P410

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Safety and Preliminary Clinical Activity of Vactosertib, a Selective TGF-β Receptor I Kinase Inhibitor, in Combination with Durvalumab in Advanced Non-small Cell Lung Cancer Patients with Low PD-L1 Expression

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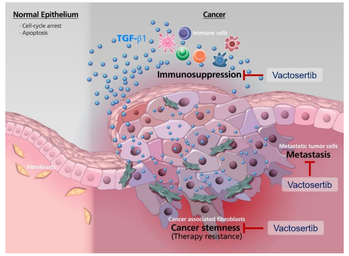
MEDPACTO

BACKGROUND

- 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
- TGF-β signaling is known to be associated with poor response to single-agent immune checkpoint inhibitors by immunosuppressive microenvironment through strong epithelial-mesenchymal transition (EMT) induction[1,2]
- Combined inhibition of immune checkpoint and TGF-β signal is anticipated as a promising therapeutic strategy because these two key pathways have independent and complementary immunosuppressive functions[3]
- Study MP-VAC-203 is a Phase 1b/2a study evaluating the combination of vactosertib with durvalumab in patients with advanced non-small cell lung cancer (NSCLC) who progressed following platinum-based chemotherapy
- Here we report the phase 1b part of the study in NSCLC patients with low PD-L1 expression (Clinical trial information: NCT03732274)

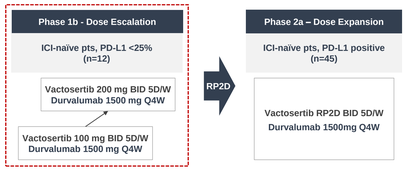


OBJECTIVES

- To evaluate the safety and tolerability of vactosertib plus durvalumab
- To characterize the pharmacokinetics of vactosertib plus durvalumab
- To document the preliminary clinical activity of vactosertib plus durvalumab

STUDY DESIGN / METHODS

Figure 1. MP-VAC-203 Study Design



Study Design

- Dose escalation assessment of the safety and tolerability of 2 doses of vactosertib (100 mg BID and 200 mg BID) given 5 days on/2 days off in combination with durvalumab (1500mg Q4W) was performed (Figure 1)
- Eligible patients are ≥19 years old, ECOG PS ≤1, and have no prior exposure to immune checkpoint inhibitors (ICIs), or TGFBR1 kinase inhibitors (Table 1)
- Tumor PD-L1 expression was evaluated in pre-treatment tissue samples by the Ventana SP263 IHC assay

STUDY DESIGN / METHODS (continued)

Study Endpoints

- Primary endpoint: safety, including adverse events per CTCAE v.5
- Secondary endpoints:
  - ✓ Tumour response was assessed per RECIST v1.1
  - ✓ Pharmacokinetic analysis of vactosertib (WinNonlin version 8.2) : Blood samples were collected at predose, 0.5, 1.5, 3, 4.5, 8, and 12 hours post dose on Day 1 and Day 5

RESULTS

Patients

Table 1. Baseline Characteristics

		100 mg BID (N= 7)	200 mg BID (N= 8)	Overall (N = 15)
Age, years, median (range)		65 (45-75)	66 (56-76)	66 (45-76)
Sex, n (%)	Male	4 (57)	5 (63)	9 (60)
	Female	3 (43)	3 (38)	6 (40)
Race, n (%)	Asian	7 (100)	8 (100)	15 (100)
No. of Prior Anticancer Therapies, n (%)	1	4 (57)	2 (25)	6 (40)
	2	1 (14)	2 (25)	3 (20)
	3 or more	2 (29)	4 (50)	6 (40)
ECOG Performance Status, n (%)	0	0	2 (25)	2 (13)
	1	7 (100)	6 (75)	13 (87)
Smoking Status, n (%)	Never	4 (57)	3 (38)	7 (47)
	Former	3 (43)	5 (63)	8 (53)
PD-L1 Expression, n (%)	Negative	3 (43)	7 (88)	10 (67)
	1-10%	4 (57)	1 (12)	5 (33)
EGFR Status, n (%)	Wild-type	3 (43)	4 (50)	7 (47)
	Mutant	1 (14)	1 (12)	2 (13)
	Unknown	3 (43)	3 (38)	6 (40)
ALK Translocation, n (%)	No	4 (57)	4 (50)	8 (53)
	Yes	0	1 (12)	1 (7)
	Unknown	3 (43)	3 (38)	6 (40)
Histology, n (%)	Squamous	3 (43)	4 (50)	7 (47)
	Non-squamous	4 (57)	2 (25)	6 (40)
	Adenocarcinoma	0	2 (25)	2 (13)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; N = number of subjects; EGFR = epidermal growth factor receptor; ALK = anaplastic lymphoma kinase

Pharmacokinetics of Vactosertib

Figure 2. PK Profile

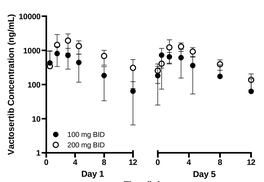


Table 2. PK Parameters

Parameters	Cycle 1 Day 1		Cycle 1 Day 5	
	100 mg BID (n=7)	200 mg BID (n=8)	100 mg BID (n=7)	200 mg BID (n=8)
T_{max} (h)*	1.5 [0.5 - 3]	3.0 [1.5 – 4.5]	0.5 [0.5 - 3]	2.3 [1.5 - 4.5]
C_{max} (μg/L)	1191 ± 272.8	2117 ± 1044.6	1018 ± 284.8	1550 ± 559.4
$AUC_{0\text{-}12h}$ (μg×h/L)	4324 ± 1567.6	11502 ± 4752.5	3999 ± 1958.9	7886 ± 1508.6
AUC_{inf} (μg×h/L)	4578 ± 1801.9	12606 ± 5475.9	4289 ± 2417.0	8674 ± 1745.5
V_d/F (L)	88 ± 29.4	84 ± 38.2	91 ± 22.0	84 ± 17.7
CL/F (L/h)	26 ± 12.5	19 ± 7.8	28 ± 10.7	24 ± 5.6
$t_{1/2}$ (h)	2.5 ± 0.40	3.2 ± 0.99	2.5 ± 0.70	2.5 ± 0.52

*Median (range); Parameters are shown as mean ± SD

RESULTS (continued)

Safety

- No dose limiting toxicity (DLT) was observed with 100 mg twice daily (BID) and 200 mg BID vactosertib in combination with durvalumab
- No cardiovascular toxicity was observed during the study
- Treatment-related adverse events (TRAE) were reported in 10 (66.7%, all grades) patients (Table 3); the most common AEs were pruritus (40.0%), rash (33.3%), nausea (20.0%), and hypothyroidism (20.0%)
- Most common adverse events of special interest (AESI) were rash (33.3%), hypothyroidism (20.0%), drug eruption (13.3%), and AST increased (13.3%)

Table 3. Summary of Treatment-related Adverse Events

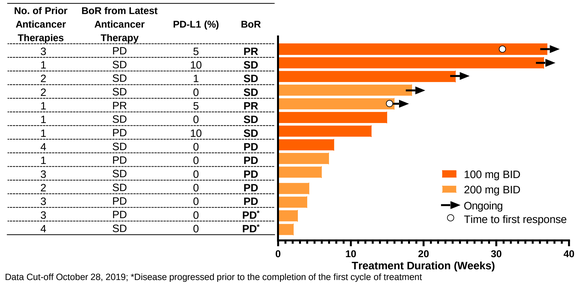
Event, n (%)	Cohort 1 100 mg BID (N=7)		Cohort 2 200 mg BID (N=8)		Overall (N=15)	
	All Grades	Grade = 3	All Grades	Grade = 3	All Grades	Grade = 3
Total	5 (71.4)	1 (14.3)	5 (62.5)		10 (66.7)	1 (6.7)
Pruritus	3 (42.9)		3 (37.5)		6 (40.0)	
Rash	3 (42.9)	1 (14.3)	2 (25.0)		5 (33.3)	1 (6.7)
Nausea	2 (28.6)		1 (12.5)		3 (20.0)	
Hypothyroidism	2 (28.6)		1 (12.5)		3 (20.0)	
Drug eruption	1 (14.3)		1 (12.5)		2 (13.3)	
AST increased			1 (12.5)		1 (6.7)	
ALT increased			1 (12.5)		1 (6.7)	
Myalgia	1 (14.3)				1 (6.7)	
Platelet count decreased			1 (12.5)		1 (6.7)	
Anorexia	1 (14.3)				1 (6.7)	
Stomatitis	1 (14.3)				1 (6.7)	
Blood TSH increased	1 (14.3)				1 (6.7)	

Data Cut-off October 28, 2019

Efficacy

- Among 12 evaluable patients, 2 patients achieved partial response (16.7%) and 5 stable disease (41.7%)
- Objective response rate (ORR) was 16.7% and 14.3% by per protocol (PP) and by intention-to-treat (ITT) analysis, respectively; disease control rate at 24-weeks (DCR 24wks) were 33.3% (PP) and 28.6% (ITT)

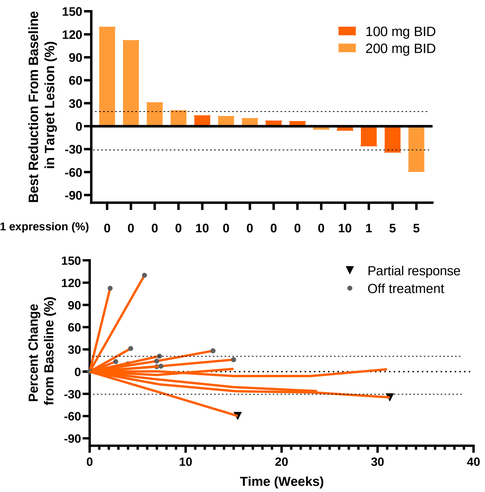
Figure 3. Duration of Treatment



Data Cut-off October 28, 2019; *Disease progressed prior to the completion of the first cycle of treatment

Efficacy (continued)

Figure 4. Overall Tumor Response (RECIST v1.1)



SUMMARY & CONCLUSION

- Safety
  - No DLT or cardiac toxicity was observed with vactosertib and durvalumab treatment
  - Most adverse events were grade 1 or 2 and generally manageable
- Pharmacokinetics
  - Vactosertib's pharmacokinetic profile supports twice daily dosing
- Efficacy: ORR (16.7%) and DCR 24wks (33.3%)
  - The chemo-free regimen of vactosertib and durvalumab showed promising early anti-tumor activity, compared to the historical data in difficult-to-treat NSCLC patients with low/negative PD-L1 expression[4-10]
- The ongoing phase 2a study is further evaluating the efficacy and safety of vactosertib in combination with durvalumab
  - Phase 2a targets ICI-naïve NSCLC patients with PD-L1 ≥ 1%

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References

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