

Vactosertib, a TGF-β signaling inhibitor, in combination with Durvalumab increased mOS in ≥2L treatment of patients with PD-L1-positive advanced NSCLC

Byoung Chul Cho¹, Ki Hyeong Lee², Ji-Youn Han³, Byoung-Young Shim⁴, Jaehyeon Kim⁵, Hyejung Yang⁵, Jungwon Woo⁵, Seong-Jin Kim⁵

¹Yonsei Cancer Center, Seodaemun-Gu, Seoul, Republic of Korea, ²Chungbuk National University Hospital, Cheongju-si, Chungcheongbuk-do, Republic of Korea, ³National Cancer Center, Goyang-si, Gyeonggi-do, Republic of Korea, ⁴The Catholic University of Korea, St. Vincent's Hospital, Suwon-si, Gyeonggi-do, Republic of Korea, ⁵MedPacto Inc., Seocho-gu, Seoul, Republic of Korea

BACKGROUND

- TGF-β signaling has been shown to enhance the efficacy of immune checkpoint inhibitors (ICIs) by boosting antitumor immunity and modifying TME to make it less conducive to cancer growth¹⁻⁵. Vactosertib, a highly selective TGF-β receptor I kinase inhibitor, has been combined with durvalumab to investigate if the combination could improve the antitumor activity of ICIs.
- Previously, a phase 1b/2a clinical study showed that the combination of vactosertib and durvalumab markedly improved ORR in patients with advanced NSCLC who had progressed after platinum-based chemotherapy (MP-VAC-203, NCT03732274)⁶.

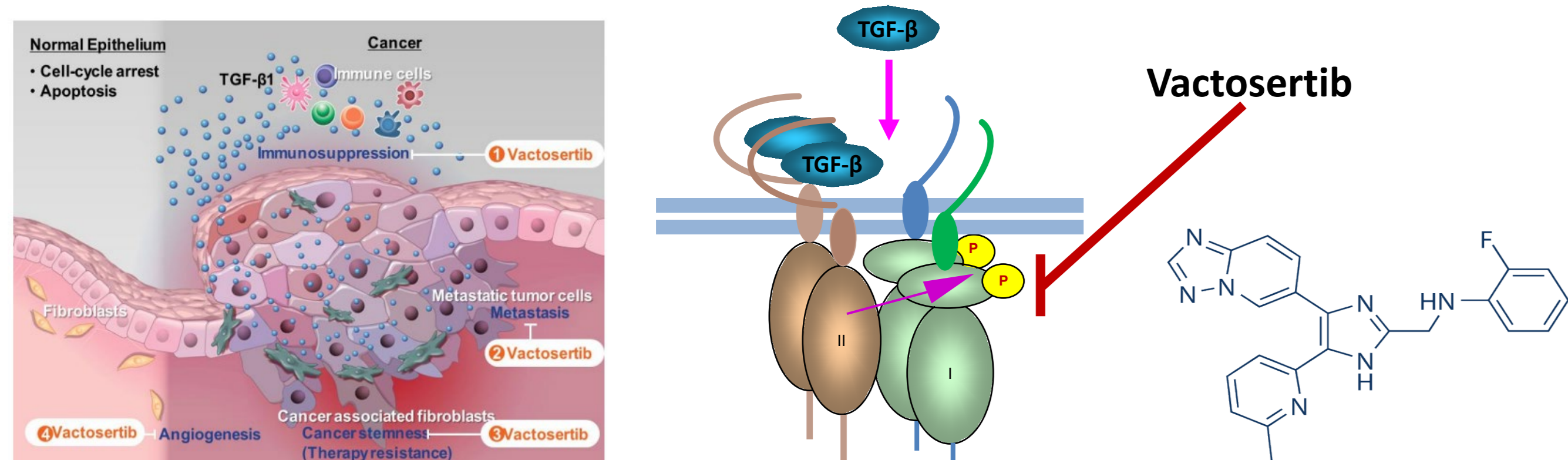


Figure 1. Mode of Action

STUDY OBJECTIVES AND METHODS

Study Objectives

- Primary Objectives:**
 - To evaluate the safety and tolerability of vactosertib in combination with durvalumab including estimation of the MTD, RP2D and/or characterization of DLTs.
- Secondary Objectives:**
 - To characterize the PK of vactosertib in combination with durvalumab to all patients assigned to dose-escalation phase and the first six patients assigned to the dose expansion phase.
 - To document the antitumor activity of vactosertib in combination with durvalumab.

Study Design and Patients

- This is an open-label, multi-centered, phase 1b/2a study in patients with advanced non-small cell lung cancer (NSCLC) who progressed following platinum-based chemotherapy. The patients were confirmed to be PD-L1 positive using the Ventana SP263 IHC assay.
- Tumor assessment was to be conducted per RECIST v1.1 every 8 weeks.
- This study consists of two parts: Phase 1b, vactosertib dose-escalation study to determine the RP2D and Phase 2a, non-randomized dose expansion study to confirm RP2D (Figure 2).

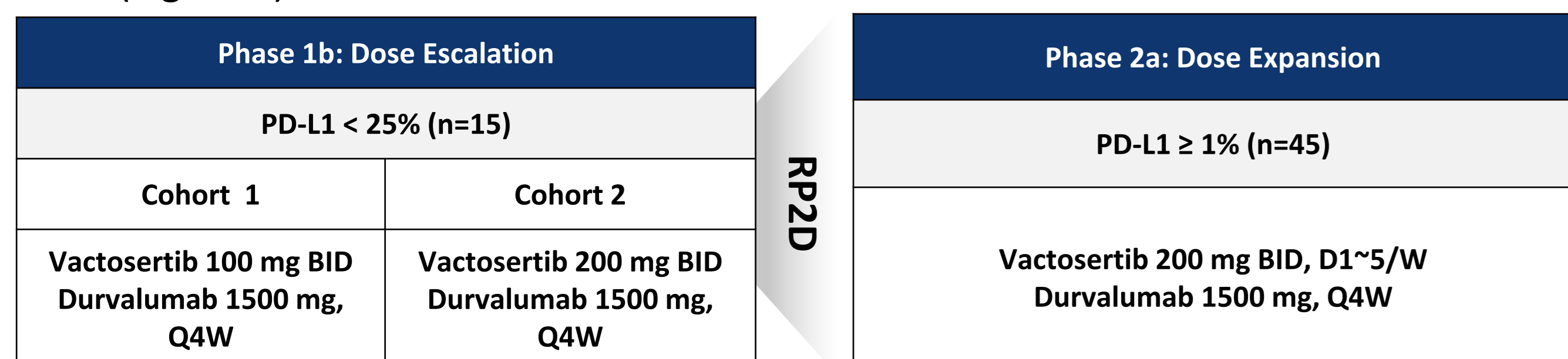


Figure 2. MP-VAC-203 Study Design

RESULTS

Patient Disposition and Characteristics

- By April 24, 2024, a total of sixty patients were analyzed: 15 patients with PD-L1<25% in Phase 1b, and 45 patients with PD-L1≥1% in Phase 2a.
- 60 patients were available for the assessment of safety and efficacy.

RESULTS (Continued)

- All patients had received at least one platinum-based chemotherapy for NSCLC (Table 1).

Table 1. Baseline Characteristics

Class	Dose Escalation (n=15)	Dose Expansion (n=45)	Total (n=60)
Age, years, median (range)	66.00 (45, 76)	63.00 (42, 83)	63.50 (42, 83)
Sex, male, n (%)	9 (60)	33 (73.33)	42 (70)
Race, n (%)	Asian 15 (100)	45 (100)	60 (100)
ECOG PS, n (%)	0 2 (13.33) 1 13 (86.67)	7 (15.56) 38 (84.44)	9 (15) 51 (85)
Histology, n (%)	Adenocarcinoma 9 (60) Squamous 5 (33.33) Non-squamous 0 (0) Unknown 1 (6.67) Others 0 (0)	27 (60) 14 (31.11) 1 (2.22) 0 (0) 3 (6.67)	36 (60) 19 (31.67) 1 (1.67) 1 (1.67) 3 (5)
Smoking Status, n (%)	Current/Former 8 (53.33) Never 7 (46.67)	32 (67.44) 13 (28.89)	40 (64.67) 20 (33.33)
Tumor driver mutations, n (%)	EGFR positive 2 (13.33) ALK positive 0 (0) KRAS positive 1 (6.67) Adjuvant 0 (0)	12 (26.67) 1 (2.22) 1 (2.22) 6 (13.33)	14 (23.33) 1 (1.67) 2 (3.33) 6 (10)
Prior line(s) of treatment, n (%)	1 7 (46.67) 2 3 (20) 3 or more 5 (33.33)	25 (55.56) 7 (15.56) 7 (15.56)	32 (53.33) 10 (16.67) 12 (20)
PD-L1 status, n (%)	<25% 15 (100) ≥25% 0 (0)	21 (46.67) 24 (53.33)	36 (60) 24 (40)

(Abbreviation) ALK, anaplastic lymphoma kinase, ECOG PS, Eastern Cooperative Oncology Group Performance Status, EGFR, epidermal growth factor receptor, KRAS, Kirsten rat sarcoma viral oncogene homolog.

Safety and Tolerability

- Overall, 54 (90.0%) patients experienced at least one TEAE.
- Treatment-related TEAEs were observed in 43 (71.7%) patients, and treatment-related TEAEs with grade 3 or higher were observed in 16 (26.7%) patients (Table 2).
- The most common treatment-related AEs were pruritus (n=24, 40.0%), rash (n=19, 31.7%), and lipase increased (n=11, 18.3%) (Table 3).
- Dose-limiting toxicity (DLT) population was 13, and there was no DLT observed.

Table 2. Summary of Treatment Emergent Adverse Events (TEAEs)

Category	Vactosertib 100mg BID N=7, n (%)	Vactosertib 200mg BID N=53, n (%)	Total N=60 n (%)
TEAE	6 (85.7)	48 (90.6)	54 (90.0)
TEAE related to study treatment	5 (71.4)	38 (71.7)	43 (71.7)
Serious TEAE	2 (28.6)	16 (30.2)	18 (30.0)
Serious TEAE related to study treatment	1 (14.3)	9 (17.0)	10 (16.7)
Grade 3 or higher TEAE	2 (28.6)	26 (49.1)	28 (46.7)
Grade 3 or higher TEAE related to study treatment	2 (28.6)	14 (26.4)	16 (26.7)
Fatal TEAE	0	3 (5.7)	3 (5.0)
Fatal TEAE related to study treatment	0	1 (1.9) ¹	1 (1.7) ¹
Discontinuation due to TEAE	0	5 (9.4)	5 (8.3)
Immune-related TEAE	4 (57.1)	29 (54.7)	33 (55.0)

(Abbreviation) TEAE, Treatment emergent adverse event
¹ Exact cause of the death is unknown, but it is suspected to be related to disease progression, as per investigator's assessment. Relationship with study treatments can't be completely ruled out.

Table 3. TEAE (Incidence ≥10%) Related To Study Treatment

Preferred Term	Vactosertib 100mg BID N=7, n (%)	Vactosertib 200mg BID N=53, n (%)	Total N=60 n (%)
Subjects with any AE related to study treatment	5 (71.4)	38 (71.7)	43 (71.7)
Pruritus	3 (42.9)	21 (39.6)	24 (40.0)
Rash	2 (28.6)	17 (32.1)	19 (31.7)
Lipase increased	0	11 (20.8)	11 (18.3)
Amylase increased	0	10 (18.9)	10 (16.7)
Nausea	2 (28.6)	6 (11.3)	8 (13.3)
Alanine aminotransferase increased	1 (14.3)	5 (9.4)	6 (10.0)
Hypothyroidism	3 (42.9)	3 (5.7)	6 (10.0)

¹ Events with lower frequency, but considered serious and important.
² Two patients (3.3%) experienced toxic-epidermal necrolysis (TEN), which were considered atypical TEN because they didn't have mucosal involvement or constitutional symptom. Their outcome was recovered/resolved and recovering/resolving, respectively.
³ Four patients (6.7%) experienced interstitial lung disease, one patient (1.7%) experienced pneumonitis.

Antitumor Activity

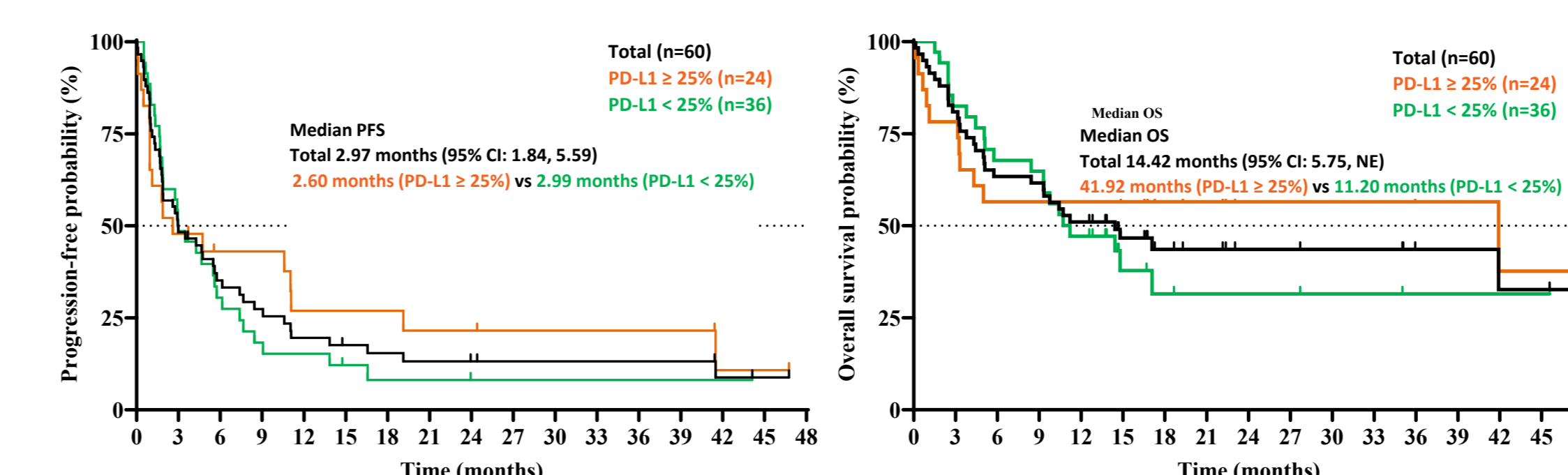
- ORR was 31.7%, with 45.8% observed in patients with PD-L1 expression ≥25% and 22.2% in those with PD-L1 expression <25%.
- DCR was 58.3%, in both patients with PD-L1 expression ≥25% and those with PD-L1 expression <25%.
- Notably, a significant difference in mOS was also found between these groups, with mOS of 41.92 months (PD-L1 ≥25%) compared to 11.20 months (PD-L1 <25%) (Figure 3).

Table 4. Overall Response Rate (%)

Response (RECIST v1.1)	Dose Escalation (n=15), n (%)	Dose Expansion (n=45), n (%)	Total (n=60), n (%)
ORR, n (%), [95%CI]	2 (13.33), [1.66, 40.46]	17 (37.78), [23.77, 53.46]	19 (31.67), [20.26, 44.96]
CR	0 (0.0)	1 (2.22)	1 (1.67)
PR	2 (13.33)	16 (35.56)	18 (30.00)
SD	5 (33.33)	11 (24.44)	16 (26.67)
PD	7 (46.67)	13 (28.89)	20 (33.33)
ND	1 (6.67)	4 (8.89)	5 (8.33)
PD-L1 <25%, n=36	2 (13.3)	6 (28.6)	8 (22.22)
PD-L1 ≥25%, n=24	-	11 (45.8)	11 (45.83)
DCR, n (%), [95%CI]	7 (46.67), [21.27, 73.41]	28 (62.22), [46.54, 76.23]	35 (58.33), [44.88, 70.93]
PD-L1 <25%, n=36	7 (46.67)	14 (66.67)	21 (58.33)
PD-L1 ≥25%, n=24	-	14 (58.33)	14 (58.33)
mDOR, mo (95% CI)	-	-	10.15 (4.40, NE)
PD-L1 <25%, n=36	NE (10.15, NE)	4.06 (1.87, NE)	7.28 (1.87, NE)
PD-L1 ≥25%, n=24	-	15.51 (2.89, NE)	15.51 (2.89, NE)
mPFS, mo (95% CI)	-	-	2.97 (1.84, 5.59)
PD-L1 <25%, n=36	2.35 (0.79, 8.44)	4.67 (1.87, 6.14)	2.99 (1.84, 5.59)
PD-L1 ≥25%, n=24	-	2.60 (0.95, 11.07)	2.60 (0.95, 11.07)
mOS, mo (95% CI)	-	-	14.42 (5.75, NE)
PD-L1 <25%, n=36	11.20 (2.50, NE)	10.71 (5.09, 17.08)	11.20 (5.75, NE)
PD-L1 ≥25%, n=24	-	41.92 (3.25, NE)	41.92 (3.25, NE)

(Abbreviation) ORR, objective response rate, DCR, disease control rate, mDOR, median duration of response, mPFS, median progression-free survival, mOS, median overall survival

Figure 3. PFS & OS by PD-L1 Expression (<25% vs ≥25%)

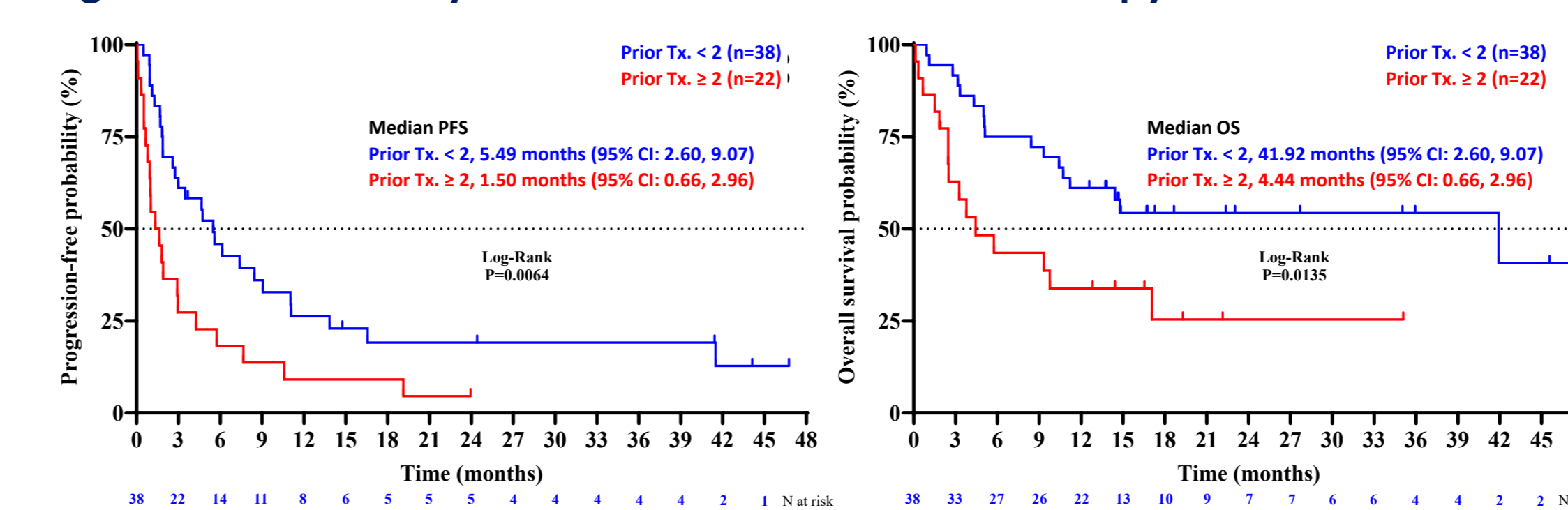


- Further investigations were conducted to identify factors influencing overall survival.
- Multivariate Cox analysis identified prior therapy (<2nd line vs ≥2nd line) as significantly associated with overall survival (HR = 2.925, 95% CI: 1.249-7.020, P = 0.0142).

Table 5. Multivariate Analysis of Survival Factors in NSCLC by COX Proportional Hazards Regression Model

Factors	Class	HR	95% CI	P-value
Age	<65 vs ≥65	1.462	0.637-3.448	0.3748
Sex	Male vs Female	0.820	0.350-1.811	0.6334
ECOG	ECOG 0 vs 1	2.007	0.555-12.881	0.3606
Staging	Local advanced vs metastatic	2.160	0.706-9.448	0.2288
PD-L1	<25% vs ≥25%	0.883	0.382-1.958	0.7638
Prior therapy	<2 nd line vs ≥2 nd line	2.925	1.249-7.020	0.0142

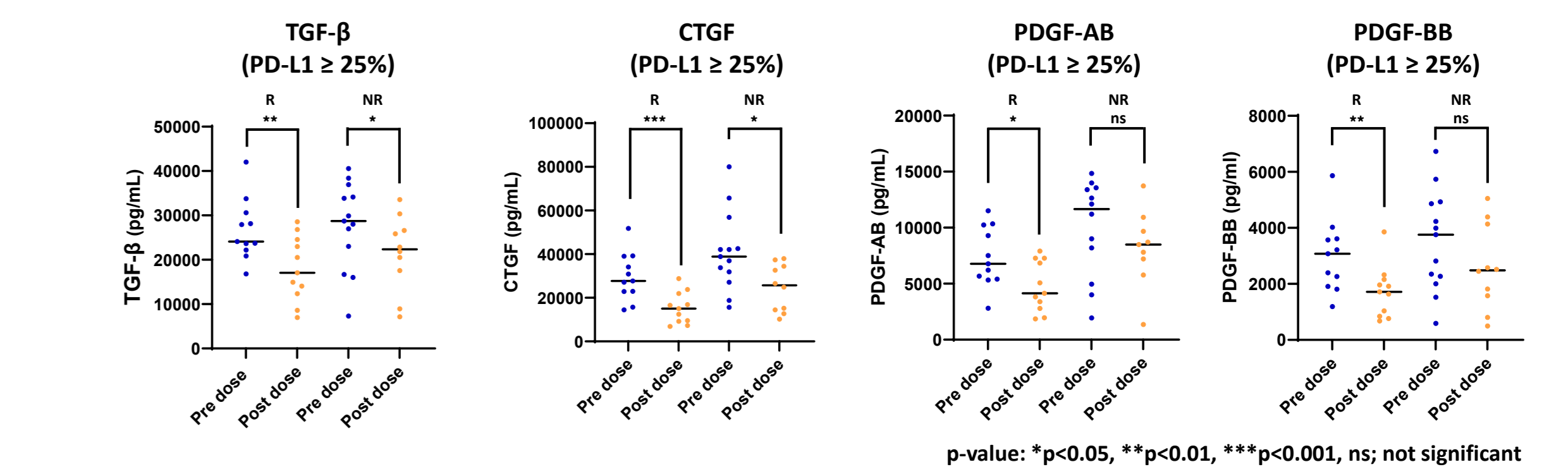
Figure 4. PFS & OS by Number of Prior Lines of Therapy



Exploratory Biomarker Analysis

- To assess the effect of vactosertib in combination with durvalumab therapy on exploratory biomarkers, including circulating cytokines such as transforming growth factor (TGF)-β, connective tissue growth factor (CTGF), platelet-derived growth factor (PDGF)-AB and PDGF-BB in patients with PD-L1 ≥25%.
- Responder is defined as CR or PR in patients by RECIST.
- After treatment, in patients classified as responders (R) compared to those classified as non-responders (NR), circulating biomarkers related to TGF-β signaling, such as TGF-β, CTGF, PDGF-AB, and PDGF-BB, significantly decreased.

Figure 5. Decrease of Circulating Biomarker in Blood After Treatment (C1D5)



CONCLUSIONS

- Safety profile of the combination of vactosertib and durvalumab was considered acceptable with stringent use of TMGs, for the pt population that has limited treatment options available.
- This combination notably improved the ORR, mDOR, and mOS, particularly among patients with high PD-L1 expression (PD-L1 ≥25%).
- Furthermore, mOS was significantly longer in patients who had received fewer than two prior lines of therapy. Multivariate analysis identified the number of prior lines of therapy as a significant predictor of survival (HR = 2.925).
- Overall, vactosertib and durvalumab combination demonstrate potential as an effective immunotherapy for patients with advanced NSCLC who have progressed following platinum-based chemotherapy.

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