Neoadjuvant botensilimab plus balstilimab (BOT/BAL) in resectable mismatch repair proficient and deficient colorectal cancer: NEST-1 clinical trial.

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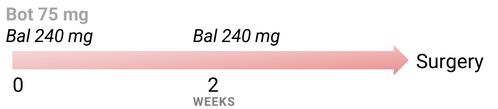
Abstract#117

Poster Board#: H2

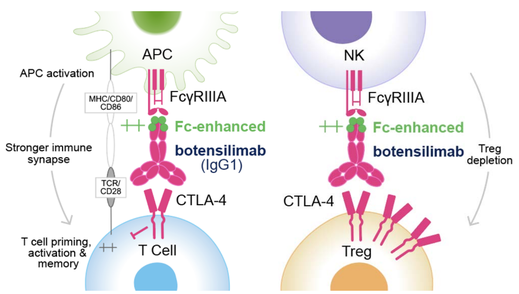
BACKGROUND/METHODS

- Effective therapies for colorectal cancer (CRC), particularly in those ~85-95% with **proficient mismatch repair/microsatellite stable (pMMR/MSS)** cancer, are a critical unmet need.[1]
- **Botensilimab (BOT),** a multifunctional next-generation **anti-CTLA-4 antibody**, with balstilimab (BAL), an anti-PD-1 antibody, has a response rate of > 20 % in patients with heavily pretreated pMMR/MSS metastatic CRC.[2]
- NEST-1 (NCT05571293) is the first study to evaluate **neoadjuvant** BOT and BAL in CRC patients eligible for surgery.
- **Investigator-initiated trial supported by Agenus Inc.**

Study schema[1]



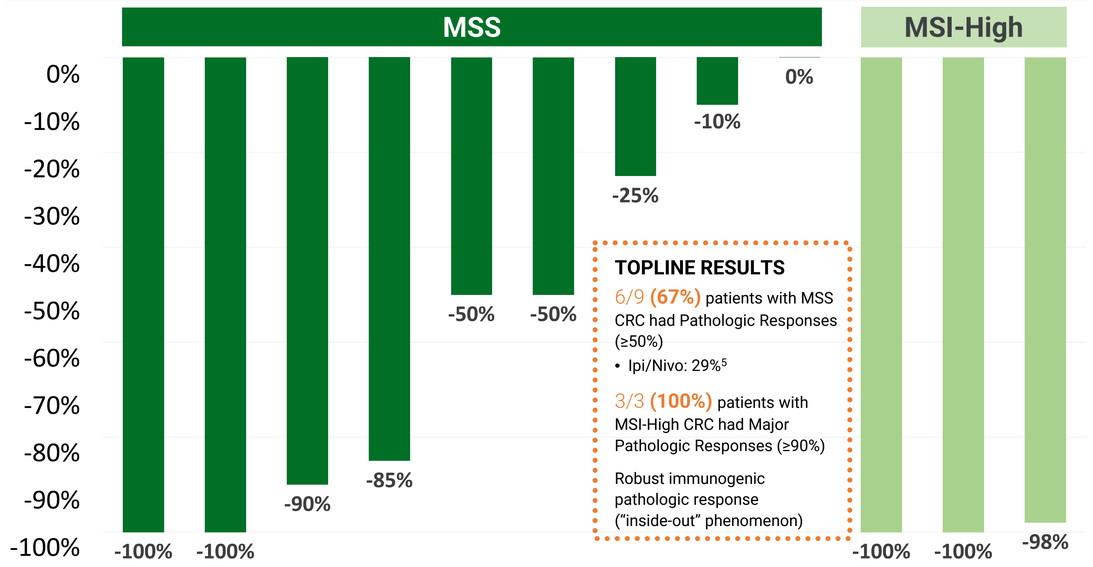
Botensilimab (BOT)[3]
Fc-enhanced CTLA-4 Inhibitor



- ↑T cell priming, expansion, memory
- ↑Frequency of activated APCs
- ↑Treg depletion
- ↓Complement mediated toxicity

References: 1. Kasi PM et al. Oncogene. 2023 Oct; 42 (44): 3252-3259. | 2. El-Khoueiry AB. Journal of Clinical Oncology 2023 41:4_suppl, LBA8. | Adapted from Wilky B, et al. Oral Presentation at CTOS 2023. Dublin, Ireland. Paper 31. | 4. Acknowledgements: DrawImpacts for the illustration. | 5. Chalabi et al. Nat Med. 2020 Apr;26(4):566-576; Verschoor et al. J Clin Oncol 40, 2022 (suppl 16; abstr 3511).

Pathologic tumor reductions (%) by patient



TOPLINE RESULTS

6/9 **(67%)** patients with MSS CRC had Pathologic Responses (≥50%)
- Ipi/Nivo: 29%[5]

3/3 **(100%)** patients with MSI-High CRC had Major Pathologic Responses (≥90%)

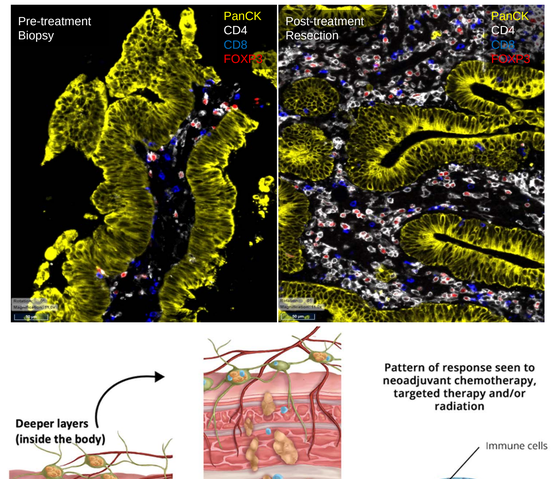
Robust immunogenic pathologic response ("inside-out" phenomenon)

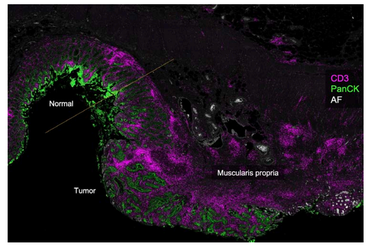
Patient ID (Sex)	11(M)	7*(M)	1(M)	2*(F)	8(F)	10(F)	4(M)	3*(F)	12(F)	5(M)	9*(M)	6(F)
Race/Origin	Caucasian	Southeast Asia	Southeast Asia	African American	Arab/Middle Eastern	Hispanic/ Mexican	African American	Caucasian	African American	Arab/Middle Eastern	Caucasian	Caucasian
Path Response	100%	100%	90%	85%	50%	50%	25%	10%	0%	100%	100%	98%
Stage Pre-treatment	T3N1a **IIIB**	T2N0 **I**	T2N1a **IIIA**	T3bN2a **IIIB**	T3bN2b **IIIC**	T3dN2b **IIIC**	T3N2a **IIIB**	T3aN1b **IIIB**	TXN0	T3N2b **IIIC**	T3dN2b **IIIC**	T3N2a **IIIB**
Stage Post-treatment	T0N0 **No tumor**	T0NX **No tumor**	T1N0 **I**	T1N0 **I**	T3N0 **IIA**	T3N0 **IIA**	T3N1b **IIIB**	T4aN2b **IIIC**	T2N1a **IIIA**	T0N0 **No tumor**	T0N0 **No tumor**	T2N0 **I**
Days until surgery(from C1D1)	38	64	30	24	36	27	21	29	29	34	57	42
ctDNA (baseline)	+	Negative	N/A	N/A	+	+	N/A	N/A	+	+	+	+
ctDNA (MRD)	Negative X 2	Negative X 3	Negative X 1	Negative X 2	Negative X 2	Negative X 1	Negative X 4	N/A	Negative X 3	Negative X 4	Negative X 2	Negative X 4
Mutations	*KRAS*^{A146}/ *HER2+*	*TP53/APC*	*TP53/ CTNNB1*	*KRAS*^{G12V}/ *APC*	*TP53/APC*	*TP53/ATM/ CTNNB1*	*APC*	*KRAS*^{A146}/ *TP53/ BRAF*^{K483T}	*KRAS*^{G12D}/ *APC/TP53*	*MSH2/ BRCA2/ KRAS*^{G12S}	*MSH2/ TP53/ KRAS*^{G12D}	*N/A*
TMB (Mut/Mb)	9.4	8.6	6.4	4.7	4.7	7.1	4.7	5.5	3.1	105	N/A	N/A
Adverse Events	*Grade-3 Diarrhea#*	*Grade 1: Chills/ Fever*	*No AEs*	*Grade 1: Chills/Headache Grade 2: Fever*	*Grade 1: Chills, Headache, Dizziness Grade 3: Fatigue*	*No AEs*	*No AEs*	*Grade 1: Flu-like symptoms, Fever*	*No AEs*	*No AEs*	*No AEs*	*Grade 1: Fatigue, Rash, Headache*

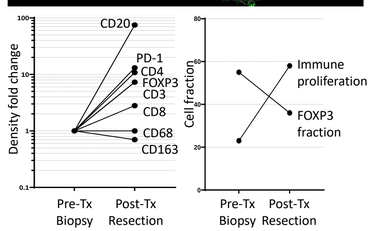
***rectal cancer**; # only 1 patient (ID-11) had grade-3 diarrhea that resolved the same day of infliximab 10 mg/kg administration 1-time dose. Surgery was performed six days later without any complications. Five patients (4 females) had fever/fatigue/flu-like symptoms within 7-10 days of BOT/BAL ("Early Immune Activation Syndrome"). Resolved with NSAIDs/symptom management.

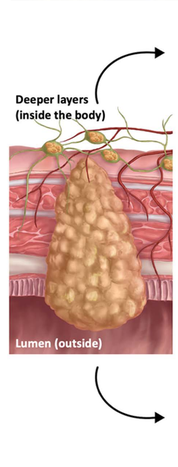
RESULTS

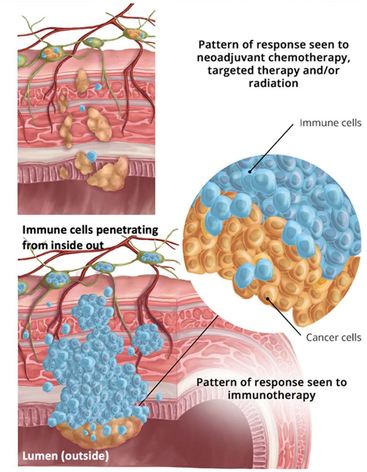
Tissue immune-microenvironment correlates assessed pre- and post-treatment with immunotherapy by RareCyte Inc. (Seattle, WA) using their 13-marker immune-oncology panel on colon and rectal cancer samples on a single paraffin-embedded slide simultaneously at 20X using the Orion instrument. Analyses show a significant increase and a diverse array of immune cells in more than one instance, shedding novel insights into the mechanism and pattern of immune responses.











CONCLUSIONS

- **The study met its primary endpoints**.
- Neoadjuvant BOT/BAL is a **safe** and **active** regimen both in pMMR/MSS and dMMR/MSI-H CRC.
  - 6/9 (67%) pMMR/MSS patients with ≥50% reduction, 2/9 with CR
  - 3/3 (100%) dMMR/MSI-H with deep response (≥98% reduction), 2/3 with CR
- **No surgery was delayed** due to any treatment-related adverse events (TRAEs).
- All patients positive for ctDNA at screening **cleared ctDNA** (7/7 – 100%). 11/11 (100%) tested have **remained ctDNA/MRD negative** on more than 30 times cumulatively.
- Post-treatment tumor IHC demonstrates **robust T cell infiltration**, T reg depletion, and dendritic cells/myeloid repolarization.
- **Clinical downstaging** and deep pathological responses provide a framework for reduced reliance on surgery and/or adjuvant chemotherapy in future studies.
- **NEST-1 trial (NCT05571293) has expanded enrollment** to evaluate an 8-week course over the current minimum 3-week course for MSS, and the necessity for surgery for MSI-High.