Intratumoral Administration of IMO-2125, a Novel TLR9 Agonist, Modulates Tumor Microenvironment and Potentiates Antitumor Activity of Anti-PD-1 mAb in Murine Colon Carcinoma and Melanoma Models

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**BACKGROUND**

**Study Objective**

- Demonstrate that modulation of the tumor microenvironment with intratumoral administration of IMO-2125, a TLR9 agonist, potentiates both antitumor activity of a anti-PD-1 checkpoint inhibitor in preclinical models.

- Cancer immunotherapies targeting immune checkpoint pathways have shown promising results in clinical trials. However, despite the promise of these therapies, only a subset of patients demonstrate antitumor activity. A key question in cancer immunotherapy is identifying predictors of response to immunotherapy, including characteristics of the tumor and its microenvironment, which will enable more precise patient selection to maximize treatment benefit.

- One approach to improve the efficacy of checkpoint inhibition involves priming the tumor microenvironment by targeting and activating immune cells with oligonucleotide-based TLR9 agonists. TLR9 agonists are known to activate dendritic cells, which process antigens and present them to T-cells, leading to the activation of anti-tumor T-cell immune responses.

- Increased immunosurveillance occurs in tumors that are immunogenic, leading to the activation of immune responses against tumor cells. TLR9 agonists can prime dendritic cells to initiate an anti-tumor immune response.

- The current study was conducted to investigate the antitumor activity of IMO-2125, a synthetic oligonucleotide-based TLR9 agonist, in combination with an anti-PD-1 checkpoint inhibitor in preclinical models.

**DISCUSSION**

**Intratumoral IMO-2125 Therapy**

- IMO-2125 is a synthetic oligonucleotide-based TLR9 agonist that activates dendritic cells, which process antigens and present them to T-cells, leading to the activation of anti-tumor T-cell immune responses.

- Intratumoral IMO-2125 monotherapy showed dose-dependent antitumor activity in a CT26 colon carcinoma model.

- Treatment with intratumoral IMO-2125 in combination with anti-PD-1 mAb induced potent systemic immune responses against disseminated lung metastases.

- Immunohistochemistry was used to evaluate the expression of TILs and checkpoint gene expression in treated and distant tumors.

- Clonal expression of PD-1 and its ligands was observed in both treated and distant tumors following combination treatment with intratumoral IMO-2125 and anti-PD-1 mAb.

**Antitumor Activity**

- Antitumor activity was observed in treated as well as distant tumors.

- Combination therapy with IMO-2125 and anti-PD-1 mAb showed potent tumor growth inhibition on treated tumors.

**Histopathology of Metastatic Lung Tumors**

- Histopathology images showed increased TILs (large figure) following treatment with intratumoral IMO-2125 and anti-PD-1 mAb combination.

- Increased TILs (large figure) were observed in both treated and distant tumors following combination therapy.

**CONCLUSIONS**

- Intratumoral IMO-2125, in combination with anti-PD-1 mAb, inhibited growth and infiltration of tumor cells, leading to potent systemic immune responses against disseminated lung metastases.

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**IDO-1, CTLA4, Ox40, BTLA, TIM3, LAG3, and CTLA4 Ox40L**

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