Poster #91 Abstract #8611

Interim Results of PDL1V (PF-08046054), a Vedotin-Based ADC Targeting PD-L1, in Patients With NSCLC in a Phase 1 Trial

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Objectives

To assess the safety, tolerability, PK, and antitumor activity of PDL1V (PF-08046054) as monotherapy in patients with metastatic R/R NSCLC, treated at the recommended pivotal dose (1.5 mg/kg 2Q3W using AiBW)

Conclusions

- Encouraging preliminary efficacy in PD-L1 positive NSCLC was observed independent of the tumor histology
- PDL1V monotherapy was generally well tolerated with a manageable safety profile
- Based on these results, a pivotal trial is in planning

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Abbreviations: 1L, first-line, 2Q3W, Days 1 and 8 every 21 days; ADC, antibody-drug conjugate; AE, adverse event; AiBW, adjusted ideal body weight; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CPS, combined positive score; CR, complete response; D, day; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; HNSCC; head and neck squamous cell carcinoma; max, maximum; min, minimum; MMAE, monomethyl auristatin E; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PK, pharmacokinetics; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; R/R, relapsed/refractory; SAE, serious adverse event; SD, stable disease; TEAE, treatment-emergent adverse event; TNBC: triple-negative breast cancer; TPS, tumor proportion score; TRAE, treatment-related adverse event.

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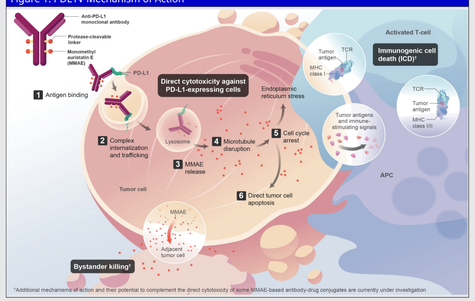
Figure 1. PDL1V Mechanism of Action



†Additional mechanisms of action and their potential to complement the direct cytotoxicity of some MMAE-based antibody-drug conjugates are currently under investigation

Introduction

- PDL1V (PF-08046054) is an ADC that binds to PD-L1–expressing tumor cells and delivers MMAE[1-4] (**Figure 1**)
- Released MMAE binds and disrupts microtubule networks, resulting in mitotic arrest and apoptotic tumor cell death;[5-7] MMAE additionally induces immunogenic cell death[6,8-10]
- In MMAE-sensitive xenograft models, PDL1V has shown antitumor activity across a range of PD-L1 expression levels[11]
- While PDL1V targets the PD-L1 immune checkpoint ligand, nonclinical data suggests checkpoint inhibition through blockade of PD-1 and PD-L1 interactions is unlikely to be a major contributor to the mechanism of action due to limitations of ADC-based dose level, schedule, and exposure
- Here, we present the safety profile and preliminary efficacy of PDL1V monotherapy at the recommended pivotal dose (1.5 mg/kg 2Q3W AiBW) in patients with locally advanced or metastatic R/R NSCLC

Methods

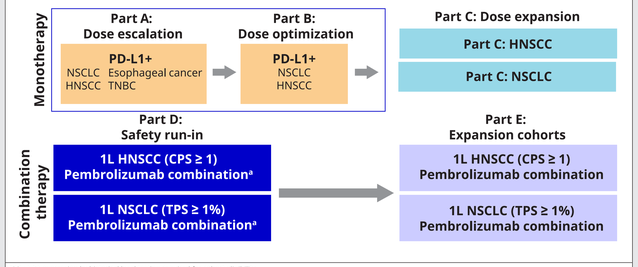
STUDY DESIGN

- CS851001 (NCT05208762) is a phase 1 study designed to evaluate the safety, tolerability, PK, and preliminary antitumor activity of PDL1V as monotherapy in patients with advanced solid malignancies and as combination therapy with pembrolizumab in patients with metastatic or unresectable head and neck squamous cell carcinoma or NSCLC (**Figure 2**)
- This study included dose escalation (Part A), dose optimization (Part B), and dose expansion (Part C)
- Here we show data of patients with R/R NSCLC enrolled in Part A, B, and C and treated at the recommended pivotal dose
- Part A and B included patients with PD-L1 expression ≥1 by CPS, TPS, or immune cell score, based on historical local testing. Part C enrolled patients independent of PD-L1 tumor expression
- Key inclusion/exclusion criteria included:
  - Patients required to have prior exposure to platinum-based chemotherapy and anti-PD-1/PD-L1 inhibitors unless intolerable or not available; known EGFR, ALK and ROS1 genomic alteration status; available archival tissue (if unavailable, a fresh biopsy required); measurable disease per RECIST v1.1; and ECOG performance status 0 or 1
  - Patients with known active central nervous system metastases, leptomeningeal disease, preexisting neuropathy ≥ grade 2 per NCI CTCAE v5.0. or any other serious underlying medical condition or previous receipt of an MMAE-containing agent are excluded

TREATMENT

- Patients received PDL1V monotherapy at the recommended pivotal dose of 1.5 mg/kg 2Q3W AiBW

Figure 2. PDL1V Phase 1 Study Schema



[a]PD-L1 ≥1 expression by historical local testing required for cohort eligibility.

Results

PATIENTS

- At the data cutoff of December 20, 2024, a total of 30 patients with R/R NSCLC (Parts A and B, n = 15; Part C, n = 15) were treated at the recommended pivotal dose (**Table 1**).

Table 1: Baseline Demographics and Disease Characteristics of Patients With R/R NSCLC

	PDL1V 1.5 mg/kg 2Q3W AiBW dosing (N = 30)
Age (years), median (min, max)	60.0 (44, 73)
Female sex, n (%)	17 (56.7)
ECOG performance status, n (%)	
0	10 (33.3)
1	20 (66.7)
Histology, n (%)	
Non-squamous	23 (76.7)
Squamous	7 (23.3)
PD-L1 status, n (%)	
Positive	25 (83.3)
Negative[a]	5 (16.7)
Prior lines of systemic treatment in recurrent or metastatic settings, median (min, max)	2.0 (1, 7)
Prior treatment in any setting, n (%)	
PD-1/PD-L1	29 (96.7)
Taxanes	20 (66.7)

[a]After the data cut off 1 additional patient was found to be PD-L1 negative

SAFETY AND TOLERABILITY

- Safety was assessed for all treated patients in Parts A, B, and C who received PDL1V 1.5 mg/kg 2Q3W AiBW dosing (N = 92)
- No dose-limiting toxicities were reported at the recommended pivotal dose
- No Grade 5 events occurred due to TRAEs (**Table 2**)

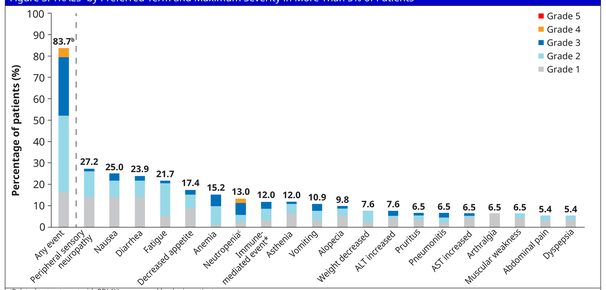
Table 2. Summary of Adverse Events

n (%)	PDL1V 1.5 mg/kg 2Q3W AiBW dosing (N = 92)
Any TEAE[a]	92 (100)
Any TRAE[b]	77 (83.7)
Grade ≥3 TEAE	52 (56.5)
Grade ≥3 TRAE	29 (31.5)
Any SAE	40 (43.5)
Any treatment-related SAE	13 (14.1)
Discontinued treatment due to TEAE	11 (12.0)
Discontinued treatment due to TRAE	5 (5.4)
TEAE leading to death	8 (8.7)
TRAE 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.

- The most common TRAEs were peripheral sensory neuropathy (27.2%), nausea (25.0%), diarrhea (23.9%), and fatigue (21.7%) (**Figure 3**)
- The majority of TRAEs were grade 1 or 2 in severity
- Grade ≥3 TRAEs occurred in 29 (31.5%) patients and the most common grade ≥3 TRAE was anemia (5.4%)

Figure 3: TRAEs[a] by Preferred Term and Maximum Severity in More Than 5% of Patients



[a]Related to treatment with PDL1V as assessed by the investigator.
[b]Any AEs reported across all patients.
[c]Composite of related preferred terms.
*See **Table 3** for details of immune-mediated events.

Table 3. Summary of Treatment-Related Immune-Mediated AEs by Preferred Term and Maximum Severity Occurring in 1 or More Patients[a,b,c]

	PDL1V 1.5 mg/kg 2Q3W AiBW dosing (N = 92)			
n (%)	**Grade 1**	**Grade 2**	**Grade 3**	**Total**
Any AE	3 (3.3)	5 (5.4)	3 (3.3)	11 (12.0)
Pneumonitis	2 (2.2)	2 (2.2)	2 (2.2)	6 (6.5)
Hypothyroidism	1 (1.1)	1 (1.1)	0	2 (2.2)
Arthritis	1 (1.1)	0	0	1 (1.1)
Hepatitis	0	0	1 (1.1)	1 (1.1)
Interstitial lung disease	0	1 (1.1)	0	1 (1.1)
Thrombocytopenia	0	1 (1.1)	0	1 (1.1)

[a]Immune mediated adverse events 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).
[b]AE grades are based on the NCI CTCAE, v5.0.
[c]At each preferred term, multiple occurrences of AEs within a patient were counted only once at the highest severity grade.

ANTITUMOR ACTIVITY IN NSCLC

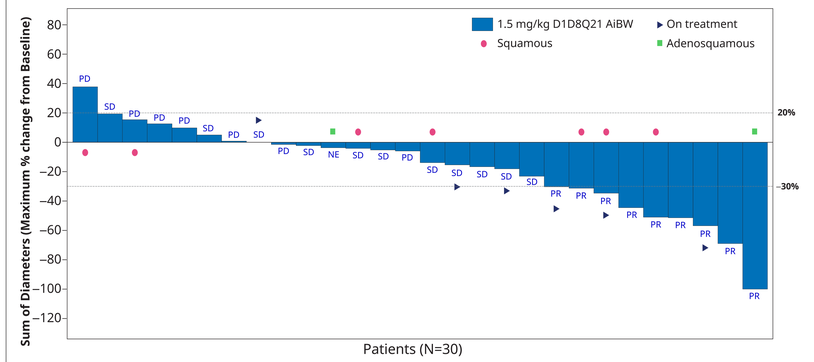
Table 4. Confirmed Best Overall Response

	PDL1V 1.5 mg/kg 2Q3W AiBW dosing		
	TPS <1% (n = 6)	**TPS ≥1% (n = 24)**	**Total (N = 30)**
Best overall response,[a,b] n (%)			
CR	0	0	0
PR	0	8 (33.3)	8 (26.7)
SD	4 (66.7)	9 (37.5)	13 (43.3)
PD	2 (33.3)	4 (16.7)	6 (20.0)
Not evaluable[c]	0	1 (4.2)	1 (3.3)
No assessment	0	2 (8.3)	2 (6.7)
ORR (CR + PR), n (%)	0	8 (33.3)	8 (26.7)
(95% CI)[d]	(0.0–45.9)	(15.6–55.3)	(12.3–45.9)
DCR (CR + PR + SD), n (%)	4 (66.7)	17 (70.8)	21 (70.0)
(95% CI)[d]	(22.3–95.7)	(48.9–87.4)	(50.6–85.3)

[a]Assessed per RECIST v1.1. CR or PR were confirmed with repeat scans ≥28 days after the initial response.
[b]CR, PR, SD, PD, 'Not evaluable' and 'No assessment' are mutually exclusive
[c]Patients had post-baseline assessment and the best overall response was determined to be not evaluable per RECIST v1.1
[d]Two-sided 95% exact CI computed using the Clopper–Pearson method.

- The confirmed ORR in patients with TPS ≥1% among squamous (n = 5) and non-squamous (n = 19) tumors was 40.0% and 31.6%, respectively
- A waterfall plot showing the maximum percentage reduction in the sum of diameters of target lesions from baseline is shown in **Figure 4**

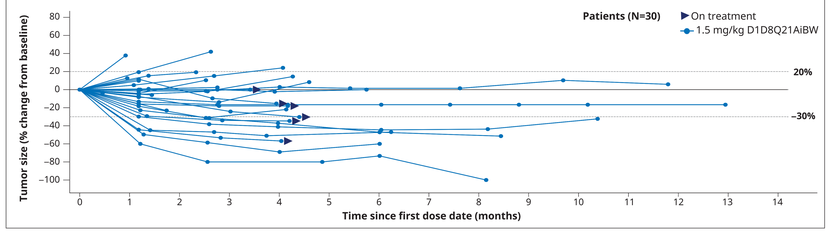
Figure 4: Waterfall Plot Showing the Maximum Percentage Reduction in Sum of Diameters of Target Lesions From Baseline[a]



[a]2 subjects are not displayed due to lack of post-baseline assessment that is eligible for the efficacy analysis.
Each column represents a patient according to investigator-assessed best overall response per RECIST v1.1.

- Spider plot depicting the percentage change in lesions from baseline is shown in **Figure 5**

Figure 5: Spider Plots Depicting the Percentage Change in Lesions From Baseline



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