P377

SITC
Annual Meeting
November 6-10, 2019
National Harbor, MD

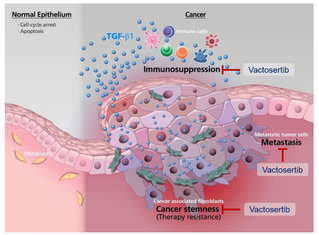
Safety and Preliminary Clinical Activity of Vactosertib, a Selective TGF-β Receptor I Kinase Inhibitor, in Combination with Pembrolizumab in Patients with Metastatic Colorectal or Gastric Cancer

Keun-Wook Lee [1], Young Suk Park [2], Joong Bae Ahn [3], Sun Young Rha [3], Hark Kyun Kim [4], Young Iee Park [4], Min-Hee Ryu [6], Jeeyun Lee [2], Jin Kyung Lee [5], Sunjin Hwang [5], Seong-Jin Kim [5], Tae Won Kim[6]

[1]Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Republic of Korea, [2]Samsung Medical Center, Seoul, Republic of Korea, [3]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea, [4]National Cancer Center, Goyang, Republic of Korea, [5]MedPacto Inc., Seocho-gu, Seoul, Republic of Korea, [6]Asan Medical Center, Seoul, Republic of Korea.

BACKGROUND

- To date, anti-tumor efficacy by immune checkpoint inhibitors in colorectal or gastric/gastroesophageal cancer as monotherapy is known to be limited[1]
- Recent studies have revealed that inhibition of transforming growth factor beta (TGF-β) signaling reverses immunosuppressive tumor microenvironment and poor responses to cancer immunotherapy[2,3]
- 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
- Study MP-VAC-204 is a Phase 1b/2a study evaluating the combination of vactosertib with pembrolizumab in metastatic colorectal cancer (mCRC) or diffuse gastric cancer (GC) or gastro-esophageal junction cancer (GEJC)
- Here we report the phase 1b dose escalation part of the study (Clinical trial information: NCT03724851)



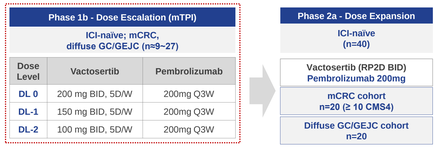
OBJECTIVES

- To evaluate the safety and tolerability of vactosertib in combination with pembrolizumab
- To characterize the pharmacokinetics of vactosertib in combination with pembrolizumab
- To document the anti-tumor activity of vactosertib in combination with pembrolizumab

STUDY DESIGN / METHODS

- Eligible patients are 1) mCRC patients who have disease progression after treatment with all available therapies including fluoropyrimidine and oxaliplatin or irinotecan, or 2) metastatic diffuse-type GC/GEJC patients who have disease progression after at least two lines of chemotherapy including fluoropyrimidine and platinum

Figure 1. MP-VAC-204 Study Design



Study Endpoints

- Primary endpoint: safety, including adverse events per CTCAE v5.0
- Secondary endpoints:
  - ✓ Tumor response was assessed per RECIST v1.1 and iRECIST
  - ✓ Pharmacokinetic analysis of vactosertib (WinNonlin version 8.2) : Blood samples were collected at pre-dose, 0.5, 1.5, 3, 4.5, 8 and 12 hours post-dose on Day 1 and Day 5
- Exploratory endpoints:
  - ✓ Tumor biomarkers including microsatellite instability (MSI) and epithelial-to-mesenchymal transition (EMT) in serial tumor samples

RESULTS

Patients

Table 1. Baseline Characteristics

		mCRC (N=8')	GC/GEJC (N=6)	Overall (N=14)
Age, years, median (range)		58 (39-62)	53 (46-71)	56 (39-71)
Sex, n (%)	Male	3 (37)	4 (67)	7 (50)
	Female	5 (63)	2 (33)	7 (50)
Race, n (%)	Asian	8 (100)	6 (100)	14 (100)
No. of Prior Anticancer Therapies, median (range)		4 (3-6)	3 (2-4)	4 (2-6)
ECOG Performance Status, n (%)	0	6 (75)	2 (33)	8 (57)
	1	2 (25)	4 (67)	6 (43)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; N = number of subjects; GC/GCJC = Gastric and gastroesophageal junction cancer;
* two patients with dosing error were only included in safety analysis population

Safety

- There was no dose limiting toxicity (DLT) in 200 mg twice daily (BID) vactosertib in combination with pembrolizumab
- No cardiac toxicity was observed during the study
- Treatment-related adverse events (TRAE) were reported in 10 (71.4%) patients; the most common AEs were fatigue (28.6%), decreased appetite (28.6%), diarrhea (21.4%), and anemia (21.4%)

Table 2. Summary of Treatment-related Adverse Events

Event, n (%)	mCRC (N=8)		GC/GEJC (N=6)		Overall (N=14)	
	All Grades	Grade = 3	All Grades	Grade = 3	All Grades	Grade = 3
Total	6 (75.0)	2 (25.0)	4 (66.7)		10 (71.4)	2 (14.2)
Hematologic						
Anemia	1 (12.5)	1 (12.5)	2 (33.3)		3 (21.4)	1 (7.1)
Non-hematologic						
Fatigue	4 (50.0)				4 (28.6)	
Decreased appetite	3 (37.5)		1 (16.7)		4 (28.6)	
Diarrhea	3 (37.5)				3 (21.4)	
Headache	1 (12.5)		1 (16.7)		2 (14.3)	
Rash	2 (25.0)				2 (14.3)	
Hypothyroidism	2 (25.0)				2 (14.3)	
Nausea	1 (12.5)		1 (16.7)		2 (14.3)	
Muscle spasms	1 (12.5)				1 (7.1)	
Drug Eruption	1 (12.5)	1 (12.5)			1 (7.1)	1 (7.1)
Abdominal pain	1 (12.5)				1 (7.1)	
Pyrexia	1 (12.5)				1 (7.1)	
Dry mouth	1 (12.5)				1 (7.1)	
Pruritus			1 (16.7)		1 (7.1)	
Paresthesia			1 (16.7)		1 (7.1)	
Hypokalemia			1 (16.7)		1 (7.1)	

Data cut-off October 28, 2019

Efficacy Overview

- Among 6 evaluable mCRC patients in 200 mg BID vactosertib in combination with pembrolizumab, responses were 2 partial responses
  - Confirmed objective response rate (ORR) was 16.7% (RECIST v1.1) and 33.3% (iRECIST)
  - Disease control rate at 24 weeks (DCR 24wks) was 33.3%
- Among GC/GEJC patients, there was 1 patient with stable disease while 5 had progressed

Efficacy of mCRC patients

Figure 2. Duration of Treatment

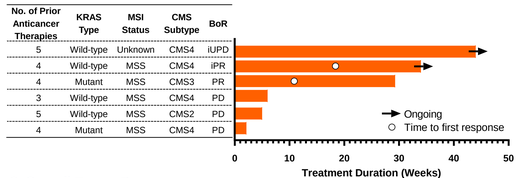


Figure 3. Overall Tumor Response

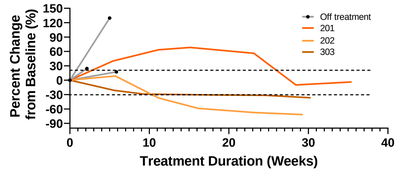


Figure 4. Serum Levels of Carcinoembryonic Antigen (CEA)

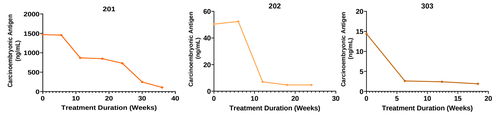
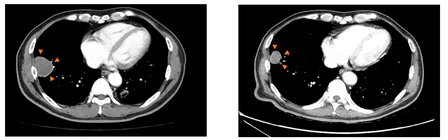


Figure 5. Changes in Target Lesion of Subject 202 (mCRC)



Pharmacokinetics of Vactosertib

Figure 6. PK Profile

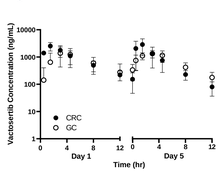


Table 3. PK Parameters

Parameters	Cycle 1 Day 1		Cycle 1 Day 5	
	mCRC (n=6)	GC/GEJC (n=6)	mCRC (n=6)	GC/GEJC (n=6)
T_{max} (h)*	1.5 [1.5 - 3]	3.0 [1.5 - 8]	1.0 [0.5 - 1.5]	3.0 [1.5 - 4.5]
C_{max} (μg/L)	2538 ± 870	1934 ± 810	3577 ± 1726	1473 ± 393
$AUC_{0\text{-}12h}$ (μg×h/L)	11947 ± 4017	8850 ± 3508	10075 ± 4872	8816 ± 2777
AUC_{inf} (μg×h/L)	13219 ± 3574	8891 ± 1383	10421 ± 4756	9563 ± 3165
V_z/F (L)	84 ± 46	83 ± 28	90 ± 50	101 ± 45
CL/F (L/h)	16 ± 3	23 ± 4	23 ± 9	25 ± 11
$t_{1/2}$ (h)	3.6 ± 1.5	2.5 ± 0.7	2.6 ± 1.0	2.8 ± 0.5

Mean ± standard deviation; *, median (range); parameters are shown from 0 to 12 hr.

Pharmacodynamic Marker Analysis of mCRC patients

Figure 7. Expression Level of Tumor Infiltrating CD8⁺ T cells, Granzyme B⁺CD8⁺ T cells, and E-cadherin (n=6)

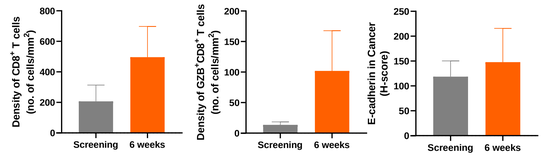


Figure 8. Representative Image of Tumor Infiltrating CD8⁺ T cells and Granzyme B

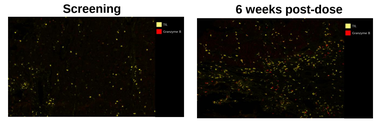
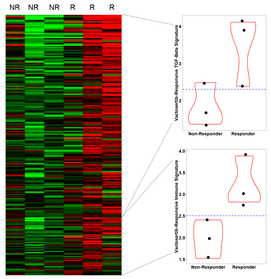


Figure 9. Vactosertib Response Gene Signature



SUMMARY & CONCLUSION

- The combination of vactosertib and pembrolizumab had an acceptable tolerability with a manageable safety profile without any cardiac toxicities
- The chemo-free regimen of vactosertib and pembrolizumab showed promising early anti-tumor activity in MSS mCRC patients
  - Confirmed ORR 16.7% by RECIST v1.1 and 33.3% by iRECIST
- The ongoing phase 2a study is further evaluating efficacy and safety of vactosertib in combination with pembrolizumab

For more information, please contact us at sarahskim@medpacto.com, +82-10-4213-3926

References

[1]Hugo et al., Cell. 2016;165(1):35-44.
[2]Luo et al., Translational Oncology. 2019;12(3):475-484.
[3]Colak et al., Trends in Cancer. 2017;3(1):56-71.