Intratumoral Administration of IMO-2125, a Novel TLR9 Agonist, Modulates the Tumor Microenvironment and Exerts Systemic Antitumor Activity Alone and in Combination with an Anti-CTLA-4 mAb

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INTRODUCTION

- Cancer immunotherapy combination regimens aim to stimulate host antitumor immune responses and break tumor-related immune tolerance with the potential of curative treatment.
- Potential immunotherapeutic targets include Toll-like receptors (TLRs), which are key receptors of the innate immune system and play an important role in regulating adaptive immune responses.
- IMO-2125 is a potent and selective agonist of endosomal TLR9 that induces interferon-a and the maturation of dendritic cells (DC).
- In the setting of cancer immunotherapy, we hypothesized that intratumoral (i.t.) administration of IMO-2125 has the potential to stimulate DC maturation and T cell activation in the tumor microenvironment, leading to increased local and systemic antitumor immune responses and tumor regression, and may potentiate the activity of checkpoint inhibitors.

METHODS AND RESULTS

Systemic IMO-2125 induced dose-dependent immune responses in a Phase I Trial

Intratumoral IMO-2125 treatment elicited specific cytotoxic T cell responses to tumor antigens

Intratumoral IMO-2125 and anti-CTLA-4 mAb combination demonstrated improved growth inhibition in treated tumors versus monotherapies with either agent

Conclusions

- Intratumoral IMO-2125 monotherapy led to dose-dependent decreases in treated and distant tumor volumes, an increase in infiltrating CD8+ T cells, and specific cytotoxic T cell responses against tumor antigens.
- The antitumor activity of intratumoral IMO-2125 was associated with the presence of infiltrating CD8+ T cells.
- Intratumoral IMO-2125 induced durable and tumor-specific immune memory, as demonstrated by antitumor activity against a tumor rechallenge.
- Combination of intratumoral IMO-2125 and an anti-CTLA-4 mAb resulted in improved inhibition of tumor growth, regression of systemic lung metastases and infiltration of TILs versus monotherapy with either agent.
- Collectively, these data demonstrated the potent antitumor activity of IMO-2125, a novel immunomodulatory TLR9 agonist, alone and in combination with a checkpoint inhibitor.
- Planning for a clinical trial of intratumoral IMO-2125 in combination with sipuleucel-T, an anti-CTLA-4 mAbs, could represent a new combination strategy in patients with metastatic prostate cancer is currently underway with study initiation expected in Q4, 2015.

Study design to evaluate antitumor activity of intratumoral IMO-2125 treatment in CT26 colon carcinoma tumor model

Study design to evaluate antitumor activity of intratumoral IMO-2125 treatment at right tumor on Days 6, 10 and 13.

Placebo group: PBS (50 g/mouse), i.p.

IMO-2125 group: IMO-2125 (50 g/mouse), i.t.

Anti-CD4+ or CD8+ mAb, 25 mg/kg (500 g/mouse), i.p.

6 syngeneic, non-organ-related B cell lymphoma A20 cells by s.c. inoculation at the upper back area.

Tumor regressed

Antitumor activity of intratumoral IMO-2125 treatment was dependent on CD8+ T cells

Intratumoral IMO-2125 induced durable and tumor-specific immune memory

Study design to evaluate duration and specificity of the antitumor response induced by intratumoral IMO-2125 treatment

Study design to evaluate the antitumor activity of intratumoral IMO-2125 in combination with anti-CTLA-4 mAb on treated tumors and systemic lung metastases

Intratumoral IMO-2125 and anti-CTLA-4 mAb combination inhibited growth of systemic lung metastases versus monotherapy with either agent

Intratumoral IMO-2125 and anti-CTLA-4 mAb combination increased tumor infiltrating lymphocytes in metasatastic nodules

Intratumoral IMO-2125 treatment led to dose-dependent decreases in tumor volume in both treated and distant tumors

Antitumor activity was associated with induction of tumor-infiltrating lymphocytes (TILs)

Intratumoral IMO-2125 treatment increased infiltration of CD8+ T cells in tumors

Study design to evaluate the antitumor activity of intratumoral IMO-2125 in combination with anti-CTLA-4 mAb on treated tumors and systemic lung metastases

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