#3706

Safety and Efficacy of Vactosertib, a TGFBR1 Kinase Inhibitor, in Combination with Paclitaxel in Patients with Metastatic Gastric Adenocarcinoma

Minkyu Jung[1], Choong-kun Lee[1], Hyo Song Kim[1], Chan-Young Ock[2], Jin Bum Bae[2], Jin Kyung Lee[2], Jiyeon Ryu[2], Bitna Oh[2], Dong Woo Kang[2], Sunjin Hwang[2], Ki Baik Hahm[2], Seong-Jin Kim[2], Hyun Cheol Chung[1], Sun Young Rha[1]

[1]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea, [2]MedPacto, Inc., Seoul, Korea

BACKGROUND

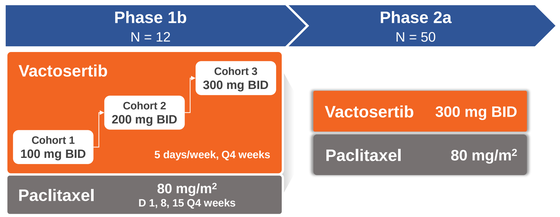
- High levels of transforming growth factor (TGF)-β in the tumor microenvironment (TME) represents a primary mechanism for induction of epithelial-to-mesenchymal transition, immune evasion, and cancer stem-like cells (CSC) formation, resulting in resistance to chemotherapy
- Elevated serum levels of TGF-β were shown in gastric cancer and were correlated to poor overall survival and poor prognosis [1)]
- Previous studies demonstrated that vactosertib, a highly selective and potent oral TGF-β inhibitor, can augment the cytotoxic effect of paclitaxel by suppressing CSC formation [2)]
- The results of a phase I study of vactosertib in combination with paclitaxel as a second-line treatment in metastatic gastric cancer (mGC) are presented (NCT03698825)

OBJECTIVES

- To evaluate the tolerability, safety, and preliminary clinical efficacy of vactosertib plus paclitaxel

STUDY DESIGN

Figure 1. Study Scheme



Key Inclusion criteria

- Eastern Cooperative Oncology Group performance status of 0-1
- Patients have progressed on the 1st line fluoropyrimidine and platinum class combination therapy, or in case of HER2-positive, additional Trastuzumab combination therapy
- Patients with an evaluable lesion according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)

Key Exclusion criteria

- Patients who had a major surgery or radiation therapy within 4 weeks, had chemotherapy within 2 weeks, or had TGF-β inhibitor

RESULTS

Table 1. Baseline Characteristics

Event, n (%)		100 mg BID (N=6)	200 mg BID (N=3)	300 mg BID (N=3)	Overall (N=12)
Age, years, median (range)		55 (39-65)	47 (45-54)	45 (45-52)	49 (39-65)
Sex	Male	3 (50)	2 (67)	1 (33)	6 (50)
	Female	3 (50)	1 (33)	2 (67)	6 (50)
Race	Asian (Korean)	6 (100)	3 (100)	3 (100)	12 (100)
HER2 Expression	Positive	1 (17)			1 (8)
	Negative	5 (83)	3 (100)	3 (100)	11 (92)
Histology	Adenocarcinoma (MD)	1 (17)	0	0	1 (8)
	Adenocarcinoma (PD)	3 (50)	3 (100)	2 (67)	8 (67)
	Signet ring cell carcinoma	2 (33)	0	1 (33)	3 (25)
Operation History	Total Gastrectomy	2 (33)	2 (67)	2 (67)	6 (50)
	Subtotal Gastrectomy	1 (17)	1 (33)	1 (33)	3 (25)
	None	3 (50)	0	0	3 (25)
ECOG Performance Status	0	5 (83)	2 (67)	3 (100)	10 (83)
	1	1 (17)	1 (33)	0	2 (17)

HER2, human epidermal growth factor receptor 2; MD, moderately differentiated; PD, poorly differentiated; ECOG, Eastern Cooperative Oncology Group

Safety

Table 2. Treatment-related Adverse Events (observed in more than 10%)

Event, n (%)	100 mg BID (N=6)		200 mg BID (N=3)		300 mg BID (N=3)		Overall (N=12)	
	All Grades	Grade = 3	All Grades	Grade = 3	All Grades	Grade = 3	All Grades	Grade = 3
Anemia	3 (50)		1 (33)	1 (33)	3 (100)	3 (100)	7 (58)	4 (33)
Anorexia	3 (50)	1 (17)	2 (67)				5 (42)	1 (8)
Fatigue	2 (33)		1 (33)		1 (33)		4 (33)	
Dyspepsia	3 (50)				1 (33)		4 (33)	
Urticaria	2 (33)				2 (67)		4 (33)	
Weight loss	3 (50)						3 (25)	
Alopecia	1 (17)				2 (67)		3 (25)	
AST increased	2 (33)						2 (17)	
ALP increased	2 (33)						2 (17)	
Myalgia	1 (17)		1 (33)				2 (17)	
Tingling sense	1 (17)				1 (33)		2 (17)	
Hypotension	1 (17)		1 (33)				2 (17)	
Thrombocytosis			1 (33)		1 (33)		2 (17)	
Diarrhea			1 (33)		1 (33)		2 (17)	
Headache					2 (67)		2 (17)	
Fever					2 (67)		2 (17)	
Constipation					2 (67)		2 (17)	
Mucositis	1 (17)				1 (33)		2 (17)	

Data Cut-off Aug 20, 2020

- No Grade 4 or 5 treatment-related adverse event (TRAE) was observed

Safety (continued)

- There was no dose-limiting toxicity (DLT) in all doses of vactosertib in combination with paclitaxel and no cardiac toxicity was observed
- Most common TRAEs were anemia (58%), followed by anorexia (42%)
- An anorexia (Gr3) case was reported as a serious adverse event (SAE), possibly related to vactosertib and paclitaxel
- There was one AE of Gr3 vomiting leading to permanent vactosertib discontinuation in Cohort 1 (100 mg BID)

Efficacy

Figure 2. Duration of Treatment

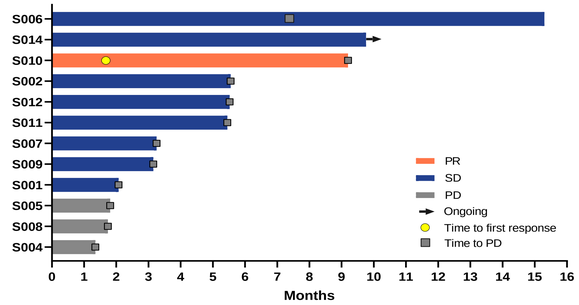
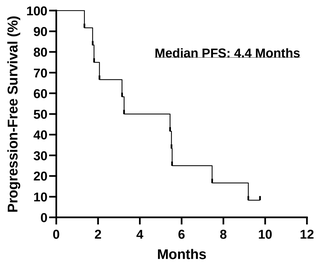


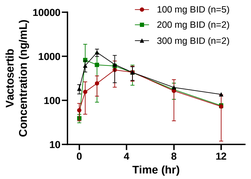
Figure 3. Progression-Free Survival



- Best overall response was 1 partial response, 8 stable diseases, and 3 progressive diseases
- Median progression-free survival (PFS) was 4.4 months

Pharmacokinetics and Pharmacodynamic Markers

Figure 4. Pharmacokinetics of Vactosertib

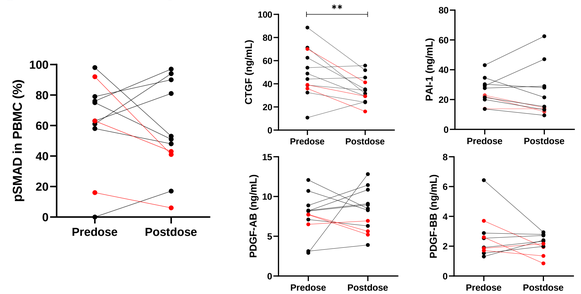


	100 mg BID (n=5)	200 mg BID (n=2)	300 mg BID (n=2)
$AUC_{0\text{-}inf}$ (h*ng/mL)	3803 ± 1537	4440	5879
C_{max} (ng/mL)	594 ± 151	1072	1225
T_{max} (h)*	3.1 [1.5-4.5]	2.6 [0.6, 4.6]	1.6 [1.6,1.6]
$T_{1/2}$ (h)	2.6 ± 1.0	3.1	4.5

Mean ± standard deviation; *, median (range); Parameters from 2 patients were reported as mean
Note: Since PK parameters relating terminal phase from three patients were not able to be estimated due to outlet obstruction, delayed absorption, and dosing error, data were not included in the analysis

- Pharmacokinetic analysis demonstrated a dose-dependent exposure of vactosertib on day 5

Figure 5. Pharmacodynamic Markers



- Levels of phosphorylated SMAD in PBMC were decreased after 300 mg BID vactosertib (marked in red)
- Concentrations of CTGF in plasma were significantly decreased in overall patient analysis

SUMMARY & CONCLUSION

- The combination of vactosertib and paclitaxel was demonstrated a manageable safety profile and durable efficacy
- Based on overall results of the phase I study, 300 mg BID was chosen for RP2D
- The phase 2a study is ongoing to further evaluate efficacy and safety of vactosertib in combination with paclitaxel as a 2L treatment in patients with mGC

For more information, please contact us at sarahskim@medpacto.com

References: *1) Hepato-Gastroenterology. 2014; 61(129) 245-250 ; 2) Oncotarget. 2015;6(35):37526-37543*