Agonistic Death Receptor 5 (DR5) IgM antibody IGM-8444 induces tumor cell apoptosis in vitro and in vivo and has a favorable in vitro safety profile

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Background
- Tumor necrosis factor receptor (TNFR) superfamily member death receptor DR5 requires multimerization to induce apoptosis and tumor cytotoxicity (Pan et al., 2019, Cell 176, 1477).
- While agonistic IgG antibodies targeting DR5 have demonstrated evidence of preclinical efficacy, limited clinical efficacy was observed likely due to insufficient receptor multimerization in the tumor microenvironment.
- Some multivalent DR5 agonists have shown signs of clinical efficacy but also liver toxicity.
- We have developed IGM-8444, a novel multivalent anti-DR5 IgM antibody that effectively clusters DR5 to induce tumor cytotoxicity in vitro and in vivo.

IGM-8444 Does Not Induce Killing of Primary Human Hepatocytes

Combination of IGM-8444 with Chemotherapy Results in Enhanced Tumor Cytotoxicity in Vitro

ABT-199 Enhances Efficacy In Vivo

IGM-8444 Induces Cytotoxicity Across Multiple Tumor Cell Line Indications

IGM-8444 Induces Cytotoxicity in Tumor Cells

IGM-8444 Binds and Induces Apoptosis in Tumor Cells

Combination of IGM-8444 with Chemotherapy and ABT-199 Enhances In Vivo Efficacy

Summary
- Anti-DR5 antibodies showed > 5000-fold increased in vitro potency as IgMs compared to IgGs.
- When compared to an IgG, IGM-8444 induces more rapid and profound apoptosis in vitro; IGM-8444 is highly potent across 38 cell lines and PDXs evaluated from 21 tumor types but does not kill primary human hepatocytes in vitro at concentrations well above those required to kill tumor cell lines.
- As a monotherapy, IGM-8444 induces anti-tumor efficacy in CDX and PDX models in vivo, including durable and dose-dependent tumor regressions in a gastric PDX.
- Combinations of IGM-8444 with standard of care chemotherapy and targeted agents enhance tumor cytotoxicity both in vitro and in vivo.
- These data support the development of IGM-8444 to treat solid and hematologic cancers and an IND is projected to be filed in 2020.