The combination of gemcitabine/nab-paclitaxel with an anti-DLL4 monoclonal antibody demcizumab produces synergetic growth inhibition, delays tumor recurrence and reduces tumorigenicity of tumor initiating cells in pancreatic cancer

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ABSTRACT

Clinical management of pancreatic cancer is challenging and this disease remains the fourth most common cause of cancer-related death. Conventional chemotherapeutic agents, including gemcitabine, commonly used in the treatment of pancreatic cancer, have low response rates and limited effects on improving patient survival. A recent phase III clinical trial has demonstrated that nab-paclitaxel (Abraxane®), a protein-bound paclitaxel in combination with gemcitabine significantly improved the response rate and overall survival compared to patients receiving gemcitabine alone. We previously demonstrated that targeting Notch signaling by anti-DLL4 (demcizumab) inhibits tumor growth, reduces tumor initiating cell frequency and induces differentiation in patient-derived pancreatic xenograft tumors. To further explore the utility of demcizumab in the setting of pancreatic cancer, we evaluated anti-DLL4 combination with gemcitabine/nab-paclitaxel in a panel of pancreatic xenograft models. We found that anti-DLL4 in combination with gemcitabine plus nab-paclitaxel resulted in striking tumor regression, whereas tumors treated with chemotherapeutic agents grew continuously. The effect of the triple combination in some tumors was quite durable and persisted after both antibody and chemotherapeutic treatments were discontinued. The significant growth inhibitory effect of the combination of anti-DLL4 with gemcitabine/nab-paclitaxel was associated with a decrease in cancer stem cell frequency and an increase in apoptosis and tumor cell differentiation. The triple combination of anti-DLL4, gemcitabine and nab-paclitaxel was generally more efficacious compared with anti-DLL4 plus gemcitabine alone. Notably, in a xenograft established from a patient that previously did not respond to demcizumab plus gemcitabine, the triple combination was highly effective. We are currently evaluating demcizumab in combination with gemcitabine/nab-paclitaxel in a phase 1b clinical trial in pancreatic cancer.

BACKGROUND

• Pancreatic cancer is the fourth leading cause of cancer death in the United States with 5-year survival rate of only 3% and a median survival of less than 6 months. Conventional chemotherapeutic agents, including gemcitabine, commonly used in the treatment of pancreatic cancer, have low response rates and limited effects on improving patient survival.


• Evidence has accumulated suggesting that tumors may arise and grow as a result of the formation of a subset of cells termed cancer stem cells (CSC) or tumor initiating cells; this cell population may also be involved in tumor recurrence and resistance to radiation and chemotherapy.

• The Notch signaling pathways play an important role in controlling cell fate, self-renewal and cell proliferation and differentiation.

• Delta-like 4 ligand (DLL4) is an important component of Notch-mediated stem cell self-renewal and vascular development. DLL4 over-expression is found in tumor vasculature and in tumor cells to activate Notch signaling in cancer stem cells.

• The objective of this study is to evaluate the effect of an anti-DLL4 monoclonal antibody in combination with gemcitabine/nab-paclitaxel in patient-derived pancreatic xenograft models.

MATERIALS and METHODS

The anti-DLL4 antibodies were generated at OncoMed Pharmaceuticals, Inc. The pancreatic tumors OMP-PN8 and OMP-PN13 were obtained from University of Michigan. OMP-PN42 was obtained from a patient that failed to respond to demcizumab plus gemcitabine from Phase 1b trial and generated at OncoMed Pharmaceuticals, Inc. Tumors were passaged subcutaneously in NOD/SCID mice up to 4 passages.

• For efficacy studies, treatments were initiated when tumors reached 100 mm³. Animals were treated with gemcitabine or gemcitabine plus nab-paclitaxel or with anti-DLL4 antibody.

• Histologic analysis used formalin-fixed, paraffin-embedded sections. Slides were scanned using Imagescope (Scanscope AT, Aperio).

• For Limiting Dose Dilution (LDD) study, single cell suspensions from control and treated tumors were diluted to appropriate cell doses and injected subcutaneously in NOD/SCID mice. Mice were followed up for up to 3 months and sacrificed before tumor volume reached 2,000 mm³. Cancer stem cell frequency was determined using L-Select 1.1.2 software program (StemCell Technologies, Inc., Vancouver, Canada).

• Data are expressed as means±SEM. Differences of p<0.05 are considered significantly different.

• An ongoing Phase 1b dose escalation study of demcizumab plus gemcitabine with or without nab-paclitaxel evaluates in 1st line pancreatic cancer patients.

RESULTS

• Anti-DLL4 in combination with gemcitabine/nab-paclitaxel was efficacious against pancreatic xenograft tumor growth.

• The significant growth inhibitory effect of the triple combination was associated with a decrease in cancer stem cell frequency and an increase in apoptosis and tumor cell differentiation.

• The triple combination was highly effective against tumor growth in a xenograft derived from a patient that previously did not respond to demcizumab plus gemcitabine.

• Three of the 6 (50%) evaluable patients who received DEM/GEM/nab-paclitaxel had a RECIST partial response and 2 had stable disease resulting in a clinical benefit rate of 83%. The Kaplan Meier estimated median progression free survival for this cohort has not been reached.

• A randomized Phase 2 trial in 1st line pancreatic cancer is planned for 2014.