Cellular Therapy for Solid Tumors

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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 ICI ± chemotherapy presents a challenge in the treatment of metastatic NSCLC[1]
- TIL cell therapy with lifileucel alone demonstrated an ORR of 21% in patients with refractory metastatic NSCLC previously treated with an ICI[2]
- ORR for pembrolizumab monotherapy in NSCLC is dependent on PD-L1 expression, with ORR of ~10% reported for PD-L1 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, *EGFR*-wt subgroup in particular has a high unmet need, as ICI does not add benefit and targeted therapy is not available[1,2]
- We report updated efficacy and safety results for lifileucel combined with pembrolizumab in patients with ICI-naive metastatic NSCLC

EGFR-wt, endothelial growth factor receptor gene wild-type; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD-L1, programmed death-ligand 1;- TIL, tumor-infiltrating lymphocyte; TPS, tumor proportion score.

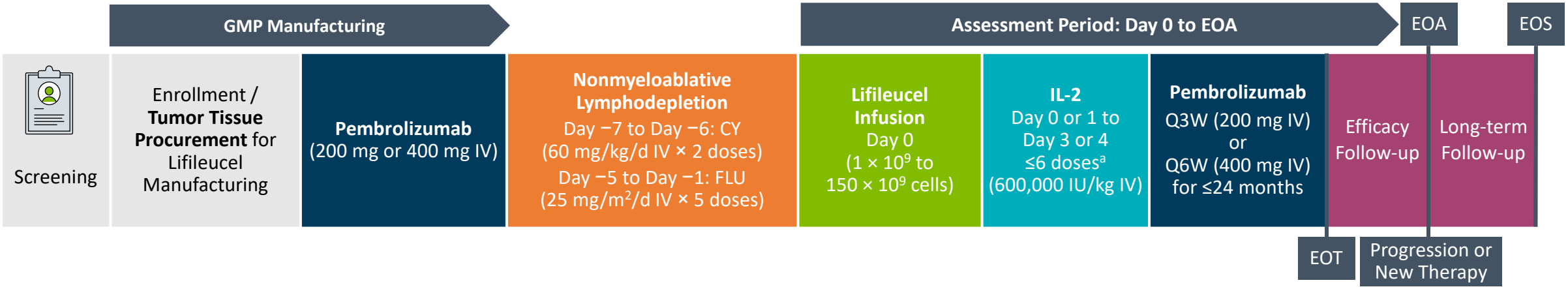
1. Zhou S, et al. *Front Immunol*. 2023;14:1129465. 2. Schoenfeld AJ, et al. *Cancer Discov*. 2024;14:1389–402. 3. Garon B, et al. *N Engl J Med*. 2015;37:2018–28.

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 RECIST v1.1
  - Patients were allowed to have received up to 3–4 prior lines[a] of therapy excluding ICI
- Patients received nonmyeloablative lymphodepletion (cyclophosphamide and fludarabine), followed by a single lifileucel infusion, and ≤6 doses of high-dose IL-2
- 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 TEAEs
- Single-cell RNA and TCR sequencing were performed on TIL at baseline (day 0), day 11, and day 22 of the manufacturing process

[a]Patients could receive up to 4 lines if 2 or more of the lines were TKI therapy for those with tumors that harbored actionable mutations. ICI, immune checkpoint inhibitor; IL-2, interleukin-2; ORR, objective response rate; RECIST v1.1; Response Evaluation Criteria in Solid Tumors version 1.1; TCR, T-cell receptor; TEAE, treatment-emergent adverse event; TIL, tumor-infiltrating lymphocytes; TKI, tyrosine kinase inhibitor.

Study Treatment Schema



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

CY, cyclophosphamide; EOA, end of assessment; EOS, end of study; EOT, end of treatment; FLU, fludarabine; GMP, Good Manufacturing Practices; IL-2, interleukin-2; IU, international units; IV, intravenous; Q3W, every three weeks; Q6W, every six weeks.

Demographic and Baseline Characteristics

Characteristic		*EGFR* wt (n=14)	*EGFR* Mutated Post-TKI (n=8)	All (N=22)[a]
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)
Former tobacco use,[b] n (%)		13 (92.9)	1 (12.5)	14 (63.6)
ECOG PS, n (%)	0, 1	6 (42.9), 8 (57.1)	6 (75.0), 2 (25.0)	12 (54.5), 10 (45.5)
Nonsquamous cell carcinoma, n (%)		13 (92.9)	8 (100)	21 (95.5)
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)
Skin/Subcutaneous		1 (7.1)	0	1 (4.5)
Other		2 (14.3)	2 (25.0)	4 (18.2)
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)
≥3 baseline target and nontarget lesions, n (%)		9 (64.3)	5 (62.5)	14 (63.6)
PD-L1 tumor proportion score, n (%)	<1, 1–49, ≥50	11 (78.6), 0, 3 (21.4)	6 (75), 2 (25), 0	17 (77.3), 2 (9.1), 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, 1, ≥2	6 (42.9), 7 (50.0), 1 (7.1)	0, 3 (37.5), 5 (62.5)	6 (27.3), 10 (45.5), 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)

- 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
- 14 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 to 57.6×10^9)

[a]At the data cutoff date of August 12, 2024, 22 patients had received lifileucel infusion. [b]Other category is "Never used" tobacco.
ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*-wt, endothelial growth factor receptor gene wild-type; PD-L1, programmed death-ligand 1; SOD, sum of diameters; TKI, tyrosine kinase inhibitor; TPS, tumor proportion score.

The Majority of Patients in the *EGFR*-wt Group Responded to Lifileucel Treatment

Response Outcomes by *EGFR* Mutation Status

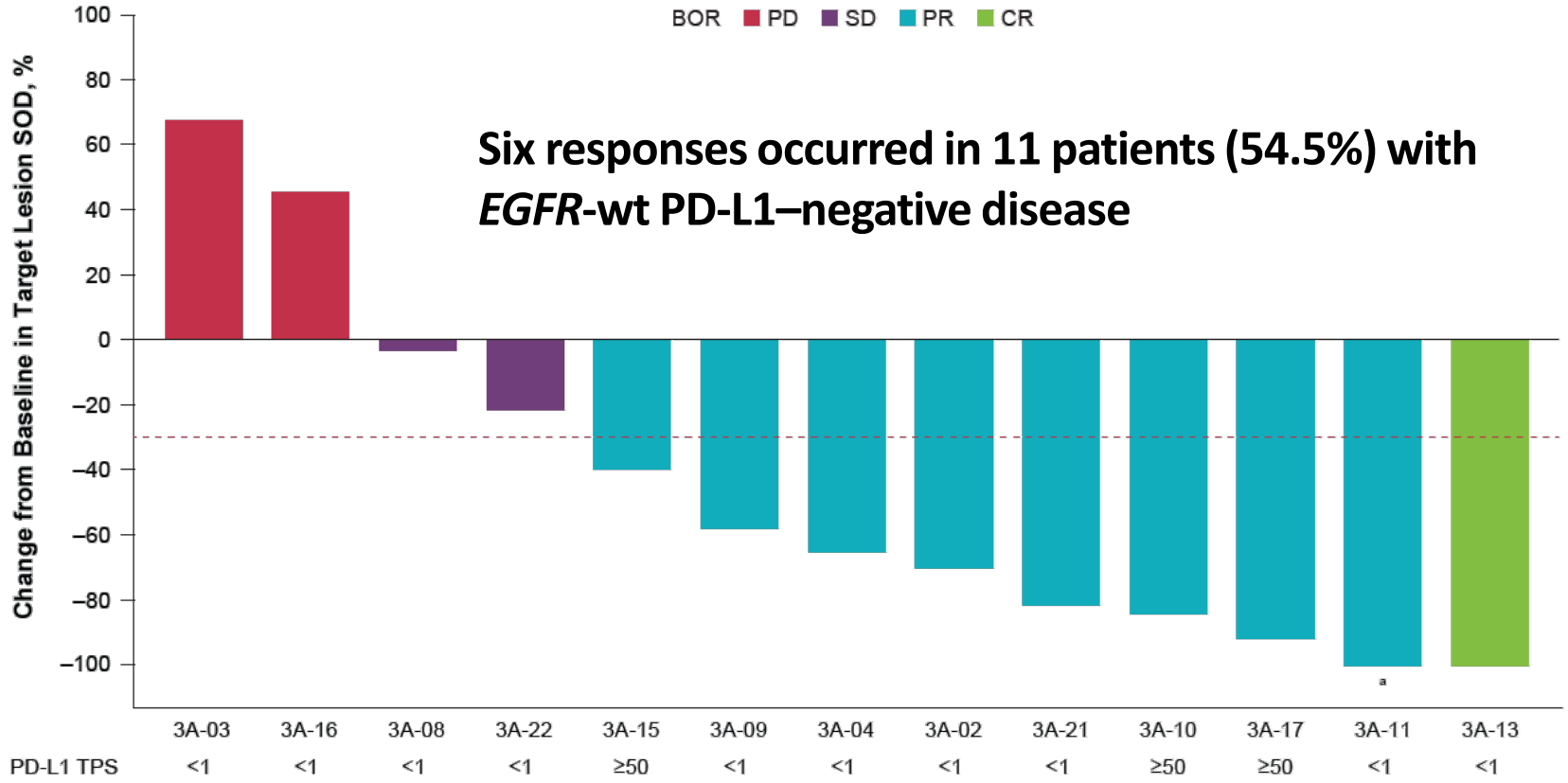
Response Parameter	*EGFR* wt (n=14)	*EGFR* Mutated Post-TKI (n=8)
ORR, n (%)	9 (64.3)	1 (12.5)
DCR, n (%)	11 (78.6)	7 (87.5)
BOR, n (%)		
CR	1 (7.1)	1 (12.5)
PR	8 (57.1)	0
SD	2 (14.3)	6 (75.0)
PD	2 (14.3)	0
NE	1 (7.1)	1 (12.5)
Median DOR (95% CI), months	NR (3.7, NR)	13.7 (NR–NR)

- 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)
  - Median duration of response was not reached in the *EGFR*-wt subgroup (95% CI: 3.7 months–NR)
- One of the 8 patients with *EGFR*-mutated post-TKI disease had a complete response

BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; *EGFR*, endothelial growth factor receptor gene; *EGFR*-wt, endothelial growth factor receptor gene wild-type; NE, not evaluable; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.

Most Patients in the *EGFR*-wt Subgroup Had Target Lesion Regression

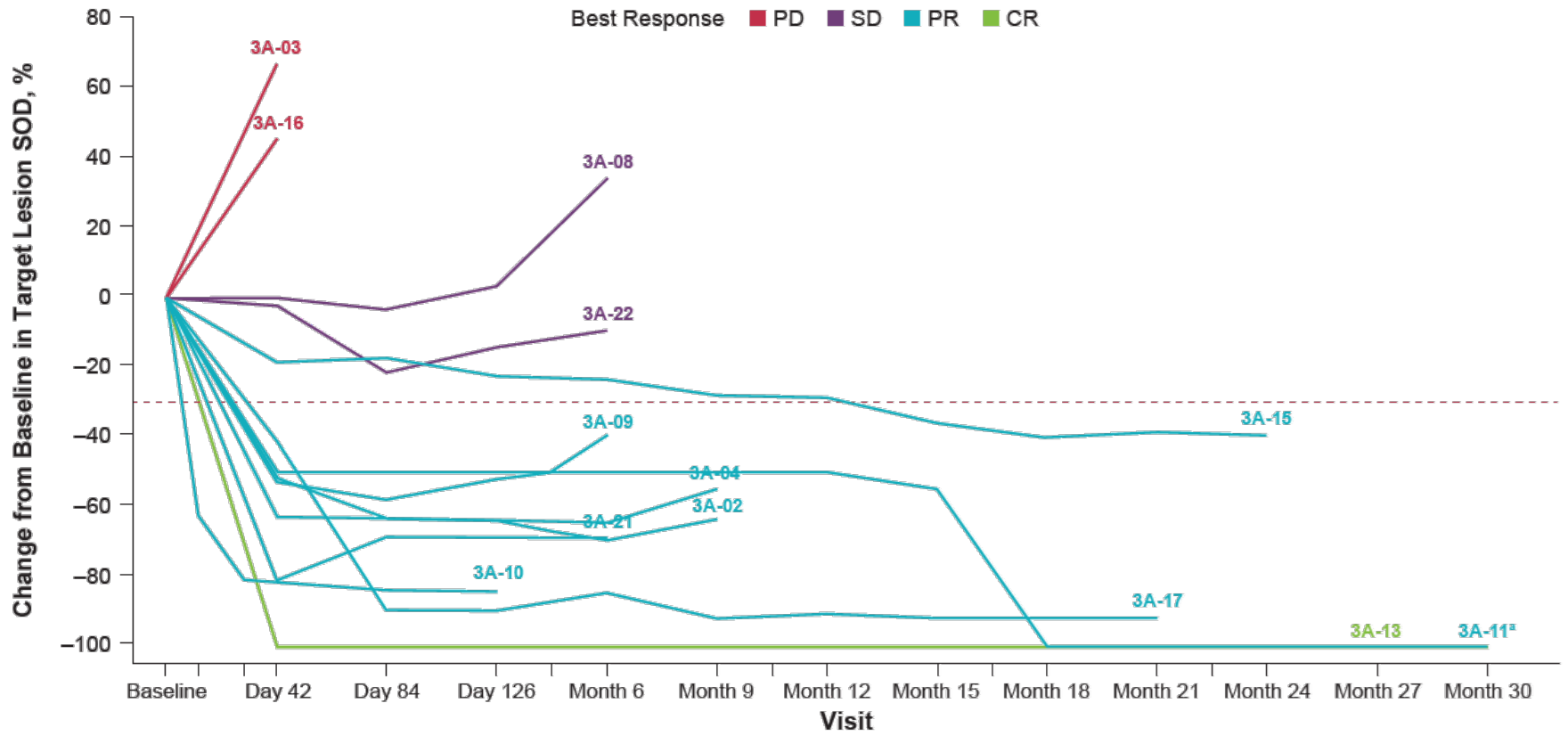
Best Percentage Change from Baseline in Target Lesion SOD in the *EGFR*-wt Subgroup



One patient in EGFR-wt PD-L1–negative group who did not have post-dose tumor response assessment was not included in the plot. [a]A response of PR for this patient was based on a target lesion reduction of 100% with the persistence of nontarget lesions. BOR, best overall response; CR, complete response; *EGFR*-wt, endothelial growth factor receptor gene wild-type; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease; SOD, sum of diameters; TPS, tumor proportion score.

Tumor Responses in the *EGFR*-wt Subgroup Were Durable

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

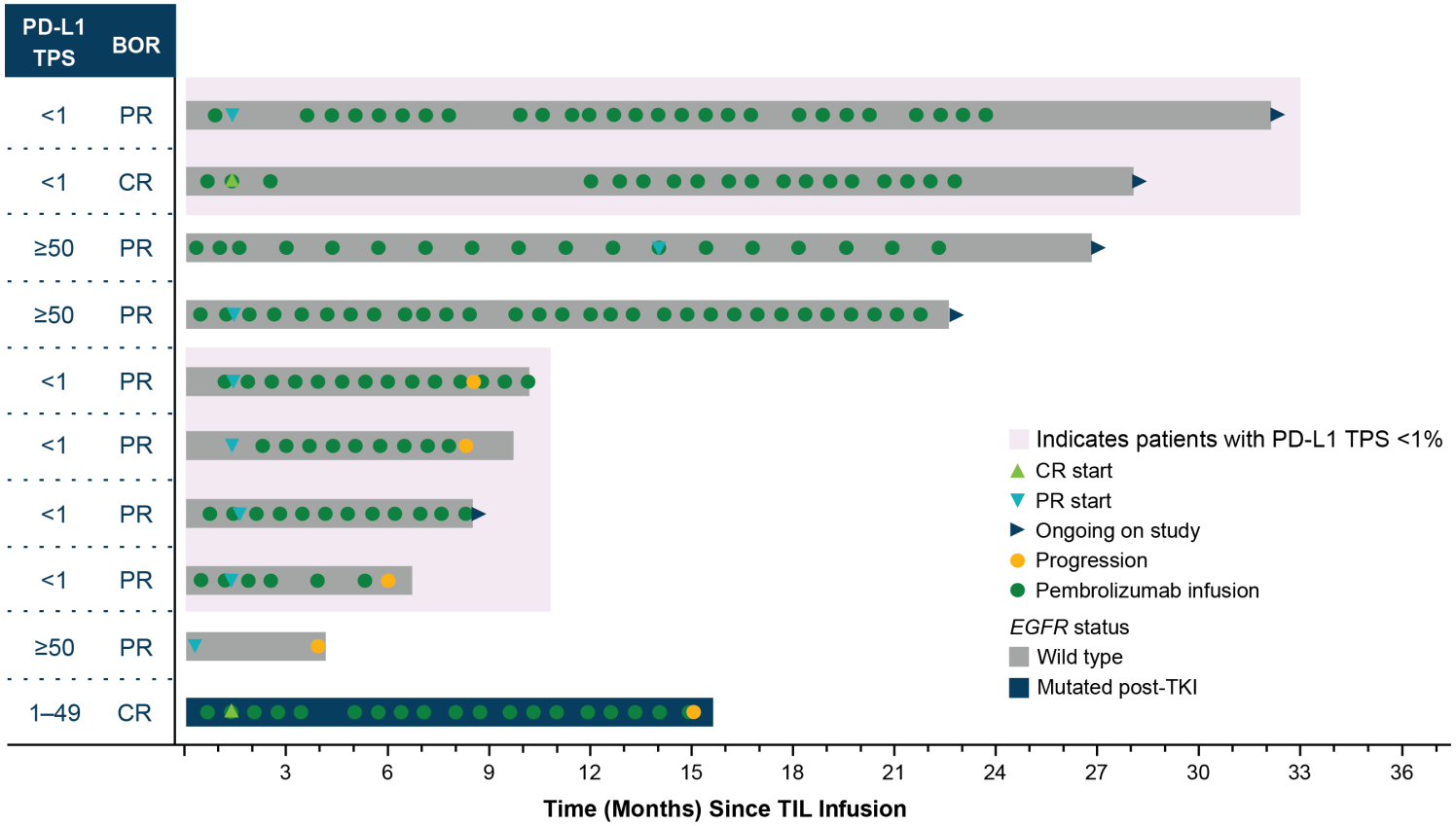


[a]A response of PR for this patient was based on a target lesion reduction of 100% with the persistence of nontarget lesions.

CR, complete response; *EGFR*-wt, endothelial growth factor receptor gene wild-type; PD, progressive disease; PR, partial response; SD, stable disease; SOD, sum of diameters.

Responses in PD-L1–Negative Tumors Were Durable

Time on Study for Responders



- 5 patients with *EGFR*-wt disease had ongoing responses at the last follow-up visit, which included 3 patients with PD-L1–negative disease
  - 4 of these patients maintained response beyond 20 months from the start of TIL infusion
    - 2 of these responders had no prior treatment; 2 previously received chemotherapy
    - In the 3 patients who completed 2 years of pembrolizumab treatment, responses have continued
- The one complete responder with *EGFR*-mutated post-TKI disease had disease recurrence after 15 months

Pink boxes denote patients with PD-L1–negative disease. BOR, best overall response; CR, complete response; *EGFR*, endothelial growth factor receptor gene; *EGFR*-wt, endothelial growth factor receptor gene wild-type; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; SOD, sum of diameters; TIL, tumor-infiltrating lymphocyte; TKI, tyrosine kinase inhibitor; TPS, tumor proportion score.

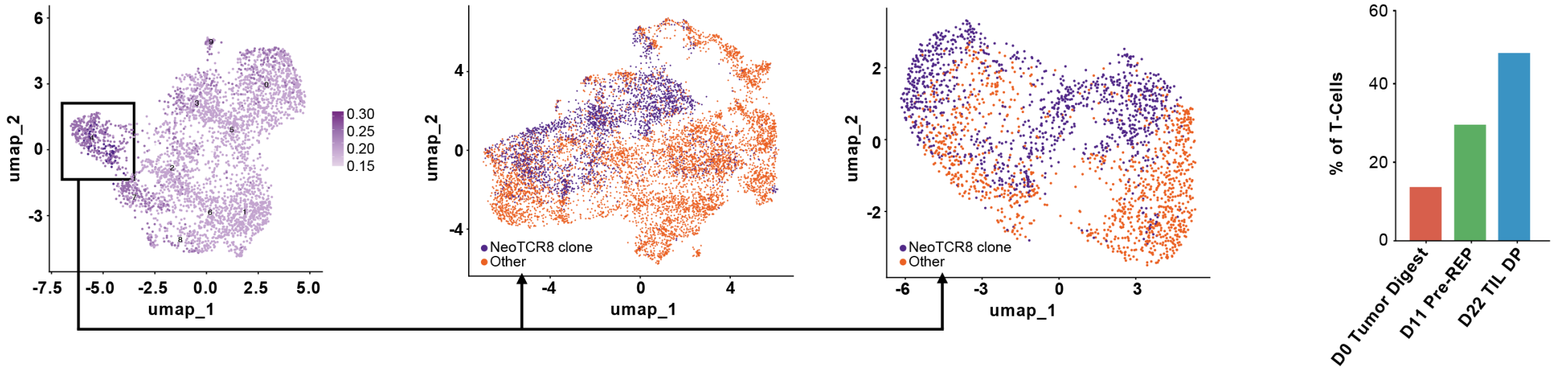
TIL Manufacturing Process Expands Putative Tumor-Reactive T Cells in Patient with Durable Complete Response

Day 0 Tumor Digest
NeoTCR8 Gene Signature

Day 11 Pre-REP
NeoTCR8 TCR Clones

Day 22 TIL DP
NeoTCR8 TCR Clones

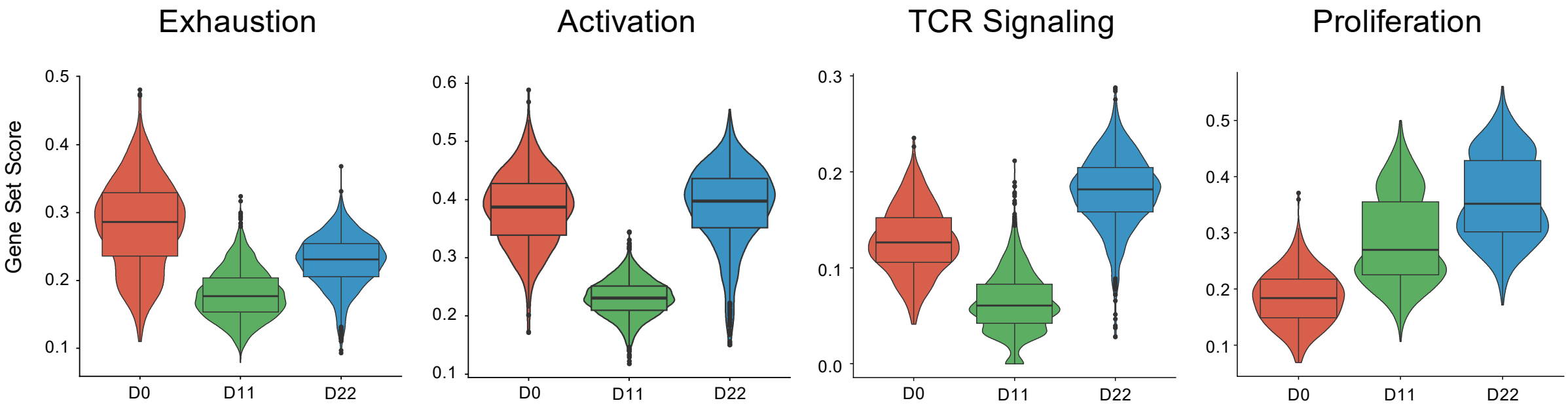
NeoTCR8 T-Cell Proportion



Data are from 1 patient with a durable complete response. D, day; DP, drug product; REP, rapid expansion process; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocyte; UMAP, Uniform Manifold Approximation and Projection.

Lowery FJ, et al. *Science*. 2022;375:877-84.

In a Complete Responder, Tumor-Reactive T Cells Evolved into Activated, Proliferating, Effector Memory-Like Cells



Data are from 1 patient with a durable complete response. The violin plots are per cell.
D, day; TCR, T-cell receptor.
Yost KE, et al. *Nat Med*. 2019;25:1251-9.

TEAEs Were Consistent With Underlying Disease and Known Profiles of Pembrolizumab, NMA-LD, and IL-2

Nonhematologic TEAEs in ≥30% of Patients[a] (N=22)

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)

TEAEs by Preferred Term, n (%)	Any Grade	Grade ≥3
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)

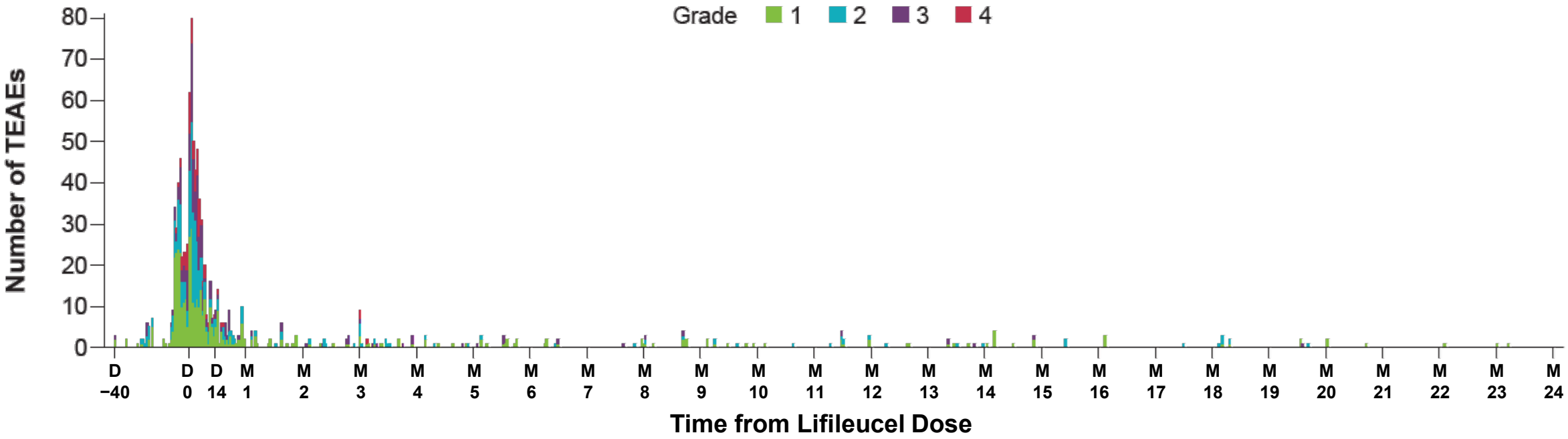
- The most common grade ≥3 nonhematologic TEAEs were hypoxia (54.5%), febrile neutropenia (45.5%), and hypophosphatemia (31.8%)

[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.

AE, adverse event; IL-2, interleukin-2; NMA-LD, nonmyeloablative lymphodepletion; TEAE, treatment-emergent adverse event.

TEAEs Mostly Occurred During the First 2 Weeks After Lifileucel Infusion

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.

AE, adverse event; D, day; M, month; TEAE, treatment-emergent adverse event.

Hematologic Abnormalities Resolved to Grade ≤2 Within the First 30 Days After Lifileucel Treatment in Most Patients

Grade 3/4 Hematologic Laboratory Abnormalities (N=22)

Preferred Term	Events, n (%)	Events Resolved to Grade ≤2 by 30 Days After Lifileucel Infusion, n (%)[a]
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)

- All patients experienced grade 3/4 hematologic laboratory abnormalities

[a]Percentage is calculated based on n, not N.

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
  - Median DOR was not reached in patients with *EGFR*-wt NSCLC, and there are 4 patients with ongoing responses over 20 months
- Data from 1 patient with a durable CR indicated that the TIL manufacturing process reinvigorates and expands putative tumor-reactive T cells, shifting their phenotype away from exhaustion towards activated, effector, proliferating, antitumor T cells
- 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

CR, complete response; DOR, duration of response; *EGFR*-wt, endothelial growth factor receptor gene wild-type; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD-L1, programmed death-ligand 1; PR, partial response; TIL, tumor-infiltrating lymphocyte.

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