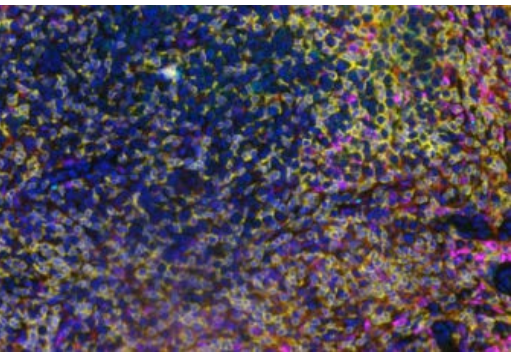
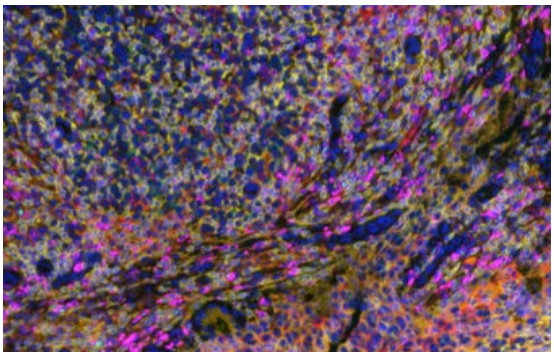
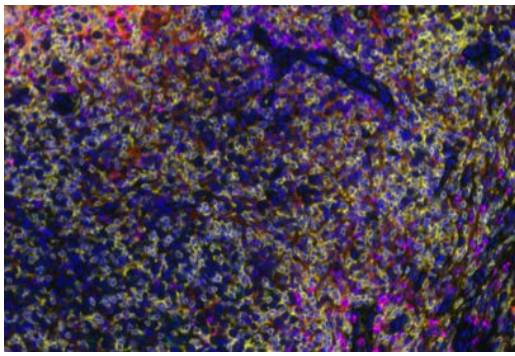

PHASE II STUDY OF INTRATUMORAL PLASMID INTERLEUKIN 12 (pIL-12) WITH ELECTROPORATION IN COMBINATION WITH PEMBROLIZUMAB IN STAGE III/IV MELANOMA PATIENTS WITH LOW TUMOR INFILTRATING LYMPHOCYTES

Adapted from Poster No. 203921, presented at SITC 2016

Alain P. Algazi[1], Katy Tsai[1], Michael D. Rosenblum[2], Prachi Nandoskar[1], Robert H. Andtbacka[3], Amy Li[1], John Nonomura[4], Toshimi Takamura[4], Mary A. Dwyer[4], Erica Browning[4], Reneta Talia[4], Chris Twitty[4], Sharron Gargosky[4], Jean S. Campbell[4], Carmen Ballesteros-Merino[5], Carlo B. Bifulco[5], Bernard A. Fox[5], Mai H. Le[4], Robert H. Pierce[4], Adil I. Daud[1]

[1] University of California, San Francisco Medical Center-Mt. Zion, 1600 Divisadero St, San Francisco, CA 94115 [2] University of California, San Francisco [3] Huntsman Cancer Institute, 1950 Circle of Hope Drive, Salt Lake City, Utah 84112 [4] Oncosec Medical Inc., 5820 Nancy Ridge Drive San Diego CA 92121 [5] Earle A. Chiles Research Institute at Providence Portland Medical Center, Portland, Oregon 97213

PROVIDENCE Cancer Center

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BACKGROUND

Low tumor infiltrating lymphocytes (TIL) are predictive of a poor response to immunotherapy with anti-PD-1/PD-L1 agents. We have shown that melanoma patients with $CD8^+$TIL that have a low frequency of CTLA-4^{hi} PD-1^{hi} are unlikely to respond to pembrolizumab (Daud 2016). Intratumoral electroporation of pIL-12 (IT-pIL12-EP) leads to induction of an IFN-γ signature suggestive of increased TIL as well as regression in both treated and untreated lesions. We hypothesize that combination IT-pIL12-EP and pembrolizumab will improve clinical outcomes in this low-response population. Preliminary results from a multi-center, Phase II, open-label trial testing this hypothesis are presented.

DESIGN

Eligible patients will be treated with IT-pIL12-EP in accessible lesions on Days 1, 5 and 8 every six weeks (cycles 1, 3, 5, 7, 9, 11, and 13) and with IV pembrolizumab (200 mg) on Day 1 of each 3-week cycle shown in Figure 3.

Eligibility restricted adults with a <25% CTLA-4^{hi} PD-1^{hi} in the $CD8^+CD45^+$ gate (low TIL) based on flow cytometry of the tissue biopsy and histological or cytological diagnosis of melanoma with progressive locally advanced or metastatic disease that is not amenable to definitive local therapy with curative intent (Figure 1).

Primary Objective:
To assess the anti-tumor efficacy (defined as the best overall response rate using RECIST v1.1) of the combination of intratumoral pIL-12 EP and pembrolizumab in patients with low TIL melanoma.

Secondary Objectives:
To assess safety and tolerability of the combination of intratumoral pIL-12 EP and pembrolizumab; duration of response; twenty-four week landmark progression free survival; median progression free survival; overall survival; and best overall objective response rate by immune related-Response Criteria (irRC) in low TIL melanoma patients treated with the combination of intratumoral pIL-12 EP and pembrolizumab.

Patients' pre- and post-treatment blood and tumor specimens were used for immune monitoring with multispectral IHC (msIHC) and Nanostring analysis.

FIGURE 1 Flow Cytometry (Daud JCI 2016)

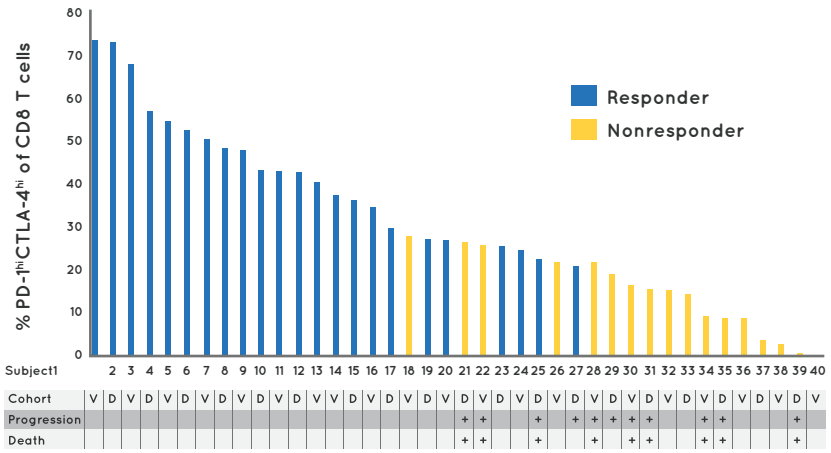
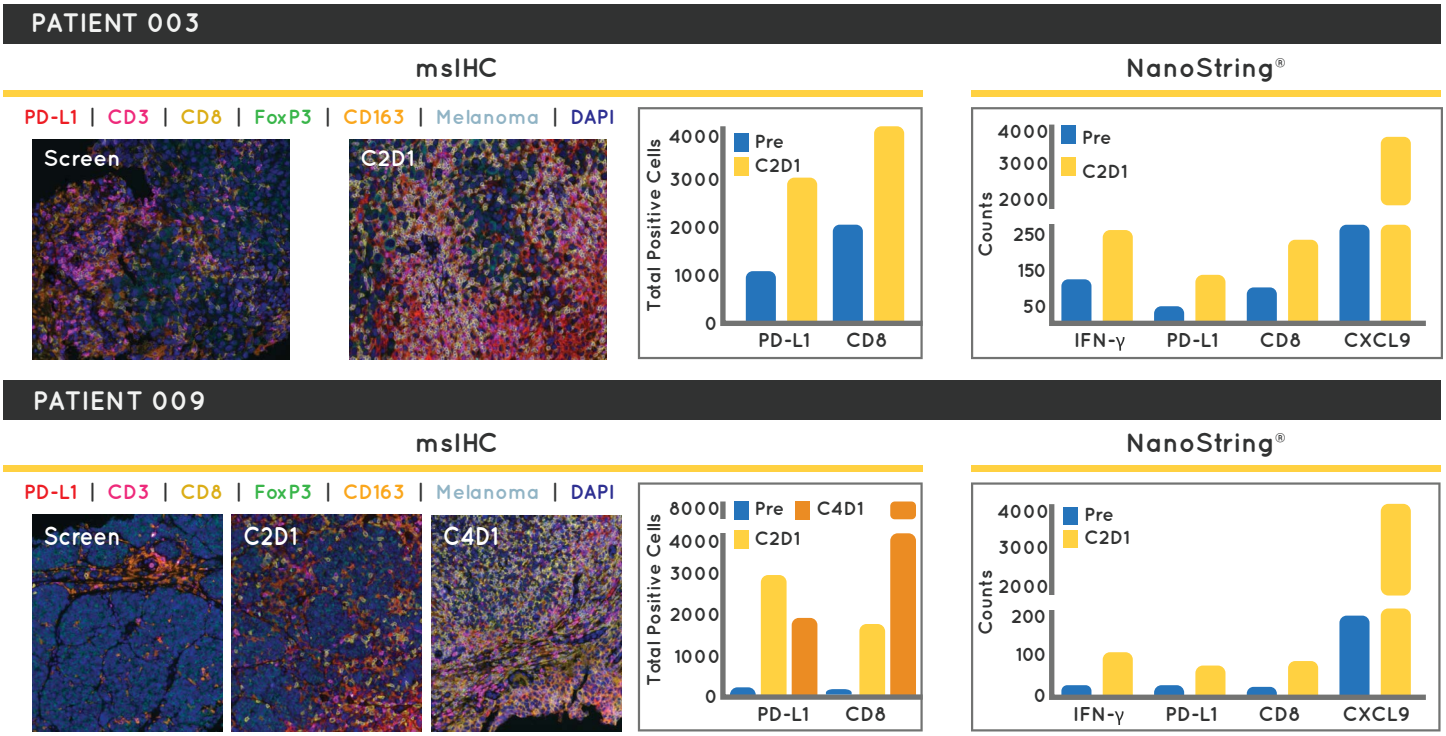


Figure 1: Histogram showing flow cytometric quantification of the percentages of CTLA-4^{hi}PD-1^{hi} tumor-infiltrating T cells in the $CD8^+$ CTL gate versus characteristics of individual patients. Responders included patients with tumor target lesions that met RECIST 1.1 criteria for a CR or a PR. Nonresponders included patients with tumor target lesions that met RECIST 1.1 criteria for progressive (≥20% increase in the target lesions) or stable disease (<30% reduction or <20% increase in tumor target lesions). n = 40 patients.

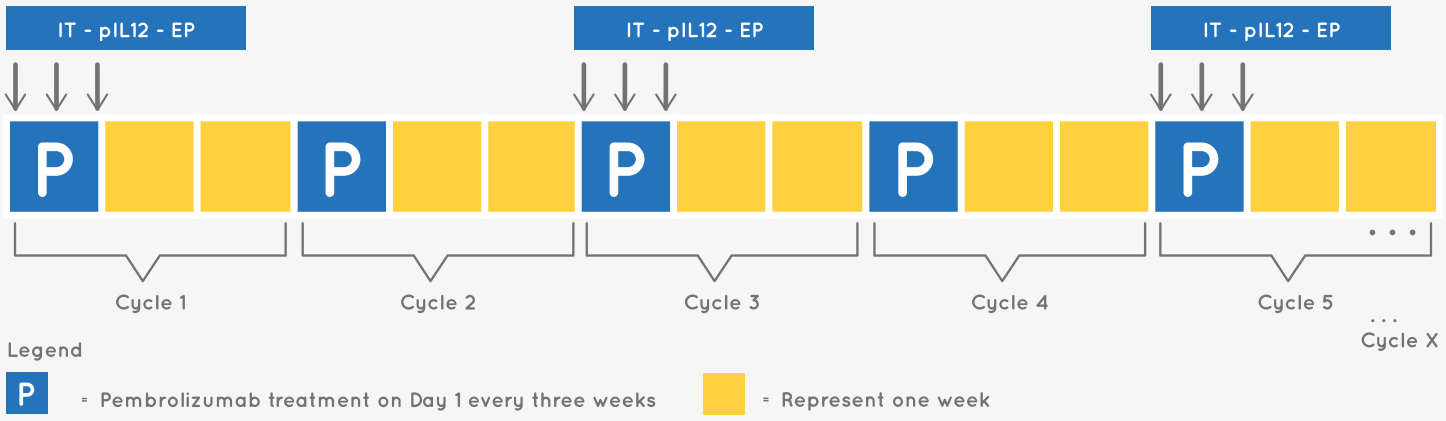
FIGURE 2 Immunohistochemistry



IMMUNE MONITORING RESULTS

Formalin fixed paraffin embedded (FFPE) tumor biopsies from two patients undergoing a complete response (CR) were used for msIHC and NanoString® analysis. msIHC analysis illustrates that immunologically inactive tumors become highly activated, evident by an increase in PD-L1^{+} cells and a brisk CD8^{+} T cell infiltrate after 1 (C2D1) or 3 (C4D1) cycles of combination IT-pIL12-EP plus pembrolizumab. A similar increase in both IFN-γ-related and CD8 gene expression was also measured with NanoString® analysis.

FIGURE 3 Study Design



RESULTS

DEMOGRAPHICS

These 15 patients, ages 39-89 years, were 53% male, 66% Stage III and 34% Stage IV.

SAFETY

Combination treatment was well tolerated; 38% of adverse events (AE) were classified as treatment site reactions (grade 1-2) that resolved.

- One reported serious adverse event (SAE) of grade-3 cellulitis resolved with 5d antibiotics.
- One reported grade-2 event of clinical interest (ECI) of diarrhea resolved with corticosteroids.
- One reported grade 3 ECI of elevated transaminases (AST, ALT) and alkaline phosphatase was likely due to 6 grams daily of acetaminophen for back-pain and unrelated to study procedures.

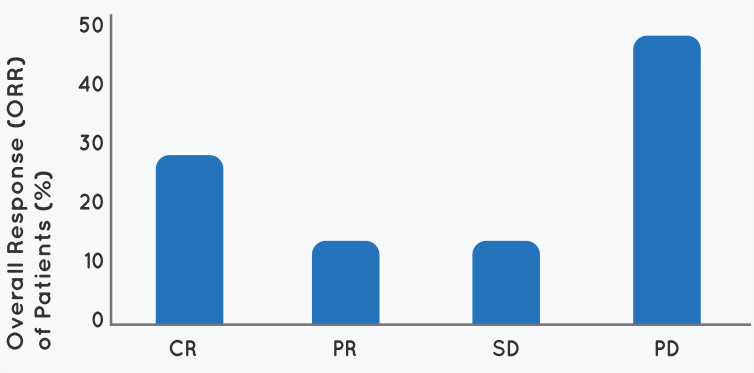
Regarding grade 3 AE:

(a) One patient (004) repeatedly experienced transient grade 3 pain with the electroporation procedure when pre-treated with systemic analgesics and lidocaine application at the treatment sites. These treatment-associated symptoms improved substantially after pre-treatment nerve blocks were initiated.

(b) Another patient (022) had a single episode of transient, grade 3 procedural pain associated with EP with no recurrence after optimization of the standard pre-medications described in the clinical trial protocol.

(c) One patient (013) had elevated liver function test (LFT), biliary colic & high AST considered unrelated to treatments.

FIGURE 4 Overall Response



RESULTS - BORR (Efficacy): Best overall response rate evaluated using RECIST v1.1 by investigator evaluation at each re-staging assessment performed approximately every 12 weeks showed a 40% ORR (13% PR, 27% CR) in this non responder population (N=15).

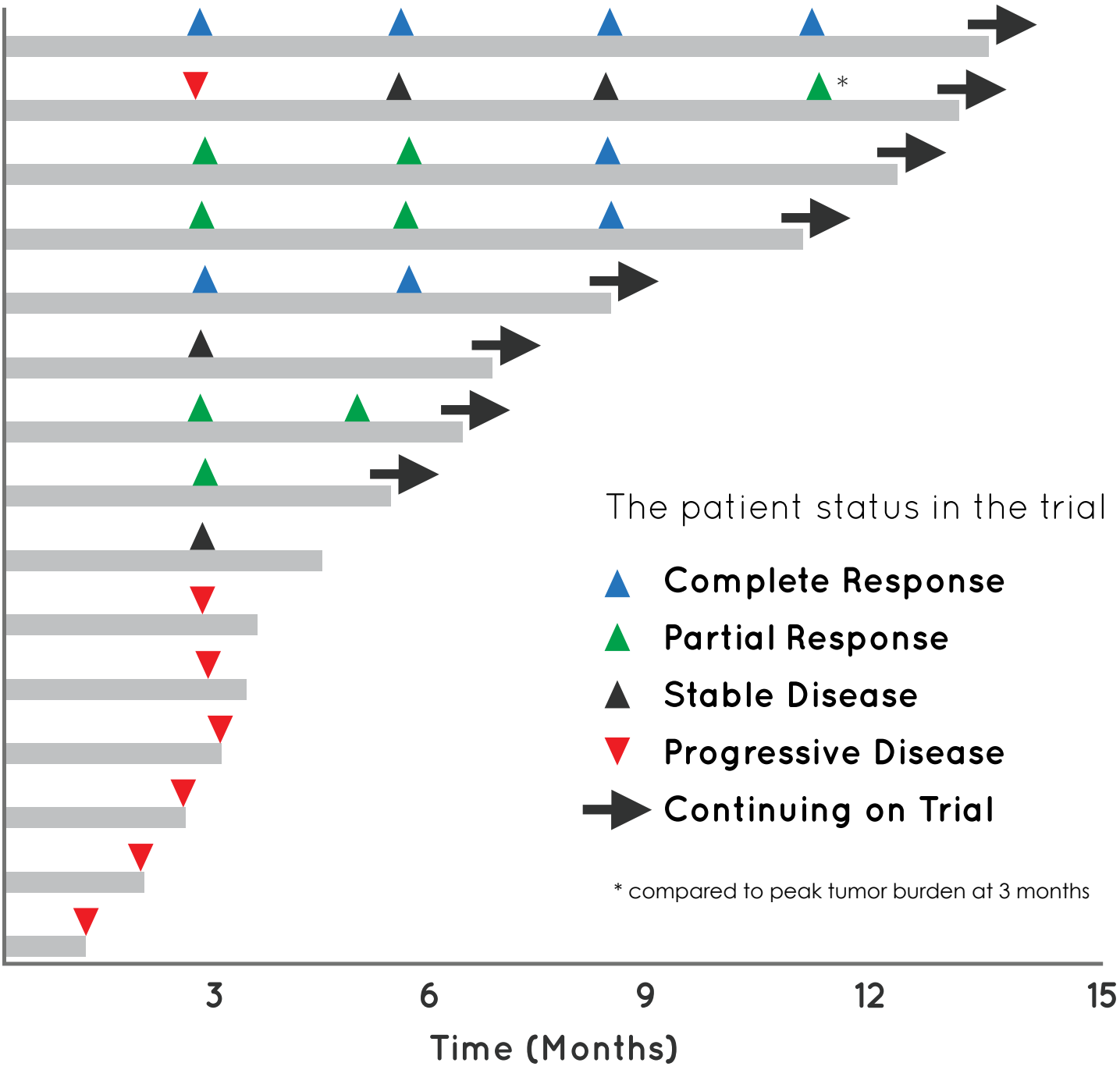
The best overall response rates of patients is indicated over the trial period. Note one patient who had PD by RECIST but continues therapy became a PR but is captured here as PD.

TABLE 1 TIL Frequency and Patient Response

Patient #	% CTLA-4^{hi} PD-1^{hi} CD8^{+} TIL<25% = non responder	Observed Response to IT-pIL12-EP + Pembro
001	21.8	PD^{+}
022	21.6	PR
023	18.7	PD
003	11	CR
026	11	PR
016	8.61	PD
009	7.99	CR
013	4.07	CR^{+}
019	1.57	PD^{+}
011	.918	PD^{+}
007	0.14	PD^{+}
017	<LLD	SD
020	<LLD	CR
004	<LLD	PD^{+}
024	<LLD	SD

+ previously treated with pembrolizumab

FIGURE 5 Patient Response



CONCLUSION

The combination IT-pIL12-EP with pembrolizumab in melanoma patients, selected to represent an anti-PD-1 non-responsive phenotype, was associated with a 40% clinical response. The combination therapy demonstrated an excellent safety profile and tumor-based biomarker analysis supports the hypothesis that IT-pIL12-EP can increase TIL, leading to an enhanced pembrolizumab response.

These data suggest that IT-pIL12-EP modulates the tumor microenvironment to enable an effective anti-PD-1mAb response in patients otherwise unlikely to respond.

NOTES

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