
- Given that ICB is generally more tolerable than the current SOC chemotherapy combinations, further study is warranted. In patients who do progress on immunotherapy alone, the addition of chemotherapy may enhance responses and has been safely done in other trials.
- Up to 30% of patients with colon cancer will present with synchronous liver metastasis. Metastatic disease to the liver has diminished the response to current ICB strategies in colon cancer and other malignancies.
- Trials of ICB in MSS CRC have occurred in later lines of therapy, where immune checkpoint blockade has been shown to be less efficacious. This raises the possibility that patients with MSS CRC who lack liver metastases may have a favorable response to immunotherapy if exposed prior to other treatments.
- Avoidance of chemotherapy promises to reduce long-term side effects in patients. Moreover, with the advent of circulating tumor DNA (ctDNA) technology, response to immunotherapy can be monitored more closely than with radiographic response and CEA alone.
- Therefore, we hypothesize that a subset of patients with metastatic colorectal cancer lacking liver metastasis will potentially respond to ICB alone.



Yofe et al Nat Cancer 2022
Chand et al Cancer Disc 2024
Bullock et al Nat Medicine 2024



Botensilimab

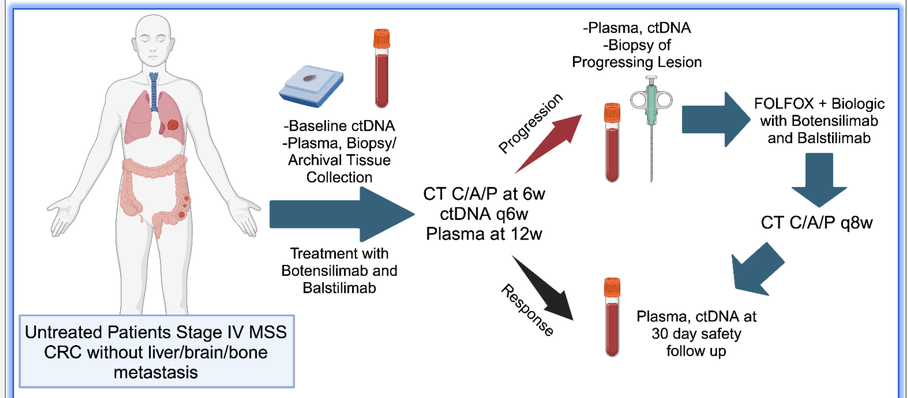
Botensilimab is a fragment crystallizable (Fc)-engineered human immunoglobulin G subclass 1 (IgG1) monoclonal antibody (mAb) that targets co-inhibitory protein cytotoxic T lymphocyte-associated protein 4 (CTLA-4), expressed on recently activated T cells. Botensilimab is thought to employ two primary mechanisms-of-action: 1) binding to and blockade of CTLA-4 expressed on T cells and 2) binding to and activation of Fc gamma receptors (FcγRs) expressed on antigen-presenting and phagocytic cells. Both mechanisms are expected to bring about a cascade of downstream effects to augment tumor immunity. In addition to blockade of CTLA-4 binding to endogenous ligands cluster of differentiation (CD)80 and CD86, botensilimab leverages a novel mechanism (mediated by its increased Fc binding activity to FcγRs expressed by antigen-presenting cells and natural killer [NK] cells) to enhance T-cell priming and regulatory T cell (Treg) depletion. Further, Fc modifications to botensilimab effectively abolish binding to C1q complement protein, thereby reducing the risk of drug-induced complement-related toxicities. Taken together, the composite properties of botensilimab are anticipated to improve efficacy by promoting antigen-specific effector T-cell responses while also demonstrating an improved safety profile as compared with current CTLA-4 targeted therapies for the treatment of cancer.

References

1. 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. e1168-e1194.
2. 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. e2115416.
3. Wilky, B., et al., *Botensilimab, a Novel Innate/Adaptive Immune Activator, Plus or Minus Balstilimab (Anti-PD-1) in "Cold" and I-O Refractory Metastatic Solid Tumors.* Journal for Immunotherapy of Cancer, 2022. **10**: p. A810-A810.
4. Morris, V.K., et al., *Treatment of Metastatic Colorectal Cancer: ASCO Guideline.* J Clin Oncol, 2023. **41**(3): p. 678-700.
5. 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**(3).
6. Lenz, H.J., et al., *Nivolumab (NIVO)+5-fluorouracil/leucovorin/oxaliplatin (mFOLFOX6)/bevacizumab (BEV) versus mFOLFOX6/BEV for first-line (1L) treatment of metastatic colorectal cancer (mCRC): Phase 2 results from CheckMate 9X8.* Journal of Clinical Oncology, 2022. **40**(4).
7. Falchi, M., et al., *Regorafenib, Ipilimumab, and Nivolumab for Patients With Microsatellite Stable Colorectal Cancer and Disease Progression With Prior Chemotherapy: A Phase 1 Nonrandomized Clinical Trial.* JAMA Oncol, 2023. **9**(5): p. 627-634.
8. Thibaudin, 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**(9): p. 2087-2098.
9. Janjigian, Y.Y., et al., *Pembrolizumab plus trastuzumab and chemotherapy for HER2-positive gastric or gastro-oesophageal junction adenocarcinoma: interim analyses from the phase 3 KEYNOTE-811 randomised placebo-controlled trial.* Lancet, 2023. **402**(10418): p. 2197-2208.
10. Sun, J.M., et al., *Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study.* Lancet, 2021. **398**(10302): p. 759-771.
11. Paz-Ares, L., et al., *First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial.* Lancet Oncol, 2021. **22**(2): p. 198-211.
12. Narita, Y. and K. Muro, *Updated Immunotherapy for Gastric Cancer.* J Clin Med, 2023. **12**(7).
13. Tabernero, J., et al., *MODUL cohort 2: an adaptable, randomized, signal-seeking trial of fluoropyrimidine plus bevacizumab with or without atezolizumab maintenance therapy for BRAFv(e) metastatic colorectal cancer.* ESMO Open, 2022. **7**(5): p. 100559.
14. Antoniotti, C., et al., *Upfront FOLFOXIRI plus bevacizumab with or without atezolizumab in the treatment of patients with metastatic colorectal cancer (AtezoTRIBE): a multicentre, open-label, randomised, controlled, phase 2 trial.* Lancet Oncol, 2022. **23**(7): p. 875-887.
15. Rebuzzi, N., et al., *Incidence and Survival in Synchronous and Metachronous Liver Metastases From Colorectal Cancer.* JAMA Netw Open, 2022. **5**(10): p. e2236666.
16. Yu, J., et al., *Liver metastasis restrains immunotherapy efficacy via macrophage-mediated T cell elimination.* Nat Med, 2021. **27**(1): p. 152-164.
17. 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**(12): p. e2349094.
18. Pires da Silva, I., et al., *Site-specific response patterns, pseudoprogression, and acquired resistance in patients with melanoma treated with ipilimumab combined with anti-PD-1 therapy.* Cancer, 2020. **126**(1): p. 86-97.
19. Qu, F.J., Y. Zhou, and S. Wu, *Progress of immune checkpoint inhibitors therapy for non-small cell lung cancer with liver metastases.* Br J Cancer, 2024. **130**(2): p. 165-175.
20. Atkins, M.B., et al., *Combination Dabrafenib and Trametinib Versus Combination Nivolumab and Ipilimumab for Patients With Advanced BRAF-Mutant Melanoma: The DREAMseq Trial-ECOG-ACRIN EA6134.* J Clin Oncol, 2023. **41**(2): p. 186-197.
21. Carretero-Gonzalez, A., et al., *Analysis of response rate with ANTI PD1/PD-L1 monoclonal antibodies in advanced solid tumors: a meta-analysis of randomized clinical trials.* Oncotarget, 2018. **9**(39): p. 8706-8715.
22. Roccuzzo, B., et al., *Early plasma circulating tumor DNA (ctDNA) changes predict response to first-line pembrolizumab-based therapy in non-small cell lung cancer (NSCLC).* J Immunother Cancer, 2021. **9**(3).
23. *Botensilimab (AGEN1181) Investigator's Brochure.* 2023. **5 ed.**

Trial Design

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 will start botensilimab and balstilimab treatment. Eligible subjects cannot have received prior systemic therapy for colorectal cancer since diagnosis with metastatic/unresectable disease, though adjuvant therapy > 6 months is acceptable. They will receive botensilimab (75 mg every 6 weeks x 4 doses) and balstilimab (240 mg every 2 weeks) in 6-week cycles and in the event of progression, mFOLFOX6 and bevacizumab or panitumumab will be added to the regimen. Subjects will have safety testing at baseline and every two weeks while on study drug. Study treatment with botensilimab and balstilimab, mFOLFOX6, and bevacizumab or panitumumab will be continued until radiographic or clinical progression, toxicity, or patient withdrawal. Subjects will have one safety 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 first-line botensilimab and balstilimab in MSS CRC without liver, brain, or bone metastasis followed by botensilimab and balstilimab in combination with mFOLFOX6 plus bevacizumab or panitumumab upon progression.
- To evaluate the disease control rate (DCR) of first-line botensilimab and balstilimab in MSS CRC without liver, brain, or bone metastasis.
- To confirm the safety and tolerability of botensilimab and balstilimab in the first-line setting.

Secondary Objectives

- To describe the overall survival and progression free survival of patient treated with first-line botensilimab and balstilimab.
- To determine the best overall response (BOR) of botensilimab and balstilimab in patients with MSS CRC without liver, brain, or bone metastasis.

Exploratory Objectives

- To identify tumor-mediated pathways of resistance to botensilimab and balstilimab.
- To determine the utility of ctDNA and CEA as dynamic biomarkers of response to immunotherapy in CRC.

Adverse Event Management

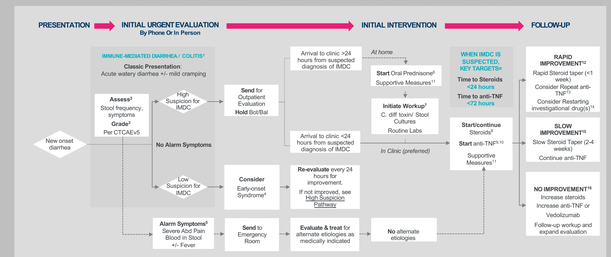
EARLY-ONSET SYNDROME

Presentation
- 0-14 days post infusion
- Intermittent fever
- Chills, Rigors
- Fatigue/malaise
- Occasionally mild self-limited N/V or diarrhea
- May recur w/subsequent infusions
- Resolves within a few days

Workup
- Infectious workup if indicated
- Consider evaluating inflammatory markers

Management
- Acetaminophen PRN
- NSAIDs (e.g. Naproxen 500mg BID w/meals if tolerated, consider PPI as well)
- Anti-motility agents (If ineffective, consider alternative diagnosis)
- If doesn't resolve within a few days, consider alternate etiologies

AGENUS ALGORITHM FOR MANAGEMENT OF IMMUNE-MEDIATED DIARRHEA/ COLITIS



BBOpCo Patients will have a prednisone prescription to reduce time to IMDC treatment and instructions to call their provider

Progress and Future Directions

- **Two of 15 patients have been treated so far without clear irAEs, and we are awaiting restaging.**
- **Plans for correlative biomarker analysis will be further developed at interim futility/data analysis based on a DCR of at least 50% at 8 patients. Expansion beyond 15 patients will be considered at this time.**
- **Future directions will address liver metastasis in the first line with novel therapeutics in part based on exploratory objectives in this study**

Support

GI Cancer Immunotherapy Research Fund
QR code to support our work:

Gateway Foundation for Cancer Research
CRUSH CRC
Join our 5K in Durham, NC!

Valeriani Family
Agenus (Drug only support)

CRUSH COLORECTAL CANCER DUKE 5K
March 22, 2025
Ben Franklin Blvd Durham 8:30 am
Registration http://dukecrc5k.org/

GATEWAY FOR CANCER RESEARCH

Duke Cancer Institute 50th Anniversary
Nicholas.DeVito @Duke.edu
VuMeDi https://www.vumedi.com/accounts/86f1411b-909b-47e3-85ef-eccf162b87b3/
Bluesky LinkedIn @ndevitomd