Intratumoral IMO-2125, a TLR9 Agonist, is Active in Combination with Ipilimumab in PD-(L)1 Refractory Melanoma

While checkpoint inhibitor therapy (CPI) has improved metastatic melanoma (MM) treatment, many patients remain refractory and fail to achieve durable responses. We reasoned that combining CPI with an agent that activates antigen presenting cells and improves T cell infiltration may result in improved clinical responses.

Our approach is to modulate the tumor microenvironment through intratumoral (i.t.) injection of a TLR9 agonist, IMO-2125, in combination with either ipilimumab (ipi) or pembrolizumab (pembro). In preclinical studies, it administered IMO-2125 stimulated plasmacytoid dendritic cells to induce high amounts of interferon alpha and helper T cell cytokines, leading to increased immune cell infiltration in the tumor microenvironment. In addition, the combination of i.t. IMO-2125 with either an anti-CTLA-4 or anti-PD-1 antibody resulted in improved systemic tumor control compared with either agent alone.

Based on these data, we hypothesized that i.t. IMO-2125 will synergize with ip or pembro to overcome tumor immune escape and improve systemic anti-melanoma activity. We initiated a Phase 1/2 clinical trial in patients with anti-PD-1 refractory MM accordingly. Here, we describe updated preliminary clinical activity in PD-1 refractory melanoma.

**CONCLUSIONS**

- The combination of IMO-2125 and ipilimumab is tolerable at all dose combinations studied and has clinical activity in PD-1 refractory melanoma.
- There is evidence for immune activation in both the injected and distant tumor biopsies that correlates with clinical outcomes.
- Further investigation of the IMO-2125 + pembrolizumab combination in PD-1 refractory melanoma warranted; the planned Phase 2 expansion will begin soon.
- Dose escalation of IMO-2125 + pembrolizumab is also ongoing.

**Patient and disease characteristics**

**Safety summary**

**Most frequent TEAE**

**Maximum decrease in target lesions by RECIST v1.1**

**Proof of mechanism in responding patient 003**

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