Local treatment with novel TLR9 agonist IMO-2125 demonstrates antitumor activity in preclinical models of pancreatic cancer

Daqing Wang, Evren Kocabas Argon, Fugang Zhu, & Sudhir Agarwal

ideraPharmaceuticals Inc., Cambridge, MA

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INTRODUCTION

Background

- Pancreatic cancer is the fourth leading cause of cancer-related deaths in the US, with a 3 year survival rate of less than 7%.
- No standard of care exists for patients who have progressed on front line chemotherapy.
- Checkpoint inhibitors, such as anti-PD1/PDL1 and anti-CTLA4, have shown promising clinical results in multiple tumor types; however, they have not shown clinical benefit in pancreatic cancer.
- The efficacy of checkpoint inhibitors relies largely on the infiltration of the tumor by tumor-infiltrating lymphocytes (TIL).
- Unlike other cancers, pancreatic cancer has a non-invasive tumor microenvironment (TME) due to a high level of desmoplasia, which results in a dense fibrosis of stromal cells surrounding the tumor, rendering checkpoint inhibitors ineffective.

Mechanism of action

- IMO-2125 is a synthetic agonist of Toll-like receptor (TLR) 9.
- In preclinical studies, intratumoral (i.t.) administration of IMO-2125 maintains the TME by engaging dendritic cells and B-cells, and induces Th1 cytokines, including high levels of interferon alpha (IFN-alpha), and modulating the expression of checkpoints compared to vehicle control treated tumor.

Study design to evaluate antitumor activity of IMO-2125

- Local treatment with novel TLR9 agonist IMO-2125 demonstrates antitumor activity in preclinical models of pancreatic cancer

- Study design to evaluate duration and specificity of the antitumor activity induced by IMO-2125 i.p. treatment

- Study design to evaluate IMO-2125 i.p. administration in combination with PD1/PDL1 blockade

- Study design to evaluate IMO-2125 in combination with CAR T-cells

- Study design to evaluate IMO-2125 in combination with checkpoint inhibitors

- Study design to evaluate IMO-2125 in combination with immunomodulatory agents

- Study design to evaluate IMO-2125 in combination with vaccines

- Study design to evaluate IMO-2125 in combination with other novel therapeutic agents

- Study design to evaluate IMO-2125 in combination with gene therapy

DISCUSSION

Study design to evaluate antitumor activity of IMO-2125 treatment

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CONCLUSIONS

- Intratumoral IMO-2125 showed dose-dependent tumor regression and infiltration of TILs in both implanted and distant tumors, with no toxicity observed.
- IMO-2125 is an effective treatment in this pancreatic cancer model.

- Our results support a novel, localized, potent antigen-specific activity when compared to both systemic and subcutaneous treatment, and inhibited tumor growth.

- These data demonstrate that i.t. or i.p. treatment with IMO-2125 modulates the tumor microenvironment and increases infiltration of TILs. These changes are associated with antitumor activity in pancreatic cancer models and indicate that IMO-2125 may potentiate checkpoint inhibitor therapy for the treatment of pancreatic cancer.

- The efficacy of checkpoint inhibitors relies largely on the infiltration of the tumor by tumor-infiltrating lymphocytes (TIL).

REFERENCES