of interferon (IFN)-gamma or CD8+ tumor cells. In addition, these subgroups were further broken down based on the proportion of programmed death-ligand 1 (PD-L1)-expressing tumor-infiltrating cells as PD-L1+ (≥1%) or PD-L1− (<1%).

Results Patients treated with P+V+C with high and low TMB had similar PFS outcomes. However, the magnitude of the PFS benefit with A+V+C vs P+V+C was markedly higher in patients with high TMB (≥10 mutations/Mb) compared with patients with low TMB (<10 mutations/Mb) in whom the benefit between treatment arms was comparable (figure 1A). The magnitude of the PFS benefit with A+V+C was further enhanced in patients with high TMB and PD-L1− compared with patients with high TMB and PD-L1+. Overall, patients with potential for increased antitumor immunity (IFN-gamma ≥ median or CD8+ ≥ median) who received A+V+C had more favorable outcomes compared with their counterparts with IFN-gamma < median or CD8+ < median. In general, the PFS benefit with A+V+C vs P+V+C was more readily apparent in PD-L1− subgroups. Similar trends were seen with DOR (figure 1B).

Conclusions There was a trend of larger magnitude of PFS benefit with A+V+C vs P+V+C in PD-L1− patient subgroups, who benefit less with single-agent immunotherapy. The PFS and DOR benefits were more evident in patients with high IFN-gamma or TMB >10 mutations/Mb. Additional multivariate analyses are ongoing to delineate the PFS trends observed.

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INDIRECT TREATMENT COMPARISON OF NIVOLUMAB VERSUS PLACEBO AS ADJUVANT TREATMENT FOR MELANOMA

Abstract 307 Figure 1  Forest plot of PFS (A) and DOR (B). mo, months; NE, not evaluable; Neg, negative; NE, not estimable; Pos, positive.
Background The sentinel lymph node (SLN) is the first node to receive lymphatic drainage from the primary tumor and the site where naïve T cells are first primed. As such it is of great importance in initiating an effective anti-tumor immune response and an attractive target for immunomodulatory agents. Pre-clinical studies have reported that i.t. administration of anti-CTLA-4 is as effective in inducing tumor eradication as systemic delivery, without the risk of treatment related side effects. However, it remains unclear whether this is due primarily to modulation of the tumor microenvironment or of tumor-draining lymph nodes (TDLN). Here, we have evaluated the safety, tolerability and immunomodulatory effects in the SLN and peripheral blood mononuclear cells (PBMC) of anti-CTLA-4/tremelimumab, delivered locally at the tumor excision site in patients with early-stage melanoma. This unique setting (post tumor excision but prior to SLN biopsy) allowed us to clinically assess the role of TDLN in the biological efficacy of CTLA-4 blockade.

Methods In this phase 1 dose-escalation trial, patients with clinical stage I-II melanoma received one intradermal injection of tremelimumab at four dose levels (2, 5, 10 [n=3 each] or 20 mg [n=4]) around the primary excision site of the tumor, seven days prior to re-excision and SLN biopsy. Flow cytometry was performed to study viable cells from melanoma SLN and PBMC (prior to tremelimumab administration [day 0], and at 7 days, 3 weeks and 3 months after tremelimumab injection). Systemic melanoma antigen (MART-1/NY-ESO-1)-specific T cells responses were assessed by IFN-γ ELISPOT assay.

Results Intradermal delivery of tremelimumab was safe and well tolerated. In terms of biological efficacy it selectively induced profound and durable decreases in Treg frequencies in both SLN and PBMC, decreased systemic MDSC rates, activated migratory dendritic cell subsets in the SLN, and induced T cell activation (by HLA-DR and ICOS up-regulation), both in SLN and PBMC. Moreover, systemic anti-melanoma T cell responses were induced (n=5) or boosted (n=2), in association with T cell activation and central-memory T cell differentiation. Of note, tumor recurrences so far were only observed in two patients who did not develop a systemic anti-tumor T cell response.

Conclusions These findings indicate that i.d. administration of anti-CTLA-4 may offer a safe and promising adjuvant treatment strategy for patients with early-stage melanoma. Moreover, they demonstrate a central role for TDLN in the biological efficacy of CTLA-4 blockade and warrant the development of TDLN-targeted delivery methods for anti-CTLA-4.

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