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 receptors 1, 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 to anti-PD1 refractory advanced melanoma. 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/m² 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 correlational 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.

Results N/A

Conclusions N/A

REFERENCES