ESMO IMMUNO-ONCOLOGY
Annual Congress

NUMBER OF IL-2 DOSES AND CLINICAL OUTCOMES OF TUMOR-INFILTRATING LYMPHOCYTE (TIL) CELL THERAPY: POST HOC ANALYSIS OF THE C-144-01 TRIAL OF LIFILEUCEL IN PATIENTS WITH ADVANCED MELANOMA

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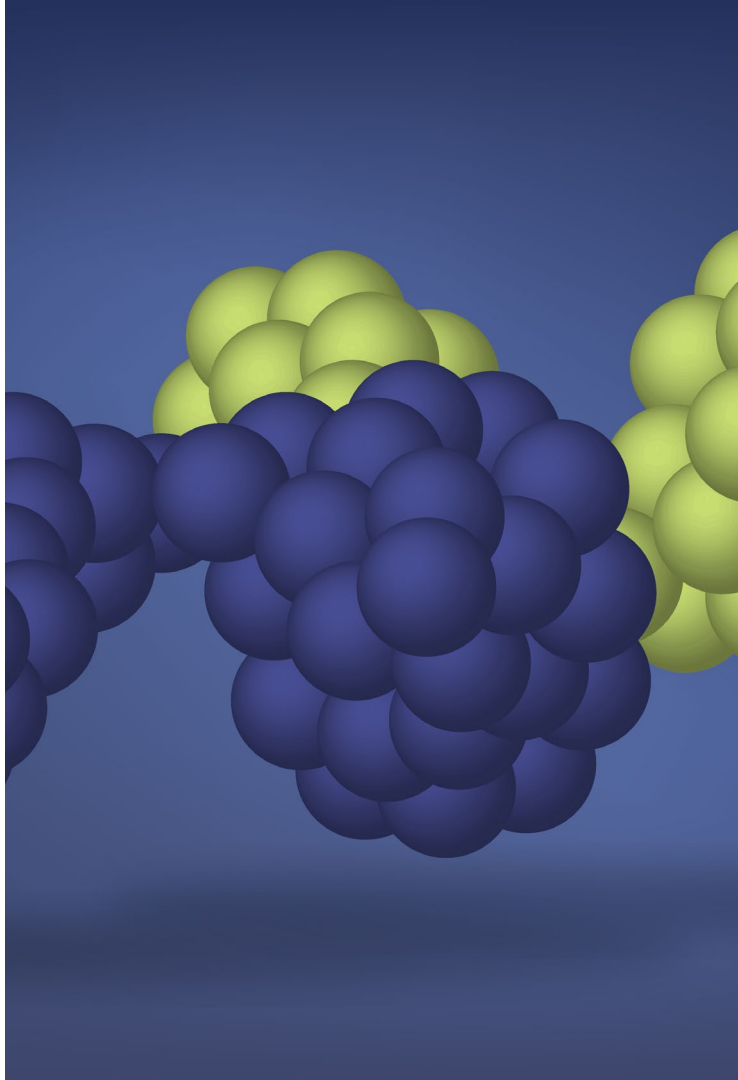
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE



DECLARATION OF INTERESTS

Jessica C. Hassel

Honoraria: Almirall, Amgen, Bristol Myers Squibb, GSK, MSD, Novartis, Pierre Fabre, Roche, Sanofi, and Sun Pharma
Consulting or advisory role: GSK, MSD, Pierre Fabre, and Sun Pharma
Research funding: Bristol Myers Squibb, Sun Pharma, and Sanofi
Travel, accommodations, and expenses: Sun Pharma

BACKGROUND

- High-dose aldesleukin (IL-2) is approved as monotherapy in metastatic melanoma
  - Its activity is mediated through endogenous T cell activation; however, IL-2 monotherapy shows limited efficacy and considerable toxicity[1,2]
- Lifileucel, a polyclonal one-time investigational TIL cell therapy, showed encouraging activity in 153 patients with advanced melanoma who progressed after ICI and targeted therapy, if indicated (C-144-01 trial)[3]
  - **31.4% IRC-assessed ORR**
  - **Median DOR not reached at median study follow-up of 36.5 months**
- An abbreviated course of high-dose IL-2 (600,000 IU/kg, ≤6 doses) is used as part of the lifileucel regimen to promote T-cell activity, rather than providing independent anti-neoplastic activity[4]
  - Prior studies found no association between IL-2 dose and TIL cell therapy efficacy[5,6]
- This post hoc analysis explores the association between number of IL-2 doses and clinical outcomes of lifileucel

1. Atkins, et al. *J Clin Oncol*. 1999;17(7):2105-16. **2.** Rosenberg, et al. *J Exp Med*. 1985;161:1169-88.
3. Sarnaik, et al. Presented at SITC 2022. **4.** Dudley, et al. *J Immunother*. 2002;25(3):243-51.
5. Goff, et al. *J Clin Oncol*. 2016;34(20):2389-97. **6.** Seitter, et al. *Clin Cancer Res*. 2021;27(19):5289-98.
Abbreviations: DOR, duration of response; ICI, immune checkpoint inhibitor; IL-2, interleukin 2; IRC, independent review committee; ORR, objective response rate; TIL, tumor-infiltrating lymphocyte.

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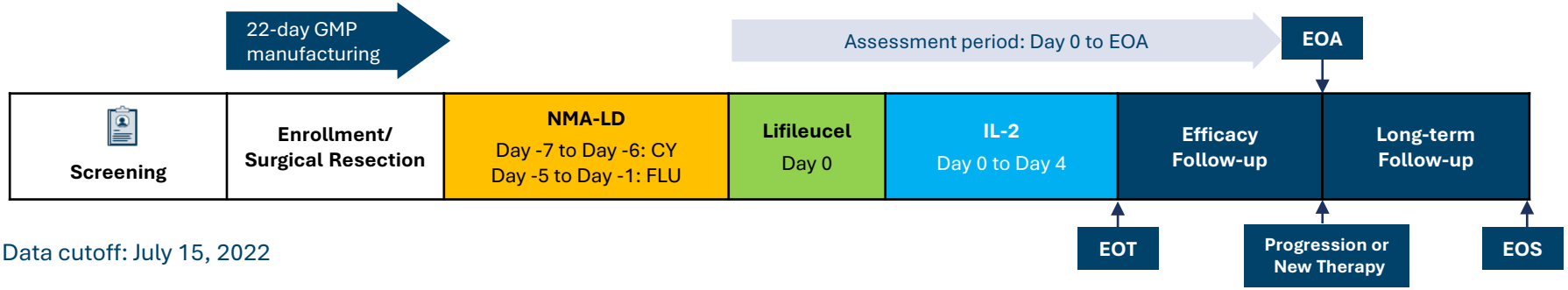
METHODS (C-144-01 TRIAL)



Data cutoff: July 15, 2022

IL-2 Dosing Per Protocol

- 600,000 IU/kg IV starting 3–24 hours after lifileucel infusion and every ~8–12 hours for up to 6 doses
  - Allowed for up to 4 days after lifileucel infusion for IL-2 toxicity management
  - Number of doses based on tolerance
  - If toxicities could be easily reversed within 24 hours by supportive measures, then additional doses of IL-2 (up to maximum of 6 doses) were given[1-3]
  - Held or stopped at the discretion of the investigator; skipping IL-2 doses was permitted in the event of Grade 3 or 4 toxicity[1-3]

Analyses

- Association of number of IL-2 doses with lifileucel ORR (RECIST v1.1 per IRC), DOR, safety, and TCR repertoire was explored
- TCR repertoire of tumors, TIL infusion product, and pre- and post-infusion patient blood samples were assessed using RNAseq

1. Proleukin® (aldesleukin) Prescribing Information. **2**. Dutcher J, et al. *J Immunother Cancer*. 2014;2:26. **3**. Schwartz et al. *Oncology*.2002;16(Suppl 13):11-20.
Abbreviations: CY, cyclophosphamide; DOR, duration of response; EOA, end of assessment; EOS, end of study; EOT, end of treatment; FLU, fludarabine; GMP, Good Manufacturing Practice; IL-2, interleukin-2; IRC, independent review committee; NMA-LD, nonmyeloablative lymphodepletion; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocytes.

PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Characteristic	Full Analysis Set* (N=153)
Median age, years (range)	56.0 (20, 79)
Sex, n (%)	
Male	83 (54.2)
Female	70 (45.8)
Median target lesion SOD (range), mm	97.8 (13.5, 552.9)
>3 baseline target and nontarget lesions,† n (%)	116 (75.8)
LDH, n (%)	
≤ULN	70 (45.8)
1–2 × ULN	54 (35.3)
>2 × ULN	29 (19.0)
Prior systemic therapies, n (%)	
Median number of therapies (range)	3.0 (1, 9)
Anti–PD-1/PD-L1	153 (100)
Anti–CTLA-4	125 (81.7)
Anti–PD-1 + anti–CTLA-4 combination	82 (53.6)
BRAF ± MEK inhibitor	39 (25.5)
IL-2 (monotherapy or combination)	13 (8.5)
IL-2 in metastatic setting, n‡	5 (3.3)
Median number of TIL cells infused (range), (× 10^9)	21.1 (1.2, 99.5)
IL-2 doses §	
Median IL-2 doses (range)	6.0 (0, 6)
1–2 doses, n (%)	16 (10.5)
3–4 doses, n (%)	26 (17.0)
5–6 doses, n (%)	109 (71.2)
Median cumulative IL-2 dose (×10^3 IU/kg)¶	3528.3
Median relative dose intensity, %**	100

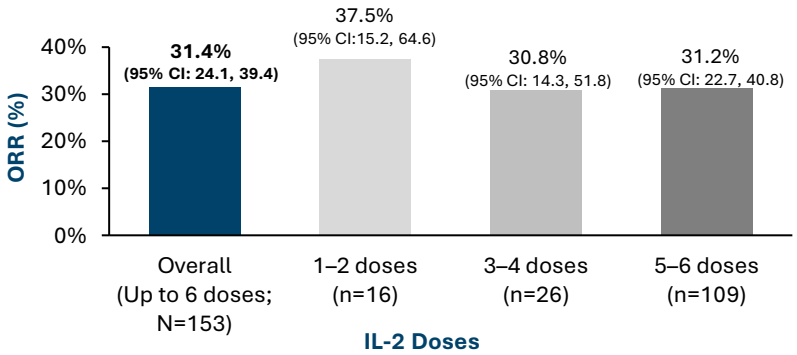
- Median number of IL-2 doses administered in the lifileucel regimen was 6
  - 1–2 doses: n=16 (10.5%)
  - 3–4 doses: n=26 (17.0%)
  - 5–6 doses: n=109 (71.2%)
  - Did not receive IL-2: n=2‡ (1.3%)

*The Full Analysis Set included patients who had received lifileucel that met the manufacturing product specification, including minimum TIL cell dose of 1 × 10^9 and less than 150 × 10^9.
†1 patient had missing data on number of baseline target and non-target lesions.
‡Not including investigational IL-2 agents administered as part of combination regimen.
§ 2 patients in the Full Analysis Set did not receive IL-2 due to clinical condition.
¶ 79% lower than the maximum cumulative dose of 1 full treatment course (two 5-day cycles separated by a rest period) of IL-2 monotherapy.
**Up to maximum of 6 doses of IL-2 at 600,000 IU/kg.

Abbreviations: CTLA-4, cytotoxic T-lymphocyte–associated protein 4; IL-2, interleukin-2; LDH, lactate dehydrogenase; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; SOD, sum of diameters; ULN, upper limit of normal.

LIFILEUCEL ORR AND DOR WERE INDEPENDENT OF NUMBER OF IL-2 DOSES

ORR, by Number of IL-2 Doses



DOR, by Number of IL-2 Doses

	Median DOR, months (95% CI)	DOR ≥12 months, by number of IL-2 doses, n/N1 (%)
Overall (Up to 6 doses)	**NR (8.3, NR)**	**26/48 (54.2)**
1–2 doses	NR (2.7, NR)	4/6 (66.7)
3–4 doses	NR (8.3, NR)	6/8 (75.0)
5–6 doses	24.6 (4.1, NR)	16/34 (47.1)

- No significant difference in ORR by number of IL-2 doses (***p*=0.87**)
- ORR was 40% in 5 patients who received prior IL-2 in metastatic setting (all had progressed on or after prior IL-2 therapy)

- No significant difference in DOR by number of IL-2 doses (***p*=0.25**)

Abbreviations: DOR, duration of response; IL-2, interleukin-2; N1, number of patients in subgroup; NR, not reached; ORR, objective response rate.

SAFETY WAS INDEPENDENT OF NUMBER OF IL-2 DOSES

Expected Non-Hematologic IL-2 Toxicities[1] in ≥10% of Patients in Any Subgroup, by Number of IL-2 Doses*†

Preferred Term, n (%)	1–2 IL-2 Doses (n=16)		3–4 IL-2 Doses (n=26)		5–6 IL-2 Doses (n=111)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Chills	10 (62.5)	1 (6.3)	18 (69.2)	2 (7.7)	89 (80.2)	5 (4.5)
Pyrexia	10 (62.5)	2 (12.5)	14 (53.8)	5 (19.2)	57 (51.4)	10 (9.0)
Hypotension	8 (50.0)	2 (12.5)	9 (34.6)	3 (11.5)	34 (30.6)	12 (10.8)
Decreased appetite	6 (37.5)	1 (6.3)	3 (11.5)	1 (3.8)	21 (18.9)	1 (0.9)
Diarrhea	6 (37.5)	1 (6.3)	8 (30.8)	0	34 (30.6)	1 (0.9)
Dyspnea	6 (37.5)	1 (6.3)	5 (19.2)	1 (3.8)	19 (17.1)	5 (4.5)
Nausea	6 (37.5)	1 (6.3)	3 (11.5)	0	27 (24.3)	2 (1.8)
Hypertension	4 (25.0)	2 (12.5)	5 (19.2)	3 (11.5)	17 (15.3)	9 (8.1)
Vomiting	3 (18.8)	0	8 (30.8)	0	22 (19.8)	1 (0.9)
Somnolence	3 (18.8)	0	0	0	2 (1.8)	1 (0.9)
Confusional state	2 (12.5)	0	4 (15.4)	1 (3.8)	8 (7.2)	1 (0.9)
Oliguria	2 (12.5)	1 (6.3)	3 (11.5)	2 (7.7)	4 (3.6)	3 (2.7)
Weight increased	2 (12.5)	0	4 (15.4)	0	20 (18.0)	2 (1.8)
Edema	1 (6.3)	0	4 (15.4)	0	4 (3.6)	0
Pleural effusion	1 (6.3)	1 (6.3)	5 (19.2)	1 (3.8)	10 (9.0)	1 (0.9)
Capillary leak syndrome	1 (6.3)	0	3 (11.5)	2 (7.7)	16 (14.4)	5 (4.5)

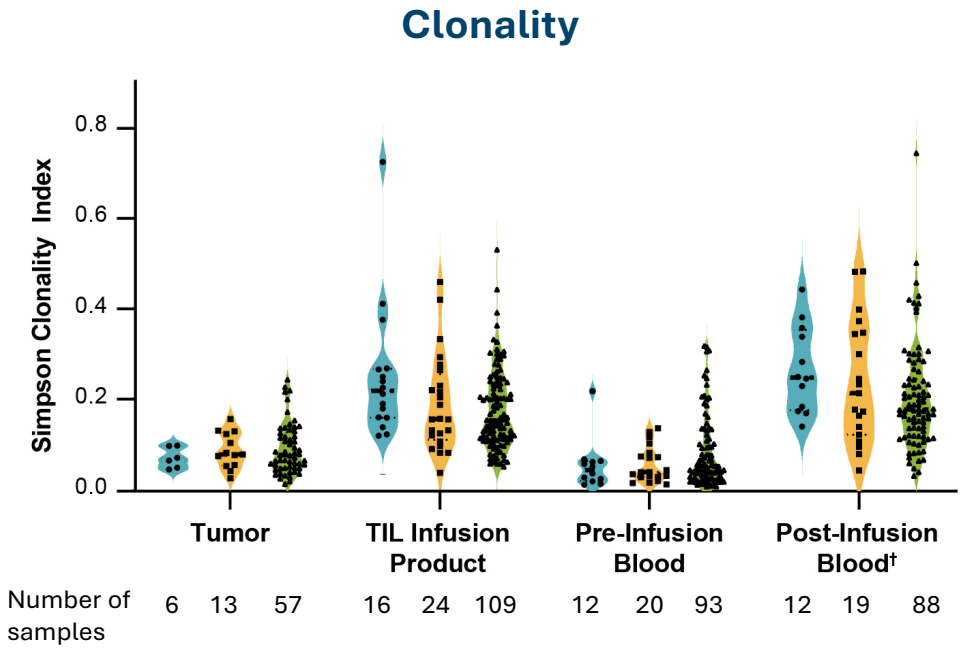
Grade 3/4 Lab Hematologic Abnormalities, by Number of IL-2 Doses*

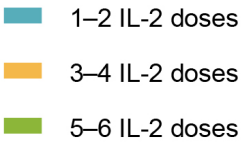
Preferred Term, n (%)	1–2 IL-2 Doses (n=16)	3–4 IL-2 Doses (n=26)	5–6 IL-2 Doses (n=111)
Leukopenia	16 (100)	26 (100)	111 (100)
Lymphopenia	16 (100)	26 (100)	111 (100)
Neutropenia	16 (100)	26 (100)	111 (100)
Thrombocytopenia	16 (100)	25 (96.2)	103 (92.8)
Anemia	12 (75.0)	22 (84.6)	74 (66.7)

- IL-2 discontinuation was guided by clinical tolerance, thus limiting safety comparisons across dose groups
- Reported Grade 3/4 TEAEs were similar across IL-2 dose groups and consistent with those of the overall population[2]
- All patients developed Grade 3/4 lymphopenia (per lab values) after NMA-LD (Day 0–4)
- Three Grade 5 TEAEs occurred‡ (5–6 IL-2 dose group)
  - Pneumonia (n=1)
  - Acute respiratory failure (n=1)
  - Intra-abdominal hemorrhage (n=1)

*3 patients in the Safety Analysis Set (defined as patients who received any lifileucel infusion) did not receive IL-2.
†Other relevant events: Grade 3/4 cytokine release syndrome (CRS; investigator-assessed, no confirmatory serum cytokine levels measured) was reported for 1 patient receiving 5–6 IL-2 doses. Any-grade CRS was reported for 1 patient receiving 3–4 IL-2 doses and 3 patients receiving 5–6 IL-2 doses.
‡An additional Grade 5 TEAE occurred in a patient who did not receive IL-2.
1. Proleukin® (aldesleukin) Prescribing Information. **2**. Sarnaik, et al. SITC 2022. Abstract 789.
Abbreviations: IL-2, interleukin 2; NMA-LD, nonmyeloablative lymphodepletion; TEAE, treatment-emergent adverse event.

TCR CLONALITY WAS INDEPENDENT OF NUMBER OF IL-2 DOSES



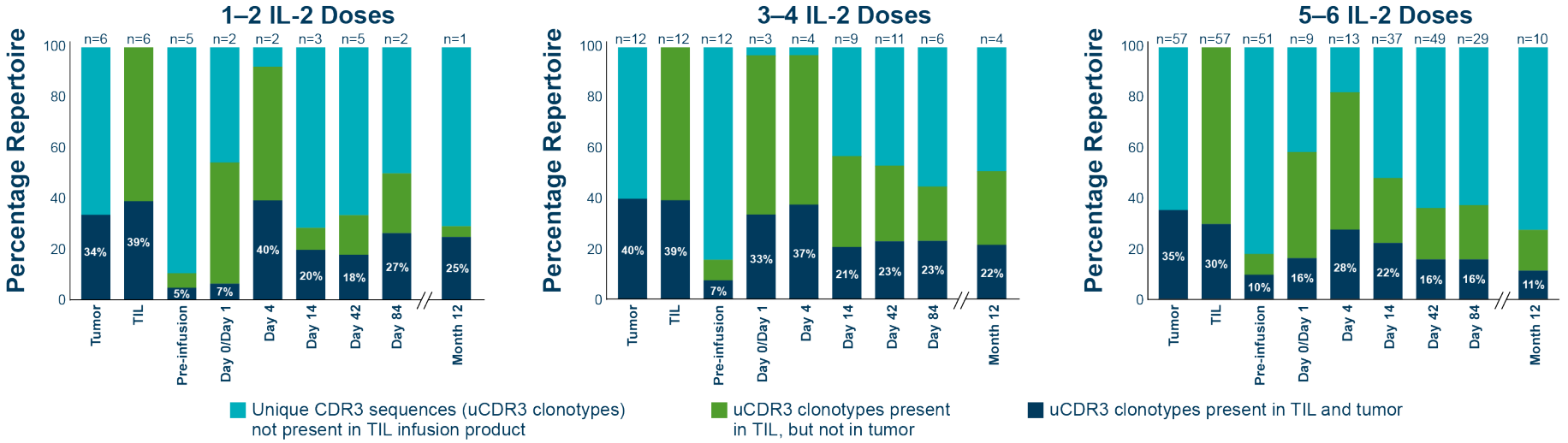


- Polyclonality* was similar between IL-2 dose groups within each sample type

*As measured by the Simpson Clonality Index, which reflects the mono- or poly-clonality of a sample. Values can range from 0 (evenly distributed, polyclonal sample) to 1 (monoclonal sample).
†Day 42 visit.

Abbreviations: IL-2, interleukin-2; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocytes.

TCR CLONAL EXPANSION AND PERSISTENCE WERE OBSERVED IN ALL IL-2 DOSE GROUPS



- uCDR3 clonotypes identified in both tumor and TIL infusion product likely reflect tumor-associated clonotypes captured in the TIL infusion product
- These shared uCDR3 clonotypes expanded and persisted to a similar degree, regardless of number of IL-2 doses

Abbreviations: IL-2, interleukin-2; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocyte; uCDR3, unique CDR3.

CONCLUSIONS

- Up to 6 doses of aldesleukin were planned in the lifileucel regimen with discontinuation recommended for IL-2 side effects
  - The median number of IL-2 doses tolerated was 6
  - Median cumulative dose administered was 79% lower than the approved maximum cumulative dose of 1 full treatment course of aldesleukin monotherapy for melanoma
- The number of administered IL-2 doses did not show association with clinical outcomes
  - Safety profile, ORR, and DOR were comparable across the range of IL-2 doses
  - Responses to lifileucel were observed despite IL-2 administration during lymphopenia and in patients who progressed after prior IL-2 monotherapy
  - TCR clonality data suggest similar clonal expansion and persistence of TIL-derived clones across all IL-2 dose groups

Protocol-guided abbreviated high-dose IL-2 dosing after lifileucel, with discontinuation driven by clinical tolerance, is feasible and does not independently contribute to anti-neoplastic activity

Abbreviations: DOR, duration of response; IL-2, interleukin-2; ORR, objective response rate; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocyte.

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