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ASCO
Annual Meeting
June 1-5, 2018
Chicago, IL

TGF- β RESPONSIVE SIGNATURE IS ASSOCIATED WITH ANTI-TUMOR EFFECT OF VACTOSERTIB, A POTENT ORAL TGF-β RECEPTOR TYPE I (TGFBRI) INHIBITOR IN PATIENTS WITH ADVANCED SOLID TUMORS

Vicki Keedy,[1] Todd Bauer,[2] Jeffrey Clarke, [3] Herbert Hurwitz,[3] Insun Baek,[4] Ilho Ha,[4] Chan-Young Ock,[4] Su Youn Nam,[4] Mina Kim,[5] Neunggyu Park,[5] Jung Yong Kim,[5] Seong-Jin Kim[4]

[1]Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN, USA., [2]Sarah Cannon Research Institute / Tennessee Oncology, PLLC., Nashville, TN, USA.

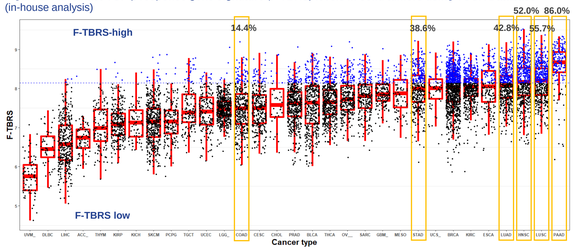
[3]Department of Medicine, Duke University School of Medicine, Durham, NC, USA., [4]MedPacto Inc., Suwon, Gyeonggi-do, Republic of Korea., [5]National OncoVenture, National Cancer Center, Goyang-si, Gyeonggi-do, Republic of Korea.

BACKGROUND

- Therapeutic antibodies that block the programmed death-1 (PD-1) – programmed death-ligand 1 (PD-L1) pathway can induce robust and durable responses in patients with various cancers [1]. However, these responses only occur in a subset of patients. Elucidating the determinants of response and resistance is key to improving outcomes and developing new treatment strategies.
- Stromal signature regulated by TGF-β pathway is one of the major mechanisms of tumor immune surveillance, leading to resistance to immune checkpoint inhibitors (ICI). This occurred particularly in patients with tumors, which showed exclusion of CD8+ T cells from the tumor parenchyma that were instead found in the fibroblast- and collagen-rich peritumoral stroma. Moreover, TGF-β responsive signatures (TBRS) of stromal cells have been associated with poor prognosis [2].
- Vactosertib (TEW-7197) is a potent, highly selective, oral inhibitor of TGF-β type I receptor (TGFBRI) that has shown promise as a drug candidate for the treatment of various solid tumors and hematological malignancies.

Multiple solid tumors show high expression level of Fibroblast-TGF-β response gene signature (F-TBRS)

Figure 1. Fibroblast-TGF-β response gene signature (F-TBRS) levels in solid tumors using TCGA Database*
(in-house analysis)

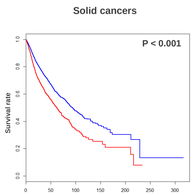


	Cancer type	F-TBRS-high		Cancer type	F-TBRS-high
PAAD	Pancreatic adenocarcinoma	86.0%	LUAD	lung adenocarcinoma	42.8%
LUSC	Lung SqCC	55.7%	STAD	Stomach adenocarcinoma	38.6%
HNSC	Head and neck SqCC	52.0%	COAD	Colorectal adenocarcinoma	14.4%

*arbitrary cut-off level used. adjusted hazard ratio 1.27; P=1.06 x 10-8

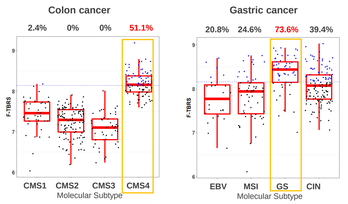
Colorectal (CMS4) and diffuse gastric cancer with high-TBRS are associated with poor prognosis [3), 4)]

Figure 2. TBRS is associated with poor prognosis*



*using TCGA database;
75% cut-off level used

Figure 3. F-TBRS levels in CRC and GC using TCGA database



GC patients with high levels of stromal super-module expression had a poorer prognosis (p=0.004) [4)]

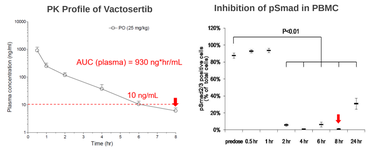
In Vitro activity of Vactosertib well translated into *in vivo* anti-tumor effects

Table 1. *In vitro* potency of Vactosertib

Potency	Vactosertib	Galunisertib
Kinase assay, K_d (nM)		
TGFBR1 (ALK5)	6.6	130
ACVR1B (ALK4)	2.4	90
TGF-βRII	18	140
Reporter cell assay, IC_{50} (nM)		
HaCaT 3TP-lux	16.5	>100
4T1 3TP-lux	12.1	>100

Selectivity		Vactosertib	Galunisertib
IC_{50} (nM)	TGFBR1	13	86
	p38α	1,775	320
	Selectivity (p38α/TGFBR1)	140	4

Figure 4. PK/PD Correlation observed in animal model



In a B16F10 melanoma mouse model with 5 days on, 2 days off oral once daily dosing of vactosertib (25 mg/kg), the exposure was LLOQ at 8 hrs and pSmad was inhibited through 24 hours (~30% inhibition) at a C_{trough} level of 10 ng/mL. The AUC at steady state ranged between 900~1000 ng*hr/mL. In addition, the anti-tumor effects of oral once daily dosing of vactosertib (25 mg/kg) in combination with anti-PD-1 were observed in a Braf mut/Pten(-) tg mouse model.

Vactosertib treated with anti-CTLA-4 induces robust T-cell immunity in a poorly immunogenic melanoma model [5)]

Figure 5. Tumor volume growth curve

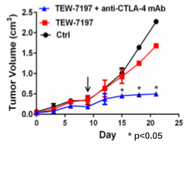
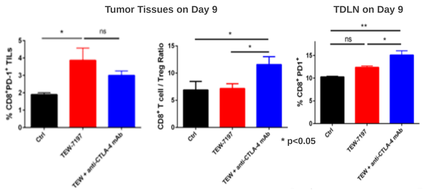


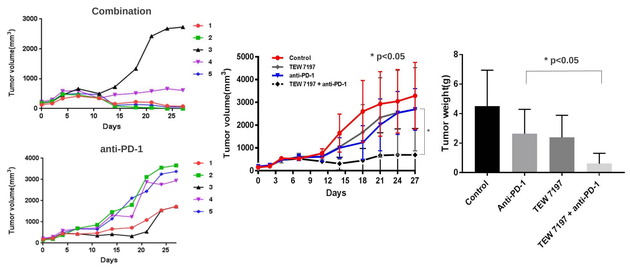
Figure 6. Lymphocyte flow cytometry analysis showed increase in TIL



- Tyr:CreER;Braf^{CA};Pten$^{lox/lox}$ Inducible transgenic melanoma mouse model is a poorly immunogenic melanoma model and did not show a therapeutic effect with checkpoint inhibitor monotherapy in the previous study.

Vactosertib is synergistic with anti-mouse PD-1 in a mouse syngeneic gastric cancer cell line model (NCC-S1M) [6), 7)]

Figure 7. Anti-tumor effect following 4-week treatment with intraperitoneal anti-mouse PD-1, oral vactosertib (TEW 7197) or combination in syngeneic gastric cancer cell line NCC-S1M allografts



METHODS

- A total of 34 patients aged 19 and older with histologically confirmed locally advanced or metastatic solid tumors were enrolled in a phase I modified 3+3 dose-escalating study (NCT02160106)
- Vactosertib was orally administered at the dose range of 30~340 mg QD and 200mg BID for 5 days with 2 days off every week.
- Inhibition of pSmads in peripheral blood mononuclear cells (PBMCs) was evaluated during Cycle 1
- RNA sequencing of pre-treatment tumor samples in 16 patients were analyzed to evaluate F-TBRS defined as geometric mean values of 171 corresponding gene expressions.

RESULTS

Table 2. Patient Characteristics

		Cohort 1~7 QD (N=29)	Cohort 1-3 (N=12), QD 30mg, 60mg, 100mg	Cohort 4-7 (N=17), QD 140mg, 200mg, 260mg, 340mg	Cohort 8 (N=5)*, BID 200mg BID
Sex (n, %)	Male	16, 55%	7, 58%	9, 53%	2, 40%
	Female	13, 45%	5, 42%	8, 47%	3, 60%
Age (yrs)	Median	62	62	64	66
	Range	34 – 80	40 – 80	34 – 70	58 – 76
ECOG Performance Status	0	9, 31%	3, 25%	6, 35%	3, 60%
	1	20, 69%	9, 75%	11, 65%	2, 40%
Prior Therapies	Median	3	3	4	3
	Range	0 - 9	0 – 6	0 – 9	2 - 5
	Chemotherapy	29, 100%	12, 100%	17, 100%	5, 100%
	ICI	5, 17%	1, 8%	4, 24%	0

* Preliminary data

Table 3. List of Treatment Emergent Adverse Events (TEAEs)

MedDRA SOC	Adverse Events (n, %)	Cohort 1~8 (N=34)		Cohort 1-3 (N=12), QD 30mg, 60mg, 100mg		Cohort 4-7 (N=17), QD 140mg, 200mg, 260mg, 340mg		Cohort 8 (N=5)*, BID 200mg BID	
		All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3
General disorders and admin. site conditions	FATIGUE	10 (29%)	-	1 (8%)	-	7 (41%)	-	2 (G1/2)	-
	FEVER	2 (6%)	-	1 (8%)	-	1 (6%)	-	-	-
Gastrointestinal disorders	NAUSEA	9 (26%)	-	3 (25%)	-	3 (18%)	-	3 (G1)	-
	CONSTIPATION	4 (12%)	-	2 (17%)	-	2 (12%)	-	-	-
	VOMITING	4 (12%)	-	1 (8%)	-	2 (12%)	-	1 (G1)	-
	DIARRHEA	4 (12%)	-	2 (17%)	-	1 (6%)	-	1 (G1)	-
	ABDOMINAL PAIN	2 (6%)	1 (3%)	-	-	2 (12%)	1 (6%)	-	-
Nervous system disorders	HEADACHE	5 (15%)	-	2 (17%)	-	2 (12%)	-	1 (G1)	-
	DYSGEUSIA	2 (6%)	-	-	-	2 (12%)	-	-	-
	STROKE	1 (3%)	1 (3%)	1 (8%)	1 (8%) [1)]	-	-	-	-
Metabolism and nutrition disorders	ANOREXIA	6 (18%)	-	-	-	5 (29%)	-	1 (G1)	-
	HYPOPHOSPHATEMIA	2 (6%)	-	-	-	2 (12%)	-	-	-
Skin and subcutaneous tissue disorders	SKIN RASH	4 (12%)	-	1 (8%)	-	1 (6%)	-	2 (G1)	-
Blood and lymphatic system disorders	ANEMIA	3 (9%)	-	2 (17%)	-	1 (6%)	-	-	-
	HYPOTENSION	2 (6%)	-	1 (8%)	-	1 (6%)	-	-	-
Cardiac disorders	CHEST WALL PAIN	2 (6%)	-	1 (8%)	-	1 (6%)	-	-	-
Investigations	ALT/AST/GGT INC	3 (9%)	1 (3%)	-	-	1 (6%)	1 (6%)	2 (G1/2)	-
Respiratory disorders	PULMONARY EDEMA	1 (3%)	1 (3%)	1 (8%)	1 (8%) [2)]	-	-	-	-

* Preliminary data,
1) A 75-yr-old penile cancer patient with diabetes mellitus and hypertension developed stroke on C1D7 and was hospitalized with diagnosis of brain infarction. After standard treatment, he recovered on C1D8 with minor motor dysfunction
2) A 63-yr-old chondrosarcoma patient with diabetes mellitus and hypertension was hospitalized on C2D15 with the diagnosis of non-cardiogenic pulmonary edema. After one week of supportive care, he fully recovered and was discharged.

Figure 8. PK profiles

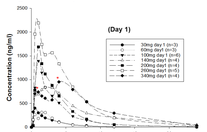


Table 4. PK profiles

Cohort		1	2	3	4	5	6	7	8
Dose (n)		30 mg (3)	60 mg (3)	100 mg (6)	QD 140 mg (4)	200 mg (4)	260 mg (5)	340 mg (4)	BID*** 200 mg (4)
T_{max} (hr)*	D1	0.5 (0.5-1.5)	1.5 (0.5-1.5)	1.1 (1.0-3.0)	1.8 (0.5-3.0)	1.2 (1.0-4.0)	1.0 (0.5-4.0)	1.1 (0.5-4.0)	0.8 (0.5-1.1)
	D5	1.0 (1.0-3.0)	1.3 (0.5-1.5)	1.3 (0.5-2.0)	1.5 (1.0-1.6)	1.5 (1.0-1.5)	1.5 (0.5-4.0)	0.5 (0.2-2.1)	1.1 (0.6-1.2)
$T_{1/2}$ (hr)**	D1	2.5 [38]	1.9 [74]	2.8 [47]	5.5 [59]	3.1 [40]	2.9 [56]	4.3 [38]	3.1 [17]
	D5	1.9 [52]	1.6 [59]	4.5 [81]	2.7 [30]	2.4 [32]	3.5 [85]	6.8 [68]	4.0 [27]
C_{max}** (ng/mL)	D1	327 [112]	437 [12]	1,308 [64]	1,006 [68]	1,328 [138]	2,949 [46]	1,487 [35]	2,544 [92]
	D5	318 [63]	481 [44]	866 [70]	1,461 [40]	1,899 [57]	2,249 [51]	1,842 [32]	1,886 [53]
C_{trough}* (ng/mL)	D5	LLOQ[1)]	LLOQ	LLOQ (LLOQ-59)	5.9 (LLOQ-14)	LLOQ (LLOQ-25)	LLOQ (LLOQ-46)	17.7 (LLOQ-174)	178 (82-266)
AUC_{0-last}** (ng.hr/mL)	D1	980 [59]	979 [40]	4,395 [27]	5,967 [68]	4,910 [93]	10,598 [58]	6,954 [83]	8,838 [61]
	D5	875 [56]	831 [130]	3,505 [33]	5,337 [49]	4,697 [44]	8,419 [45]	7,438 [47]	7,058 [30]

*Median (range) ** Geometric Mean [Geometric CV%] *** Preliminary data, Parameters are shown from 0 to 12 hr.
1) LLOQ: lower limit of quantitation

Figure 9. Inhibition of pSMAD[8)]

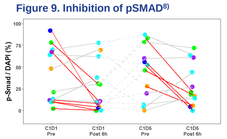


Figure 10. Best Overall Response with Vactosertib monotherapy

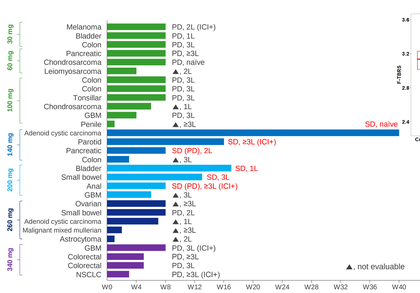
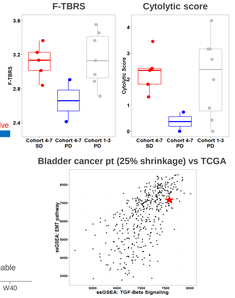


Figure 11. F-TBRS levels and cytolytic score



SUMMARY & CONCLUSION

- **Vactosertib, a potent and highly selective oral TGFBR1 inhibitor, was safe and well tolerated and the maximum tolerated dose was not determined.**
- **In per-protocol analysis, 6 out of 17 patients who received ≥140 mg achieved stable disease (35.3%) and showed higher F-TBRS levels than those with progressive disease.**
- Based on PK profiles observed, a BID dosing regimen would allow for better maintenance of plasma levels of vactosertib in the biologically active range and enhance the potential for antitumor activity. Therefore, the proposed RP2Ds are 100 mg BID or 200 mg BID which now are being evaluated in combination with other therapeutic options in multiple solid tumors and hematologic malignancies.
- Since high F-TBRS levels are well recognized as one of the main mechanisms related to resistance to ICI, **vactosertib would be an ideal therapeutic strategy in combination with ICIs or conventional anti-tumor therapies for solid tumors with high F-TBRS levels.**

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

Discovery of vactosertib was supported by Ministry of Education and Science, Korea (2008 – 2013)
Study was partially funded by National OncoVenture (NOV), Korea.

[1)]Hedge PS, Clin Cancer Res. 2016 5;22(8):1865-74., [2)]Calon A, Cancer Cell. 2012 13; 22(5): 571–584., [3)]Muller, M.F. Virchows Arch, 2016.469(2),125-34E, [4)]Wu Y, et al. Gut 2013;62:1100–1111, [5)]Conducted by Brent Hanks, Duke Cancer Institute, USA, [6)]Conducted by Hark Kim, National Cancer Center, South Korea, [7)]Park et al. Mol Carcinog 2015 Nov;54(11):1521, [8)]Drug Des Devel Ther. 2015; 9: 4479–4499