Preclinical and Clinical Activity of Anti-DLL4 (Demcizumab) in Combination with Gemcitabine Plus nab-Paclitaxel in Pancreatic Cancer


START, Madrid; Spain; CNIO, Madrid; Spain; CIOCC, Madrid, Spain; Oncomed Pharmaceuticals Inc, Redwood City, CA

Abstract

In a Phase I/II clinical trial of Demcizumab (DEM) in combination with gemcitabine (GEM) and nab-paclitaxel in advanced pancreatic cancer, we observed early clinical activity and a manageable safety profile. Preclinical data has indicated that targeting DLL4 with DEM is likely to improve the activity of standard of care regimens in pancreatic cancer models. We evaluated the antitumor activity and safety of DEM in combination with GEM and nab-paclitaxel in xenograft models of human pancreatic cancer. Depletion of stem-like cells in these xenograft models was associated with improved survival. We also evaluated the impact of DEM on tumor cell gene expression, specifically genes associated with stemness and apoptosis.

Methods

Xenograft models of human pancreatic cancer were established in immunodeficient mice. Treatment groups included either GEM or nab-paclitaxel (500 mg/kg) alone, or in combination with DEM (5 mg/kg). Treatment schedules were q2w (2 week) for GEM and q2w for DEM. Total doses were administered over 150 days. Treatment groups included both control and DEM treated animals. Tumor growth and survival were monitored. Tumors were excised at 34 days post treatment and analyzed for gene expression changes using a microarray analysis.

Results

In all xenograft models, DEM+GEM+nab-paclitaxel was associated with improved survival compared to GEM or nab-paclitaxel alone. A subset of gene expression changes was observed in tumors treated with DEM+GEM+nab-paclitaxel, specifically genes associated with stemness and apoptosis. In particular, DEM treatment depleted the tumor stem cell population, which correlated with improved survival.

Conclusion

DEM+GEM+nab-paclitaxel was associated with improved survival compared to GEM or nab-paclitaxel alone. These findings support the potential of DEM to improve the efficacy of standard of care regimens in pancreatic cancer.

Background

Pancreatic cancer remains one of the most lethal malignancies and there is a need for more effective treatment options. The Notch pathway plays a critical role in the development and progression of pancreatic cancer. DLL4 is a Notch ligand that is expressed in pancreatic cancer stem cells (CSCs). Targeting DLL4 with DEM is expected to improve the efficacy of standard of care regimens in pancreatic cancer.

Preclinical Xenograft Data

Reversible Cardiopulmonary Toxicity* (Any Grade) (N=47)

Duration on Study and Median Progression Free Survival

AEs Occurring in >25% of Pts (N=47)

All Grades by Dose Level (maplog)

% Change in RECIST Target Lesion Size All Patients (N=47)

% Change in RECIST Target Lesion Size DEM/GEM/nab-Paclitaxel Patients

Summary

- Anti-DLL4+gemcitabine/nab-paclitaxel was evaluated in a phase I clinical trial of pancreatic cancer xenograft models and tissue act in the safety and efficacy of this regimen, and in the treatment of recurrent disease. Notably, the combination of DEM and GEM was associated with improved survival compared to GEM or nab-paclitaxel alone. These findings support the potential of DEM to improve the efficacy of standard of care regimens in pancreatic cancer.

- In a phase II clinical study of DEM+GEM in patients with 1st line pancreatic cancer, DEM+GEM+nab-paclitaxel was associated with improved survival compared to GEM or nab-paclitaxel alone. These findings support the potential of DEM to improve the efficacy of standard of care regimens in pancreatic cancer.

- In the ongoing Phase I/II dose escalation study of demcizumab, we are evaluating the clinical activity and safety of this regimen in pancreatic cancer patients. The combination of DEM and GEM is expected to improve the efficacy of standard of care regimens in pancreatic cancer.