IGM-8444 as 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:**
Death receptor 5 (DR5) is a member of the tumor necrosis factor (TNF) receptor superfamily that multimerizes when bound to its ligand, TNF-related apoptosis inducing ligand (TRAIL), to activate the extrinsic apoptotic pathway. DR5 is broadly expressed on solid and hematologic cancers and has been targeted with both recombinant TRAIL and agonistic antibodies in the clinic. However, these therapeutics have generally been unsuccessful due to toxicity or lack of efficacy. We have developed a multivalent IgM DR5 agonist, IGM-8444, that multimerizes DR5 to selectively and potently induce tumor cell apoptosis while maintaining tolerability.

**Methods:**
IGM-8444 is an engineered, pentameric IgM antibody with 10 binding sites specific for DR5. Human tumor cell lines or hepatocytes were evaluated *in vitro* for dose dependent IGM-8444 induced cytotoxicity. The efficacy of IGM-8444 was evaluated with or without chemotherapy, in cell line-derived xenograft (CDX) and patient-derived xenograft (PDX) mouse tumor models, with IGM-8444 administered at various dose levels and schedules when tumors reached approximately 100 mm³. Sera and tumors were analyzed for biomarkers of tumor apoptosis.

**Results:**
In vitro cytotoxicity assays identified IGM-8444 activity across cell lines from 18 solid and hematologic malignancies. In IGM-8444 partially resistant cell lines, combination with chemotherapy or a Bcl2 inhibitor enhanced in vitro cytotoxicity. IGM-8444 was efficacious as a monotherapy in CDX and PDX tumor models including colorectal, lung, and gastric indications. In a gastric PDX model, IGM-8444 induced complete and durable dose-dependent tumor regressions. In vivo, combination of IGM-8444 with standard-of-care chemotherapies, such as irinotecan, led to enhanced efficacy. IGM-8444 administration increased markers of tumor apoptosis, identifying potential clinical pharmacodynamic biomarkers. At doses several log-fold higher than efficacious doses, IGM-8444 demonstrated a favorable single agent in vitro safety profile, with little to no in vitro cytotoxicity observed using primary human hepatocytes from multiple donors.

Conclusions:
These data support the clinical development of IGM-8444 in both solid and hematological malignancies as a single agent and in combination with standard of care therapy. IGM-8444 is projected for IND filing in 2020.

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