Phase 1 results from the combination of an immune-activating anti-CD27 antibody (varilimumab) in combination with PD-1 blockade (nivolumab): activation across multiple immune pathways without untoward immune-related adverse events

Rachel E Sanborn1, Michael J Pishvain1, Margaret K Callahan2, Naiyer Rizvi3, Harriet Kluger4, Michael Yellin5, Tracey Rawls6, Laura Vitali6, Abdel Halim7, Thomas Davis8, Tibor Keler9
1.Earle A. Chiles Research Institute, OR; 2. Georgetown University Medical Center, DC; 3. Memorial Sloan Kettering Cancer Center, NY; 4. Columbia University, NY; 5. Yale Cancer Center, CT; 6.Celldex Therapeutics, NJ

Abstract # CT023

Background

CD27 is a key costimulatory molecule uniquely expressed on CD4+ and CD8+ T cells and plays roles in T cell activation, proliferation, and effector function, including generation of cytokine CD8+ T cells, and differentiation to memory T cells.

Varilimumab is a fully human IgG1 anti-CD27 mAb that has demonstrated biological and clinical activity in a Phase 1 study.

Phase 1 Trial Design & Patient Characteristics

A 3+3 design with escalating doses of varilimumab (0.1, 0.5, 1.0, 5.0, 10 mg/kg) in combination with nivolumab (3 mg/kg) for patients with advanced solid tumors with metastatic colorectal cancer (CRC), melanoma (MEL), ovarian cancer, renal cell carcinoma (RCC), or a head and neck squamous cell carcinoma (SCC/HN). Before 6 of 8 additional patients per cohort was permitted, for a total of 12 patients per cohort. The 1.0 mg/kg and 10 mg/kg cohorts were lead-in

Primary Objectives:
1. Phase 1: to assess the safety and tolerability of varilimumab in combination with nivolumab, and to identify dose (either toxicities or toxic effects) and the recommended Phase 2 dose.
2. Phase 2: to assess the preliminary antitumor activity of the combination of varilimumab and nivolumab, as measured by objective response rate (ORR), in all tumor types except GBM which will be measured by overall survival at 12 months (OSD).

All dose levels of the combination therapy were well tolerated, without identification of a MTD.

Treatment-related AEs included infusion reactions, lymphopenia, fatigue, nausea, vomiting, rash, and elevated pancreatic enzymes. One patient had grade 4 hepatitis. Two patients with drug-related SAEs

Grade 4 hepatitis (1013) and grade 3 renal insufficiency in a patient with melanoma cancer (varilimumab 10 mg/kg cohort).

Grade 2 hypertension (2540) in a patient with CRC (varilimumab 10 mg/kg cohort).

Varilimumab PK profile

Pharmacodynamic data suggests that a combination of varilimumab with checkpoint blockade will have synergistic antitumor activity. This Phase 1/2 clinical study explores the biological and clinical activity of combining varilimumab, a fully human anti-CD27 mAb. We present safety and immune biomarker data from the Phase 1 portion of the study.

Changes in Tumor Infiltrating Lymphocytes

Patients with responses from pre- and on study biopsies (n=17)

Examples of Patients with Increase in TIL and PD-L1 Expression

● Increase in TILs observed at all varilimumab dose levels.
● Trend increased in PD-L1 expression and CD26+ TILs in patients with SD or better response.

Changes in Circulating Lymphocytes

The combination of varilimumab and nivolumab was well tolerated at all varilimumab dose levels in 8 of 12 patients. Toxicity has been similar to what was seen with nivolumab or varilimumab monotherapy.

Circulating biomarkers showed increase in inflammatory chemokines and decrease in CD4 and Treg cells.

Biomarker changes not related to varilimumab dose level.

Biomarker changes generally consistent with varilimumab monotherapy.

Marked increases in tumor infiltrating lymphocytes.

Observed in selected patients at each varilimumab dose level.

May correlate with clinical outcome.

Summary