Poster #441
Abstract #6033

Initial safety and efficacy of PDL1V (PF-08046054), a vedotin-based ADC targeting PD-L1, in combination with pembrolizumab in patients with recurrent or metastatic (R/M) HNSCC

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Objectives

- To assess the safety/tolerability, PK, and preliminary antitumor activity of PDL1V in combination with pembrolizumab in patients with PD-L1 positive, R/M HNSCC who have not received therapy with anti-PD-1/PD-L1 inhibitors

Conclusions

- The combination of PDL1V and pembrolizumab appeared tolerable with a manageable safety profile at the recommended expansion doses with no DLTs
- Early encouraging objective confirmed responses were observed in 2 different dose levels of PDL1V, including a notable 28.6% complete response rate
- Enrollment in multiple combination expansion cohorts with PD-L1 expressing tumors is ongoing

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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; C, cycle; CI, confidence interval; CPS, combined positive score; CR, complete response; D, day; DCR, disease control rate; DLTs, dose-limiting toxicities; ECOG, Eastern Cooperative Oncology Group; HNSCC, head and neck squamous cell carcinoma; HPV, human papilloma virus; ICD, immunogenic cell death; ILD, interstitial lung disease; IMAE, immune-mediated adverse event; max, maximum; min, minimum; MMAE, monomethyl auristatin E; 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; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; PSN, peripheral sensory neuropathy; RECIST, Response Evaluation Criteria in Solid Tumors; R/M, recurrent/metastatic; 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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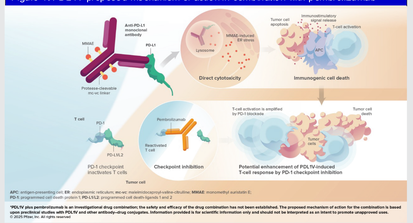
Figure 1. PDL1V proposed mechanism of action in combination with pembrolizumab



APC: antigen-presenting cell; ER: endoplasmic reticulum; mc-vc: maleimidocaproyl-valine-citrulline; MMAE: monomethyl auristatin E; PD-1: programmed cell death protein 1; PD-L1/L2: programmed cell death-ligand 1 and 2.

*PDL1V plus pembrolizumab is an investigational drug combination; the safety and efficacy of the drug combination has not been established. The proposed mechanism of action for the combination is based upon preclinical studies with PDL1V and other antibody–drug conjugates. Information provided is for scientific information only and should not be interpreted as an intent to promote unapproved uses.

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Introduction

- PD-L1 is a transmembrane protein highly expressed across a variety of malignancies, including HNSCC[1,2]
- PDL1V (PF-08046054) is a vedotin-based ADC against PD-L1 expressing tumor cells and delivers MMAE;[3,4] MMAE binds and disrupts microtubule networks resulting in mitotic arrest and apoptotic tumor cell death[4,5]
- MMAE additionally induces ICD,[3-5] which can be further amplified by traditional immune checkpoint inhibitors, providing strong scientific rationale for combination with pembrolizumab[3,5] (**Figure 1**)
- Based on the preclinical and clinical data,[7,8] there is a strong rationale for combining vedotin-based ADCs with PD1 inhibitors; this trial is evaluating PDL1V and pembrolizumab in 1L HNSCC, an area of unmet need
- Here we present safety for all HNSCC patients treated with the combination and efficacy for those patients with complete evaluation of response

Methods

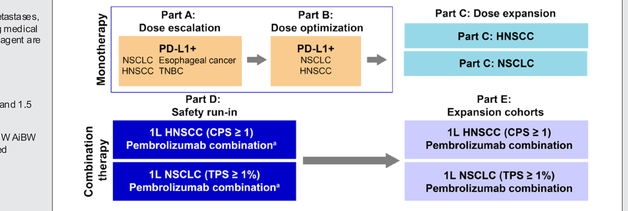
STUDY DESIGN

- C5851001 (NCT05208762) is a phase 1 study designed to evaluate the safety, tolerability, PK, and preliminary antitumor activity of PDL1V as monotherapy and in combination (eg, with pembrolizumab) in patients with advanced solid malignancies (**Figure 2**)
- The study includes Part D (**Figure 2**) (safety run-in cohort) and Part E (expansion cohort) in patients with PD-L1 positive, R/M HNSCC
- For Part D, key inclusion/exclusion criteria included:
  - PD-L1 expression by combined positive score (CPS) ≥ 1 based on historical local testing
  - No prior therapy with anti-PD-1/PD-L1 antibodies in any setting or cytotoxic therapy in the locally advanced or metastatic setting
  - Measurable disease per RECIST v1.1, and ECOG performance status ≤ 1 at baseline are required
  - Patients with known active central nervous system metastases, leptomeningeal disease, any other serious underlying medical condition, or previous receipt of an MMAE-containing agent are excluded

TREATMENT

- In Part D, 2 doses of PDL1V were evaluated (1.25 mg/kg and 1.5 mg/kg 2Q3W using AIBW dosing)
- Once safety was demonstrated at 1.25 mg/kg, 1.5 mg/kg 2Q3W AIBW (ie, the recommended pivotal dose) dose cohort was initiated
- All patients in Part D received pembrolizumab at 200 mg every 3 weeks
- Administration of the combination agents was by intravenous dosing of pembrolizumab first, followed by PDL1V

Figure 2. PDL1V phase 1 study schema



*PD-L1 ≥1 expression by historical local testing required for cohort eligibility.

Results

PATIENTS

- At the data cutoff of April 10, 2025, 25 patients were dosed; 8 patients received PDL1V at 1.25 mg/kg and 17 received 1.5 mg/kg (**Table 1**)
- Efficacy data are presented in the 14 patients enrolled in the safety run-in as these cohorts have the most mature duration of follow-up.

Table 1. Baseline demographics and disease characteristics of patients with R/M HNSCC

	PDL1V 2Q3W AIBW dosing		
	1.25 mg/kg (n = 8)	1.5 mg/kg (n = 17)	Total (N = 25)
Age, years, median (min, max)	56.5 (36, 70)	67.0 (54, 76)	66.0 (36, 76)
Male sex, n (%)	8 (100)	10 (58.8)	18 (72.0)
ECOG performance status, n (%)			
0	5 (62.5)	10 (58.8)	15 (60.0)
1	3 (37.5)	7 (41.2)	10 (40.0)
Primary tumor location, n (%)			
Oral cavity	2 (25.0)	9 (52.9)	11 (44.0)
Oropharyngeal	6 (75.0)	8 (47.1)	14 (56.0)
P16 positive	5/6 (83.3)	6/8 (75.0)	11/14 (78.6)
P16 negative	0/6	1/8 (12.5)	1/14 (7.1)
P16 status unknown	1/6 (16.7)	1/8 (12.5)	2/14 (14.3)
PD-L1 positive, n (%)	8 (100)	17 (100)	25 (100)
CPS score, n (%)			
1 to 19	5 (62.5)	10 (58.8)	15 (60.0)
≥ 20	3 (37.5)	7 (41.2)	10 (40.0)
Received prior line of systemic treatment in (neo)adjuvant setting,[a] n (%)	1 (12.5)	1 (5.9)	2 (8.0)

[a]One patient received taxane-containing therapy and platinum therapy; one patient received platinum therapy.

SAFETY AND TOLERABILITY

- Overall, low incidence of high-grade TRAEs (**Table 2**)
- Low incidence of treatment discontinuation due to TRAEs with no grade 5 TRAEs
- No DLTs seen at either dose in the safety run-in cohort

Table 2. Summary of TEAEs[a] and TRAEs[b]

	PDL1V 2Q3W AIBW dosing		
n (%)	1.25 mg/kg (n = 8)	1.5 mg/kg (n = 17)	Total (N = 25)
Any TEAE	8 (100)	15 (88.2)	23 (92.0)
Any TRAE	8 (100)	15 (88.2)	23 (92.0)
Grade ≥ 3 TEAE	3 (37.5)	8 (47.1)	11 (44.0)
Grade ≥ 3 TRAE	2 (25.0)	5 (29.4)	7 (28.0)
Any SAE	3 (37.5)	4 (23.5)	7 (28.0)
Any treatment-related SAE	3 (37.5)	2 (11.8)	5 (20.0)
Discontinued treatment due to TEAE	2 (25.0)	1 (5.9)	3 (12.0)
Discontinued treatment due to TRAE	2 (25.0)	0	2 (8.0)
TEAE leading to death	0	0	0
TRAE leading to death	0	0	0

[a]TEAEs are newly occurring adverse events or adverse events that worsen after the first dose of study treatment through 90 days after the last dose of study treatment.
[b]Related to treatment with either PDL1V or pembrolizumab as assessed by the investigator..

- Preliminary safety events are comparable with individual profile of vedotin-based ADCs and pembrolizumab with no unexpected toxicity signals (**Table 3** and **Table 4**)
- The incidence of treatment-related IMAEs was 24.0% (4.0% grade 3); the IMAEs were pneumonitis, hypothyroidism, colitis, thrombocytopenia, and uveitis; no grade 4 or 5 IMAEs were observed

Table 3. Summary of TRAEs[a] by preferred term (occurring in > 1 patient in total population)

	PDL1V 2Q3W AIBW dosing		
n (%)	1.25 mg/kg (n = 8)	1.5 mg/kg (n = 17)	Total (N = 25)
Any event	8 (100)	15 (88.2)	23 (92.0)
Fatigue	5 (62.5)	8 (47.1)	13 (52.0)
Nausea	5 (62.5)	6 (35.3)	11 (44.0)
Peripheral sensory neuropathy[b]	5 (62.5)	5 (29.4)	10 (40.0)
Diarrhea	4 (50.0)	4 (23.5)	8 (32.0)
Anemia	2 (25.0)	2 (11.8)	4 (16.0)
Pneumonitis[c]	1 (12.5)	3 (17.6)	4 (16.0)
Abdominal pain	1 (12.5)	2 (11.8)	3 (12.0)
Alanine aminotransferase increased	1 (12.5)	1 (5.9)	2 (8.0)
Alopecia	0	2 (11.8)	2 (8.0)
Aspartate aminotransferase increased	1 (12.5)	1 (5.9)	2 (8.0)
Constipation	1 (12.5)	1 (5.9)	2 (8.0)
Decreased appetite	2 (25.0)	0	2 (8.0)
Dyspnea	1 (12.5)	1 (5.9)	2 (8.0)
Headache	0	2 (11.8)	2 (8.0)
Hypothyroidism	1 (12.5)	1 (5.9)	2 (8.0)
Muscle spasms	2 (25.0)	0	2 (8.0)
Oral candidiasis	0	2 (11.8)	2 (8.0)
Pyrexia	1 (12.5)	1 (5.9)	2 (8.0)
White blood cell count decreased	1 (12.5)	1 (5.9)	2 (8.0)

[a]Related to treatment with either PDL1V or pembrolizumab as assessed by the investigator.
[b]All peripheral sensorial neuropathy events were grade 1 and 2; 1 event ended in treatment discontinuation.
[c]All pneumonitis events resolved; one case reinitiated with no reoccurrence after 4 additional cycles; there were no grade 4 or 5 pneumonitis/ILD.

Table 4. Summary of grade ≥ 3 TRAEs[a] by preferred term (occurring in > 1 patient in total population)

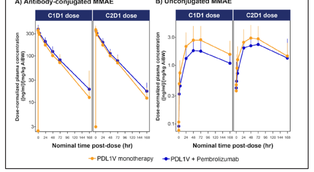
	PDL1V 2Q3W AIBW dosing		
n (%)	1.25 mg/kg (n = 8)	1.5 mg/kg (n = 17)	Total (N = 25)
Any grade ≥ 3 event	2 (25.0)	5 (29.4)	7 (28.0)
Anemia	1 (12.5)	1 (5.9)	2 (8.0)
Diarrhea	2 (25.0)	0	2 (8.0)

[a]Related to treatment with either PDL1V or pembrolizumab as assessed by the investigator.

PK

- Concentrations of PDL1V antibody-conjugated MMAE and unconjugated MMAE following the first dose (Cycle 1 Day 1) and the third dose (Cycle 2 Day 1) with either 1.25 mg/kg AIBW 2Q3W or 1.5 mg/kg AIBW 2Q3W doses are overlapping when PDL1V is administered as a monotherapy or in combination with pembrolizumab (**Figure 3**)

Figure 3. Plasma concentrations post-dose of A) antibody-conjugated MMAE and B) unconjugated MMAE



ANTITUMOR ACTIVITY IN HNSCC

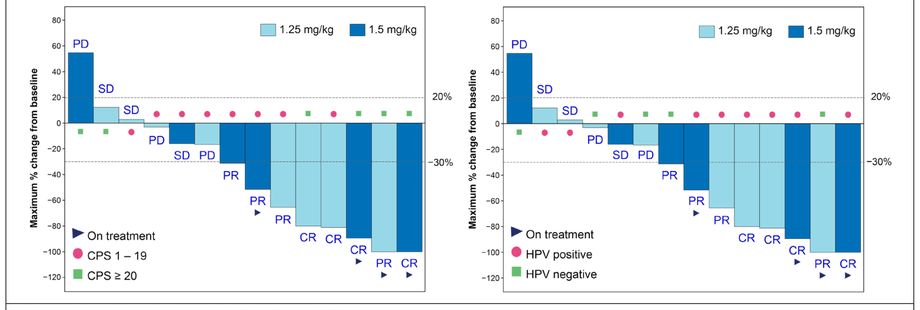
- Efficacy evaluable patients with sufficient follow-up (n = 14) are included; median follow-up was 8.3 months
- At a median PDL1V treatment duration of 3.7 months (median cycles administered = 5.0), investigator-assessed confirmed ORR for 14 patients was 57.1% (**Table 5**)
- Waterfall plots showing the maximum percentage reduction in the sum of diameter of target lesions from baseline are shown in **Figure 4**
- Overall, median PFS [95% CI] at the data cutoff was 5.6 months [1.4–not reached]

Table 5. Confirmed best overall response

	PDL1V 2Q3W AIBW dosing		
PDL1V dose	**1.25 mg/kg (n = 8)**	**1.5 mg/kg (n = 6)**	**Total (n = 14)**
Best overall response,[a] n (%)			
Complete response (CR)	2 (25.0)	2 (33.3)	4 (28.6)
Partial response (PR)	2 (25.0)	2 (33.3)	4 (28.6)
Stable disease (SD)	2 (25.0)	1 (16.7)	3 (21.4)
Progressive disease (PD)	2 (25.0)	1 (16.7)	3 (21.4)
Not evaluable	0	0	0
No assessment	0	0	0
ORR (CR + PR), n (%) [95% CI][b]	4 (50.0) [15.7–84.3]	4 (66.7) [22.3–95.7]	8 (57.1) [28.9–82.3]
DCR (CR + PR + SD), n (%) [95% CI][b]	6 (75.0) [34.9–96.8]	5 (83.3) [35.9–99.6]	11 (78.6) [49.2–95.3]
PD-L1 expression	**CPS 1 to 19 (n = 8)**	**CPS ≥ 20 (n = 6)**	
ORR (CR + PR), n (%) [95% CI][b]	4 (50.0) [15.7–84.3]	4 (66.7) [22.3–95.7]	
DCR (CR + PR + SD), n (%) [95% CI][b]	6 (75.0) [34.9–96.8]	5 (83.3) [35.9–99.6]	
HPV status	**Positive (n = 9)**	**Negative (n = 5)**	
ORR (CR + PR), n (%) [95% CI][b]	6 (66.7) [29.9–92.5]	2 (40.0) [5.3–85.3]	
DCR (CR + PR + SD), n (%) [95% CI][b]	9 (100) [66.4–100]	2 (40.0) [5.3–85.3]	

[a]Investigator assessed per RECIST v1.1. CR or PR were confirmed with repeat scans ≥ 28 days after the initial response.
[b]Two-sided 95% exact confidence interval computed using the Clopper-Pearson method.

Figure 4. Waterfall plots showing the maximum percentage change in the sum of diameter of target lesions from baseline (n = 14)



Each column represents a patient according to investigator-assessed confirmed best overall response per RECIST v1.1.
Patients with a CR may not have 100% reduction in sum of diameter because nodal target lesion(s) could be < 10mm. The line at 20% indicates progressive disease; the line at −30% indicates the threshold for a PR.

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