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

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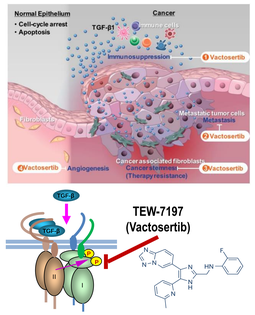
BACKGROUND

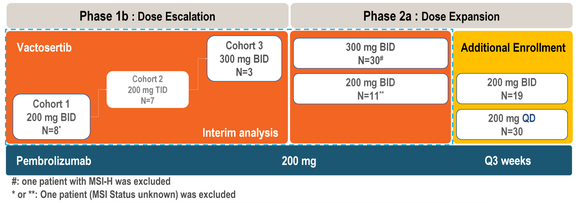
- Vactosertib (TEW-7197), a highly selective and potent inhibitor of TGF-β receptor type 1, combined with PD-1 inhibition could induce immune restoration and enhance anti-tumor responses in patients with microsatellite stable (MSS) metastatic colorectal cancer (mCRC). MP-VAC-204 is a phase 1b/2a study evaluating the combination of vactosertib with pembrolizumab in previously treated MSS mCRC. Here, we report the updated safety and efficacy data of this phase 1b/2a study (NCT03724851).



METHODS

- Eligible patients were >18 years old with ECOG performance status 0-1 and who had disease progression after treatment with all available therapies including fluoropyrimidine and oxaliplatin or irinotecan. The MSI testing was conducted by local or central tests. Tumor biomarkers including granzyme B+ CD8+T cells were measured in serial tumor samples by multiplex immunofluorescence staining and deconvolution-based immune cell analysis. Circulating proteins, TGF-β, CTGF, PAI-1 and PDGF-AB were evaluated from serial blood samples by ELISA.

Figure 1. MP-VAC-204 Study Design



- 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, TGF-β, CTGF, PAI-1, and PDGF-AB were evaluated from serial blood samples (Screening and C1D5)

RESULT

Patients

Table 1. Baseline Characteristics

		Overall, (N=105)	200mg QD, (N=30)	200mg BID, (N=36)	200mg TID, (N=7)	300mg BID, (N=32)
Age, Years	Mean(SD)	58.70 (10.55)	59.57 (10.89)	59.25 (10.02)	52.43 (10.75)	58.66 (10.82)
	Median(range)	59.00 (32-83)	59 (32-76)	59 (40-83)	58 (37-64)	60.50 (39-72)
	Q1, Q3	53, 67	55, 69	52, 67	40, 61	51.5, 68
Sex, n(%)	Male	65 (61.90)	22 (73.33)	20 (55.56)	5 (71.43)	18 (56.25)
	Female	40 (38.10)	8 (26.67)	16 (44.44)	2 (28.57)	14 (43.75)
Ethnicity, n(%)	Asian	105 (100)	30 (100)	36 (100)	7 (100)	32 (100)
ECOG Performance Status at Screening, n(%)	0	38 (36.19)	11 (36.67)	11 (30.56)	5 (71.43)	11 (34.38)
	1	67 (63.81)	19 (63.33)	25 (69.44)	2 (28.57)	21 (65.63)
KRAS mutation, n(%)	KRAS mutation	39 (37.14)	11 (36.67)	15 (41.67)	1 (14.29)	12 (37.5)
	Wild*	66 (62.86)	19 (63.33)	21 (58.33)	6 (85.71)	20 (62.5)
BRAF mutation, n(%)	BRAF mutation	4 (3.81)	2 (6.67)	2 (5.56)	0 (0)	0 (0)
	Wild*	101 (96.19)	28 (93.33)	34 (94.44)	7 (100)	32 (100)
Microsatellite Instability, n(%)	MSS(Non MSI-H)	105 (100)	30 (100)	36 (100)	7 (100)	32 (100)
CMS, n(%)	1~3	12 (11.43)	0 (0)	3 (8.33)	0 (0)	9 (28.13)
	4	27 (25.71)	0 (0)	8 (22.22)	0 (0)	19 (59.38)
	NA	66 (62.86)	30 (100)	25 (69.44)	7 (100)	4 (12.5)
Prior Anticancer Line, n(%)	0	2 (1.90)	2 (6.7)	0 (0)	0 (0)	0 (0)
	1	7 (6.67)	0 (0)	3 (8.3)	0 (0)	4 (12.5)
	2	37 (35.23)	11 (36.7)	10 (27.8)	4 (57.1)	12 (37.5)
	3	24 (22.86)	7 (23.3)	11 (30.6)	0 (0)	6 (18.8)
	4 <	35 (33.34)	10 (33.3)	12 (33.3)	3 (42.9)	10 (31.3)

Efficacy

Table 2. Overview Efficacy

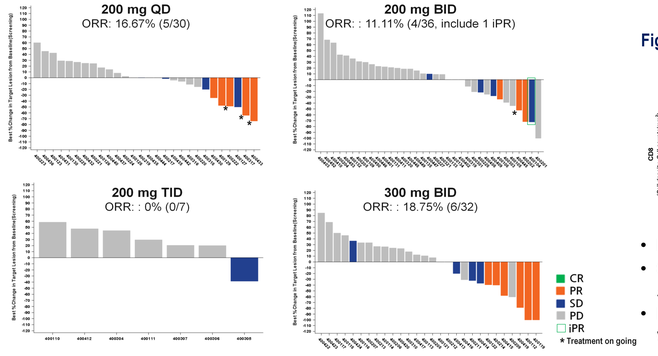
Overview of Efficacy (RECIST)	Overall, (N=105)	200mg QD, (N=30)	200mg BID, (N=36)	200mg TID, (N=7)	300mg BID, (N=32)
Objective Response Rate(ORR), n(%)	**14 (13.33)**	5 (16.67)	3 (8.33)	0 (0.00)	**6 (18.75)**
Median Progression Free Survival(mPFS), Months	**1.31**	1.40	1.31	1.22	1.22
Progression Free Survival Rate at 6 Months, n(%)	**18 (17.14)**	6 (20.00)	6 (16.67)	0 (0.00)	**6 (18.75)**
Median Overall Survival(mOS), Months	**15.80**	7.52	15.80	NC	**17.35**
Overall Survival Rate at 12 Months, n(%)	**64 (60.95)**	16 (53.33)	22 (61.11)	5 (57.14)	**22 (68.75)**
Overview of Efficacy (iRECIST)	**Overall, (N=105)**	**200mg QD, (N=30)**	**200mg BID, (N=36)**	**200mg TID, (N=7)**	**300mg BID, (N=32)**
Objective Response Rate(ORR), n(%)	**15 (14.29)**	5 (16.67)*	**4 (11.11)**	0 (0.00)	**6 (18.75)**
Median Progression Free Survival(mPFS), Months	**1.31**	1.40	1.31	1.22	1.22
Progression Free Survival Rate at 6 Months, n(%)	**20 (19.05)**	6 (20.00)	7 (19.44)	0 (0.00)	**7 (21.88)**

NC: Not Calculated

* 402222: iRECIST is not updated

- Overall response rate(ORR) was 13.3% in overall by RECIST and 14.3% by iRECIST and 18.8% in the 300 mg BID by RECIST and iRECIST.
- Overall survival rate at 12 months was 61.0% and especially, 68.8% in the 300 mg BID group.

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



Efficacy

Figure 3. Duration of Response (RECIST)

- Median duration of response (mDoR) was 5.9 months in overall and 4.2 months in the 200 mg BID group and 9.0 months in the 300 mg BID group.

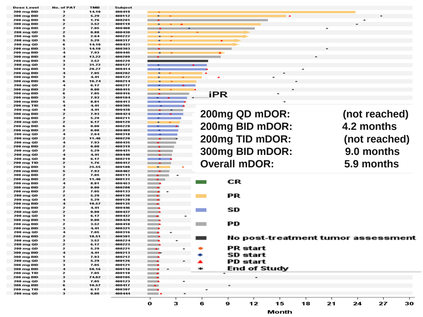


Figure 4. Overall Survival (OS)

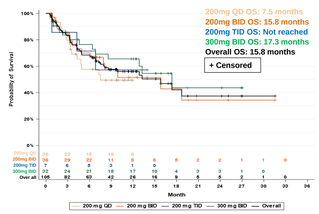
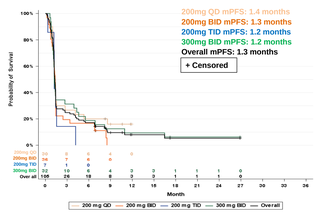


Figure 5. Progression Free Survival (RECIST)



Pharmacodynamic marker analysis

Figure 6. Decrease of Circulating Cytokines in Blood after Vactosertib Treatment

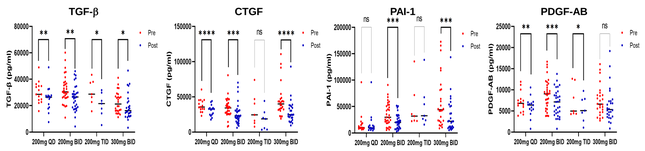
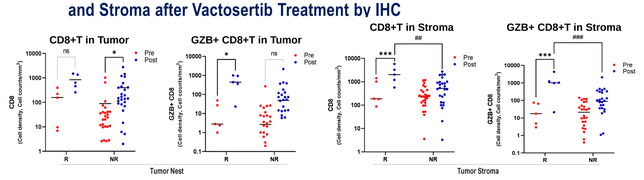


Figure 7. Increase of Infiltration of CD8+T cells and GZB+ CD8+T cells in Tumor Nest and Stroma after Vactosertib Treatment by IHC



- Responder(R) is defined as PR or PFS > 24 weeks by RECIST or iRECIST.
- Circulating biomarkers related to TGF-β signaling, CTGF, PAI-1, and PDGF-AB were significantly decreased after treatment.
- Expression of CD8 T cells and granzyme B+ CD8 T cells in tumor and stroma were elevated after treatment.

Safety

Table 3. Summary of Treatment Emergent Adverse Events

Summary of Treatment Emergent Adverse Events	Overall, (N=105) n(%), [E]	200mg QD, (N=30) n(%), [E]	200mg BID, (N=36) n(%), [E]	200mg TID, (N=7) n(%), [E]	300mg BID, (N=32) n(%), [E]
TEAE	90 (85.71), [691]	23 (76.67), [97]	31 (86.11), [272]	7 (100.00), [57]	29(90.63), [265]
TEAESI	2 (1.90), [2]	2 (6.67), [2]			
Immune-related TEAE	26 (24.76), [95]	8 (26.67), [16]	6 (16.67), [22]	1 (14.29), [1]	11 (34.38), [56]
Grade 3-5 TEAE	33 (31.43), [74]	10 (33.33), [13]	7 (19.44), [29]	4 (57.14), [9]	12 (37.50), [23]
TEAE related to Dermatology	51 (48.57), [125]	13 (43.33), [28]	17 (47.22), [28]	3 (42.86), [11]	18 (56.25), [58]
TEAE related to Adrenal Insufficiency	2 (1.90), [2]		1 (2.78), [1]		1 (3.13), [1]
Serious TEAE	20 (19.05), [27]	6 (20.00), [6]	6 (16.67), [10]	1 (14.29), [1]	7 (21.88), [10]
Serious TEAE related to Vactosertib	9 (8.57), [11]	1 (3.33), [1]	2 (5.56), [2]		6 (18.75), [8]
Discontinue due to TEAE	9 (8.57), [10]	3 (10.00), [3]	3 (8.33), [3]		3 (9.38), [4]

†Abbreviations: TEAE, treatment-emergent adverse event; n, No of subjects with adverse event; E, No of adverse event

* Empty box means "0"

- Among 105 evaluable patients, rash, headache and decreased appetite were the most frequent treatment emergent adverse events (TEAEs)
- However, all were manageable and no fatal serious TEAEs were observed in any cohort.

SUMMARY AND CONCLUSIONS

- Vactosertib in combination with pembrolizumab demonstrated promising anti-tumor efficacy in heavily treated MSS mCRC patients
  - ✓ ORR, mPFS and mOS were 13.3%, 1.3 months and 15.8 months respectively in overall and 18.8%, 1.2 months and 17.4 months respectively in the 300 mg BID group (RECIST).
  - ✓ Overall PFS rate at 6 months was 17.1% and overall survival rate at 12 months was 61.0%
- The combination of vactosertib and pembrolizumab showed manageable safety profile
- Vactosertib combined with pembrolizumab showed anti-tumor activity, prolonged overall survival and manageable safety profiles in patients with MSS mCRC. The phase 2 part is still ongoing.

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