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

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BACKGROUND

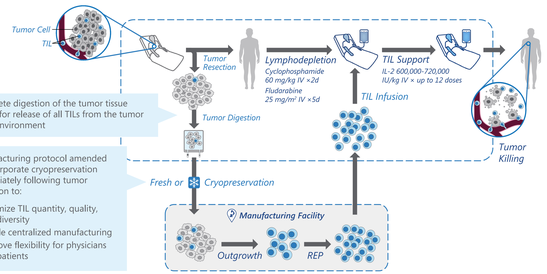
- A minority of patients with advanced melanoma achieve long-term survival with immunotherapy, and those who relapse following immune checkpoint inhibition and, if *BRAF*-mutated, BRAF inhibition have limited treatment options
- The intrinsic antitumor activity and broad T-cell receptor repertoire of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

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

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 Medicines and Healthcare Products Regulatory Agency Manufacturing Specials license (**Figure 1**)
- Twenty-one patients with advanced cutaneous melanoma and no standard of care treatment options received nonmyeloablative lymphodepleting chemotherapy (cyclophosphamide 60 mg/kg/day ×2 days, fludarabine 25 mg/m^2/day ×5 days [Cy/Flu]) followed by TIL infusion and post-TIL high-dose (HD) interleukin-2 (IL-2; 600,000-720,000 IU/kg) on a compassionate use basis (**Figure 1**)
- Patients were hospitalized for treatment
- Efficacy for 15 of 21 patients was locally assessed by computed tomography (CT)/magnetic resonance imaging (MRI) in accordance with Response Evaluation in Solid Tumors version 1.1 (RECIST v1.1). Efficacy for the remaining 6 patients was assessed using standard imaging techniques (eg, CT, positron emission tomography) and clinical monitoring (eg, history and physical examination, laboratory assessments) but did not have quantitative tumor measurement to allow RECIST v1.1 assessment
- Clinically significant adverse events (AEs) with onset post-TIL infusion were reported during the hospitalization period for all treated patients
- Data cutoff date: December 31, 2019

Figure 1. Tissue Procurement and Manufacturing



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

Table 1. 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.

RESULTS

Table 2. Treatment Exposure

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

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.

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

Table 3. Demographics and Baseline Characteristics

	RECIST-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) M1c disease, n (%) M1d disease, n (%)	4 (2-10) 10 (67) 5 (33)	4 (2-10) 14 (67) 7 (33)
Tumor burden (mm),[a] median (range)	123 (29-281)	100 (13-281)[b]
LDH, n (%) >ULN to ≤2 ×ULN >2 ×ULN	 3 (20) 3 (20)	 7 (33) 3 (14)
Prior systemic regimens (n), mean (range) Checkpoint inhibitor, n (%) PD-1 inhibitor CTLA-4 inhibitor Dual PD-1/CTLA-4 inhibitor relapsed/refractory	3 (1-5) 14 (93) 9 (60) 14 (93) 9 (60)	3 (1-9) 19 (91) 12 (57) 19 (91) 12 (57)
BRAF-mutated patients, n (%)	7 (47)	11 (52)
BRAF inhibitor ± MEK inhibitor	7 (47)	11 (52)

BRAF, B-raf proto-oncogene serine/threonine kinase; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; LDH, lactate dehydrogenase; MEK, mitogen-activated protein kinase kinase; PD-1, programmed cell death protein 1; RECIST, Response Evaluation in Solid Tumors version 1.1; ULN, upper limit of normal.
[a] Target lesions sum of diameters (local assessment per RECIST v1.1).
[b] 20 of 21 patients had tumor burden data available at baseline.

Table 4. 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)

TEAE, treatment-emergent adverse event; TIL, tumor-infiltrating lymphocyte.

- No grade 5 treatment-emergent AEs (TEAEs) were observed
- 10 patients died ≥90 days after TIL infusion and prior to data cutoff
  - 4 due to progressive disease (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)

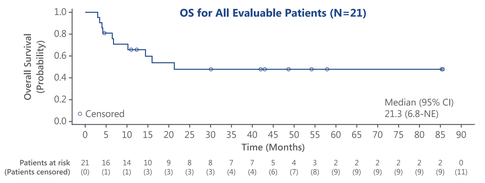
Table 5. Best Overall Response

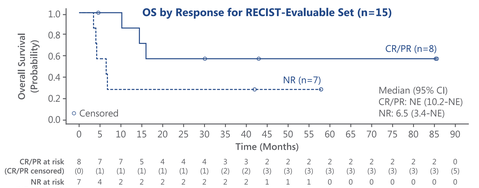
Response	RECIST-Evaluable Set[a] (n=15)	All Treated Patients[b] (N=21)
Best overall response (CR + PR), n (%) CR PR	8 (53) 2 (13) 6 (40)	14 (67) 4 (19) 10 (48)
Stable disease, n (%)	3 (20)	4 (19)
Progressive disease, n (%)	4 (27)	3 (14)
Disease control rate (CR + PR + SD), n (%)	11 (73)	18 (86)
Median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

BRAF, B-raf proto-oncogene, serine/threonine kinase; CR, complete response; CT, computed tomography; MEK, mitogen-activated protein kinase kinase; MRI, magnetic resonance imaging; PD-1, programmed cell death protein 1; PR, partial response; RECIST, Response Evaluation in Solid Tumors version 1.1; SD, stable disease; TIL, tumor-infiltrating lymphocyte.
[a] RECIST-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 include 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.

- 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

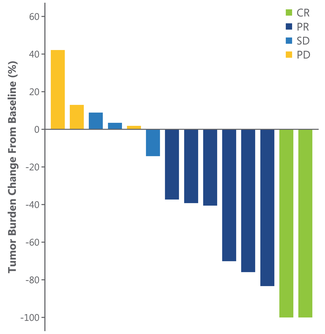
Figure 2. Overall Survival





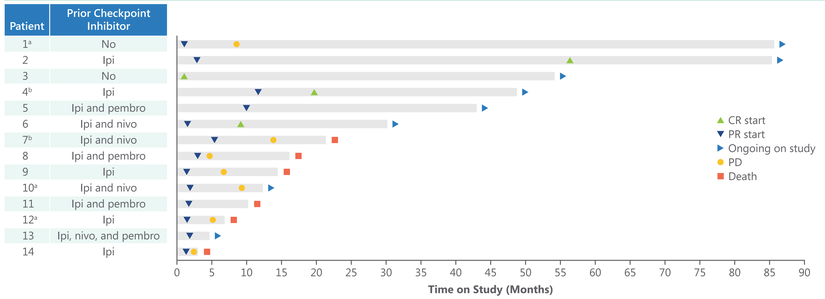
CR, complete response NE, not evaluable; NR, nonresponder; OS, overall survival; PR, partial response; RECIST, Response Evaluation in Solid Tumors version 1.1.

Figure 3. Depth of Responses in RECIST-Evaluable Set (n=14)[a]



CR, complete response; PD, progressive disease; PR, partial response; RECIST, Response Evaluation in Solid Tumors version 1.1; 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.

Figure 4. Time to Response and Overall Survival in Responding Patients (n=14)



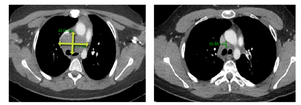
BRAF, B-raf proto-oncogene serine/threonine kinase; CR, complete response; HD, high dose; IL-2, interleukin-2; Ipi, ipilimumab; MEK, mitogen-activated protein kinase kinase; nivo, nivolumab; PD, progressive disease; PD-1, programmed cell death protein 1; pembro, pembrolizumab; PR, partial response; TIL,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

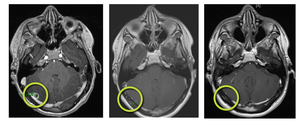
- With a median follow-up of 52.2 months, 5/21 (24%) had durable ongoing responses (>30 months post-TIL infusion)
- All patients achieving a complete response (CR) remained alive and disease free as of data cutoff

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 (sum of longest diameters 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
  - Partial response 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 were observed
  - Overall, 8 IL-2 doses were 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

Ongoing Complete Response >7 Years





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 currently enrolling patients (NCT05050006; EudraCT 2020-003862-37)

REFERENCE

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

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