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Vactosertib and Durvalumab as Second or Later Line Treatment for PD-L1 Positive Non-small Cell Lung Cancer: Interim Result

Byoung Chul Cho[1], Ki Hyeong Lee[2], Ji-Youn Han[3], Byoung Yong Shim[4], Hye Ryun Kim[1], Kyoung-Ho Pyo[1], Jae-Hwan Kim[1], Chung-Feng Xin[1], Jin Kyung Lee[5], Jiyeon Ryu[5], Bitna Oh[5], Sunjin Hwang[5], Ki Baik Hahm[5], Seong-Jin Kim[5]

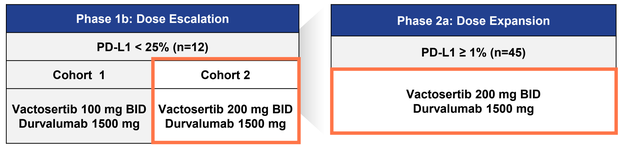
[1]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea, [2]Chungbuk National University Hospital, Cheongju, Republic of Korea, [3]National Cancer Center, Goyang, Republic of Korea, [4]ST. Vincent's Hospital, Suwon, Republic of Korea, [5]MedPacto Inc., Seoul, Republic of Korea

BACKGROUND

- Immunotherapies blocking PD-1/PD-L1 has greatly improved clinical outcomes in multiple cancers including non-small cell lung cancer (NSCLC), however, the clinical benefit is limited to only a subset of patients [1, 2]
- The unsatisfactory response of immune checkpoint inhibitors (ICIs) is mainly due to the immune-excluded phenotype, in which transforming growth factor β (TGF-β) is known to play a determinant role [3, 4]
- Vactosertib (TEW-7197) is a highly selective TGF-β receptor type 1 (TGFBR1) inhibitor, combining with ICI can be a promising strategy to overcome immunotherapy resistance as well as improve anti-tumor activity [5]
- Study MP-VAC-203 is a phase 1b/2a study evaluating the combination of vactosertib and durvalumab in patients with NSCLC who progressed following platinum-based chemotherapy (**Figure 1**)
- Here, we updated the report of safety and efficacy of patients who were administered vactosertib 200 mg BID in combination with durvalumab (NCT03732274)

STUDY DESIGN and METHODS

Figure 1. MP-VAC-203 Study Design



- Eligible patients were ≥19 years old with good performance status (ECOG 0-1) and have no prior exposure to immune checkpoint inhibitors or other TGF- β R1 kinase inhibitors
- Patients were treated with vactosertib at a dose of 200 mg twice daily (five days on and two days off) and durvalumab at a dose of 1500 mg every four weeks
- Tumor PD-L1 expression was measured by SP263 assay
- Overall response was assessed per RECIST v1.1
- Pharmacodynamic biomarkers related to TGF-β signaling was evaluated by enzyme-linked immunosorbent assay (ELISA)

RESULTS

- As of October 06, 2020, a total of 39 PD-L1 positive patients were enrolled and administered 200mg BID in phase 1b & 2a (**Table 1**)
- The median age in the overall population was 63.5 years (range 43-83) and all were Asian
- The median number of previous anti-cancer treatment was 1 (range 1-4)
- 92.3% (n=36) had ECOG performance status
- 5.1% (n=2) of the population are current smokers and 64.1% (n=25) had a smoking history
- Histologic finding showed 61.5% (n=24) of adenocarcinoma, 35.9% (n=14) of squamous, and 2.6% (n=1) of other type reported as a favor large cell carcinoma (Subject ID: 300403)

RESULTS

Patients

Table 1. Baseline Characteristics

Characteristics		PD-L1 ≥ 25% (N=19)	PD-L1 1-24% (N=20)	PD-L1 ≥ 50% (N=17)	PD-L1 1-49% (N=22)	Total (N=39)
Median age, years (range)		61 (48-83)	65 (43-81)	63 (48-83)	64.5 (43-81)	63.5 (43-83)
Sex, n (%)	Male	16 (84.2)	12 (60.0)	14 (82.4)	14 (63.6)	28 (71.8)
	Female	3 (15.8)	8 (40.0)	3 (17.6)	8 (36.4)	11 (28.2)
Race, n (%)	Asian	19 (100.0)	20 (100.0)	17 (100.0)	22 (100.0)	39 (100.0)
No. of prior anticancer therapies, median (range)		1 (1-4)	1 (1-4)	1 (1-4)	1 (1-4)	1 (1-4)
ECOG performance status, n (%)	0	1 (5.3)	2 (10.0)	0 (0.0)	3 (13.6)	3 (7.7)
	1	18 (94.7)	18 (90.0)	17 (100.0)	19 (86.4)	36 (92.3)
Smoking status, n (%)	Current	1 (5.3)	1 (5.0)	1 (5.9)	1 (4.5)	2 (5.1)
	Former	15 (78.9)	10 (50.0)	13 (76.5)	12 (54.5)	25 (64.1)
	Never	3 (15.8)	9 (45.0)	3 (17.6)	9 (40.9)	12 (30.8)
Histology, n (%)	Adenocarcinoma	12 (63.2)	12 (60.0)	10 (58.8)	14 (63.6)	24 (61.5)
	Squamous cell	7 (36.8)	7 (35.0)	7 (41.2)	7 (31.8)	14 (35.9)
	Other	0 (0.0)	1 (5.0)	0 (0.0)	1 (4.5)	1 (2.6)

Efficacy

Table 2. Objective Response Rate (ORR)

PD-L1%	ORR (n=30)
≥ 1	33.3% (10/30)
≥ 25 1 – 24	57.1% (8/14) 12.5% (2/16)
≥ 50 1 – 49	50.0% (6/12) 22.2% (4/18)

- Among 30 tumor evaluable patients, a total of 10 patients showed response resulting in 33.3% of objective response rate (ORR; **Table 2**)
  - 5 patients are soon to undergo their first tumor evaluation
  - 4 patients having no post-treatment tumor assessment were excluded (300121: consent withdrawal; 300141, 300406, and 300409: death attributed to rapid clinical disease progression)
  - 1 confirmed CR, 6 confirmed PR and 3 unconfirmed PR
- Responses are ongoing in 9 of 10 patients (30 patients having RECIST v1.1 assessment were included in the graph; **Figure 2 and 3**)
- Treatment is ongoing in 14 patients – one patient (300210) who had confirmed PR developed a new target lesion but decided to continue the treatment beyond progressive disease
- 3 patients discontinued treatment due to an adverse event: 300123 (pneumonitis), 300203 (pneumonitis) and 300407 (interstitial lung disease; ILD)
- 300119 and 300403 confirmed clinical progression
- Overall median PFS (n=34) was 4.73 months (**Figure 4**)

Efficacy (continued)

Figure 2. Duration of Treatment

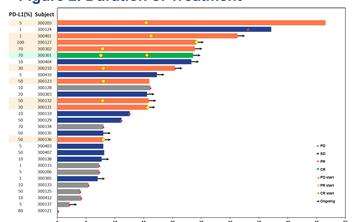


Figure 4. Progression Free Survival (PFS)

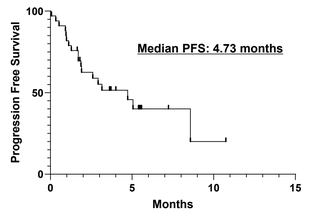
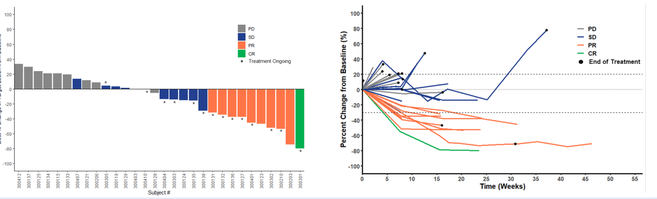
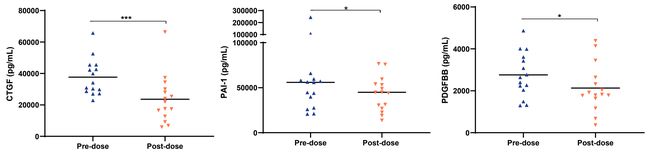


Figure 3. Overall Tumor Response



Pharmacodynamic marker analysis

Figure 5. Changes of circulating CTGF, PAI-1, and PDGF levels after treatment (C1D5)



- Circulating biomarkers related to TGF-β signaling, CTGF, PAI-1, and PDGFBB, were assessed in 15 patients and their levels were significantly decreased after treatment (**Figure 5**)

Safety

- A total of 39 patients were analyzed for safety profile
- **Table 3** is a summary of the Treatment related adverse events (TRAEs) reported in at least 2 patients (DCO: Oct 06, 2020)
- Treatment emergent adverse events (TEAEs) were reported in 79.5% (n=31) and TRAEs were reported in 66.7% (n=26)
- The most common TRAE was itching (35.9%), skin rash (30.8%) and lipase increased (20.5%)
- Grade 3 or higher TRAEs occurred in 28.2% (n=11)
  - Grade 3 (n=8): amylase increased (n=1), pneumonitis (n=1), ILD (n=1), adrenal insufficiency (n=1), anemia (n=1), colitis (n=1), pneumonic infiltration (n=1), and toxic epidermal necrolysis (TEN)-like lesion (n=1), verbatim by investigator
  - Grade 4 (n=2): lipase increased (n=1) and creatine phosphokinase (CPK) increased (n=1)
  - Grade 5 (n=1): disease progression; unlikely related to investigational products but lack of radiologic confirmation

Safety (continued)

- 7.7% (n=3) of patients were discontinued the study treatment due to AE: grade 2/3 pneumonitis (n=2) and grade 3 ILD (n=1)
- 17.9% (n=7) occurred treatment related serious adverse event (SAE)
  - Grade 3 (n=6): adrenal insufficiency (n=1), anemia (n=1), ILD (n=1), pneumonic infiltration (n=1), pneumonitis (n=1), and toxic epidermal necrolysis-like lesion (n=1)
  - Grade 5 (n=1): disease progression
- No cardiac toxicity was observed during the study

Table 3. Summary of Treatment Related Adverse Events (TRAEs)

Event	TRAEs (%)	Gr1 (%)	Gr2 (%)	Gr 3-4(%)	Vacto-related TRAE (%)	Vacto-related Gr 3-4(%)	SAE (%)	Vacto-related SAE (%)
Itching	35.9	15.4	20.5	-	33.3	-	-	-
Skin Rash	30.8	10.3	20.5	-	30.8	-	-	-
Lipase Increased	20.5	7.7	10.3	2.6	20.5	2.6	-	-
Amylase Increased	17.9	7.7	7.7	2.6	17.9	2.6	-	-
ALT Increased	7.7	-	-	-	7.7	-	-	-
AST Increased	7.7	7.7	-	-	7.7	-	-	-
GGT Increased	7.7	5.1	2.6	-	7.7	-	-	-
Nausea	7.7	2.6	5.1	-	7.7	-	-	-
TFT Abnormality	7.7	7.7	-	-	2.6	-	-	-
Abdomen Pain	5.1	-	5.1	-	5.1	-	-	-
Cardiac Troponin I Increased	5.1	5.1	-	-	2.6	-	-	-
Diarrhea	5.1	2.6	2.6	-	2.6	-	-	-
Hypothyroidism	5.1	-	5.1	-	2.6	-	-	-
ILD	5.1	-	2.6	2.6	2.6	2.6	2.6	2.6
Pneumonitis	5.1	-	2.6	2.6	2.6	2.6	2.6	2.6
Skin Erythema	5.1	5.1	-	-	5.1	-	-	-

CONCLUSIONS

- Vactosertib in combination with durvalumab demonstrated promising early anti-tumor efficacy in 2L+ NSCLC
  - 33.3% of ORR in PD-L1 positive patients with higher response rate in high PD-L1 population (PD-L1≥ 25%: ORR 57.1%; PD-L1 ≥ 50%: ORR 50.0%)
- The combination of vactosertib and durvalumab showed manageable safety profile
- The phase 2 part of enrollment is still ongoing for further evaluation of the efficacy and safety of vactosertib and durvalumab in patients with advanced NSCLC

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