A Phase 1b Study of the Anti-Cancer Stem Cell Agent Demcizumab (DEM, anti-DLL4) and Gemcitabine (GEM) with or without Nab-Paclitaxel in Patients with Pancreatic Cancer


START, Madrid, Spain; Wakato Hospital, Hamilton, New Zealand; Ramon y Cajal Hospital, Madrid, Spain; Box Hill Hospital, Box Hill, Australia; Adelaide Cancer Centre, Adelaide, Australia; Sydney Cancer Centre, Sydney, Australia; Christchurch Hospital, Christchurch, New Zealand; OncoMed, Redwood City, CA; and Austin Health, Heidelberg, Australia.

Background

There is accumulating evidence that the cell types within tumors are heterogeneous and that many cancers are resistant to existing cancer therapies. One explanation for this is the existence of cancer stem cells (CSCs), a subpopulation of tumor cells that are capable of self-renewal and differentiation into other cell types. CSCs may be responsible for therapy resistance and tumor recurrence, which highlights the need for strategies that specifically target these cells.

Methods

This is an open-label, Phase I/II dose escalation study of DEM plus GEM with or without Nab-Paclitaxel in patients with metastatic pancreatic cancer. After a 3+3 design, the dose-escalation phase included 1 patient per dose cohort until a maximum tolerated dose was determined. Following, more than 3 patients were treated at each dose level to further evaluate safety and efficacy.

Results

1. **Adverse Events (AEs)**: AEs were assessed for all 30 patients who received at least one dose of study treatment.

   - **Nonclinical Xenograft Data**: In a xenograft model, DEM and GEM showed additive antitumor activity, and 6 biomarkers of Notch signaling and CSCs were reduced.

   - **Patient Demographics (n=30)**: The median age was 65 years, and the majority of patients had adenocarcinoma of the pancreas (70%).

   - **Pharmacokinetics and Immunogenicity**: Demcizumab clears slowly in patients with a population mean half-life of 16 days.

   - **Related AEs**: AEs were manageable, with the most common being fatigue, rash, and anemia.

   - **Truncated Dosing**: In a truncated dosing scenario, 3 out of 9 patients remained on therapy for >200 days.

   - **Reversible Cardiopulmonary Toxicity**: One patient experienced reversible cardiopulmonary toxicity following >100 days of treatment, which was reversible following the discontinuation of demcizumab and medical management.

   - **Cohort Duration**: Five of these 9 patients had a PR and 3 had SD.

   - **Clinical Benefit**: Median progression-free survival was 4.7 months, with 2 out of 24 patients remaining progression-free off study.

   - **Cautionary Statement**: Due to the small sample size, the study is not powered to determine a definitive trend in survival outcomes.

Summary

This is an ongoing Phase I/II dose escalation study of demcizumab, a chemotherapeutic monoclonal antibody (targeting the DLL4 ligand in the Notch pathway) plus gemcitabine with or without nab-paclitaxel in 1st line pancreatic cancer patients.

- Demcizumab and gemcitabine with or without nab-paclitaxel were generally well tolerated with fatigue, nausea, vomiting and hypertension being the most common drug-related toxicities. The hypertension was managed with anti-hypertensives. Grade 2-3 pulmonary hypertension occurred in 2 patients and Grade 2 heart failure occurred in one patient receiving treatment for greater than 100 days.

- Patients are being followed with cardiac monitoring using B-type natriuretic peptide (BNP) and echocardiography. BNP appears to be an early indicator of cardiotoxicity. In addition, a cardioprotective medication (i.e., an angiotensin-converting enzyme inhibitor or carvedilol) was provided to patients administered to patients with rising BNP levels and this strategy appears to prevent cardiotoxicity.

- Utilizing a truncated treatment approach for demcizumab (i.e., 70 days of therapy) appears to prevent the onset of late cardiotoxicity.

- The most recent and all subsequent cohorts will receive demcizumab in combination with nab-paclitaxel.

- Concomitant gemcitabine with or without nab-paclitaxel did not appear to significantly alter the pharmacokinetics of demcizumab.

- The Kaplan-Meier estimated median progression-free survival is 5.1 months (95% CI 2.2-8.0). Five of these 9 patients had a PR and 3 had SD.

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