Clinical Feasibility and Treatment Outcomes With Unselected Autologous Tumor Infiltrating Lymphocyte Therapy in Patients With Advanced Cutaneous Melanoma

Robert E. Hawkins,[1-3] Yizhou Jiang,[1] Paul C. Lorigan,[2] Fiona C. Thistlethwaite,[2,3] Manon Pillai,[2] Martine Thomas,[1] Natalia Kirillova,[1] John S. Bridgeman,[1] Gray Kueberuwa,[1] Ryan D. Guest,[1] Zachary J. Roberts[1]

[1]Instil Bio, Inc., Dallas, TX; [2]The Christie, NHS Foundation Trust, Manchester, United Kingdom; [3]University of Manchester, Manchester, United Kingdom

Background

- A minority of patients with advanced melanoma achieve long-term survival with immunotherapy, and those who relapse following ICI and, if *BRAF*-mutated, BRAF inhibition have limited treatment options
- The intrinsic antitumor activity and broad T-cell receptor repertoire of unselected autologous TILs may provide advantages over other treatments in solid tumors, including ICI-refractory melanoma

TIL therapy has demonstrated durable complete remissions in patients with melanoma, with an estimated 41% objective response rate in advanced cutaneous melanoma[1]

BRAF, B-raf proto-oncogene; ICI, immune checkpoint inhibition; TIL, tumor infiltrating lymphocyte.

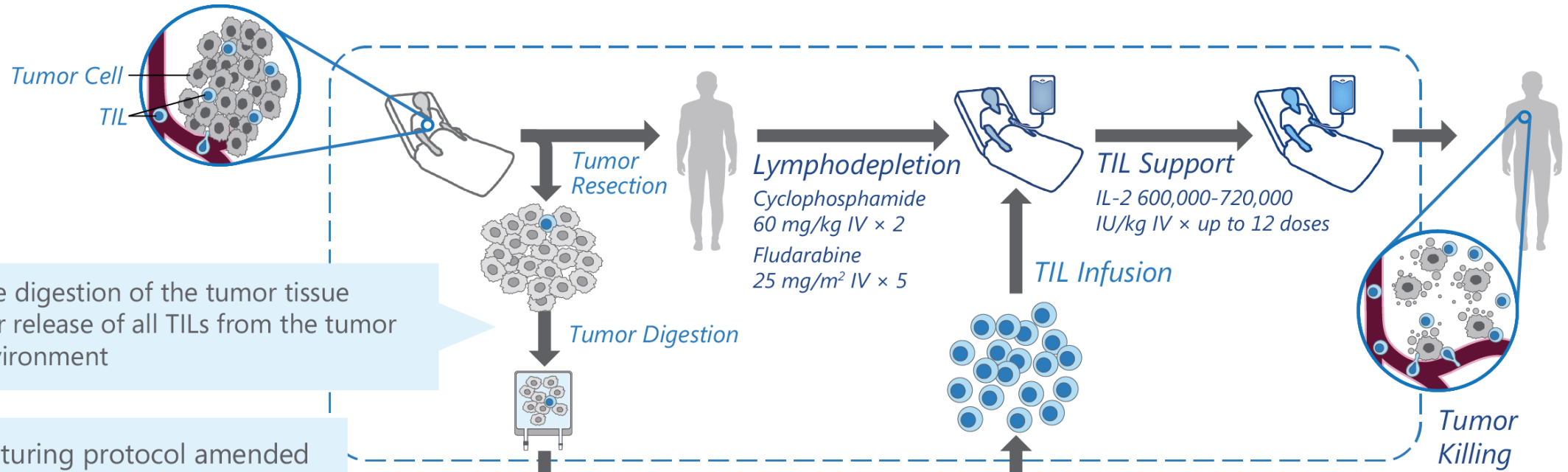
1. Dafni U, et al. *Ann Oncol.* 2019;30(12):1902-1913.

Methods

- This is a retrospective analysis of a single-center experience of TILs for compassionate use treatment of advanced cutaneous melanoma
- Unselected autologous TILs derived from digested tumor tissue were manufactured under a MHRA Manufacturing Specials license
- Twenty-one patients with advanced cutaneous melanoma and no standard of care treatment options received non-myeloablative lymphodepleting chemotherapy (cyclophosphamide 60 mg/kg/day × 2 days, fludarabine 25 mg/m^2/day × 5 days) followed by TIL infusion and post-TIL high-dose IL-2 (600,000-720,000 IU/kg) on a compassionate use basis
- Patients were hospitalized for treatment
- Efficacy for 15 of 21 patients was locally assessed by CT/MRI in accordance with RECIST version 1.1. Efficacy for the remaining 6 patients was assessed using non–RECIST 1.1 imaging (eg, PET) and clinical monitoring (eg, history and physical examination, laboratory assessments)
- Clinically significant AEs with onset post-TIL infusion were reported during the hospitalization period for all treated patients
- Data cutoff date: December 31, 2019

AE, adverse event; CT, computed tomography; IL-2, interleukin-2; MHRA, Medicines and Healthcare Products Regulatory Agency; MRI, magnetic resonance imaging; PET, positron emission tomography; RECIST, Response Evaluation Criteria in Solid Tumors; TIL, tumor infiltrating lymphocyte.

Tissue Procurement and Manufacturing



Complete digestion of the tumor tissue allows for release of all TILs from the tumor microenvironment

Manufacturing protocol amended to incorporate cryopreservation immediately following tumor digestion to:

- Optimize TIL quantity, quality, and diversity
- Enable centralized manufacturing
- Improve flexibility for physicians and patients

IL-2, interleukin-2; IV, intravenous; REP, rapid expansion protocol; TIL, tumor infiltrating lymphocyte.

Patient Selection Guidelines

Should Have	Should Not Have
• Histologically confirmed malignant melanoma with confirmed evidence of progressive metastatic disease • Satisfactory hematological and biochemical indices • Adequate cardiac function • Suitable fitness for all planned treatments and procedures (including surgery for TIL harvest, lymphodepleting chemotherapy, TILs, and IL-2) • A metastatic site that could be excised to obtain a specimen of at least 1 cm^3. For lymph nodes, these must have been >2 cm^3 • Measurable/evaluable disease after the surgical resection • No standard of care treatment options	• Prior allogeneic transplant • Symptomatic brain metastasis measuring ≥10 mm in diameter • Lymphotoxic therapy such as chemotherapy, HD steroids, or other immunosuppressive therapy within 4 weeks of harvesting • Concurrent serious infection within 28 days prior to treatment • Steroid use ≤3 weeks before treatment, except for physiological replacement doses of steroids

HD, high dose; IL-2, interleukin-2; TIL, tumor infiltrating lymphocyte.

Treatment Exposure

Treatment Exposure	All Treated Patients (N=21)
Received fludarabine lymphodepletion, n (%)	21 (100)
Received cyclophosphamide lymphodepletion,[a] n (%)	21 (100)
Total TIL cells infused ($\times 10^9$), median (range)	32 (8 – 63)
Number of IL-2 doses (n), median (range)	8 (4 – 11)

- Between October 2011 and August 2019, 21 patients with advanced cutaneous melanoma were treated
- Median duration of follow-up: 52.2 months

IL-2, interleukin-2; TIL, tumor infiltrating lymphocyte.

[a] All but 1 patient received planned doses of cyclophosphamide/fludarabine lymphodepleting chemotherapy prior to the TIL infusion. One patient received slightly reduced doses of cyclophosphamide due to prior neutropenia, generally deteriorating health, and an elevated risk of atrial fibrillation.

Demographics and Baseline Characteristics

	Imaging Evaluable Set (n=15)	All Treated Patients (N=21)
Age (y), median (range)	54 (16 – 68)	45 (16 – 68)
Male, n (%)	11 (73)	15 (71)
Stage IV, n (%)	15 (100)	21 (100)
Disease sites, median (range)	4 (2 – 10)	4 (2 – 10)
M1c disease, n (%)	10 (67)	14 (67)
M1d disease, n (%)	5 (33)	7 (33)
Tumor burden (mm),[a] median (range)	123 (29 – 281)	100 (13 – 281)[b]
LDH, n (%)		
>ULN to ≤2 × ULN	3 (20)	7 (33)
>2 × ULN	3 (20)	3 (14)
Prior systemic regimens (n), mean (range)	3 (1 – 5)	3 (1 – 9)
Checkpoint inhibitor, n (%)	14 (93)	19 (91)
PD-1 inhibitor	9 (60)	12 (57)
CTLA-4 inhibitor	14 (93)	19 (91)
Dual PD-1/CTLA-4 inhibitor relapsed/refractory	9 (60)	12 (57)
BRAF-mutated patients, n (%)	7 (47)	11 (52)
BRAF inhibitor ± MEK inhibitor	7 (47)	11 (52)

BRAF, B-raf proto-oncogene; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; LDH, lactate dehydrogenase; PD-1, programmed cell death protein 1; RECIST, Response Evaluation Criteria in Solid Tumors; ULN, upper limit of normal.

[a] Target lesions sum of diameters (local assessment per RECIST 1.1).

[b] 20 of 21 patients had tumor burden data available at baseline.

Summary of Safety

TEAEs Post-TIL Infusion ≥15%, n (%)	Any Grade (N=21)
Thrombocytopenia	13 (62)
Pyrexia	12 (57)
Rigors	9 (43)
Neutropenia	6 (29)
Tachycardia	6 (29)
Pulmonary edema	5 (24)
Vascular Leak	5 (24)
Rash	4 (19)

- No grade 5 TEAEs were observed
- 10 patients died ≥90 days after TIL infusion and prior to data cutoff
  - 4 due to PD
  - 1 possibly due to AE caused by subsequent anticancer therapy
  - 5 with documented PD prior to death but specific cause of death not available
- Cytopenias
  - Onset: ≈ -7 to 0 days (lymphodepletion)
  - Nadir: ≈ 1 to 4 days (post-TIL)
  - Recovery: ≈ 7 days (post-TIL)

AE, adverse event; PD, progressive disease; TEAE, treatment-emergent AE; TIL, tumor infiltrating lymphocyte.

Best Overall Response

Response	Imaging Evaluable Set[a] (n=15)	All Treated Patients[b] (N=21)
Best overall response (CR + PR), n (%) CR PR	8 (53) 2 (13) 6 (40)	14 (67) 4 (19) 10 (48)
Stable disease, n (%)	3 (20)	4 (19)
Progressive disease, n (%)	4 (27)	3 (14)
Disease control rate (CR + PR + SD), n (%)	11 (73)	18 (86)
Median time to response, months	1.7	1.7

- Responses were generally consistent across subgroups, including age, number of disease sites, number of prior lines of therapy, prior BRAF inhibitor, prior PD-1 inhibitor, baseline brain metastasis, and baseline tumor burden

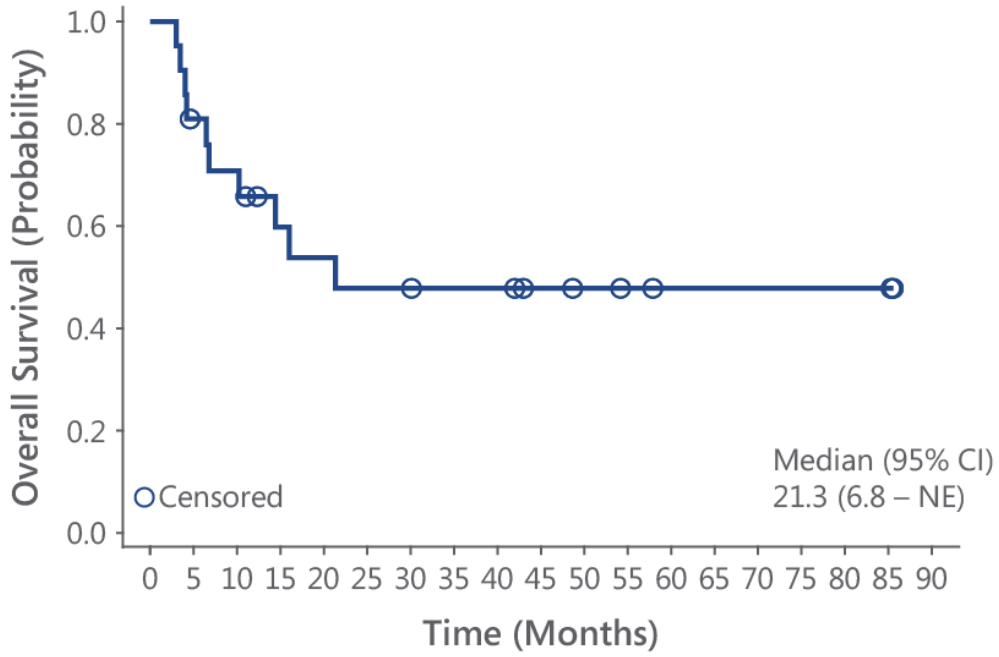
BRAF, B-raf proto-oncogene; CR, complete remission; CT, computed tomography; MEK, mitogen-activated protein kinase; MRI, magnetic resonance imaging; PD-1, programmed cell death protein 1; PR, partial remission; RECIST, Response Evaluation in Solid Tumors; SD, stable disease; TIL, tumor infiltrating lymphocyte.

[a] Imaging evaluable set includes all treated patients with a baseline CT or MRI-based disease assessment and at least 1 CT or MRI-based disease assessment per RECIST 1.1 prior to any subsequent anticancer therapy. Confirmation of response was not required.

[b] Responders includes 2 patients with dabrafenib + MEK inhibitor-refractory disease whose disease was unequivocally progressing on the combination therapy prior to TIL and who received postinfusion dabrafenib to prevent tumor flare.

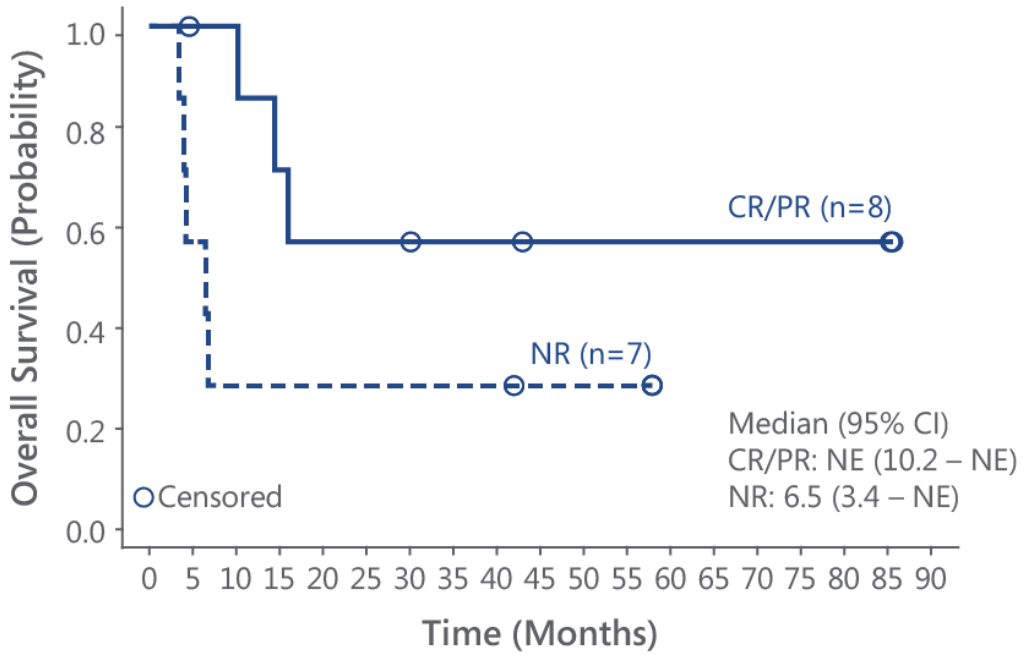
Overall Survival

OS for All Evaluable Patients (N=21)



Patients at risk	21	16	14	10	9	8	8	7	7	5	4	3	2	2	2	2	2	2	0
(Patients censored)	(0)	(1)	(1)	(3)	(3)	(3)	(3)	(4)	(4)	(6)	(7)	(8)	(9)	(9)	(9)	(9)	(9)	(9)	(11)

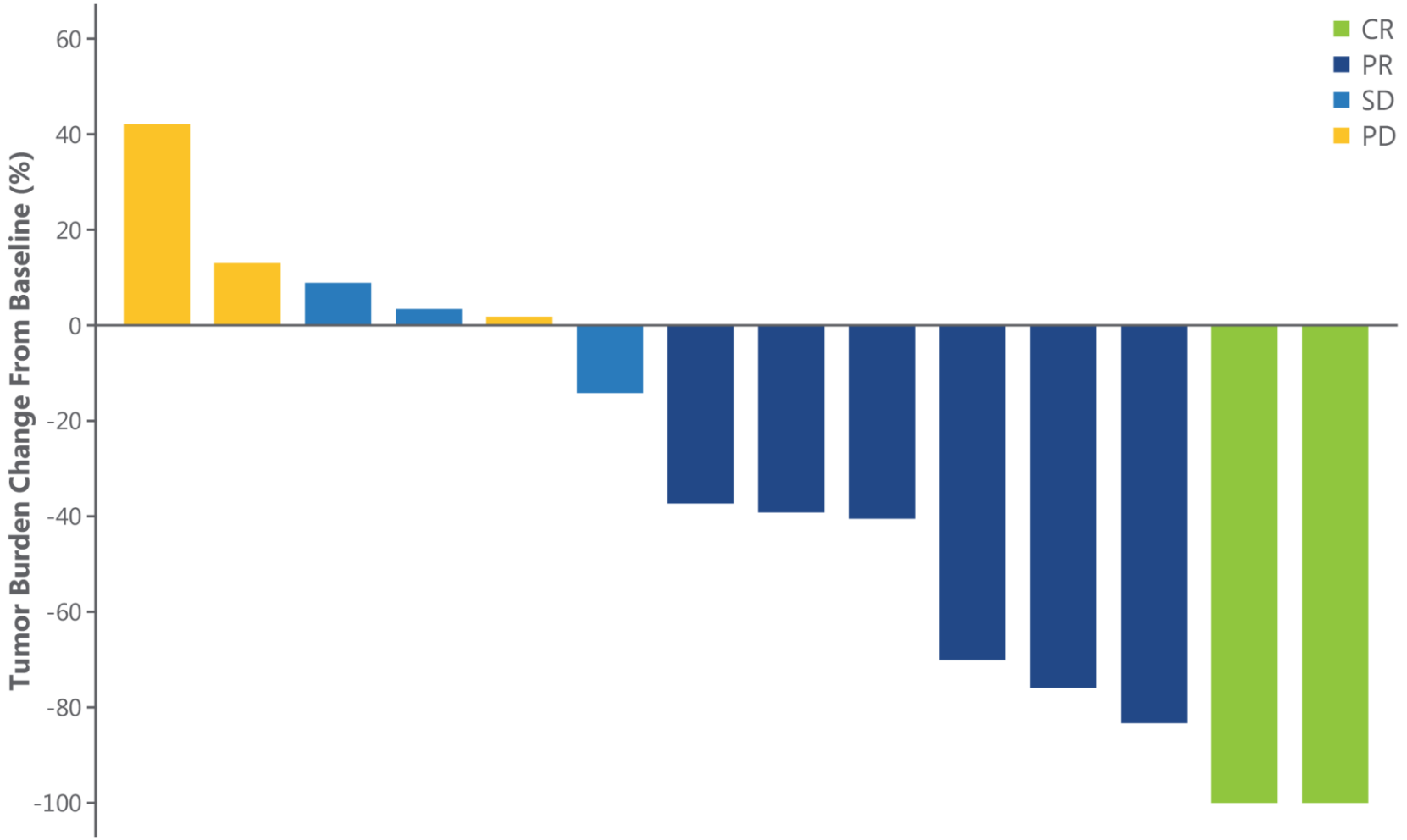
OS by Response for Imaging Evaluable Set (n=15)



CR/PR at risk	8	7	7	5	4	4	4	3	3	2	2	2	2	2	2	2	2	2	0
(CR/PR censored)	(0)	(1)	(1)	(1)	(1)	(1)	(1)	(2)	(2)	(3)	(3)	(3)	(3)	(3)	(3)	(3)	(3)	(3)	(5)
NR at risk	7	4	2	2	2	2	2	2	2	1	1	1	0	0	0	0	0	0	0
(NR censored)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(1)	(1)	(2)	(2)	(2)	(2)	(2)	(2)	(2)

CR, complete remission; NE, not evaluable; NR, nonresponder; OS, overall survival; PR, partial remission.

Depth of Responses in Imaging Evaluable Set (n=14)[a]

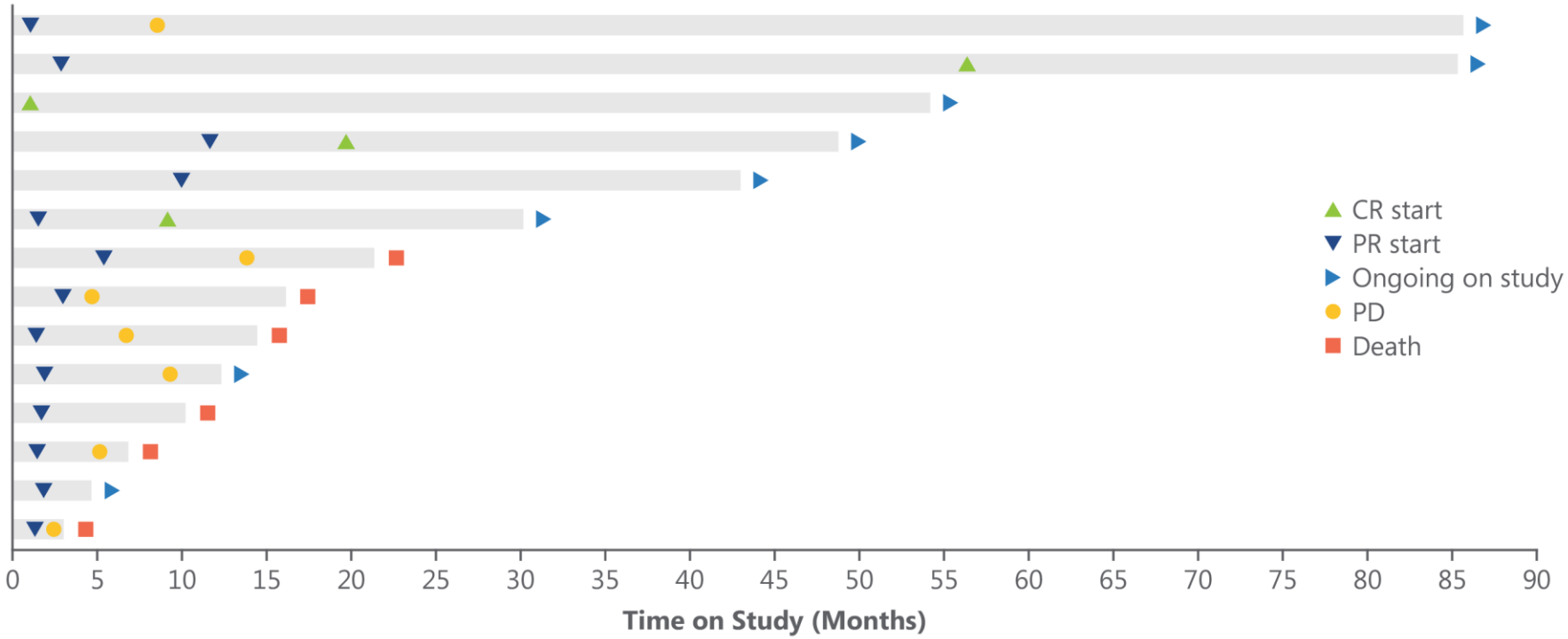


CR, complete remission; PD, progressive disease; PR, partial remission; SD, stable disease.

[a] One patient with a best overall response of PD did not have any posttreatment target lesion measures reported (progression determined by observation of new lesions) and hence was not presented in the plot.

Time to Response and OS in Responding Patients (n=14)

Patient	Prior Checkpoint Inhibitor
1[a]	No
2	Ipi
3	No
4[b]	Ipi
5	Ipi and pembro
6	Ipi and nivo
7[b]	Ipi and nivo
8	Ipi and pembro
9	Ipi
10[a]	Ipi and nivo
11	Ipi and pembro
12[a]	Ipi
13	Ipi, nivo, and pembro
14	Ipi



- With a median follow-up of 52.2 months, 5/21 (24%) had durable ongoing responses (>30 months post-TIL infusion)
- All patients achieving a CR remained alive and disease free as of data cutoff

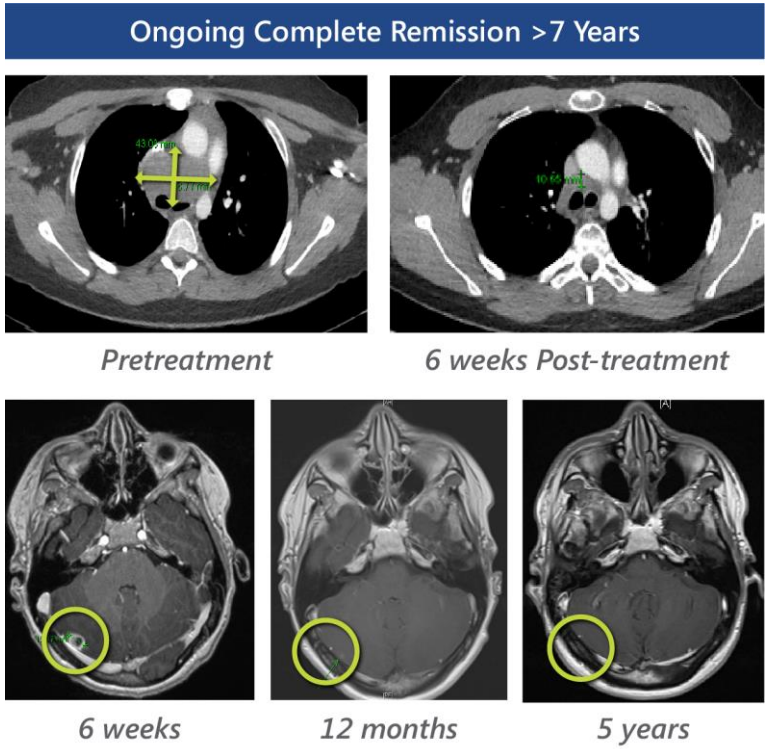
BRAF, B-raf proto-oncogene; CR, complete remission; HD, high dose; IL-2, interleukin-2; Ipi, ipilimumab; MEK, mitogen-activated protein kinase; nivo, nivolumab; PD, progressive disease; PD-1, programmed cell death protein 1; pembro, pembrolizumab; PR, partial remission; TIL, tumor infiltrating lymphocyte.

[a] Patient 1 received a checkpoint inhibitor at the time of disease progression; patients 10 and 12 received checkpoint inhibitor and HD IL-2, respectively, prior to documented disease progression.

[b] Patients 4 and 7 had unequivocally BRAF+MEK–refractory melanoma immediately prior to TIL treatment but were continued on dabrafenib, with brief interruptions for tumor harvest and TIL infusion, to prevent tumor flare upon discontinuation. Patient 4 was treated with dabrafenib for 3 months following TIL infusion, at which point the dabrafenib was stopped. Patient 7 achieved a PR that lasted approximately 14 months from TIL infusion during which time dabrafenib was continued.

Case Study: Successful Treatment of Brain Metastases

Patient and Disease Characteristics	• 16-year-old male with *BRAF*-mutated melanoma • Extensive mediastinal disease and brain metastases • Bulky disease (SLD, 103 mm)
Prior Treatment History	• Relapsed/refractory to 3 prior lines of therapy, including ipilimumab, a CTLA-4 inhibitor, and dabrafenib, a BRAF inhibitor
Response to TIL Therapy	• Rapid reduction in his disease burden observed at 6 weeks • PR achieved at 3 months • CR determined by clinical review at 56 months and confirmed with CT/MRI at month 60 post-TIL therapy • Ongoing CR at 85 months (>7 years) post-TIL therapy
TEAEs	• Expected HD IL-2–related toxicities observed • Overall, 8 IL-2 doses administered with tachycardia, fever, and cardiovascular instability observed with each dose. No evidence of infection • Seizure in the setting of high fever and tachycardia/shortness of breath after dose 6, which resolved spontaneously; 7th dose of IL-2 delayed, prophylactic levetiracetam administered, and no further seizure events observed • Symptomatic cough/shortness of breath due to disease, present prior to treatment, worsened during IL-2, and subsequently improved after IL-2 stopped • Neutropenia from days 1 to 6; no platelet support required



BRAF, B-raf proto-oncogene; CR, complete remission; CT, computed tomography; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; HD, high dose; IL-2, interleukin-2; MRI, magnetic resonance imagery; PR, partial remission; SLD, sum of longest diameters; TEAE, treatment-emergent adverse event; TIL, tumor infiltrating lymphocyte.

Conclusions

- TIL products made from digested tumors demonstrated high overall and CR rates in this retrospective analysis of a compassionate use case series conducted at the Christie Hospital in Manchester, United Kingdom
- AEs were consistent with the established safety profile[1] of Cy/Flu+TIL+IL-2 for treatment of advanced melanoma
- Autologous TIL manufacturing and administration is feasible and may offer significant clinical benefit to patients with checkpoint inhibitor– and, if applicable, BRAF±MEK inhibitor–refractory melanoma
- Additional process updates, including cryopreservation of digested tumor and process closure, have been implemented to improve the robustness, reproducibility, and scalability of the complex TIL manufacturing process to enable multicenter clinical trials with centralized manufacturing
- Results of this retrospective analysis should be interpreted with caution; further prospective clinical trials are warranted
- DELTA-1, a global phase 2 clinical trial of this therapy in patients with advanced melanoma is planned for 2021 (EudraCT, 2020-003862-37)

AE, adverse event; BRAF, BRAF, B-raf proto-oncogene; CR, complete response; Cy/Flu, cyclophosphamide/fludarabine; IL-2, interleukin-2; MEK, mitogen-activated protein kinase; TIL, tumor infiltrating lymphocytes.

1. Dafni U, et al. *Ann Oncol.* 2019;30(12):1902-1913.

Acknowledgments and Disclosures

- We would like to thank all the staff within The Christie NHS Foundation Trust and The Christie Clinic who worked tirelessly to provide high-quality care to all the patients in this report
- Medical writing support was provided by Christopher Waldapfel, PharmD of Instil Bio and Jennifer Leslie, PhD, of Nexus GG Science with funding from Instil Bio

REH: Instil Bio (UK) Ltd., Manchester, United Kingdom; Cellular Therapeutics/Immetacyte Ltd, Manchester, United Kingdom; The Christie Hospital, Manchester, United Kingdom; The University of Manchester, Manchester, United Kingdom. YJ: Instil Bio, Inc, Tarzana, CA. PCL: The Christie Hospital, Manchester, United Kingdom; The University of Manchester, Manchester, United Kingdom. FCT: Innovate Manchester Advanced Therapy Centre Hub (iMATCH); Standard Approach to atMP tissue colLEction (SAMPLE) Project; Achilles Therapeutics Ltd, London, United Kingdom. MP: The Christie Hospital, Manchester, United Kingdom; The University of Manchester, Manchester, United Kingdom. MT: Instil Bio (UK) Ltd., Manchester, United Kingdom. NK: Immetacyte Ltd, Manchester, United Kingdom. JSB: Instil Bio, Inc, Tarzana, CA. GK: Instil Bio, Inc, Tarzana, CA. RDG: Instil Bio, Inc, Tarzana, CA. ZJR: Instil Bio, Inc., Tarzana, CA.