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Efficacy and Safety of Vactosertib and Pembrolizumab Combination in Patients with Previously Treated Microsatellite Stable Metastatic Colorectal Cancer

ASCO Annual Meeting June 4-7, 2021

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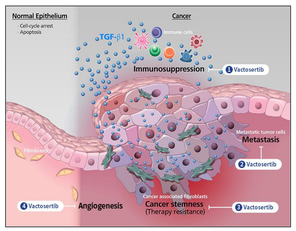
BACKGROUND

- Immune checkpoint inhibitor is an established treatment option for microsatellite instability-high (MSI-H) colorectal cancer[1,2], however, only 3.5-6.5% of metastatic colorectal cancer (mCRC) patients showed MSI-H[3,4,5]
- Recent studies have revealed that inhibition of transforming growth factor beta (TGF-β) signaling reverses immunosuppressive tumor microenvironment and poor responses to cancer immunotherapy[6,7]
- Vactosertib (TEW-7197), a highly selective and potent inhibitor of TGF-β receptor type 1, combined with PD-1 inhibition may induce immune restoration and improve anti-tumor responses[8]
- MP-VAC-204 is a phase 1b/2a study evaluating the combination of vactosertib with pembrolizumab in previously treated microsatellite stable (MSS) mCRC
- Here we report safety and efficacy data of a phase 1b/2a study (NCT03724851)



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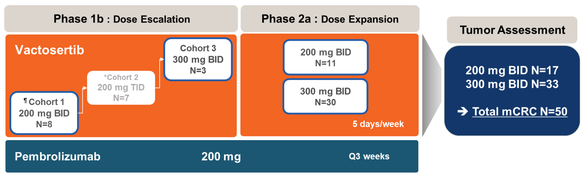
STUDY DESIGN and METHODS

Figure 1. MP-VAC-204 Study Design



¶ Two patients with dosing error (100mg BID) were excluded: 6 patients were eligible to evaluation in cohort 1 of phase 1b
*Cohort 2 (200 mg TID, n=7) patients in the phase 1b were not included in this report

- Eligible patients were >18 years old with good performance status (ECOG 0-1) and who have disease progression after treatment with all available therapies including fluoropyrimidine and oxaliplatin or irinotecan
- Tumor responses were assessed per RECIST v1.1 and iRECIST
- Safety assessment was based on CTCAE v5.0
- Tumor biomarkers including CD8+ were measured in serial tumor samples (Screening and C2 D3-6 or 10-13)
- Circulating proteins, CTGF, PAI-1, and PDGF-AB were evaluated from serial blood samples (Screening and C1D5)

RESULTS

Patients

Table 1. Baseline Characteristics

		200 mg BID (N=17)	300 mg BID (N=33)	Overall (N=50)
Age, years, median (range)		57 (39-83)	60 (33-72)	59 (33-83)
Sex, n (%)	**Male**	9 (53)	18 (55)	27 (54)
	Female	8 (47)	15 (45)	23 (46)
Race, n (%)	**Asian**	17 (100)	33 (100)	50 (100)
ECOG Performance Status, n (%)	**0**	7 (41)	10 (30)	17 (34)
	1	10 (59)	23 (70)	33 (66)
***KRAS* mutation, n (%)**		5 (29)	12 (36)	17 (34)
***BRAF* mutation, n (%)**		1 (6)	0 (0)	1 (2)
Microsatellite Instability, n (%)	**MSS**	17 (100)	33 (100)	50 (100)
CMS, n (%)	**1-3**	5 (29)	3 (9)	8 (16)
	4	12 (71)	27 (82)	39 (78)
No. of prior anticancer therapies, n (%)	**1-2**	1 (6)	17 (52)	18 (36)
	3	7 (41)	5 (15)	12 (24)
	≥ 4	9 (53)	11 (33)	20 (40)
Prior treatment regimen, n (%)	**Fluoropyrimidine**	17 (100)	33 (100)	50 (100)
	Irinotecan	17 (100)	30 (91)	47 (94)
	Oxaliplatin	17 (100)	33 (100)	50 (100)
	Bevacizumab	16 (94)	31 (94)	47 (94)
	Panitumumab/cetuximab	9 (53)	14 (42)	23 (46)
	Regorafenib	9 (53)	6 (18)	15 (30)

† Abbreviations: ECOG, Eastern Cooperative Oncology Group; KRAS, Kirsten rat sarcoma viral oncogene; BRAF, v-raf murine sarcoma viral oncogene homolog B1; MSS, Microsatellite Stable; CMS, Consensus Molecular Subtype

Efficacy

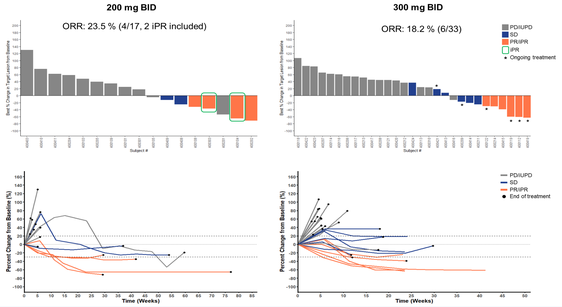
Table 2. Overview of Efficacy

	200 mg BID (N=17)	300 mg BID (N=33)	Overall (N=50)
ORR (RECIST / iRECIST, %)	11.8 / 23.5	18.2 / 18.2	16.0 / 20.0
mOS (months)	15.8	Not reached	15.8
mPFS (months)	1.3	1.2	1.3

† Abbreviations: ORR, objective response ratio; mPFS, median progression free survival; mOS, median overall survival; iRECIST, response criteria for clinical trials of cancer immunotherapy

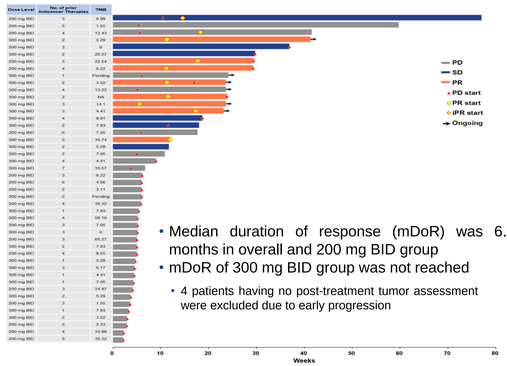
- Among 50 evaluable mCRC patients treated vactosertib in combination with pembrolizumab, 4 patients (2 iPR included) from 200 mg BID group and 6 patients from 300 mg BID group showed partial response (PR)
- Treatment is ongoing in 6 patients of the 300 mg BID group

Figure 2. Objective Response Rate (ORR) & Overall Tumor Response



Efficacy

Figure 3. Duration of Treatment



- Median duration of response (mDoR) was 6.8 months in overall and 200 mg BID group
- mDoR of 300 mg BID group was not reached
  - 4 patients having no post-treatment tumor assessment were excluded due to early progression

Figure 4. Overall Survival (OS)

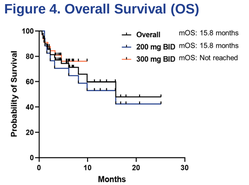
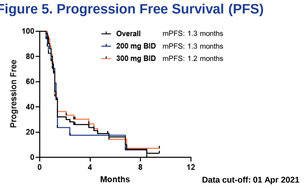
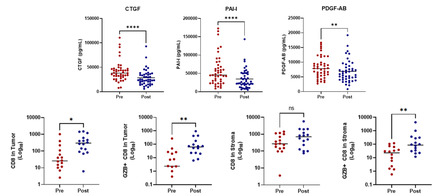


Figure 5. Progression Free Survival (PFS)



Pharmacodynamic Marker Analysis



† Abbreviations: CTGF, connective tissue growth factor; PAI-1, plasminogen activator inhibitor-1; PDGF-AB, platelet-derived growth factor–AB; pre, pre-treatment (screening); post, post-treatment
¶ CTGF, PAI-1 and PDGF-AB were measured pre-treatment (screening) and post-treatment (cycle 1 day 5) and tumor and stroma CD8 were evaluated pre-treatment (screening) and post-treatment (cycle 2 day 3-6 or day 10-13)

- Circulating biomarkers related to TGF-β signaling, CTGF, PAI-1, and PDGF-AB were assessed and their levels significantly decreased after treatment
- Tumor infiltrated CD8 T cell and granzyme B+ CD8 T cell levels were increased after treatment
- Expression of CD8 T cells and granzyme B+ CD8 T cells in tumor and stroma were elevated after treatment

Safety

Table 3. Frequency of Treatment-Related Adverse Events

Patients, n (%)	200 mg BID (N=17)	300 mg BID (N=33)	Overall (N=50)
AE	13 (76)	23 (70)	36 (72)
Grade 3-4 AE	4 (24)	7 (21)	11 (22)
Serious AE	4 (24)	6 (18)	10 (20)
Serious AE related to vactosertib	3 (18)	6 (18)	9 (18)
D/C due to AE	1 (6)	1 (3)	2 (4)

- 4% (n=2) of patients were discontinued the study treatment due to TRAEs: grade 2 pneumonitis (n=1) and grade 3 rash (n=1)
- 20% (n=10) occurred treatment related serious adverse event (SAE) :
  - ✓ Grade 2: rash (n=1), pneumonitis (n=2), diarrhea (n=1), and decreased appetite (n=1)
  - ✓ Grade 3: vomiting (n=1), tubulointerstitial nephritis (n=1), nausea (n=1), decreased appetite (n=1), asthma (n=1), and adrenal insufficiency (n=2)
  - ✓ Grade 4: hyponatremia (n=1)
- No cardiac toxicity was observed during the study

Table 4. Treatment-Related Adverse Events occurring in ≥6% of patients in overall group

Patients, n (%)	200 mg BID (N=17)		300 mg BID (N=33)		Overall (N=50)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Rash	4 (24)		10 (30)	1 (3)	14 (28)	1 (2)
Pruritus	3 (18)		10 (30)		13 (26)	
Fatigue	4 (24)		6 (18)		10 (20)	
Decreased appetite	5 (29)		5 (15)	1 (3)	10 (20)	1 (2)
Amylase increased	3 (18)		7 (21)		10 (20)	
Lipase increased	3 (18)	2 (12)	6 (18)	2 (6)	9 (18)	4 (8)
Hypothyroidism	1 (6)		6 (18)		7 (14)	
Headache	2 (12)		5 (15)		7 (14)	
Diarrhea	4 (24)		3 (9)		7 (14)	
Pneumonitis	2 (12)		2 (6)		4 (8)	
Stomatitis			3 (9)		3 (6)	
Rash maculo-papular			3 (9)	2 (6)	3 (6)	2 (4)
Pyrexia	2 (12)		1 (3)		3 (6)	
AST increased	2 (12)		1 (3)		3 (6)	

SUMMARY and CONCLUSIONS

- Vactosertib in combination with pembrolizumab demonstrated promising anti-tumor efficacy in heavily treated MSS mCRC patients
  - ✓ 64% of patients experienced more than 3 times of prior treatment and 30% of patients treated with regorafenib
  - ✓ ORR (RECIST) 16% in overall, mPFS (RECIST) 1.3 months and mOS was 15.8 months
- The combination of vactosertib and pembrolizumab showed manageable safety profile
  - ✓ Cardiac valvulopathy was not observed
- Pharmacodynamic analysis showed modulation of TGF-β signal and immune status
  - ✓ The levels of TGF-β signaling related biomarkers, CTGF, PAI-1, and PDGF-AB were significantly decreased after treatment
  - ✓ Tumor infiltrated and microenvironment CD8 T cells were increased after treatment
- The phase 2 part is still ongoing for further evaluation of the efficacy and safety of vactosertib and pembrolizumab in patients with mCRC

ACKNOWLEDGEMENTS

- We sincerely thank all patients, families, and investigators who participated in this study
- The authors thank Merck & Co. staffs for supporting this study

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