Indoximod

A methylated tryptophan with immune checkpoint inhibitory activity. Indoximod inhibits the enzyme indoleamine 2,3-dioxygenase (IDO), which degrades the essential amino acid tryptophan, and may increase or maintain tryptophan levels important to T cell function. Tryptophan depletion is associated with immunosuppression involving T cell arrest and anergy.

Pre-treatment and on-treatment α-[11C]-methyl-L-Trp (AMT) positron emission tomography (PET) with co-registered MRI was performed on patients with recurrent glioblastoma treated with the IDO1 pathway inhibitor indoximod (D1-MT) and TMZ.

Regional intratumoral variability of AMT within enhancing and non-enhancing tumor was noted at baseline. On treatment imaging revealed decreased regional uptake suggesting IDO1 pathway modulation with treatment.

Lukas et al. from the Northwestern University, Chicago validated the ability to use PET of the Trp probe, AMT, for use in visualizing and quantifying intratumoral Trp uptake in GBM patients treated with an IDO1 pathway inhibitor. These data serve as rationale to utilize AMT-PET imaging in the future evaluation of GBM patients treated with IDO1 enzyme inhibitors [1].

Phase 1b/2 single-arm trials in adult and pediatric brain cancers are being conducted in which indoximod is combined with chemotherapy or chemo-radiotherapy, with some early but intriguing efficacy data being reported. A preclinical treatment rationale was established in a robust orthotopic model of malignant brain cancer (glioblastoma), where the synergistic effects of indoximod were demonstrated in combination with temozolomide (TMZ) and radiation as a cooperative DNA damaging modality [2].

In the latest report from the adult trial (NCT02052648) [3] , 12 patients who had progressed on standard of care therapy with TMZ were enrolled in a traditional 3+3 dose escalation study of indoximod (600, 1,000, or 1,200 mg twice daily). No dose-limiting toxicity was encountered nor did indoximod cause a delay or reduction in TMZ dosing in any patient. The best responses documented were 1 patient with partial response per Response Assessment in Neuro-Oncology (RANO) criteria at 15 months and 4 patients with stable disease lasting between 4 and 11 months [4].

A phase 2 expansion of the study is ongoing at the 1,200 mg twice daily dose in combination with TMZ, bevacizumab and ateriotactic radiation (SRS) (NCT02052648).

In the pediatric brain cancer trial (NCT02502708) [5] , the first trial to evaluate indoximod both in children and in the context of radiotherapy, 17 patients from an original cohort of 29 heavily pretreated patients in the dose escalation phase 1b study who were eligible to receive further treatment were administered indoximod and radiotherapy followed by standard of care cycles of TMZ with indoximod as maintenance therapy. The other 12 patients received only indoximod and TMZ. Both treatments were well tolerated with minimal toxicity attributed to indoximod. Overall, at the time of the report, 29 patients in the dose-escalation phase of the study exhibited a median PFS of 6.2 months and median time to regimen failure (TTRF) of 11.7 months, which compares favorably with historical controls. Notably, patients receiving radiotherapy appeared to benefit significantly when

indoximod was added, with a median TTRF of 12 months observed vs. 3.2 months without radiotherapy (p = 0.04). These data suggested a dose-sparing effect of indoximod on conventional chemo-radiotherapy, potentially extending efficacious responses. The notion that targeting the IDO pathway may improve chemo-radiotherapy is supported a recent study in lung cancer [6]. Encouraged by these response data, the same regimen is now being tested in patients with diffuse intrinsic pontine glioma (DIPG), a dismal disease with no effective treatment option. Thus far, 3/6 patients enrolled are reported to have achieved good symptomatic and radiographic response [7].

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