IGM-8444 is a potent agonistic Death Receptor 5 (DR5) IgM antibody:
Induction of tumor cytotoxicity, combination with chemotherapy and in vitro safety profile
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Background

- Tumor necrosis factor receptor (TNFR) superfamily death receptor DR5 requires multimerization to induce apoptosis and tumor cytotoxicity (Pan et al., 2019, Cell 178:1477).
- 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 cytotoxicity in vitro and in vivo.

IGM-8444 binds and induces apoptosis in tumor cells.

IGM-8444 Does Not Induce Killing of Primary Human Hepatocytes In Vitro

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

IGM-8444 treatment increases M30 and M65 Serum Apoptotic and Cell Death Biomarkers

Figure 2. IGM-8444 binds and induces apoptosis in tumor cells. (A) IGM-8444 binds and induces apoptosis in Colo205, HCT15, MC3T3, and NCI-H69 cells. (B) IGM-8444 induces apoptosis in Colo205 in a dose-dependent manner.

IGM-8444 is highly potent across 27 cell lines and PDXs evaluated from 20 tumor types but does not kill primary human hepatocytes in vitro.

When compared to an IgG, IGM-8444 induces more rapid and profound apoptosis.

As a monotherapy, IGM-8444 induces anti-tumor efficacy in a combination with M65 and potent and cell death biomarkers in a dose dependent manner in vivo.

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.

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