Abstract 8609

Reduction in circulating tumor DNA in relation to radiographic response and tumor PD-L1 expression in a phase 1 study of fetrastobart vedotin (PDL1V; PF-08046054) in patients with non-small cell lung cancer

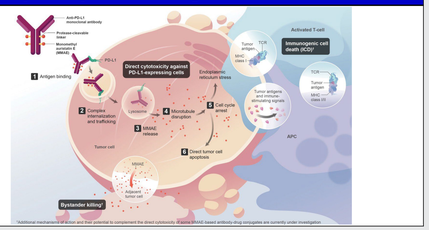
Ramy Saleh,[1] Lisle Nabell,[2] Elisa Fontana,[3] Neeltje Steeghs,[4] Nuria Kotecki,[5] Paula Sàbat,[6] Afshin Dowlati,[7] Andrea Zivi,[8] Sebastian Ochsenreither,[9] Christophe Le Tourneau,[10] Arjun Oberoi,[11] Kaissa Ouali,[12] Anna Spreafico,[13] Maura Gillison,[14] Ye Guo,[15] Jin Yao,[16] Farah Itani,[16] Shivani Gupta,[16] Rong Zhang,[16] Anna Minchom[17]

[1]McGill University Health Centre, Montreal, QC, Canada; [2]University of Alabama at Birmingham, Birmingham, AL; [3]Sarah Cannon Research Institute UK, London, UK; [4]Netherlands Cancer Institute, Amsterdam, the Netherlands; [5]Institut Jules Bordet, Bruxelles, Belgium; [6]Catalan Institute of Oncology (ICO), Barcelona, Spain; [7]Case Comprehensive Cancer Center, Cleveland, OH; [8]Azienda Ospedaliera Universitaria Integrata di Verona/Centro Ricerche Cliniche di Verona, Verona VR, Italy; [9]Charite Universitatsmedizin Berlin, Berlin, Germany; [10]Institut Curie, Paris, France; [11]Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [12]Gustave Roussy, Drug Development Department, Villejuif, France; [13]Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; [14]The University of Texas MD Anderson Cancer Center, Houston, TX; [15]Shanghai East Hospital, Shanghai, China; [16]Pfizer, Bothell, WA; [17]The Royal Marsden Hospital, London, UK

Background

- Fetra-V is an investigational ADC that binds to PD-L1–expressing tumor cells and delivers the cytotoxic agent 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]
- In MMAE-sensitive xenograft models, Fetra-V has shown antitumor activity across a range of PD-L1 expression levels[2]
- While Fetra-V targets the PD-L1 immune checkpoint ligand, nonclinical data suggest that checkpoint inhibition through blockade of PD-1/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
- Results from the phase 1 study (NCT05208762) showed promising antitumor activity and manageable safety in patients with relapsed or refractory NSCLC[6]
- In this exploratory analysis from the phase 1 study, we investigate changes in ctDNA in different subgroups of patients

Figure 1. Fetra-V Drives Antitumor Activity Through Direct Cytotoxicity and Bystander Killing



Methods

- C5851001 (NCT05208762) is a phase 1 study of Fetra-V monotherapy in patients with advanced solid tumors and in combination with pembrolizumab in patients with metastatic or unresectable head and neck squamous cell carcinoma or NSCLC
- Patients with NSCLC treated with Fetra-V monotherapy must have had prior exposure to platinum and anti–PD-(L)1 agents, targeted therapies for tumors with AGAs, and measurable disease per RECIST 1.1
- The primary objectives of this study were to evaluate the safety and tolerability of Fetra-V; a secondary objective was to assess antitumor activity
- Efficacy analyses included patients with relapsed or refractory NSCLC (phase 3 population) who received Fetra-V monotherapy at the RP3D of 1.5 mg/kg on days 1 and 8 every 21 days using adjusted ideal body weight
- Safety data were pooled across all patients treated in the study at the RP3D
- PD-L1 expression status by TPS was reported by local sites
- Paired baseline (T0) and on-treatment (T1; cycle 2, day 15 to cycle 3, day 1) ctDNA samples were used for ctDNA analyses using a methylation-based tissue-free assay (Guardant Infinity)
- Circulating tumor fraction was quantified by methylation score
- Changes in ctDNA from T0 to T1 were compared between subgroups using the Wilcoxon test

Results

- As of November 22, 2025, a total of 55 patients with relapsed or refractory NSCLC received Fetra-V at the RP3D
- In the total population, the median age was 63 years; 29.1% had squamous histology, 67.3% had TPS ≥1%, and 70.9% had an ECOG performance status of 1 (**Table 1**)
- The median number of prior lines of therapy was 2.0 (range, 1-8)
- The investigator-assessed confirmed ORR was 0% for patients with TPS <1% and 32.4% for patients with TPS ≥1% NSCLC (**Table 2**)
- Among patients with TPS ≥1% NSCLC, confirmed ORR was 33.3% (95% CI, 7.5-70.1) in those 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 AGAs
- Among all patients and all tumor types treated in the phase 1 trial at the RP3D (N=138), any-grade TEAEs occurred in 98.6% of patients; grade ≥3 TEAEs occurred in 57.2%
- The most common TEAEs were fatigue (50.0%), peripheral neuropathy (43.5%), and nausea (33.3%) (**Figure 2**)
- Median follow-up was 15.9 months (95% CI, 11.5-23.1) in patients with TPS ≥1% NSCLC
- Median duration of response was 7.2 months (95% CI, 4.4-8.0) in patients with TPS ≥1% NSCLC

Table 1. Baseline Demographics and Clinical Characteristics

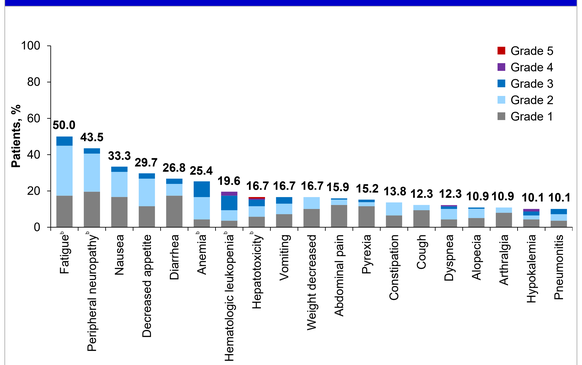
		TPS ≥1%		
	TPS <1% (n=18)	TPS 1%-49% (n=19)	TPS ≥50% (n=18)	Total (n=37)
Age, median (range), years	65 (39-84)	61 (45-74)	64 (44-79)	63 (44-79)
Sex, n (%)				
Female	11 (61.1)	6 (31.6)	9 (50.0)	15 (40.5)
Histology/subtype, n (%)				
Non-squamous	11 (61.1)	15 (78.9)	13 (72.2)	28 (75.7)
Squamous	7 (38.9)	4 (21.1)	5 (27.8)	9 (24.3)
Tumor spread, n (%)				
Metastatic	16 (88.9)	18 (94.7)	17 (94.4)	35 (94.6)
Locally advanced	2 (11.1)	1 (5.3)	1 (5.6)	2 (5.4)
Patients with any AGA, n (%)	7 (38.9)	6 (31.6)	5 (27.8)	11 (29.7)
KRAS	5 (27.8)	3 (15.8)	2 (11.1)	5 (13.5)
BRAF V600E	3 (16.7)	0	0	0
EGFR	1 (5.6)	2 (10.5)	2 (11.1)	4 (10.8)
MET	0	2 (10.5)	1 (5.6)	3 (8.1)
Median prior lines of therapy in metastatic setting (range)	2 (1-3)	2 (1-7)	2 (1-5)	2 (1-7)
Prior therapies in any setting, n (%)				
Platinum-based chemotherapy	18 (100)	18 (94.7)	17 (94.4)	35 (94.6)
PD-1/PD-L1 inhibitor	16 (88.9)	18 (94.7)	18 (100)	36 (97.3)
Taxane-containing chemotherapy	14 (77.8)	11 (57.9)	11 (61.1)	22 (59.5)
AGA targeted therapies	1 (5.6)	4 (21.1)	4 (22.2)	8 (21.6)
ECOG performance status, n (%)				
0	5 (27.8)	6 (31.6)	5 (27.8)	11 (29.7)
1	13 (72.2)	13 (68.4)	13 (72.2)	26 (70.3)

Table 2. Confirmed Best Overall Response and Duration

		TPS ≥1%		
	TPS <1% (n=18)	TPS 1%-49% (n=19)	TPS ≥50% (n=18)	Total (n=37)
Confirmed best overall response, n (%)[a]				
Complete response	0	1 (5.3)	0	1 (2.7)
Partial response	0	4 (21.1)	7 (38.9)	11 (29.7)
Stable disease	12 (66.7)	8 (42.1)	7 (38.9)	15 (40.5)
Progressive disease	5 (27.8)	4 (21.1)	3 (16.7)	7 (18.9)
Not evaluable[b]/no assessment	1 (5.6)	2 (10.6)	1 (5.6)	3 (8.1)
Objective response rate (CR + PR), n (%)	**0**	**5 (26.3)**	**7 (38.9)**	**12 (32.4)**
95% CI[c]	(0.0-18.5)	(9.1-51.2)	(17.3-64.3)	(18.0-49.8)
Disease control rate (CR + PR + SD), n (%)	12 (66.7)	13 (68.4)	14 (77.8)	27 (73.0)
95% CI[c]	(41.0-86.7)	(43.4-87.4)	(52.4-93.6)	(55.9-86.2)

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

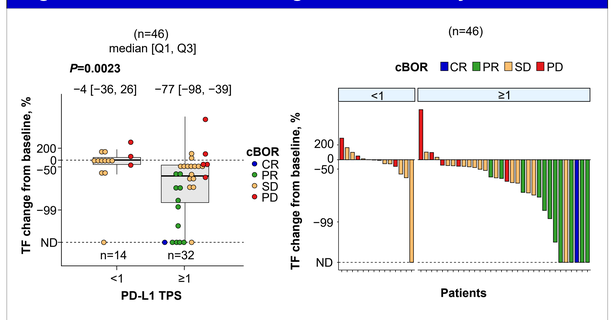
Figure 2. TEAEs by Preferred Term and Maximum Severity in >10% of Patients[a]



[a]TEAEs reported across all patients at the RP3D.
[b]Composite of related terms: fatigue [fatigue, asthenia, malaise]; peripheral neuropathy [peripheral sensory neuropathy, muscular weakness, paresthesia, peripheral motor neuropathy, neurotoxicity, burning sensation, dysesthesia, neuralgia, peripheral sensorimotor neuropathy]; hematologic leukopenia [neutropenia, neutrophil count decreased, lymphocyte count decreased, lymphopenia, leukopenia, white blood cell count decreased, febrile neutropenia]; hepatotoxicity [alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, hypertransaminasemia, blood bilirubin increased, hepatic steatosis, hepatitis, bilirubin conjugated increased, hepatic cytolysis; hepatic failure; hyperbilirubinaemia].

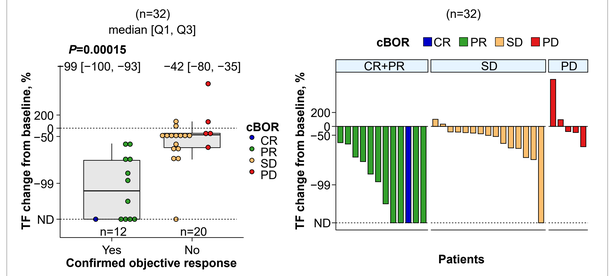
- Of the 55 patients, paired T0 and T1 samples were available for 47 patients; among these, ctDNA analysis showed that 46 (98%) had detectable ctDNA at baseline
- The median ctDNA reduction was greater in patients with TPS ≥1% NSCLC than those with TPS <1% NSCLC (−77% vs −4%; *P*=0.0023) (**Figure 3**)
- Among patients with TPS ≥1% NSCLC, the median ctDNA reduction between T0 and T1 was greater in patients with radiographic response of complete or partial responses than nonresponders (−99% vs −42%; *P*=0.00015) (**Figure 4**)
- Among patients with TPS ≥1% NSCLC, there was no significant difference in median ctDNA reduction between non-squamous and squamous histology (–73% vs –87%; *P*=0.48) (**Figure 5**)

Figure 3. Tumor Fraction Change from Baseline by TPS Status



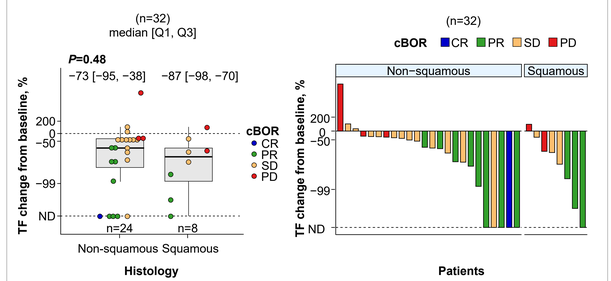
Y-axis shows log-transformed fold change of TF at T1 from T0; labels indicate percent change (100 × (fold change-1)). A small constant was added before log transformation.

Figure 4. Tumor Fraction Change from Baseline by Response Status in TPS ≥1% NSCLC



Y-axis shows log-transformed fold change of TF at T1 from T0; labels indicate percent change (100 × (fold change-1)). A small constant was added before log transformation.

Figure 5. Tumor Fraction Change from Baseline by Histology in TPS ≥1% NSCLC



Y-axis shows log-transformed fold change of TF at T1 from T0; labels indicate percent change (100 × (fold change-1)). A small constant was added before log transformation.

Conclusions

- Fetrastobart vedotin (Fetra-V) or PDL1V/PF-08046054 monotherapy at 1.5 mg/kg on days 1 and 8 every 21 days showed promising antitumor activity (ORR of 32.4%), with a manageable safety profile in patients with relapsed or refractory TPS ≥1% NSCLC
- Most patients had ctDNA reduction with Fetra-V treatment, with greater ctDNA reduction in patients with TPS ≥1% NSCLC
- Among patients with TPS ≥1% NSCLC:
  - ctDNA reduction was greater in patients with complete or partial responses than nonresponders
  - ctDNA reduction was observed in patients irrespective of tumor histology
- These results support continued use of ctDNA for response monitoring and potential early prediction of clinical benefit
- Results from this analysis support evaluation of Fetra-V in the ongoing phase 3 trial, PADL1NK-005 (NCT07144280), in patients with previously treated PD-L1–positive (TPS ≥1%) NSCLC irrespective of tumor histology

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Abbreviations: ADC, antibody-drug conjugate; AGA, actionable genomic alteration; APC, antigen-presenting cell; cBOR, confirmed best overall response; ctDNA, circulating tumor DNA; CI, confidence interval; CR, complete response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; Fetra-V, Fetrastobart vedotin; KRAS, Kirsten rat sarcoma viral oncogene homolog B; MET, mesenchymal-epithelial transition factor; MHC, major histocompatibility complex; MMAE, monomethyl auristatin E; N.D., not detected; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PD-1; programmed death protein 1; PD-L1, programmed death ligand 1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; RP3D; recommended phase 3 dose; SD, stable disease; T0, baseline; T1, after 2 cycles of treatment; TCR, T-cell receptor; TEAE, treatment-emergent adverse event; TF, tumor fraction; TPS, tumor proportion score; 2L, second line.

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Correspondence: Ramy Saleh; ramy.saleh.med@ssss.gouv.qc.ca

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