Pharmacodynamic Correlates in a Phase 1 Study of INCMGA00012, a PD-1 Antagonistic Monoclonal Antibody

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Abstract

Background: The role of the programmed cell death (PD)-1/PD-1 antagonistic cell death ligand (PD-L1) axis in limiting T cell activity has been well established. Effective blockade of this pathway has been demonstrated to lead to an increase in T cell activity and to yield clinical activity in cancer patients. INCMGA00012 is a humanized IgG4 monoclonal antibody that binds to human PD-1 and blocks its interaction with PD-L1/PD-L2. This therapeutic antibody has demonstrated acceptable tolerability with evidence of clinical activity in a phase 1 study in patients with solid tumors (NCT03396363). Pharmacodynamic markers demonstrating biological activity of INCMGA00012 were assessed in samples collected during the study.

Methods: Blood samples were collected at baseline and at various time points following treatment from patients receiving doses of either 3 mg/kg (Q2W) in the tumor-specific expansion cohort or a higher dose in the open-label cohort. PBMCs were collected to analyze flow cytometry and peripheral blood mononuclear cell (PBMC) functionality. Increased circulating serum chemokine levels (ie, CXCL10 and CXCL9) and in T cell proliferation. The role of the programmed cell death (PD)-1/programmed cell death ligand (PD-L)1 interaction with PD-L1/PD-L2. This therapeutic antibody has demonstrated acceptable tolerability with evidence of clinical activity in a phase 1 study in patients with solid tumors (NCT03396363). Pharmacodynamic markers demonstrating biological activity of INCMGA00012 were assessed in samples collected during the study.

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Regression-Occupancy for the QGMR Flat-Dosing Cohort

Receptor-Pairing on Circulating T Cells is Fully Saturated by INCMGA00012

Results: Increasing the frequency of Ki67+ T cells (CD45+/CD3+ cells) at various times in a patient with sarcoma receiving 3 mg/kg of INCMGA00012 Q2W. Whole blood was collected at various time points following treatment with INCMGA00012 and shipped overnight for analysis. Staining for CD45, CD3, CD4, CD8, CD69, CD103, CD107, and TXNIP were measured by immunoassays in serum samples collected at baseline (C1D1 pretreatment) and on treatment (C2D1: day 1, C3D1: day 15; C3D1: day 29) and compared with untreated controls (reference conditions). The authors wish to thank the participants, investigators, and site personnel who participated in this study. We also thank Deanna Kornacki and Nawel Bourayou, MD, for their contributions to data management and analysis. The authors wish to thank the participants, investigators, and site personnel who participated in this study. We also thank Deanna Kornacki and Nawel Bourayou, MD, for their contributions to data management and analysis.

Discussion and Conclusions

INCMGA00012 administration at 215 mg/m2, 330 mg/m2, and 500 mg/m2 was well tolerated and demonstrated an increase in the frequency of proliferating T cells in the blood of treated patients. INCMGA00012 chimeric antigen receptor-engineered cell therapy and with a phase 3 study in patients with melanoma in combination with nivolumab and ipilimumab. These results suggest that INCMGA00012 may be a candidate therapeutic agent for the treatment of solid tumors. INCMGA00012 administration at 215 mg/m2, 330 mg/m2, and 500 mg/m2 was well tolerated and demonstrated an increase in the frequency of proliferating T cells in the blood of treated patients. INCMGA00012 chimeric antigen receptor-engineered cell therapy and with a phase 3 study in patients with melanoma in combination with nivolumab and ipilimumab. These results suggest that INCMGA00012 may be a candidate therapeutic agent for the treatment of solid tumors.