Neoadjuvant Botensilimab (BOT) Plus Balstilimab (BAL) in Resectable Mismatch Repair Proficient (pMMR) and Deficient (dMMR) Colorectal Cancer (CRC)

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Background

Checkpoint inhibitors (CPI) have been transformative for localized dMMR CRC (microsatellite instability-high [MSI-H]), but not for localized pMMR CRC (microsatellite stable [MSS]). The combination of BOT, a novel Fc-enhanced multifunctional CTLA-4 antibody, and BAL, an anti-PD-1 antibody, has demonstrated significant activity in metastatic CRC. We examined this novel dual CPI therapy in patients with MSI-H and MSS localized CRC.

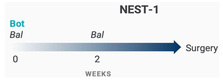
Methods

NEST Protocol (NCT05571293):

NEST-1

1 dose of 75mg Botensilimab (BOT)

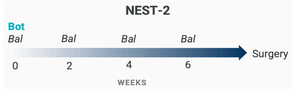
2 doses of 240mg Balstilimab (BAL) 2 weeks apart



NEST-2

1 dose of 75mg Botensilimab (BOT)

Up to 4 doses of 240mg Balstilimab (BAL) 2 weeks apart



Results

Demographics

	Total (n=24)	NEST1 (n=10)	NEST2 (n=14)	dMMR* (n=4)
Age, Median (Q1, Q3)	64 (46, 73)	57 (35, 69)	69 (59, 75)	61 (43, 72)
Male:Female	13:11	5:5	8:6	3:1
Race				
White	12	5	7	3
Asian	4	1	3	0
Black	4	2	2	0
Other	4	2	2	1
Ethnicity				
Hispanic	1	1	0	0
Non-Hispanic	21	9	12	4
Other	2	0	2	0
Clinical Stage				
Early (T1/T2)	10	1	10	1
Advanced (T3+)	14	9	4	3

*3 patients in NEST1 and 1 in NEST2

CR = Complete Pathologic Response of all invasive cancer. Residual carcinoma in situ can still constitute a complete response.

MPR = Major Pathologic Response constitutes less than 10% residual cancer cells in the pathologic specimen.

Toxicity Related to Bot/Bal

	NEST-1 (n=10)		NEST-2 (n=14)*	
	Grade 2	Grade 3	Grade 2	Grade 3
Fever	1		2	
Fatigue		1	1	
Colitis/ Diarrhea		1	3	2
Anemia			1	
Nausea			1	
Myositis			1	

*7 patients did not complete 4 cycles of balstilimab

NOTE: There were no grade 4 events, and no unresolved imAEs. No delays in surgery due to imAEs.

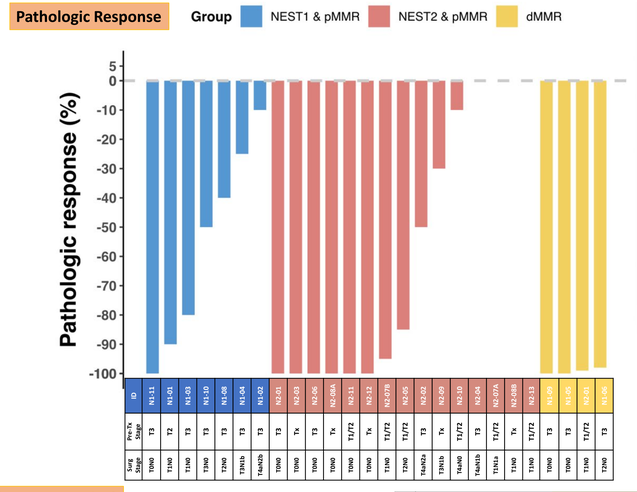
Pathologic Response

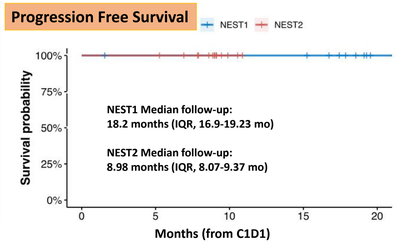
	NEST 1 n=7 MSS tumors	NEST 2 n=15 MSS tumors	MSI-H (3 NEST1, 1 NEST2)
100% (95% CI)	1 (14%, 0.4-58%)	6* (40%, 16-68%)	2** (75%, 19-99%)
≥ 90% (95%CI)	2 (29%, 4-71%)	7 (47%, 21-73%)	4 (100%, 40-100%)
≥ 50%	4 (57%)	9 (60%)	4 (100%)
Median days to Surgery (range)	29 (21-37)	57 (45-104)	46 (34-78)

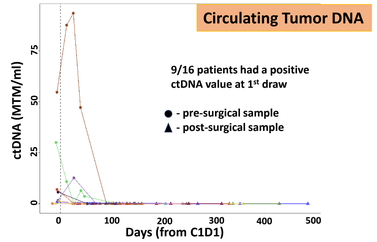
*2 with carcinoma *in situ*. **1 was rectal

Neoadjuvant BOT/BAL is safe and effective. We observed high MPR rates in both MSS and MSI-H CRC with no recurrences to date. The major pathologic response rate improved with extended time to surgery.

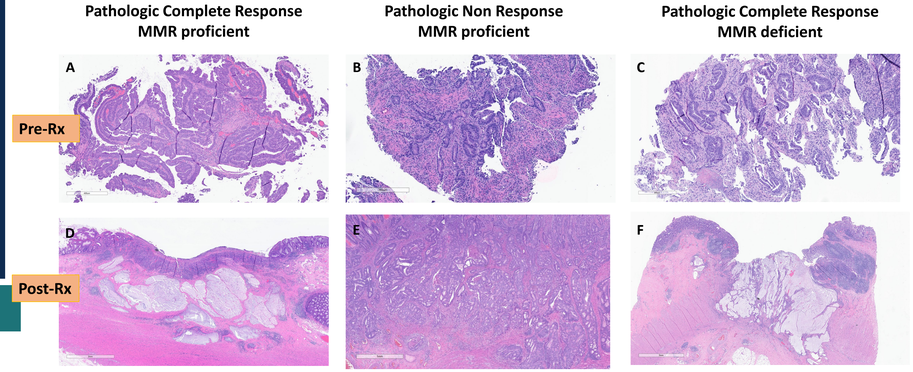
Results





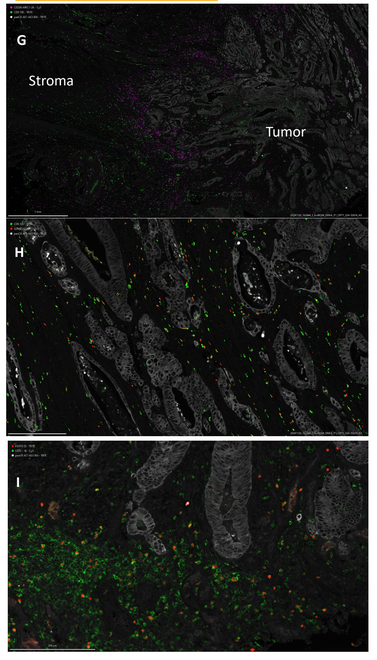


Pathology/Multiplex Imaging Analysis



H&E micrographs demonstrating the pretreatment biopsies and post-treatment matching resection specimens. (A,D) Pre- and post-Rx, mismatch repair proficient (pMMR), (B,E) Pre- and post-Rx, pMMR, (C,F) Pre- and post-Rx, dMMR. Resections demonstrate complete response with inflammation and acellular mucin pools (D), no response with diffuse sheets of adenocarcinoma in a pMMR tumor (E) and complete response in a dMMR tumor (F).

COMET Multiplex Imaging



COMET Multiplex Imaging – Future Directions

COMET is an automated, fluorescence imaging-based platform, which uses cyclical/iterative antibody-based direct immunofluorescene labeling to simultaneously visualize up to 30-40 antigens. Instead of restricted regions of interest, COMET allows for evaluation of whole tissue sections to better characterize the tumor/stromal interface.

Multiplex imaging analysis of a pMMR tumor demonstrating <50% response. Images show infiltration of CD8+ tumor cells (G:green) both within and surrounding tumor, whereas macrophages/ dendritic cells (CD68+, CD163+, CD203+) are concentrated predominantly at the leading edge of the tumor (G:magenta). A subset of the CD8+ T cell infiltrating tumor are Granzyme B+ (H:red); however, the presence of frequent intratumoral FOXp3+ T cells (I:red/green co staining) indicate an immunosuppressive microenvironment.

Future Directions: To interrogate a cohort of responders (n=4), non-responders (n=4), and dMMR samples (n=4) to identify character of TME associated with resistance.

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