A Phase I safety and pharmacokinetic (PK) study of recombinant Apo2L/TRAIL, an apoptosis-inducing protein in patients with advanced cancer.

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**Background**
- Death receptors, such as TNF-alpha receptor, Fas, and TRAIL-R (TNF-alpha Related Apoptosis Inducing Ligand Receptor)-1 and –2, can stimulate the extrinsic apoptotic pathway in tumor cells when activated by their cognate ligands.
- Stimulation of TNF-alpha receptor and Fas has been associated with unacceptable systemic toxicities, limiting the clinical utility of targeting these pathways. In contrast, pre-clinical data has shown that stimulation of the TRAIL receptor can selectively kill tumor cells without systemic toxicity.
- The ligand Apo2L/TRAIL can activate both of the human TRAIL receptors: TRAIL-R1 (DR4) and TRAIL-R2 (DR5) - Apo2L/TRAIL induces apoptosis in human tumor cell lines in vitro and in xenograft models. Its efficacy is p53-independent.
- A His-tagged preparation of TRAIL was toxic to primary human hepatocytes in culture. In contrast, the preparation of native TRAIL being developed by Genentech and Amgen has no foreign sequences and is not toxic to primary human hepatocytes, nor is it toxic in murine or primate models.
- This is the first report on the safety of Apo2L/TRAIL administered to humans.

**Materials and Methods**

**Phase I study design:**
- Open label study conducted at five centers
- 58 patients with advanced solid tumors or NHL; 586 doses administered
- Dose escalation: 0.5, 1.5, 4, 8, and 15 mg/kg i.v. administered daily for 5 days every 3 weeks
- Given concerns surrounding potential hepatotoxicity, patients without liver metastasis were treated before patients with liver metastasis in a staggered manner
- Toxicity, pharmacokinetics, immunogenicity and best responses were assessed

**Results**
- Median age: 59. Heavily pre-treated (median prior regimens = 4)
- Toxicity:
  - No dose limiting toxicities were observed in any of the cohorts.
  - Most of the adverse events were Grade 1/2 fatigue, nausea, and anemia
  - There were 2 each of Grade 3 hyperglycemia, pneumonia, and AST elevation.
  - All patients with liver toxicities had progressive disease
  - Two patients with sarcoma had adverse events related to tumor necrosis
- Best responses:
  - Of the assessable patients, 53% had stable disease, 41% had progressive disease.
  - One patient with synovial chondrosarcoma treated with 8 mg/kg had a confirmed, objective partial response (70% by RECIST criteria)
- Pharmacokinetics:
- Dose dependent and linear, which did not differ depending on presence of liver metastasis
- half-life was 0.6 hr
- No antibodies against Apo2L/TRAIL were detected.

**Author's Conclusions**
- Apo2L/TRAIL is safe and well tolerated up to 15 mg/kg. The 8 mg/kg cohort is being expanded for additional safety data.
- Combination with other chemotherapeutic agents is warranted.

**Clinical/Scientific Implications**
- There was considerable trepidation regarding liver toxicity that was engendered by in vitro results using a His-TRAIL preparation. Therefore, it is significant that there were no dose limiting toxicities in this Phase I trial, even in patients with liver metastasis.
- The partial response seen in one patient with chondrosarcoma was promising, however, like the agonistic antibodies, the majority of responses were stable disease.
- Unlike the agonistic antibodies, Apo2L/TRAIL targets both TRAIL-R1 and TRAIL-R2, which may broaden its efficacy. However, the short half-life requires an inconvenient dosing regimen (i.v. injections every day for 5 days) to get the predicted AUC required for activity.
- There is marked heterogeneity in TRAIL sensitivity in human tumor cell lines, and the mechanisms of resistance are protean. Future studies should focus on optimal combination therapies with TRAIL, as its activity as a single-agent will likely be underwhelming.