A multicenter phase 2 trial of lifileucel plus pembrolizumab in patients with checkpoint inhibitor-naive metastatic NSCLC: updated results

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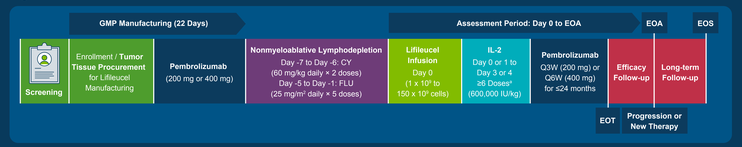
Background

- Resistance to frontline immune checkpoint inhibitor (ICI) ± chemotherapy presents a challenge in the treatment of metastatic non-small cell lung cancer (NSCLC)[1]
- Tumor-infiltrating lymphocyte (TIL) cell therapy with lifileucel alone demonstrated an objective response rate (ORR) of 21% in patients with refractory metastatic NSCLC previously treated with an ICI[2]
- ORR for pembrolizumab monotherapy in NSCLC is dependent on programmed cell death-1 ligand (PD-L1) expression, with ORR of ~10% reported for PD-L1 tumor proportion score (TPS) <1% and up to 45% for PD-L1 TPS ≥50%[3]
- Integration of TIL cell therapy in frontline regimens may improve long-term outcomes in NSCLC
- The PD-L1–negative, endothelial growth factor receptor gene wild-type (*EGFR*-wt) subgroup in particular has a high unmet need, as ICI does not add benefit and targeted therapy is not available
- We report updated efficacy and safety results for lifileucel combined with pembrolizumab in patients with ICI-naive metastatic NSCLC

Methods

- IOV-COM-202 (NCT03645928) is a global, phase 2, multicenter, multicohort, open-label study of lifileucel in patients with solid tumors
- Cohort 3A enrolled patients with ICI-naive advanced or metastatic NSCLC with disease progression
  - Patients were required to have ≥1 resectable lesion for lifileucel manufacturing and ≥1 evaluable lesion by Response Evaluation Criteria in Solid Tumors (RECIST v1.1)
  - Patients were allowed to have received up to 3–4 prior lines of therapy excluding ICI
- Patients received nonmyeloablative lymphodepletion (cyclophosphamide and fludarabine), followed by a single lifileucel infusion, and ≤6 doses of high-dose interleukin-2 (IL-2) (**Figure 1**)
- Pembrolizumab was administered once before lymphodepletion and continued for up to 2 years or disease progression or toxicity after lifileucel infusion
- Primary endpoints were ORR by RECIST v1.1 and safety including the incidence of grade ≥3 treatment-emergent adverse events (TEAEs)

Figure 1. Treatment Schema



[a]Every 8–12 hours (starting 3–24 hours after completion of lifileucel infusion).

Results

- At the data cutoff date of August 12, 2024, 22 patients had received lifileucel infusion
- Patients had a median age of 57 years (range, 30–69) and had received a median of 1 (range, 0–4) line of prior systemic therapy (**Table 1**)
- Fourteen patients had *EGFR*-wt disease, of which 11 had a PD-L1 TPS of <1%
- The most common sites of tumor resection were lung (45.5%) and lymph node (22.7%)
- The median dose of lifileucel was 22.9 × 10^9 cells (range, 1 × 10^9 – 57.6 × 10^9)

Table 1. Demographic and Baseline Characteristics

Characteristic	*EGFR*-wt (n=14)	*EGFR* Mutated Post-TKI (n=8)	All (N=22)
Median age (range), years	57.0 (30–68)	55.5 (35–69)	57.0 (30–69)
Female, n (%)	6 (42.9)	6 (75.0)	12 (54.5)
Tobacco use, n (%)			
Former use	13 (92.9)	1 (12.5)	14 (63.6)
Never used	1 (7.1)	7 (87.5)	8 (36.4)
ECOG PS, n (%)			
0	6 (42.9)	6 (75.0)	12 (54.5)
1	8 (57.1)	2 (25.0)	10 (45.5)
Histologic cell type, n (%)			
Nonsquamous cell carcinoma	13 (92.9)	8 (100)	21 (95.5)
Squamous cell carcinoma	1 (7.1)	0	1 (4.5)
Resected tumor site, n (%)			
Bone	0	1 (12.5)	1 (4.5)
Liver	1 (7.1)	0	1 (4.5)
Lung	7 (50.0)	3 (37.5)	10 (45.5)
Lymph node	3 (21.4)	2 (25.0)	5 (22.7)
Other	2 (14.3)	2 (25.0)	4 (18.2)
Skin/Subcutaneous	1 (7.1)	0	1 (4.5)
Median target lesion SOD (range), mm	56.5 (13–218)	51.5 (16–103)	56.5 (13–218)
Median number of baseline target and nontarget lesions (range)	4 (2–10)	5 (2–10)	4 (2–10)
Number of baseline target and nontarget lesions, n (%)			
<3	5 (35.7)	3 (37.5)	8 (36.4)
≥3	9 (64.3)	5 (62.5)	14 (63.6)
PD-L1 tumor proportion score, n (%)			
<1	11 (78.6)	6 (75)	17 (77.3)
1–49	0	2 (25)	2 (9.1)
≥50	3 (21.4)	0	3 (13.6)
Median number of prior lines of systemic therapy (range)	1 (0–3)	2 (1–4)	1 (0–4)
Number of prior lines of systemic therapy, n (%)			
0	6 (42.9)	0	6 (27.3)
1	7 (50.0)	3 (37.5)	10 (45.5)
≥2	1 (7.1)	5 (62.5)	6 (27.3)
Prior lines of systemic therapy by agent, n (%)			
Chemotherapy	8 (57.1)	3 (37.5)	11 (50.0)
Monoclonal antibody	0	3 (37.5)	3 (13.6)
Targeted therapy	0	8 (100)	8 (36.4)

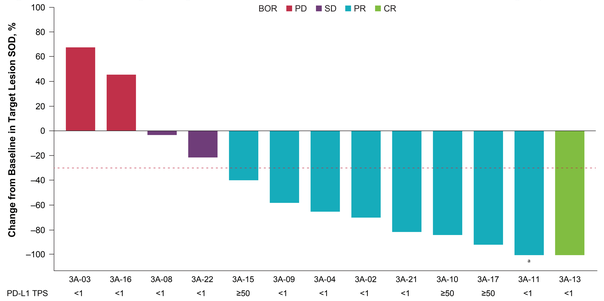
- At a median follow-up of 25.6 months, the ORR in the *EGFR*-wt subgroup was 64.3% (95% CI: 35.1–87.2) (**Table 2**)
  - Median duration of response was not reached in the EGFR-wt subgroup (95% CI: 3.7 months–NR)

Table 2. Response Outcomes by *EGFR* Mutation Status

Response Parameter	*EGFR*-wt (n=14)	*EGFR* Mutated Post-TKI (n=8)
ORR, n (%)	9 (64.3)	1 (12.5)
DCR, n (%)	11 (78.6)	7 (87.5)
BOR, n (%)		
CR	1 (7.1)	1 (12.5)
PR	8 (57.1)	0
SD	2 (14.3)	6 (75.0)
PD	2 (14.3)	0
NE	1 (7.1)	1 (12.5)
Median DOR (95% CI), months	NR (3.7, NR)	13.7 (NR–NR)

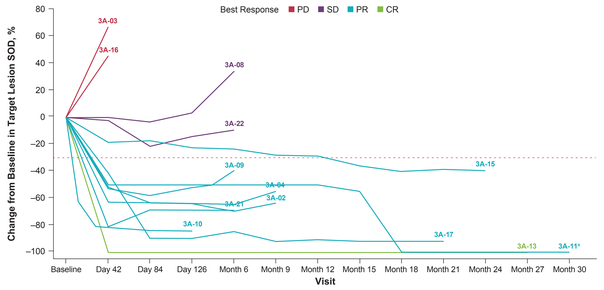
- One of the 8 patients with *EGFR* mutated post-TKI disease had a complete response
- Six responses occurred in 11 patients (54.5%) with *EGFR*-wt PD-L1–negative disease (**Figures 2** and **3**)

Figure 2. Best Percentage Change from Baseline in Target Lesion SOD in the *EGFR*-wt Subgroup



[a]A response of PR for this patient was based on a target lesion reduction of 100% with the persistence of nontarget lesions.
One patient in *EGFR*-wt PD-L1–negative group who did not have post-dose tumor response assessment was not included in the plot.

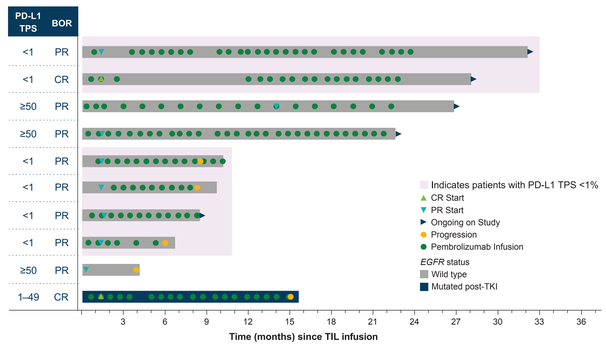
Figure 3. Percentage Change from Baseline in Target Lesion SOD Over Time in the *EGFR*-wt Subgroup



[a]A response of PR for this patient was based on a target lesion reduction of 100% with the persistence of nontarget lesions.

- Responses were durable, and 5 patients with *EGFR*-wt disease had ongoing responses at the last follow-up visit, which included 3 patients with PD-L1–negative disease (**Figure 4**)
  - 4 of these patients remained in response beyond 20 months from the start of TIL infusion
    - 2 of these responders had no prior treatment; 2 previously received chemotherapy
- The one complete responder with *EGFR* mutated post-TKI disease had disease recurrence after 15 months

Figure 4. Time on Study for Responders



- TEAEs were consistent with underlying disease and known profiles of pembrolizumab, nonmyeloablative lymphodepletion, and IL-2
- The most common grade ≥3 nonhematologic TEAEs were hypoxia (54.5%), febrile neutropenia (45.5%), and hypophosphatemia (31.8%) (**Table 3**)

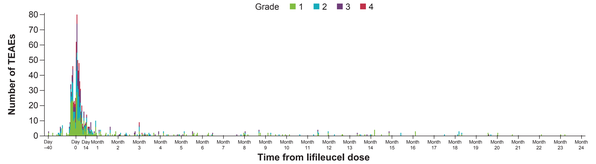
Table 3. Nonhematologic TEAEs in ≥30% of Patients[a]

TEAEs by Preferred Term, n (%)	Any Grade	Grade ≥3
Chills	17 (77.3)	0
Pyrexia	17 (77.3)	1 (4.5)
Hypoxia	17 (77.3)	12 (54.5)
Fatigue	14 (63.6)	3 (13.6)
Nausea	14 (63.6)	1 (4.5)
Dyspnea	13 (59.1)	5 (22.7)
Diarrhea	11 (50.0)	0
Hypotension	11 (50.0)	3 (13.6)
Sinus tachycardia	11 (50.0)	0
Febrile neutropenia	10 (45.5)	10 (45.5)
Arthralgia	9 (40.9)	2 (9.1)
Constipation	9 (40.9)	0
Decreased appetite	9 (40.9)	1 (4.5)
Hypoalbuminemia	9 (40.9)	1 (4.5)
Hyponatremia	9 (40.9)	3 (13.6)
Cough	9 (40.9)	0
Hypertension	9 (40.9)	3 (13.6)
Vomiting	8 (36.4)	0
Hypophosphatemia	8 (36.4)	7 (31.8)
Rash maculopapular	8 (36.4)	0
Musculoskeletal chest pain	7 (31.8)	0
Headache	7 (31.8)	0
Peripheral edema	7 (31.8)	1 (4.5)

[a]TEAEs refer to AEs regardless of causality that occur from the first dose of pembrolizumab or lifileucel infusion (whichever is earlier) and ≤30 days after the last dose of pembrolizumab or lifileucel (whichever is later) or up to start of new anticancer therapy.

- TEAEs peaked during the first 2 weeks after lifileucel infusion and rapidly declined thereafter

Figure 5. Incidence of TEAEs Over Time[a]



[a]TEAEs refer to AEs regardless of causality that occur from the first dose of pembrolizumab or lifileucel infusion (whichever is earlier) and ≤30 days after the last dose of pembrolizumab or lifileucel (whichever is later) or up to start of new anticancer therapy. All occurrences are counted if a patient experiences the same TEAE, but the event is counted with the highest grade.

- All patients experienced grade 3/4 hematologic laboratory abnormalities (**Table 4**)
  - In the majority of patients, hematologic abnormalities resolved to grade ≤2 within the first 30 days after lifileucel treatment

Table 4. Grade 3/4 Hematologic Laboratory Abnormalities

Preferred Term	Events, n (%)	Events Resolved to Grade ≤2 by 30 Days After Lifileucel Infusion, n (%)
Neutropenia	22 (100)	21 (96)
Leukopenia	22 (100)	21 (96)
Lymphopenia	22 (100)	20 (91)
Thrombocytopenia	20 (91)	19 (95)
Anemia	15 (68)	15 (100)

Conclusions

- **In patients with ICI-naive metastatic *EGFR*-wt NSCLC, lifileucel plus pembrolizumab demonstrated robust antitumor activity and durable responses, including in patients with difficult to treat *EGFR*-wt PD-L1–negative tumors**
  - **ORR was 64.3% and responses included a CR and a deep PR; ORR was 54.5% in patients with *EGFR*-wt PD-L1–negative disease**
- **No new safety signals beyond what was expected with either lifileucel or pembrolizumab were observed**
- **These results support further investigation of lifileucel as part of frontline therapy in metastatic *EGFR*-wt NSCLC**

References
1. Zhou S, *et al. Front Immunol.* 2023;14:1129465. 2. Schoenfeld AJ, *et al. Cancer Discov.* 2024;14:1389–402. 3. Garon B, *et al. N Engl J Med.* 2015;37:2018–28.

Abbreviations
AE, adverse event; BOR, best overall response; CI, confidence interval; CR, complete response; CY, cyclophosphamide; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EGFR, endothelial growth factor receptor; EOA, end of assessment; EOS, end of study; EOT, end of treatment; FLU, fludarabine; GMP, Good Manufacturing Practice; ICI, immune checkpoint inhibitor; IL-2, interleukin-2; NE, not evaluable; NR, not reached; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PD-L1, programmed cell death-1 ligand; PR, partial response; PS, performance status; Q3W, every 3 weeks; Q6W, every 6 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SOD, sum of diameters; TEAE, treatment-emergent adverse event; TIL, tumor-infiltrating lymphocytes; TKI, tyrosine kinase inhibitor; TPS, tumor proportion score; wt, wild type.

Disclosures
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