

Efficacy and Safety of Lfileucel and Pembrolizumab in Patients with Immune Checkpoint Inhibitor-Naïve Advanced Melanoma: Final Results from IOV-COM-202 Study

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October 23, 2026



Declaration of Interest

Andrew J.S. Furness: Reports speaking fees from Bristol Myers Squibb, Eisai, Iovance Biotherapeutics, Ipsen, Merck, and Pfizer; support for attending meetings and/or travel from Achilles Therapeutics, Adaptimmune, ESMO, and Iovance Biotherapeutics; advisory board participation with Achilles Therapeutics, Aivita, GSK, Immunocore, and Neogene; consulting fees from Iovance Biotherapeutics and BioNTech; and is a co inventor on a pending patent (WO2019008375A1) related to methods of identifying responders to cancer treatment.

Helen Gogas: Reports honoraria from Bristol Myers Squibb, MSD Oncology, Pierre Fabre, Sanofi/Regeneron, and Genesis Pharmaceuticals; consulting/advisory roles with Bristol Myers Squibb, MSD Oncology, Pierre Fabre, and Sanofi/Regeneron; institutional research funding from Bristol Myers Squibb, Roche, MSD Oncology, Amgen, Novartis, Iovance Biotherapeutics, and Replimune; and travel support from MSD, Pfizer, and Sanofi.

Bernard Doger de Speville Uribe, Donald Lawrence, Theresa Medina: Nothing to disclose.

Gino K. In: Reports institutional research funding from Pfizer, Regeneron, Replimune, Bicara, Merck, Georgiamune, Obsidian, Immunocore, Iovance Biotherapeutics, and Xencor; and consulting/advisory roles with Pfizer, Bristol Myers Squibb, Regeneron, and Replimune.

Sajeve Thomas: Employment with and stock or stock options with Iovance Biotherapeutics.

Young Ki Hong: Consulting/Advisory Role: Amgen, AstraZeneca, BioNTech SE, Bristol Myers Squibb, Iovance Biotherapeutics, Lyell Immunopharma, Mirati Therapeutics, Perthera, Pfizer, Obsidian Therapeutics, Eli Lilly, OncoC4, and SyntheKine; Research Funding (Institutional): A2bio, AbbVie, Adaptimmune, Amgen, BioNTech SE, Bristol Myers Squibb, Genentech/Roche, GSK, Iovance Biotherapeutics, Marengo Therapeutics, Mirati Therapeutics, Obsidian Therapeutics, OncoC4, Servier, SyntheKine.

Juan Martin-Liberal: Honoraria from Astellas, Bristol-Myers Squibb, MSD, Novartis, Pierre Fabre, Pfizer Regeneron, Roche, and Sanofi; advisory board with Bristol-Myers Squibb, Highlight Therapeutics, Ipsen, Novartis, Pierre Fabre, Roche, and Sanofi; and travel support from Bristol-Myers Squibb, MSD, Novartis, PharmaMar, Pierre Fabre, Pfizer, Roche, and Ipsen.

Kai He: Reports institutional research funding and clinical trial support from Bristol Myers Squibb, Mirati Therapeutics, Adaptimmune, Genentech/Roche, GlaxoSmithKline, Amgen, Iovance Biotherapeutics, AbbVie, OncoC4, SyntheKine, Obsidian, Marengo Therapeutics, and Servier; and personal advisory board participation with multiple biopharmaceutical companies including Amgen, Bristol Myers Squibb, Iovance Biotherapeutics, BioNTech, Pfizer, and others.

Marta Sotelo Garcia: Reports support for attending meetings and/or educational courses from MSD and Sun Pharma.

Sylvia Lee: Reports institutional research funding from Iovance Biotherapeutics, Lyell, Seagen, Kite, and Black Diamond, and travel expenses from DAVA Oncology.

Friedrich Graf Finckenstein: Employee of Iovance Biotherapeutics and reports stock or stock options, travel/accommodation support from Iovance Biotherapeutics, and patents/royalties with Bristol Myers Squibb and Iovance Biotherapeutics; Reports stock with Roche and BMS

Simon Häfliger: Reports advisory board participation with Novartis and Takeda, invited speaker role with Roche, expert testimony role with Roche.

Morganna Vance, Rana Fiaz, Melissa Catlett, Siyu Zhu, Rongsu Qi, Brian Thompson, Joe Dean, Brian Gastman, Frederick G. Vogt: Employees of Iovance Biotherapeutics, Inc., San Carlos, CA, USA, and may own stock and have no other financial relationships to disclose.

Patrick Terheyden: Reports consulting fees from Almirall, Biotest, Bristol Myers Squibb, Sanofi, L'Oréal, Novartis, Pierre Fabre, Merck Serono, Roche, Kyowa Kirin, Biofrontera, and 4SC; honoraria from Bristol Myers Squibb and Pierre Fabre; and support for attending meetings and/or travel from Bristol Myers Squibb and Pierre Fabre.

Advanced Melanoma: Unmet Need for Frontline Treatments That Provide Long-Term Benefit

- *Approximately half of patients who receive frontline combination ICI therapy do not achieve long-term benefit, representing a population in need of new strategies¹*
- *Lifileucel was approved as a second-line treatment for advanced melanoma based on results from the C-144-01 trial^{2,3}*
 - *ORR for the heavily pretreated patients was 31.4%²*
 - *Longest duration of IRC-assessed response was ongoing at 55.8 months*
 - *Responses continued to deepen in many patients even beyond 2.5 years*
- *Prior data supports earlier use of lifileucel in the frontline/ICI-naïve setting*
 - *In a retrospective analysis of 192 patients with ICI-naïve metastatic melanoma treated with TIL cell monotherapy at the National Cancer Institute, the ORR was 56%, with a CR rate of 25% and 10-year survival rate of 96% who achieved CR⁴*
- *Lifileucel plus ICI therapy may hold promise as a first-line combination therapy for advanced disease*

CR, complete response; ICI, immune checkpoint inhibitor; IRC, independent review committee; ORR, objective response rate; PD-1, programmed cell death protein-1; TIL, tumor-infiltrating lymphocyte.

1. Larkin J, et al. *N Engl J Med*. 2019;381:1535–46. 2. Chesney J, et al. *J Immunother Cancer*. 2022;10:e005755. 3. Amtagvi™: Prescribing Information, 2024. 4. Seitter SJ, et al. *Clin Cancer Res*. 2021;27:5289–98.

IOV-COM-202: Phase 2, Multicohort, Multicenter Study of Lifileucel + Pembrolizumab in Patients with Solid Tumors

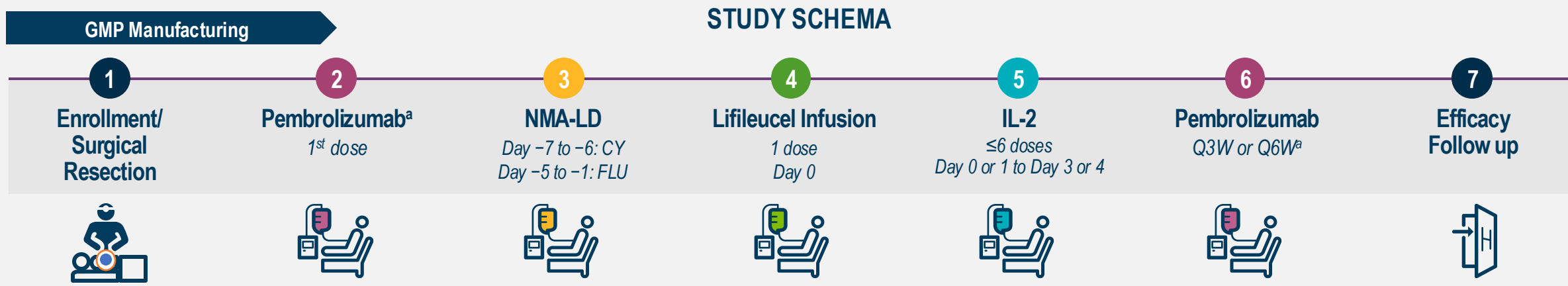
Cohort 1A of IOV-COM-202 (NCT03645928) assesses the efficacy and safety of lifileucel + pembrolizumab in patients with ICI-naïve unresectable or metastatic melanoma

- Patients may have received BRAF/MEK inhibitor treatment if they are BRAF mutation positive
- Patients may have received no prior therapies

Eligible patients must have:

- ≥ 1 resectable lesion (≥ 1.5 cm diameter) and
- ≥ 1 measurable lesion for response assessment per RECIST v1.1

Trial was designed as a proof-of-concept study to support a registrational study in the frontline treatment setting



^aFirst administration of single-dose pembrolizumab IV 200 mg or 400 mg, followed by pembrolizumab IV 200 mg Q3W or 400 mg Q6W for 24 months or until disease progression or unacceptable toxicity.

BRAF, B-Raf proto-oncogene; CY, cyclophosphamide; FLU, fludarabine; GMP, Good Manufacturing Practice; ICI, immune checkpoint inhibitor; IL-2, interleukin-2; IV, intravenous;

MEK, mitogen-activated extracellular signal-regulated kinase; NMA-LD, non-myeloablative lymphodepletion; Q3W, every 3 weeks; Q6W, every 6 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

Baseline Patient and Disease Characteristics

Characteristics	N=27
Median age, y (min, max)	53.0 (18–68)
Male sex, n (%)	18 (66.7)
White	27 (100)
Melanoma type, n (%)	
<i>Cutaneous</i>	18 (66.6)
Acral	1 (3.7)
Mucosal	3 (11.1)
<i>Other</i>	5 (18.5)
Metastatic staging at study entry, n (%)	
<i>M0</i>	2 (7.4)
<i>M1a</i>	8 (29.6)
<i>M1b</i>	5 (18.5)
M1c	12 (44.4)
Screening ECOG status	
0	21 (77.8)
1	6 (22.2)

Characteristics	N=27
PD-L1 TPS (central labs), n (%)	
<1	6 (22.2)
≥1	14 (51.9)
Missing	7 (25.9)
Median target lesion SOD, mm (min, max)	50.0 (14–355)
>3 baseline target and nontarget lesions, n (%)	18 (66.7)
Liver metastasis, n (%)	9 (33.3)
Brain metastasis, n (%)	0
LDH, n (%)	
<ULN	17 (63.0)
1–2 × ULN	9 (33.3)
>2 × ULN	1 (3.7)
BRAF V600 mutated, n (%)	10 (37.0)
Prior BRAF/MEK inhibitor treatment	3 (11.1)
Median number of prior therapies (min, max) ^a	0 (0–2)

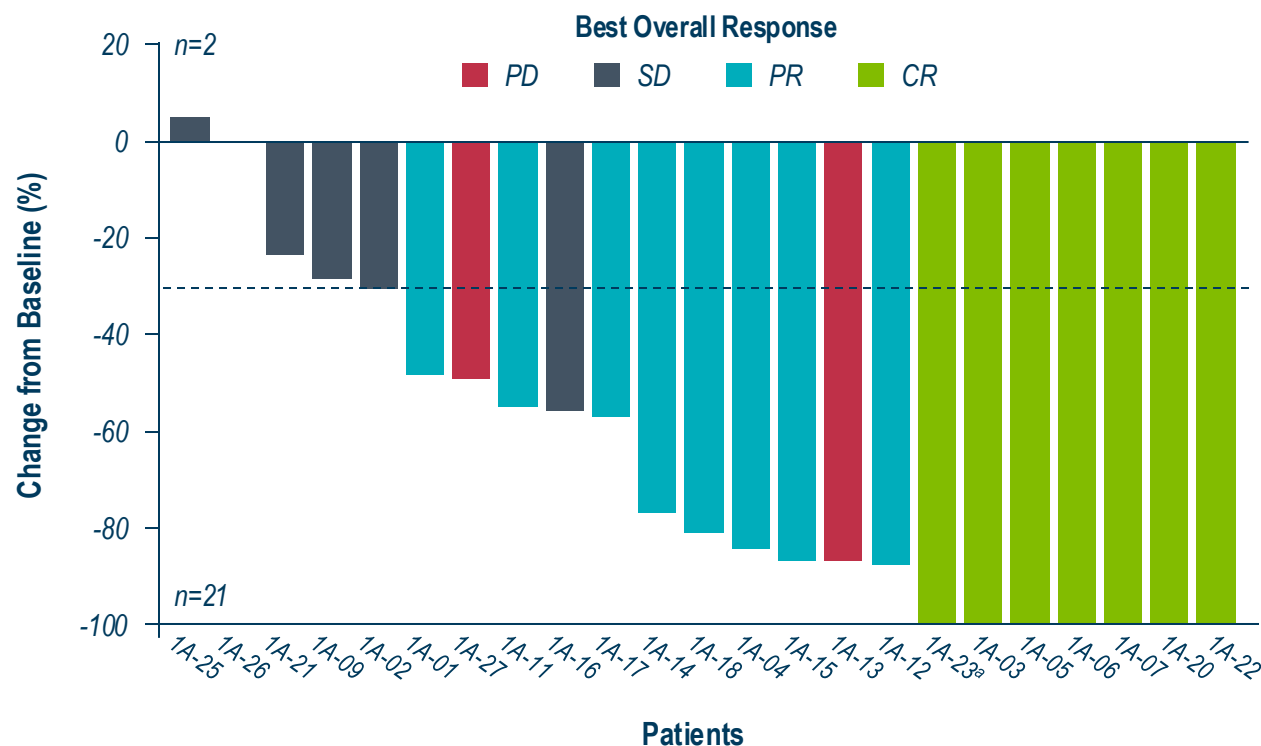
^a3 patients received prior chemotherapy; 2 other patients received prior adjuvant ICI >12 months prior to enrollment, which was not counted as a line of prior therapy per protocol.

BRAF, B-Raf proto-oncogene; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; LDH, lactate dehydrogenase; MEK, mitogen-activated extracellular signal-regulated kinase; PD-L1, programmed death-ligand 1; SOD, sum of diameters; TPS, tumor proportion score; ULN, upper limit of normal.

Efficacy

Lifileucel with Pembrolizumab results in 62.5% ORR and CR rate of 29.2%

Best Percentage Change from Baseline in Target Lesion SOD



Investigator-Assessed Response (RECIST v1.1) (n=24)^a

Objective Response Rate, n (%)	15 (62.5)
(95% CI)	(40.6, 81.2)
Disease Control Rate, n (%)	20 (83.3)
(95% CI)	(62.6, 95.3)
Best Overall Response, n (%)	
CR	7 (29.2)
PR	8 (33.3)
SD	5 (20.8)
PD	3 (12.5)
NE	1 (4.2) ^b

95% CI was calculated using the Clopper-Pearson Exact test.

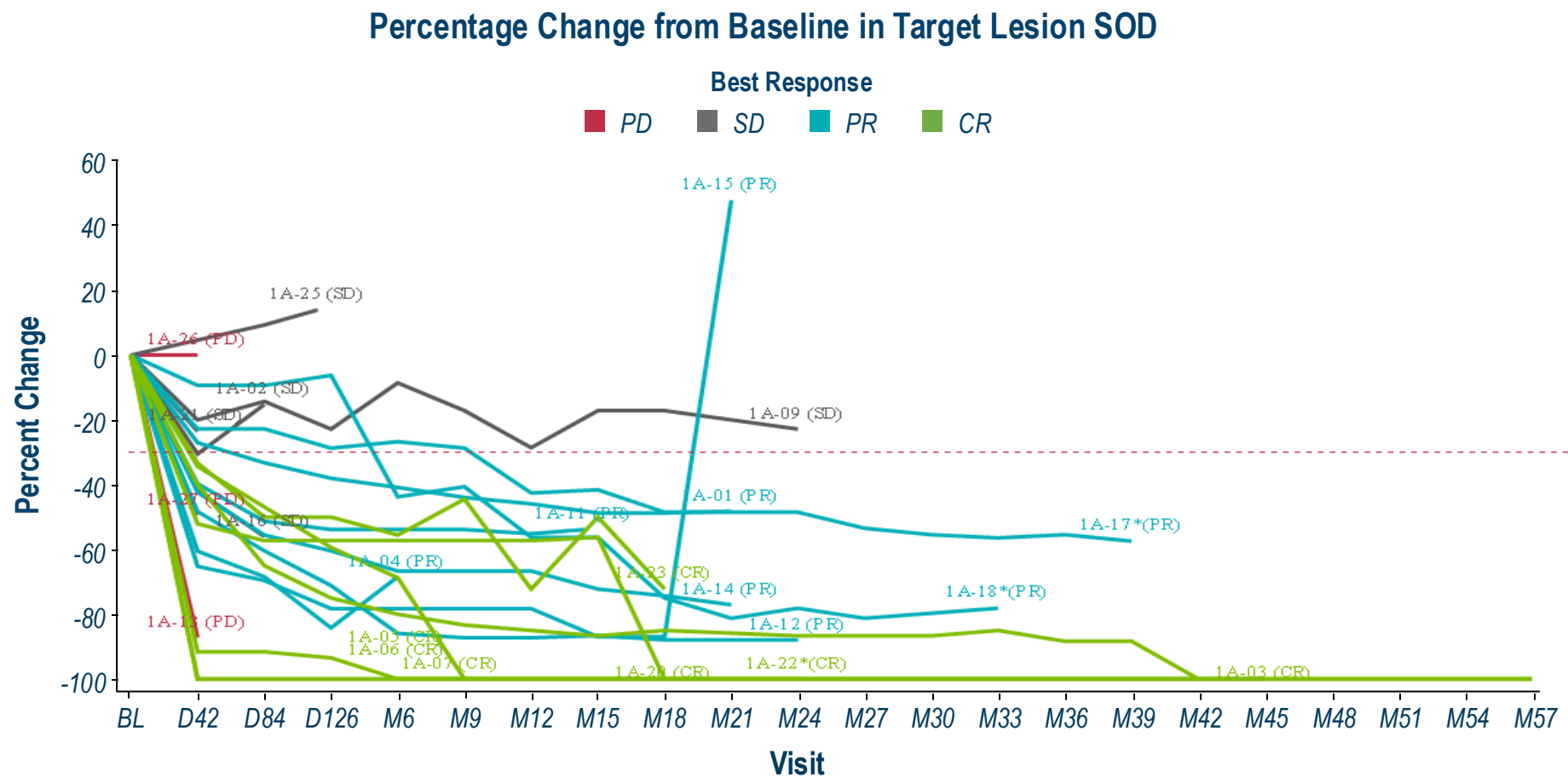
^aIOV-COM-202 Cohort 1A Full Analysis Set included all patients who received TIL ≥ 5.58 billion that met the manufacturing product specifications.

^bPatient 1A-10 is included as NE and did not have a post-dose tumor response assessment.

CI, confidence interval; CR, complete response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SOD, sum of diameters; TIL, tumor-infiltrating lymphocyte.

Efficacy

Lifileucel with Pembrolizumab mediates durable and deepening responses



IOV-COM-202 Cohort 1A Full Analysis Set includes all patients who received ≥ 5.58 billion TILs meeting manufacturing product specifications.

For percentage change from baseline to post-baseline timepoints, the SOD at baseline is used as the denominator.

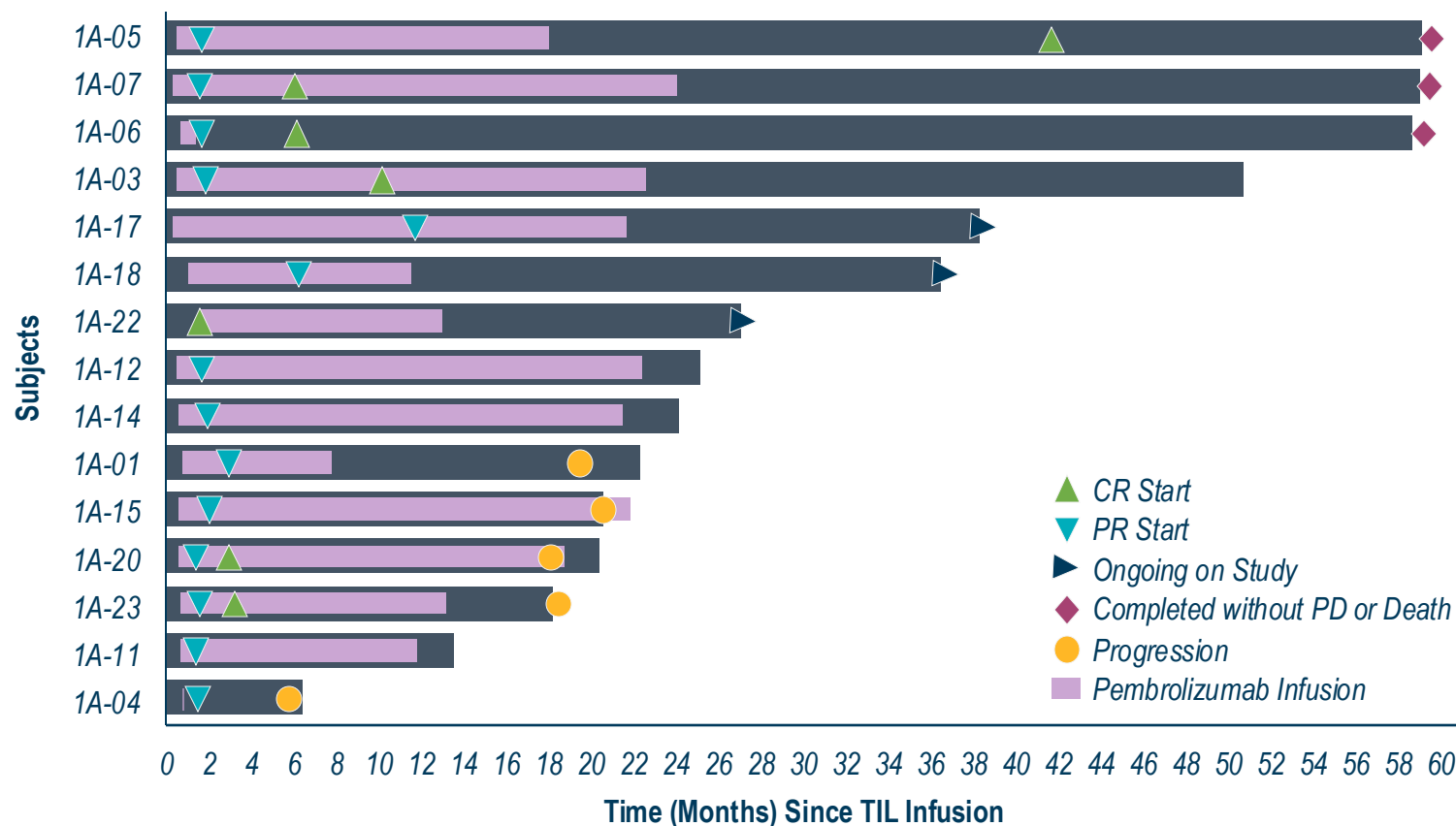
Patient 1A-10 did not undergo post-dose tumor response assessment and was not included.

*Ongoing patients without PD.

BL, baseline; CR, complete response; D, day; M, month; PD, progressive disease; PR, partial response; SD, stable disease; SOD, sum of diameters; TIL, tumor-infiltrating lymphocyte.

Efficacy

Lifileucel with Pembrolizumab demonstrates durable and deepening responses



- *mDOR not reached^a*
(min, max: 4.3 mo, 57.7+ mo)
- *Median f/u for DOR^b: 26.9 mo*
- *3 of 15 responders completed 5-year response assessment w/o PD or death (DOR range, 57+ to 57.7+ mo)*
- *In addition, 3 of 15 responders still ongoing at data cut (DOR range, 25.3+ to 26.9+ mo)*

IOV-COM-202 Cohort 1A Full Analysis Set includes all patients who received ≥ 5.58 billion TILs meeting manufacturing product specifications.

Each bar is presented for each patient starting from date of TIL infusion up to date of new anti-cancer therapy, end of assessment, death, or data cutoff date, whichever occurs earlier.

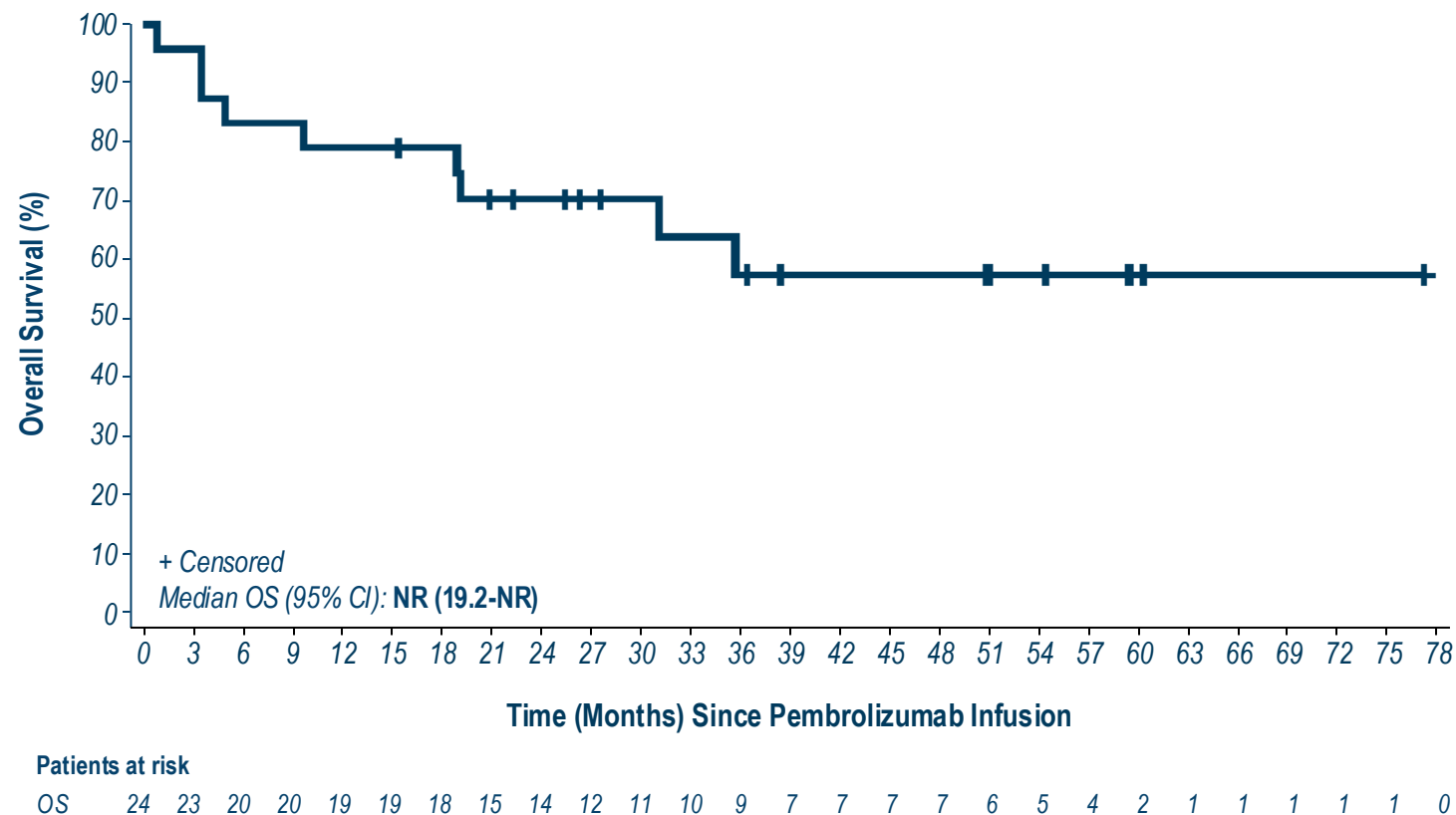
Patients 1A-03 and 1A-11 withdrew consent during assessment phase while still in response. Patient 1A-12 discontinued from study while still in response to continue pembrolizumab off-study. Patient 1A-14 was in response during assessment phase before moving to long-term follow-up phase due to relocation from the investigative site.

^aBased on Kaplan-Meier product-limit estimates. ^bBased on reverse Kaplan-Meier method.

CR, complete response; DOR, duration of response; mDOR, median duration of response; Pembro, pembrolizumab; PD, progressive disease; PR, partial response; TIL, tumor-infiltrating lymphocyte.

Efficacy

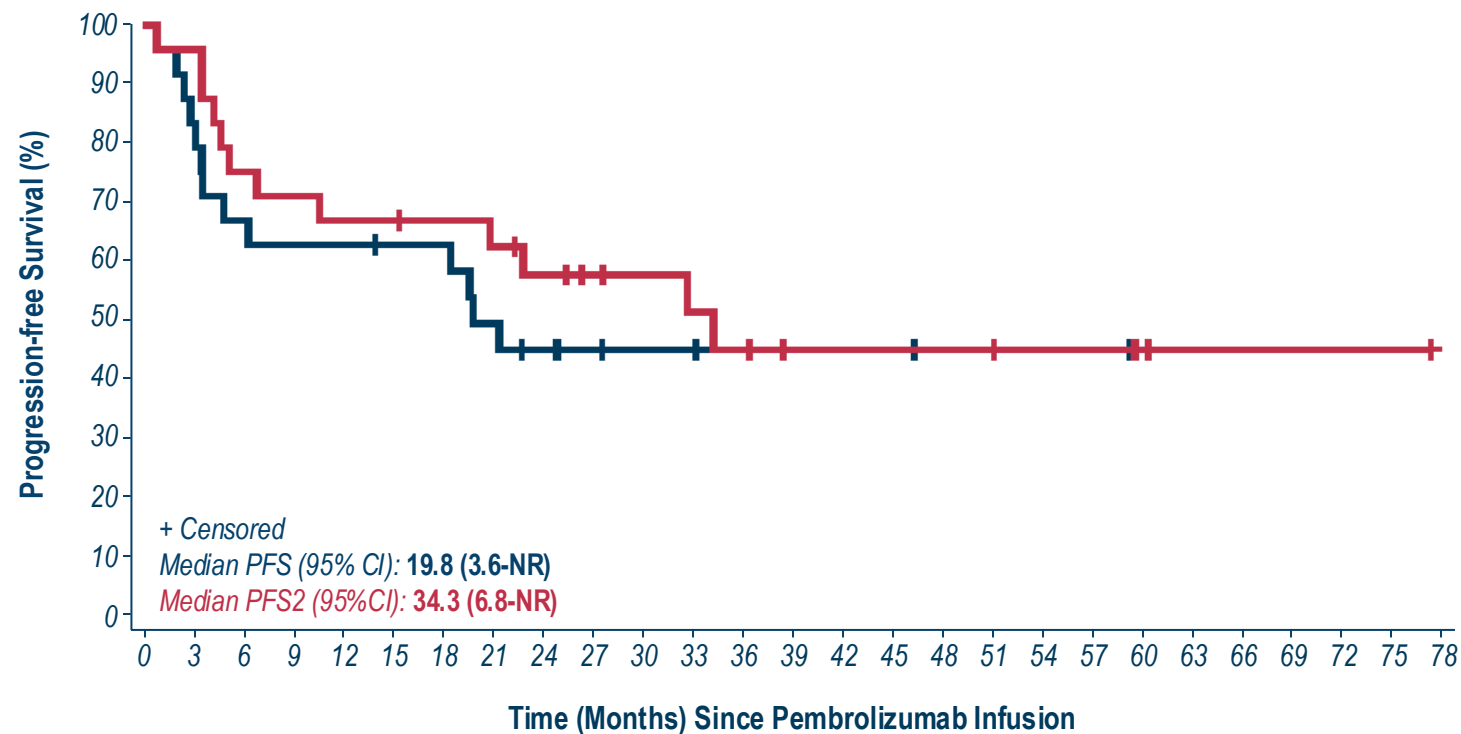
Median OS was not reached with median study follow-up of 50.9 months



IOV-COM-202 Cohort 1A Full Analysis Set includes all patients who received ≥ 5.58 billion TILs meeting manufacturing product specifications.
CI, confidence interval; NR, not reached; OS, overall survival; TIL, tumor-infiltrating lymphocyte.

Efficacy

Lifileucel with Pembrolizumab results in median PFS of 19.8 months and median PFS2 of 34.3 months



PFS2 suggests feasibility of systemic therapies in later lines with frontline use of lifileucel

Patients at risk

PFS	24	20	16	15	15	14	14	11	9	7	6	6	5	4	4	4	3	3	3	3	1	0					
PFS2	24	23	18	17	16	16	15	14	12	10	9	8	7	5	5	5	5	5	4	4	2	1	1	1	1	1	0

Successful Salvage after Lifileucel + Pembrolizumab

4 Patient examples with 4 different ways to salvage following lifileucel + Pembrolizumab therapy

1

Patient 1 (1A-01) — Retreatment with Lifileucel

BOR of PR (DOR 16.8 mos) in initial treatment; retreated with lifileucel, BOR of PR

PFS2 77.4+ mos

2

Patient 2 (1A-15) — Subsequent ICI therapy

BOR of PR (DOR 18.7 mos); progression in target lesions and new lesion → ipilimumab + nivolumab

PFS2 22.8 mos

3

Patient 3 (1A-20) — Subsequent BRAFi/MEKi

BOR of CR (DOR 16.8 mos); progression due to new lesion → dabrafenib + trametinib

PFS2 26.3+ mos

4

Patient 4 (1A-23) — Subsequent local resection

BOR of CR (DOR 17 mos); progression due to new local metastasis, which was resected

PFS2 22.3+ mos

Safety: Treatment-Emergent Adverse Events in $\geq 30\%$ of Patients^a

Safety of lifileucel with pembrolizumab consistent with disease and safety profiles of study regimen

Preferred Terms, n (%)	N=27	
	Any grade	Grade 3/4
Thrombocytopenia	24 (88.9)	18 (66.7)
Pyrexia	22 (81.5)	4 (14.8)
Chills	21 (77.8)	3 (11.1)
Nausea	21 (77.8)	0
Anemia	19 (70.4)	13 (48.1)
Vomiting	17 (63.0)	0
Neutropenia	15 (55.6)	15 (55.6)
Fatigue	14 (51.9)	1 (3.7)
Headache	13 (48.1)	0
Cough	12 (44.4)	0
Decreased appetite	12 (44.4)	0
Diarrhea	12 (44.4)	2 (7.4)
Febrile neutropenia	11 (40.7)	10 (37.0)
Rash (maculopapular)	11 (40.7)	5 (18.5)
Alopecia	10 (37.0)	0
Dyspnea	10 (37.0)	2 (7.4)
Hypokalemia	9 (33.3)	0

Safety was consistent with the underlying disease and known safety profiles of pembrolizumab, NMA-LD, lifileucel, and IL-2

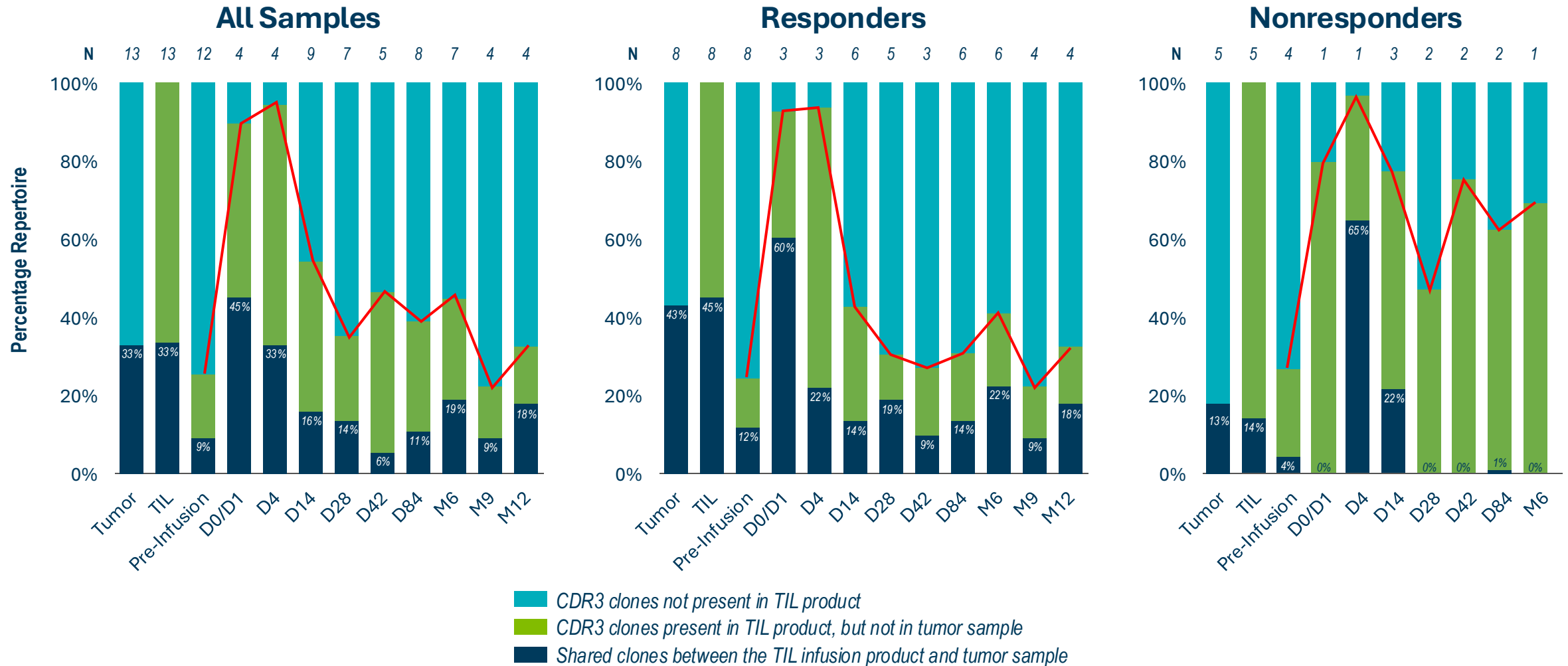
- AEs consistent with the lifileucel regimen occurred and resolved early
- AEs occurring later than 30 days after lifileucel infusion were generally consistent with the safety profile of pembrolizumab monotherapy

N=27 (safety analysis set includes all patients who received lifileucel). One patient had a grade 5 TEAE of sepsis.

^aTEAEs refer to adverse events that occurred from the first dose of pembrolizumab or lifileucel infusion (whichever occurred first) up to 30 days after the last dose of pembrolizumab or lifileucel infusion (whichever occurred later) or up to the start of a new anti-cancer therapy.

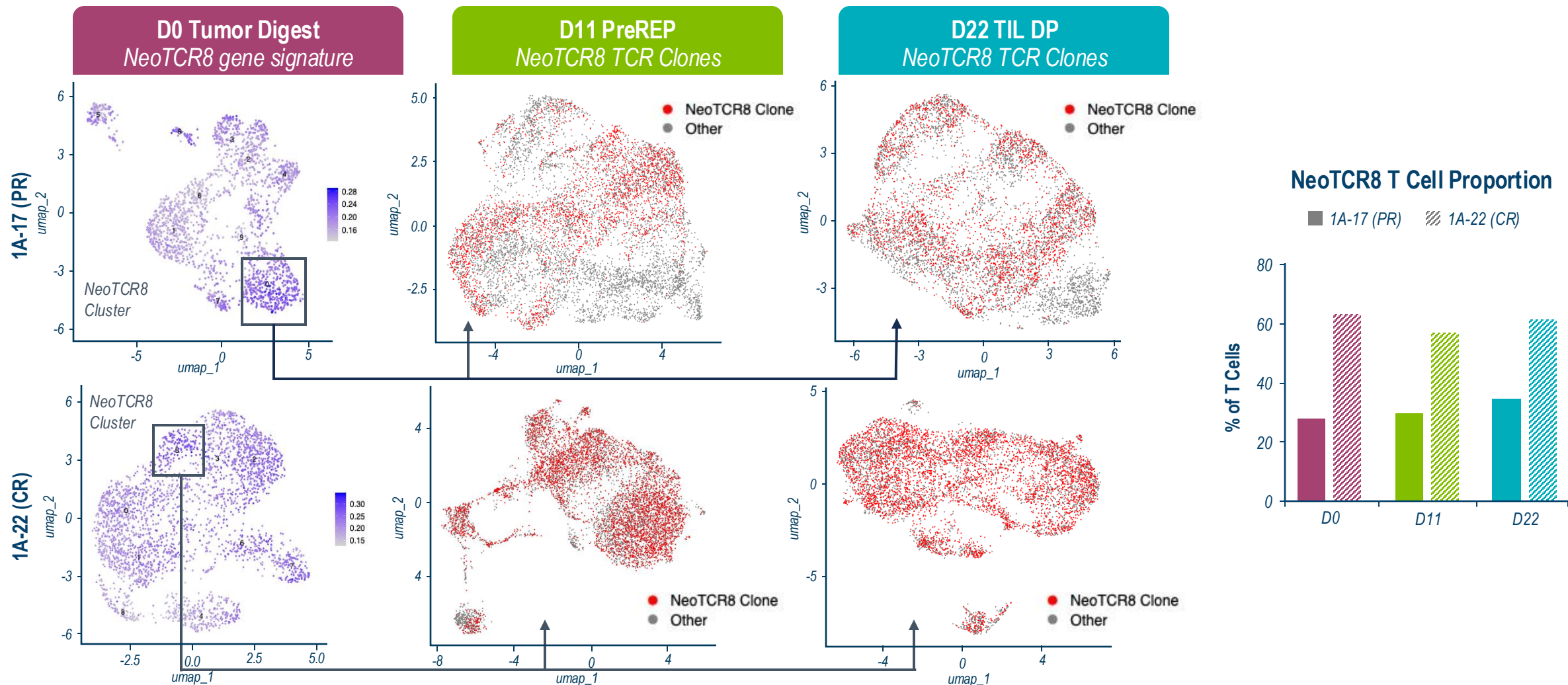
AE, adverse event; IL-2, interleukin-2; NMA-LD, non-myeloablative lymphodepletion; TEAE, treatment-emergent adverse event.

Longitudinal analysis of TCR Clones from the Infused Lifileucel Drug Product in the Periphery



D, day; M, month; TIL, tumor-infiltrating lymphocyte;

Putative Tumor-Reactive T Cells Are Maintained Throughout the TIL Manufacturing Process in Two Patients with Durable Responses



CR, complete response; D, day; DP, drug product; PR, partial response; PreREP, pre-Rapid Expansion Protocol; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocyte; UMAP, Uniform Manifold Approximation and Projection. Lowery FJ, et al. Science. 2022;375:877–84.

Conclusions

In this phase 2 trial, a single administration of lifileucel combined with pembrolizumab in patients with ICI-naïve advanced melanoma demonstrated:

Efficacy and durability of responses

- *ORR was 62.5%; CR rate was 29.2%*
- *91.3% evaluable patients demonstrated regression of target lesions*
- *Median DOR was not reached (range: 4.3 mo to 57.7+ mo), with median follow-up of 26.9 months*
- *ORR and DOR compare favorably with ICI monotherapy and combination regimens for first-line treatment of melanoma*

Manageable and expected safety profile

- *TEAEs consistent with the underlying disease and known, manageable safety profiles of single administration of the lifileucel regimen and continued pembrolizumab*
- *Late AEs consistent with anti-PD-1 monotherapy, differentiated from ICI combination therapies*
- **No identified barriers evident to subsequent systemic therapy**

These results serve as rationale for TILVANCE-301, an ongoing registrational, randomized trial assessing lifileucel + pembrolizumab in frontline advanced melanoma

TILVANCE-301 Global Phase 3 and Confirmatory Trial

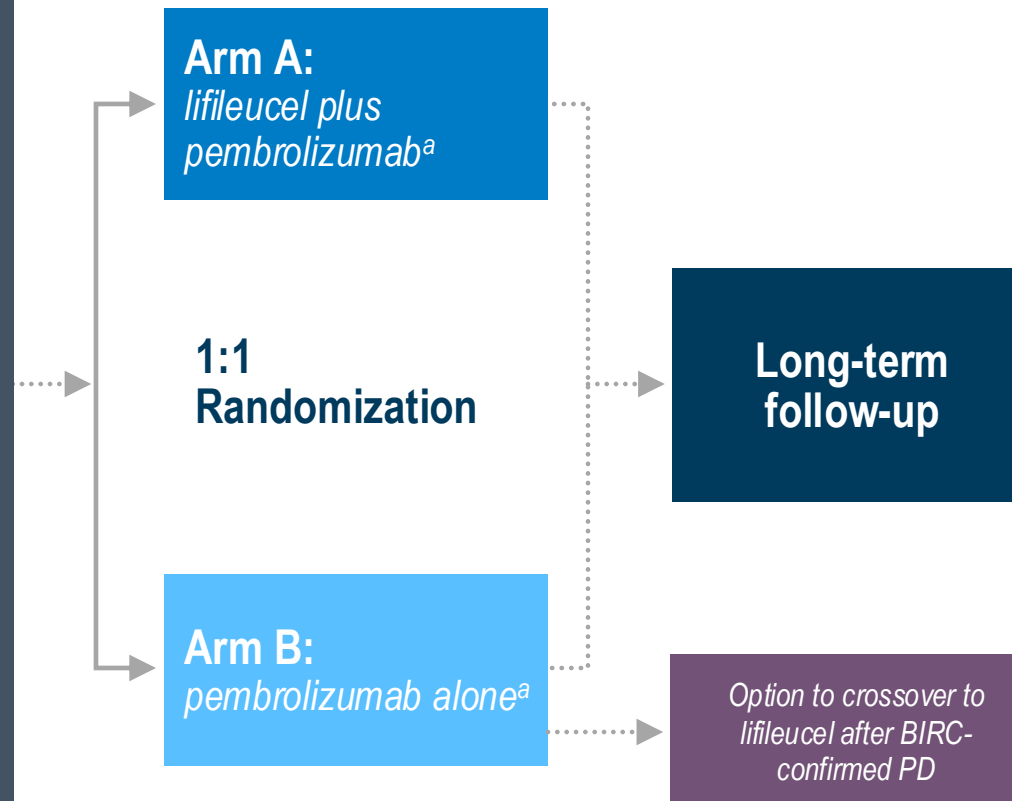
Randomized, multicenter study with optional crossover to lifileucel (NCT05727904)

Patient Population

Unresectable or metastatic melanoma; no prior therapy for metastatic disease

N=670

80+ sites in U.S., Canada, Europe, APAC



Study Design

- Dual primary endpoints: ORR & PFS
- Interim analysis on ORR
- Final analysis on PFS
- **Registrational for frontline melanoma**
- **Confirmatory for full approval of lifileucel in post-anti-PD-1 melanoma in the U.S.**

^aPembrolizumab in both arms is started at the same time after randomization.

BIRC, blinded independent review committee; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein-1; PFS, progression-free survival.

Acknowledgments

*The authors thank the **patients and their families**, as well as the **investigators and study site team members**, for their participation in the study.*

This study was sponsored by lovance Biotherapeutics, Inc. (San Carlos, CA, USA).

Medical writing and editorial support was provided by lovance Publications team and SlideSource and funded by lovance.



Thank You

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