A Phase 1b Study of Navicixizumab & Weekly Paclitaxel in Heavily Pre-Treated Platinum Resistant Ovarian, Primary Peritoneal or Fallopian Tube Cancer

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Methods

This is an ongoing Phase 1b dose escalation and expansion study of navicixizumab in combination with paclitaxel in heavily pretreated platinum resistant ovarian cancer patients. Patients with measurable disease were included. The starting dose level was 1 mg/kg and was escalated by a step of 1 mg/kg up to a maximum of 15 mg/kg in the Phase 1a trial. The escalation as per a protocol defined standardized anti-tumor activity or dose limiting toxicity (DLT) was based on the 28-day cycle. If a patient experienced a DLT at a dose + 3 mg/kg, the patient was enrolled at a dose - 3 mg/kg. The PLL 80 mg/kg was given in 1/2 of cycle 1, 2/5 and 3/2 of cycle 2 was given in cycle 2. Paclitaxel (30 mg/m²) was administered on days 1, 8 and 15. The maximum recommended phase 2 dose is 3 mg/kg, following an expansion cohort enrolment of a total of 40 patients. The expansion cohort was predicated with 3 mg/kg of navicixizumab as a higher dose did not show increased activity, but did result in more pronounced adverse events.

Patient Demographics (n=34)

Best % Change in RECIST Target Lesion Size - Bevacizumab Treated Patients

Preclinical Xenograft Data

- Efficacy in ovarian xenograft models as a single agent and in combination with paclitaxel
- Reduces tumor growth and tumorigenicity

Background

Inhibition of tumor angiogenesis has proven to be a successful approach to treating cancer and two ligands responsible for tumor angiogenesis are vascular endothelial growth factor (VEGF) and delta-like ligand 4 (DLL4) which is one of the 5 ligands in the Notch pathway. In addition, inhibition of DLL4 reduces the tumorigenicity of a tumor in xenograft models by reducing the number of tumor initiating cells. Navicixizumab is an IgG4, humanized bispecific monoclonal antibody directed against both human DLL4 and VEGF. Navicixizumab was carefully designed such that the anti-VEGF and anti-DLL4 arms have roughly equivalent affinity for their respective ligands. Navicixizumab was efficacious in all xenograft models in all dose levels tested, including breast, colon, gastric, glioblastoma, non-small cell lung cancer, pancreatic, ovary, and renal cell carcinomas. Finally, navicixizumab had a response rate of 25/ (3/12) in heavily pretreated ovarian cancer pts who were treated in an earlier single agent phase 1b trial.

Clinical Response

- Overall Response Rate: 22/26 (85%)
- Partial Response: 14/23 (61%)
- Stable Disease: 9/23 (39%)
- No response: 0/23 (0%)
- Median Duration of Response: 19 months

Toxicity

- Grade 1/2: Hypertension (53%), Peripheral edema (33%), Headache (21%), Back Pain (18%), GI Perforation (18%), Thrombocytopenia (18%), Peripheral neuropathy (18%), WBC decreased (18%), GERD (18%)
- Grade 3/4: Hypertension (16%), Peripheral edema (16%), Headache (16%), Back Pain (16%), GI Perforation (16%), Thrombocytopenia (16%), Peripheral neuropathy (16%), WBC decreased (16%), GERD (16%), GERD (16%)

% Change from Baseline

- RECIST Best Overall Response
- GCIG Best CA-125 Response

Adverse Events of Special Interest

- Hypertension
- Pneumonitis
- Heart Failure
- Hypothyroidism
- Hypothyroidism

Immunogenicity (n=25)

- ADA+ Patients post-baseline
- ADA+ Patients post-baseline

Summary

The most common related adverse events were hypertension (53%), fatigue (33%), diarrhea (21%) and headache (16%). The hypertension was managed with a protocol standardized anti-hypertensive treatment algorithm.

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