advanced melanoma. Improved objective response rate (ORR) was observed for T-VEC plus IPI compared to IPI alone (39% vs. 18%; OR 2.9; 95% Cl, 1.5–5.5; P=0.002).[1] At 3-year follow-up, median OS was not reached in either arm (HR, 0.85; 95% CI, 0.55–1.32; P=0.480).[2] Here we present 4-year interim analysis results including BRAF V600 mutation subgroup analysis.

Methods Patients with unresectable or metastatic (IIIB-IV) melanoma were randomized 1:1 to receive T-VEC plus IPI or IPI alone. T-VEC was injected day 1, week 1, at 106 PFU/mL, followed by 108 PFU/mL on day 1, week 4, and Q2W thereafter. IPI (3 mg/kg) was given Q3W starting day 1, week 6, up to 4 doses, for T-VEC arm; day 1, week 1 for IPI alone. Response was assessed per immune-related response criteria (irRC) Q12W until disease progression. The primary endpoint was ORR; key secondary endpoints were overall survival (OS), progression-free survival (PFS), durable response rate (DRR), and safety (NCT01740297).

Results A total of 198 patients (98 combination, 100 IPI alone) were randomized. As of February 25, 2020, median follow-up was 48.3 months for combination and 35.7 months for IPI alone. DRR improved for combination vs. IPI (33.7% vs. 13.0%; OR 3.4; 95% CI, 1.7–7.0; P=0.001). Median PFS was 13.5 months with combination and 6.4 months with IPI (HR 0.81; 95% Cl, 0.57–1.15; P=0.23). Median OS was not reached for combination and was 50.1 months for IPI (HR 0.82; 95% CI, 0.54–1.25; P=0.36). For combination, 47 (48.0%) patients received subsequent anti-cancer therapy vs. 64 (64.0%) for IPI; median time from randomization to first subsequent therapy was 27.7 months and 8.3 months, respectively. In subgroup analysis, patients without BRAF V600 mutation (63% combination, 60% IPI) improved DRR and PFS for combination vs. IPI alone (DRR: 33.9% vs. 5.0%; median PFS: 18.0 months vs. 4.5 months); BRAF V600 mutation positive patients (36% combination, 34% IPI) were similar between arms (DRR: 34.3% vs. 26.5%; median PFS: 4.2 months vs. 6.4 months). No additional safety signals observed in follow-up.

Conclusions The improved PFS and DRR for the combination arm at 4-year follow-up indicates continued benefit of combination therapy. Patients receiving IPI alone were more likely to receive subsequent anti-cancer therapy in a shorter time. Subsequent anticancer therapies may confound OS analysis. The BRAF mutant post-hoc analysis requires further mechanistic investigation.

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Trial Registration NCT01740297

Ethics Approval The study was approved by all institutional ethics boards.

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434 UPDATED CLINICAL DATA FROM THE MELANOMA EXPANSION COHORT OF AN ONGOING PH1/1B STUDY OF EGANELISIB (FORMERLY IPI-549) IN COMBINATION WITH NIVOLUMAB

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Background Eganelisib is a first-in-class, oral, selective PI3K-γ inhibitor. Preclinically, eganelisib reprograms macrophages/myeloid derived suppressor cells (MDSCs) from an immune-suppressive to an immune-activating phenotype and enhances efficacy of checkpoint inhibitors. Efficacy of eganelisib + nivolumab in patients with advanced melanoma resistant to immediate prior anti-PD(L)1 therapy is presented.

Methods IPI-549-01 (NCT02637531) evaluates eganelisib in advanced solid tumors, as monotherapy and in combination with nivolumab. The combination expansion dose was eganelisib 40 mg QD PO + nivolumab 240 mg Q2W IV. Combination expansion cohorts include unresectable stage III/IV melanoma patients resistant to immediate prior anti-PD(L)1 therapy. Safety, preliminary clinical activity, PK, and correlative study of blood and tumor biopsy samples were mandated.

Results As of June 1, 2020, 180 patients were treated with eganelisib + nivolumab including 40 with melanoma.The most common (>20% of patients) treatment-emergent adverse events in patients treated with eganelisib + nivolumab (N = 180) were fatigue (34.4%), increased AST (30.0%), increased ALT (26.7%), nausea (25.0%), pyrexia (25.0%), anemia (22.8%), decreased appetite (20.6%), and cough (20.6%). 85 (47.2%) patients experienced at least 1 treatment-emergent serious adverse event (SAE) and 19 (10.6%) had a treatment-related SAE. There was no toxicity unique to the melanoma cohort, and no treatment-related death as assessed by investigators.Preliminary data from the melanoma cohort show that in the efficacy-evaluable population which includes all patients (n=39) who had at least 1 post-baseline response assessment or discontinued treatment due to disease progression, the overall response rate (ORR, ie. CR [complete response] or PR [partial response] per RECIST v1.1) is 7.7%, the disease control rate (DCR, ie. CR, PR, or SD [stable disease]) is 35.9%, and the clinical benefit rate (CBR, ie. CR, PR, or SD of at least 24 weeks from first treatment) is 17.9%, per RECIST v1.1. For patients that received ≤ 2 lines of prior systemic therapy (n=19), the ORR is 15.8%, the DCR is 52.6%, and the CBR is 36.8%. In total, there are 3 patients with PR (duration of response 4–12 months) and 4 with SD > 6 months' treatment duration.Translational data evaluating blood MDSCs, cytokines, and proliferation of previously exhausted CD8 memory T-cells as well as changes in immune cell infiltrates from tumor biopsies will be presented.

Conclusions Eganelisib + nivolumab demonstrates an acceptable safety profile and clinical activity in patients with melanoma who were resistant to immediate prior anti-PD(L)1 therapy. Updated clinical and translational data will be presented.

Ethics Approval The study was approved by WIRB, Study Number 1188591 and IRB Tracking Number: 20180297.

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435 A PHASE II TRIAL OF NIVOLUMAB PLUS AXITINIB IN PATIENTS WITH ANTI-PD1 REFRACTORY ADVANCED MELANOMA

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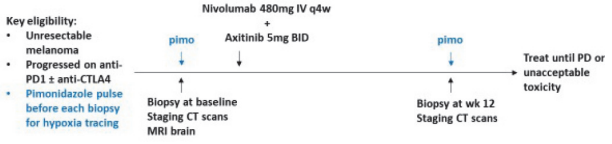
Background Immunotherapy has changed the treatment landscape for melanoma, although many patients (pts) do not respond to treatment. While there are likely multiple mechanisms of resistance at play, one key mechanism is the generation of an immunosuppressive and metabolically harsh tumor microenvironment (TME).[1] This is likely the result of an altered angiogenic pattern along with dysregulated metabolism of the tumor itself, which leads to hypoxia.[2] CD8+ tumor infiltrating lymphocytes (TIL) isolated from tumors with high oxidative metabolism have an exhausted phenotype and decreased functionality (decreased IFN-γ and TNF-α production).[3] Thus, TIL may be blunted due to failure to meet their metabolic needs. Vascular endothelial growth factor (VEGF) is a critical mediator of angiogenesis and is overexpressed in many solid tumors, including melanoma. Axitinib has high inhibitory activity for VEGF receptors1, 2, and 3. In a preclinical B16 melanoma model, we found that anti-PD1 plus axitinib provided an improved and durable response compared to monotherapy with either agent. We hypothesize that by modulating angiogenesis, axitinib will reduce intra-tumoral hypoxia and resultant T cell dysfunction, which will re-sensitize melanoma to anti-PD1 therapy.

Methods This is an investigator-initiated, phase II trial of nivolumab plus axitinib for pts with unresectable stage III or IV melanoma who have progressed on prior anti-PD1 therapy with or without concomitant anti-CTLA4. Prior treatment with BRAF/MEK inhibitors is permitted. Pts with brain metastases are permitted if they are asymptomatic and have stable disease 2 weeks after CNS-directed treatment. Pts will receive nivolumab 480 mg IV every 4 weeks and axitinib PO 5 mg twice daily for up to two years or until progression or unacceptable toxicity. Timing of biopsies is reported in figure 1, with an optional biopsy at progression. Pts will receive an oral dose of pimonidazole 0.5 mg/m^2 before each biopsy to permit in vivo evaluation of intra-tumoral hypoxia. Primary endpoint: overall response rate (ORR). Secondary endpoints: safety, progression-free survival, overall survival, and correlative analyses (evaluation of hypoxia in the TME, TIL function, immune phenotype, and tumor cell metabolism). Statistical analysis includes Simon's minimax two-stage design. The null hypothesis is that the true ORR is 10%, tested against a one-sided alternative of 25% or higher. N=31 patients with a type I error rate of 0.08 and power 0.81 when the true response rate is 0.25.



Abstract 435 Figure 1 Study schema

Results N/A

Conclusions N/A

Trial Registration NCT04493203

Ethics Approval The study was approved by the University of Pittsburgh Institutional Review Board, approval number HCC 20-101.

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Combination immunotherapies

436 RATIONAL SEQUENCING OF IMMUNE-ONCOLOGY THERAPIES ACHIEVES DURABLE RESPONSE AND IMMUNOLOGIC MEMORY

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Background Oncologically-sound standard of care therapy often indicates ablation of draining lymphatic basins to eradicate repositories of metastatic disease. However, emerging cancer immunotherapies often necessitate intact secondary lymphoid organs to achieve maximum effect. Therefore, multimodal immune-oncology (IO) therapeutic approaches introduce an inherent paradox into the clinical management of the cancer patient: how to reconcile the clinical benefit of lymphatic ablation with the destruction of an indispensable immune organ.

Methods Here, we leverage a novel preclinical model of tobacco-signature head and neck squamous cell carcinoma (HNSCC) to examine the impact of lymphatic ablation on the efficacy of immunotherapy and to identify sequences of therapy that maximize durable response without compromising oncologically-sound standard of care therapy.

Results We show that cervical lymphatic ablation in tumor bearing animals abolishes the response to CTLA- 4 blockade by eradicating lymph-node associated conventional dendritic cells and restricting CD8 T cell priming and subsequent tumor infiltration. By modelling recurrent HNSCC, we find that upfront, elective cervical lymphatic ablation eliminates the tumor response to adjuvant CTLA-4 blockade in contrast to a lymphatic-sparing approach, which preserves sensitivity to CTLA-4 blockade. In the neoadjuvant setting, we show that delayed, but not early, cervical lymphatic ablation leads to durable response after CTLA-4 blockade. Lastly, we demonstrate that a successful tumor response to CTLA-4 blockade begets long-lasting immunologic memory, resistant to delayed cervical lymphatic ablation.

Conclusions Collectively, this work addresses an inherent paradox in the delivery of combination IO therapy, informs