A Phase I Trial of Folinic Acid, Fluorouracil, Oxaliplatin, Bevacizumab, Botensilimab, Balstilimab (FOLFOX-3B) in Microsatellite Stable Metastatic Colorectal Cancer

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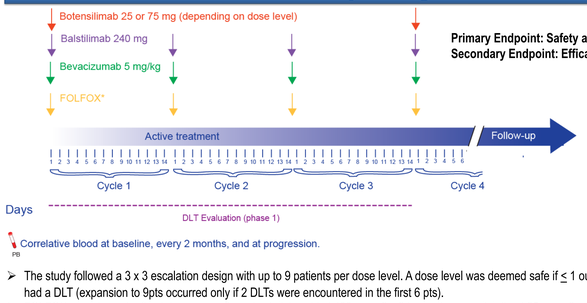
Background

- Botensilimab is an Fc-enhanced multifunctional CTLA4 antibody with differential mechanisms of action designed to extend therapy to 'cold' or poorly immunogenic solid tumors.
- The combination of Botensilimab and the PD-1 antibody balstilimab has been associated with durable and deep responses in microsatellite stable (MSS) metastatic colorectal cancer (mCRC).
- Given the potential synergistic activity between checkpoint inhibitors and oxaliplatin and VEGF(R) inhibitors, we performed a phase 1 clinical trial of folinic acid, fluorouracil, oxaliplatin, bevacizumab, botensilimab, and balstilimab (FOLFOX-3B).

Study Design



Primary Endpoint: Safety and Tolerability
Secondary Endpoint: Efficacy (ORR, PFS and OS)

- The study followed a 3 x 3 escalation design with up to 9 patients per dose level. A dose level was deemed safe if ≤ 1 out of 6 pts or ≤ 2 out of 9 pts had a DLT (expansion to 9pts occurred only if 2 DLTs were encountered in the first 6 pts).
- FOLFOX was given at a fixed dose, every 2 weeks: folinic acid at 400 mg/m2 x 2 hours (hrs), oxaliplatin at 85 mg/m2 x 2 hrs, and fluorouracil at 2400 mg/m2 x 46 hrs. Bevacizumab was given at 5mg/kg IV prior to FOLFOX.
- Up to 2 prior lines of therapy was allowed, including oxaliplatin-based therapy, as long as PD did not occur within 3 months from prior oxaliplatin.

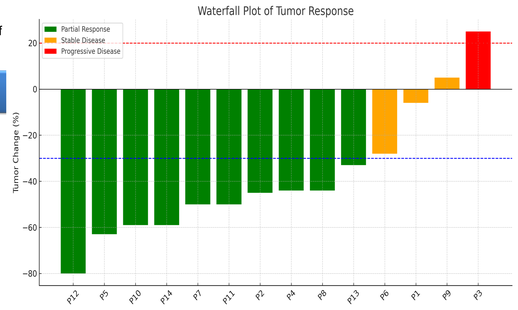
Patient Characteristics (n=14)

Patient	ECOG status	Dose Level	Primary tumor	Liver metastases	Prior therapy		TMB	RAS	RAF	Time From Stage IV diagnosis (months)
					1st Line	2nd Line				
Pt 01	0	1	Left	No	FOLFOXIRI + Pmab	Capecitabine + Bev	9	WT	WT	56
Pt 02	0	1	Left	Yes	FOLFIRI + Bev	None	4	WT	WT	14
Pt 03	1	1	Left	Yes	Chemoradiation	None	1	NRAS Q61H	WT	3
Pt 04*	0	1	Left	Yes	FOLFOXIRI + Bev	FOLFIRI + Pmab	4	WT	WT	29
Pt 05	0	1	Left	Yes	FOLFOXIRI+ Pmab	Capecitabine + Bev	3.5	WT	WT	23
Pt 06	0	1	Left	Yes	FOLFOXIRI + Bev	FOLFIRI + Bev	2	KRAS G12V	WT	8
Pt 07	0	1	Left	Yes	None	None	NA	WT	WT	1
Pt 08	0	2	Right	No	FOLFOX	FOLFIRI	4	KRAS G12V	WT	63
Pt 09	0	2	Left	Yes	FOLFOX + Pmab	FOLFIRI + Bev	1	WT	WT	37
Pt 10	0	2	Left	No	FOLFOX	None	2	WT	WT	39
Pt 11	1	2	Left	No	FOLFOX	None	7.8	KRAS G12D	WT	5
Pt 12	0	2	Left	No	FOLFOX + Bev	None	5	WT	WT	14
Pt 13#	0	2	Left	Yes	FOLFOX + Bev	FOLFIRI + Bev	NA	WT	BRAF D594G	42
Pt 14	0	2	Left	Yes	None	None	NA	KRAS G12V	WT	1

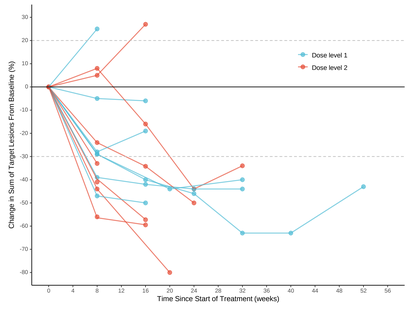
Bev = Bevacizumab: Pmab = Panitumumab
*Patient was replaced due to inability to dose all intended doses of balstilimab due to transient colitis and non-DLT defining hepatitis.
#Patient was replaced as he was not able to receive all intended doses of FOLFOX in the first 6 weeks secondary to thrombocytopenia.

Clinical Activity

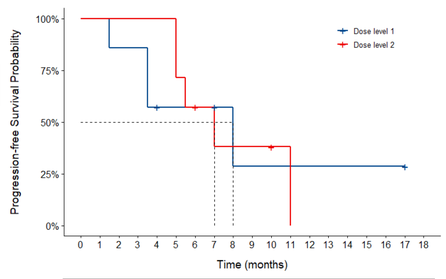
A. Waterfall plot



B. Spider plot

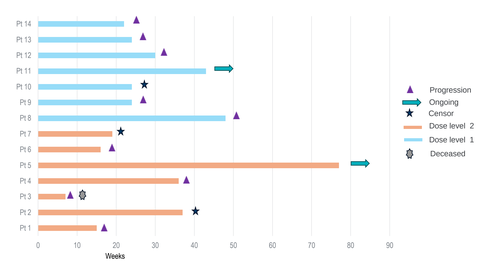


C. Progression-free Survival



	Overall	DL-1	DL-2
Median PFS (months)	7	8	7

D. Swimmer plot



E. Objective response

	Overall (n=14)		Patient with liver metastases (n=9)		Patient without liver metastases (n=5)		2nd/3rd setting (n=12)	
	Dose level 1 (n=7)	Dose level 2 (n=7)	Dose level 1 (n=6)	Dose level 2 (n=3)	Dose level 1 (n=1)	Dose level 2 (n=4)	Dose level 1 (n=6)	Dose level 2 (n=6)
PR	57% (n=4)	86% (n=6)	67% (n=4)	67% (n=2)	0	100% (n=4)	50% (n=3)	83% (n=5)
SD	29% (n=2)	14% (n=1)	17% (n=1)	33% (n=1)	100% (n=1)	0	33% (n=2)	17% (n=1)
PD	14% (n=1)	0	17% (n=1)	0	0	0	17% (n=1)	0

Adverse Event

Immune–related AEs

	Dose 1			Dose 2		
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Hypothyroidism		14% (1)		14% (1)		
Hyperthyroidism					14% (1)	
Colitis		14% (1)	14% (1)			
Mucositis-oral	14% (1)	14% (1)				
Fever	14% (1)	14% (1)				
ALT/AST elevation	43% (3)		14% (1)			
ALP elevation	29% (2)					
Hyperhidrosis	29% (2)			14% (1)		
Pruritus	14% (1)					
Rash maculo-papular				43% (3)		

For non-immune-related AEs, G1/2 more than once, and any G3 and above was included in the table.

DL1: no DLT, 1 patient was non-evaluable due to not receiving all 3 dose of balstilimab for non-DLT defining immune related AE
DL2: no DLT, 1 patient non-evaluable due to not receiving 3 cycles of Oxaliplatin
All patients on DL2 received the 2 intended doses of botensilimab (caped at 2 doses)

Non-Immune–related AEs

	Dose 1			Dose 2		
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Anemia	43% (3)					14% (1)
Abdominal pain	43% (3)					
Allergic reaction						14% (1)
Anorexia	29% (2)	43% (3)				
Constipation	57% (4)			57% (4)		
Diarrhea	71% (5)			71% (5)		
Mucositis oral		29% (2)		54% (4)		
Nausea	43% (3)	29% (2)		86% (6)		
Rectal pain			14% (1)			
ANC decrease			14% (1)			
Lymphocyte decrease			14% (1)			14% (1)
Weight loss	29% (2)					
Fatigue	29% (2)	57% (4)		29% (2)		
Platelet decrease	29% (2)					
Neutrophil count decrease					29% (2)	
Hyperglycemia			29% (2)			
Hypertriglyceridemia			14% (1)			
Paresthesia				71% (5)		
Peripheral sensory neuropathy	29% (2)					
Proteinuria		29% (2)				

Conclusion

1. Botensilimab at 75mg IV Q6 weeks x 2 doses plus balstilimab 240 mg IV Q2 weeks and FOLFOX bevacizumab is the recommended phase 2 dose of FOLFOX-3B
2. The study demonstrated encouraging ORR of 71% in 14 patients with MSS MCRC and translated into 66% ORR in the 12 patients who had received prior 1-2 lines of therapy
3. Severe immune-related side effects were rare and only one patient required immune suppression for colitis and hepatitis
4. This combination can be considered for further development in the first-line treatment of MSS metastatic colorectal cancer
5. Additional cohorts of botensilimab of 150 mg IV x 2 doses and 75 mg IV x 4 doses in the setting of FOLFOX-3B are currently under investigation under a protocol amendment

References

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ClinicalTrials.gov ID: NCT05627635
https://clinicaltrials.gov/study/NCT05627635

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