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Encouraging antitumor activity of PDL1V (PF-08046054) monotherapy, an ADC targeting PD-L1, correlates with antigen expression in patients with NSCLC

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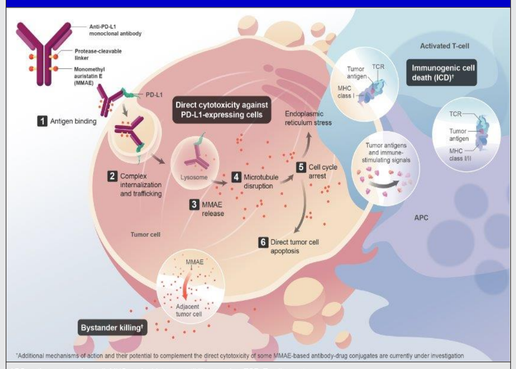
Introduction

- PDL1V (PF-08046054) is an investigational antibody-drug conjugate (ADC) that binds to PD-L1–expressing tumor cells and delivers cytotoxic agent monomethyl auristatin E (MMAE) through proteolytic cleavage of the MMAE drug linker[1,2] (**Figure 1**)
- Released MMAE binds and disrupts microtubule networks, resulting in mitotic arrest and apoptotic tumor cell death;[3-5] MMAE additionally induces immunogenic cell death[4,6-8]
- In MMAE-sensitive xenograft models, PDL1V has shown antitumor activity across a range of PD-L1 expression levels[2]
- While PDL1V targets the PD-L1 immune checkpoint ligand, nonclinical data suggest that checkpoint inhibition through blockade of programmed cell death 1 (PD-1)/PD-L1 interactions is unlikely to be a major contributor to the mechanism of action due to limitations of dose levels, schedules, and exposure with ADCs
- Encouraging preliminary efficacy was observed with PDL1V along with a manageable safety profile in patients with R/R PD-L1–positive NSCLC[9]
- Here, we present updated results from this study in patients with metastatic R/R NSCLC

Figure 1. PDL1V drives antitumor activity through direct cytotoxicity, bystander killing, and immunogenic cell death

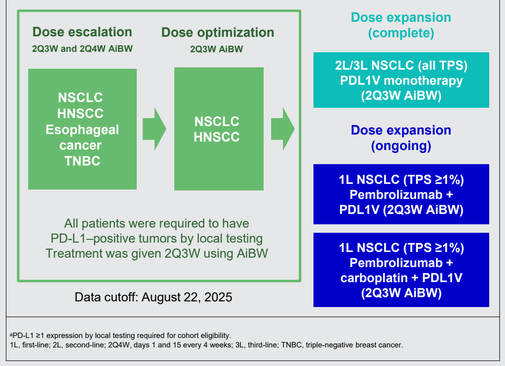


APC, antigen-presenting cell; MHC, major histocompatibility complex; TCR, T-cell receptor.

Methods

- C5851001 (NCT05208762) is a phase 1 study of PDL1V monotherapy in patients with advanced solid tumors and in combination with pembrolizumab in patients with metastatic or unresectable head and neck squamous cell carcinoma (HNSCC) or NSCLC
- This analysis included dose escalation, dose optimization, and dose expansion cohorts that included patients with R/R NSCLC independent of PD-L1 expression by TPS (**Figure 2**)
- Key inclusion criteria included ≥18 years of age, histologically- or cytologically-confirmed NSCLC, measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
  - Patients who received prior taxane were included in the trial
- Efficacy analyses included patients with NSCLC who received PDL1V at the recommended phase 3 dose of 1.5 mg/kg 2Q3W using adjusted ideal body weight (AiBW)
- Safety data were pooled across all patients treated in the study at the recommended phase 3 dose
- The primary objectives of this analysis were to evaluate the safety and tolerability of PDL1V; a secondary objective was to assess antitumor activity

Figure 2. PDL1V Phase 1 Study Schema (NCT05208762)



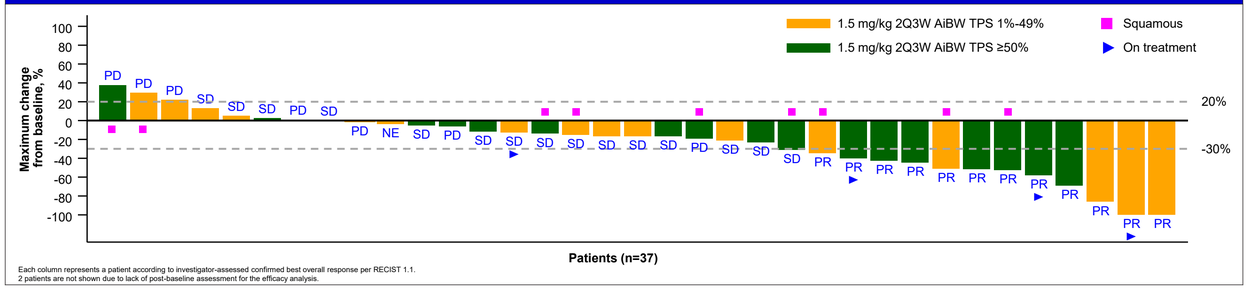
Data cutoff: August 22, 2025

[a]PD-L1 ≥1 expression by local testing required for cohort eligibility.
1L, first-line; 2L, second-line; 2Q4W, days 1 and 15 every 4 weeks; 3L, third-line; TNBC, triple-negative breast cancer.

Results

- As of August 22, 2025, a total of 55 patients with NSCLC received PDL1V in the 2L+ setting at the recommended phase 3 dose of 1.5 mg/kg 2Q3W
- The median age was 63 years; 47.3% were female, 29.1% had squamous histology, 65.5% had prior taxane-containing therapy, and 70.9% had an ECOG performance status of 1 (**Table 1**)
- Confirmed ORR was 32.4% in patients with TPS ≥1% NSCLC (**Table 2**)
  - Confirmed ORR was 33.3% (95% CI, 7.5-70.1) in patients with squamous NSCLC, 40.9% (95% CI, 20.7-63.6) in those with prior taxane, and 45.5% (95% CI, 16.7-76.6) in those with actionable genomic alterations (AGAs)
- Responses were observed in both non-squamous and squamous histology in patients with TPS ≥1% NSCLC (**Figure 3**)
- Percentage change in target lesions from baseline in patients with TPS ≥1% NSCLC is shown in **Figure 4**
- Median duration of response was 7.2 months (95% CI, 4.4-8.0) in patients with TPS ≥1% NSCLC

Figure 3. Maximum percentage reduction in sum of diameters of target lesions from baseline in patients with TPS ≥1% NSCLC



Each column represents a patient according to investigator-assessed confirmed best overall response per RECIST 1.1.
2 patients are not shown due to lack of post-baseline assessment for the efficacy analysis.

Table 1. Baseline demographics and clinical characteristics

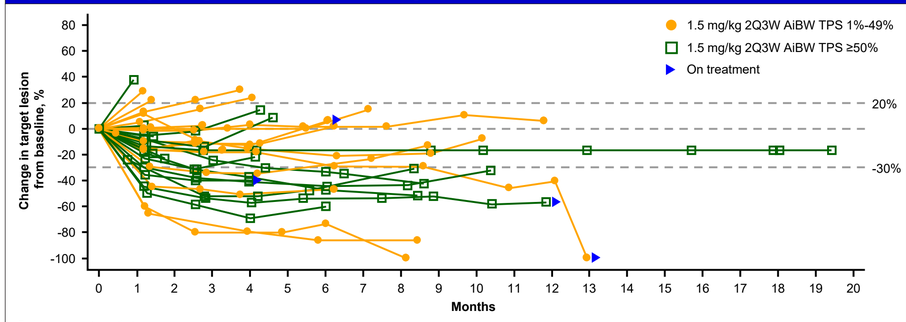
	TPS <1% (n=18)	TPS ≥1%			Total (n=55)
		TPS 1%-49% (n=19)	TPS ≥50% (n=18)	Total (n=37)	
Age, median (range), years	65 (39-84)	61 (45-74)	64 (44-79)	63 (44-79)	63 (39-84)
Sex, n (%)					
Female	11 (61.1)	6 (31.6)	9 (50.0)	15 (40.5)	26 (47.3)
Histology/subtype, n (%)					
Non-squamous	11 (61.1)	15 (78.9)	13 (72.2)	28 (75.7)	39 (70.9)
Squamous	7 (38.9)	4 (21.1)	5 (27.8)	9 (24.3)	16 (29.1)
Tumor spread, n (%)					
Metastatic	16 (88.9)	18 (94.7)	17 (94.4)	35 (94.6)	51 (92.7)
Locally advanced (LA)	2 (11.1)	1 (5.3)	1 (5.6)	2 (5.4)	4 (7.3)
Patients with any AGA, n (%)	7 (38.9)	6 (31.6)	5 (27.8)	11 (29.7)	18 (32.7)
KRAS	5 (27.8)	3 (15.8)	2 (11.1)	5 (13.5)	10 (18.2)
BRAF V600E	3 (16.7)	0	0	0	3 (5.5)
EGFR	1 (5.6)	2 (10.5)	2 (11.1)	4 (10.8)	5 (9.1)
MET	0	2 (10.5)	1 (5.6)	3 (8.1)	3 (5.5)
No. of prior treatment lines in LA or metastatic setting, median (range)	2 (1-3)	2 (1-7)	2 (1-5)	2 (1-7)	2 (1-7)
Prior therapies in any setting, n (%)					
Platinum-based therapy	18 (100)	18 (94.7)	17 (94.4)	35 (94.6)	53 (96.4)
PD-1/PD-L1 inhibitor	16 (88.9)	18 (94.7)	18 (100)	36 (97.3)	52 (94.5)
Taxane-containing therapy	14 (77.8)	11 (57.9)	11 (61.1)	22 (59.5)	36 (65.5)
AGA-targeted therapy	1 (5.6)	4 (21.1)	4 (22.2)	8 (21.6)	9 (16.4)
ECOG performance status, n (%)					
0	5 (27.8)	6 (31.6)	5 (27.8)	11 (29.7)	16 (29.1)
1	13 (72.2)	13 (68.4)	13 (72.2)	26 (70.3)	39 (70.9)

Table 2. Confirmed best overall response

	TPS <1% (n=18)	TPS ≥1%			Total (n=55)
		TPS 1%-49% (n=19)	TPS ≥50% (n=18)	Total (n=37)	
Confirmed best overall response,[a] n (%)					
Complete response (CR)	0	0	0	0	0
Partial response (PR)	0	5 (26.3)	7 (38.9)	12 (32.4)	12 (21.8)
Stable disease (SD)	12 (66.7)	8 (42.1)	7 (38.9)	15 (40.5)	27 (49.1)
Progressive disease (PD)	5 (27.8)	4 (21.1)	3 (16.7)	7 (18.9)	12 (21.8)
Not evaluable[b]/no assessment	1 (5.6)	2 (10.5)	1 (5.6)	3 (8.1)	4 (7.3)
Objective response rate (CR + PR), n (%)	0	**5 (26.3)**	**7 (38.9)**	**12 (32.4)**	12 (21.8)
95% CI[c] for objective response rate	(0.0-18.5)	**(9.1-51.2)**	**(17.3-64.3)**	**(18.0-49.8)**	(11.8-35.0)
Disease control rate (CR + PR + SD), n (%)	12 (66.7)	**13 (68.4)**	**14 (77.8)**	**27 (73.0)**	39 (70.9)
95% CI[c] for disease control rate	(41.0-86.7)	**(43.4-87.4)**	**(52.4-93.6)**	**(55.9-86.2)**	(57.1-82.4)

[a]Per RECIST 1.1; CR or PR were confirmed with repeat scans at least 28 days after the initial response.
[b]Patients had post-baseline assessment, and the best overall response was determined to be not evaluable per RECIST 1.1.
[c]Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method.

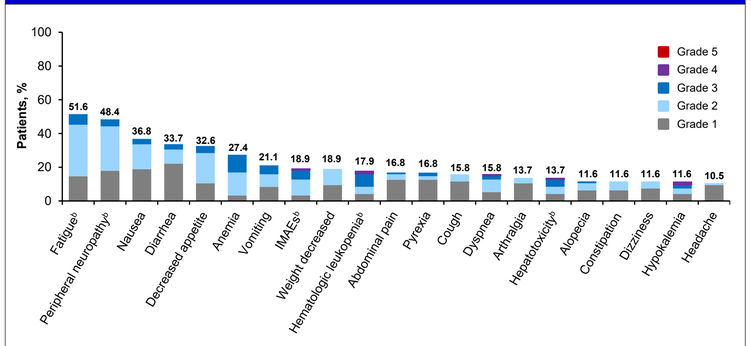
Figure 4. Percentage change in sum of diameters of target lesions from baseline in patients with TPS ≥1% NSCLC



Each line represents a patient.

- Most common TEAEs were fatigue (51.6%), peripheral neuropathy (48.4%), and nausea (36.8%) (**Figure 5**)
  - Grade 3 peripheral neuropathy occurred in 4.2% of patients; none had a grade 4 or 5 event
- Any-grade treatment-related peripheral neuropathy occurred in 40.0% of patients; grade 3 occurred in 2.1%
- Treatment-emergent immune-mediated adverse events (IMAEs) occurred in 18.9% of patients; most common were pneumonitis (8.4%) and hypothyroidism (5.3%) (**Table 4**)
- Any-grade treatment-related pneumonitis/interstitial lung disease occurred in 8.4% of patients; grade 3 occurred in 3.2%; none had a grade 4 or 5 event

Figure 5. TEAEs by preferred term and maximum severity in >10% of patients[a]



[a]Any AEs reported across all patients at the recommended phase 3 dose.
[b]Composite of related terms.
Fatigue included preferred terms fatigue, asthenia, and malaise.
Peripheral neuropathy included preferred terms peripheral sensory neuropathy, muscular weakness, paresthesia, peripheral motor neuropathy, neurotoxicity, burning sensation, dysesthesia, and neuralgia.
IMAEs included preferred terms pneumonitis, hypothyroidism, hepatitis, thrombocytopenia, antiphospholipid syndrome, arthritis, enterocolitis, and interstitial lung disease.
Hematologic leukopenia included preferred terms neutropenia, neutrophil count decreased, lymphocyte count decreased, lymphopenia, leukopenia, white blood cell count decreased, and febrile neutropenia.
Hepatotoxicity included preferred terms alanine aminotransferase increased, aspartate aminotransferase increased, hypertransaminasemia, gamma-glutamyltransferase increased, blood bilirubin increased, hepatic stenosis, and hepatitis.

- Among all patients treated in the phase 1 trial at the recommended phase 3 dose (N=95), any-grade treatment-emergent adverse events (TEAEs) occurred in all patients; grade ≥3 TEAEs occurred in 62.1% of patients (**Table 3**)
- TEAEs led to dose delay in 38.9%, dose reduction in 27.4%, and treatment discontinuation in 15.8% of patients
  - The most common reason for dose modifications was peripheral sensory neuropathy with dose delay in 8.4%, dose reduction in 12.6%, and treatment discontinuation in 3.2% of patients
- 8.4% of treatment discontinuations were treatment related

Table 3. Safety summary

	1.5 mg/kg 2Q3W (N=95), n (%)
Any TEAEs[a]	95 (100)
Treatment-related TEAEs[b]	81 (85.3)
Grade ≥3 TEAEs	59 (62.1)
Grade ≥3 treatment-related TEAEs	33 (34.7)
Any treatment-emergent SAEs	44 (46.3)
Treatment-related treatment-emergent SAEs	15 (15.8)
Discontinued treatment due to TEAEs	15 (15.8)
Discontinued treatment due to treatment-related TEAEs	8 (8.4)
TEAEs leading to death	9 (9.5)
Treatment-related TEAEs leading to death	0

[a]TEAEs are newly occurring AEs or AEs that worsen after the first dose of study treatment through 90 days after the last dose of study treatment.
[b]TEAEs related to treatment with PDL1V as assessed by the investigator.
SAE, serious adverse event.

Table 4. Treatment-emergent IMAEs by preferred term[a]

	1.5 mg/kg 2Q3W (N=95), n (%)				
	Grade 1	Grade 2	Grade 3	Grade 4	Total
Any IMAE	3 (3.2)	9 (9.5)	5 (5.3)	1 (1.1)	18 (18.9)
Pneumonitis	2 (2.1)	3 (3.2)	3 (3.2)	0	8 (8.4)
Hypothyroidism	2 (2.1)	3 (3.2)	0	0	5 (5.3)
Hepatitis	0	0	2 (2.1)	0	2 (2.1)
Thrombocytopenia	0	1 (1.1)	0	1 (1.1)	2 (2.1)
Antiphospholipid syndrome	0	1 (1.1)	0	0	1 (1.1)
Arthritis	1 (1.1)	0	0	0	1 (1.1)
Enterocolitis	0	0	1 (1.1)	0	1 (1.1)
Interstitial lung disease	0	1 (1.1)	0	0	1 (1.1)

[a]IMAEs include preferred terms from the Immune-mediated/autoimmune disorders (SMQ) with broad scope minus 4 preferred terms (Neuropathy peripheral, Peripheral motor neuropathy, Peripheral sensorimotor neuropathy, and Peripheral sensory neuropathy). AE grades are based on the NCI CTCAE, v5.0. At each preferred term, multiple occurrences of AEs within a patient were counted only once at the highest severity grade.
NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; SMQ, Standardised MedDRA Queries.

Conclusions

- PDL1V monotherapy at 1.5 mg/kg on days 1 and 8 every 21 days (2Q3W) showed a confirmed objective response rate (ORR) of 32.4% in patients with tumor proportion score (TPS) ≥1% in relapsed or refractory (R/R) non-small cell lung cancer (NSCLC); responses were durable, with a median duration of response of 7.2 months
- Responses were observed in patients with (TPS) ≥1% NSCLC regardless of TPS score; no responses were observed in patients with TPS <1% NSCLC, indicating that programmed cell death ligand 1 (PD-L1)–expressing tumors may be required for measurable antitumor activity
- PDL1V monotherapy was well tolerated with a manageable safety profile
- Treatment discontinuation rates were low (15.8%) and only 8.4% of discontinuations were treatment related
- No treatment-related deaths were reported
- These data support the pivotal phase 3 trial in patients with R/R metastatic NSCLC

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