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518 / 2 - 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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Presenter/Authors

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Disclosures

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Abstract

Death receptor 5 (DR5) is a member of the tumor necrosis factor (TNF) receptor superfamily that binds TNF-related apoptosis inducing ligand (TRAIL) to induce receptor trimerization and activate extrinsic apoptotic pathways. DR5 is expressed on a broad range of solid tumors as well as leukemias and lymphomas and has been targeted therapeutically with DR5 IgG antibodies and recombinant TRAIL agonists. However, agonistic IgG antibodies and TRAIL molecules targeting DR5 have been largely unsuccessful in clinical trials either in monotherapy or combination studies with chemotherapy due to insufficient receptor clustering to induce apoptotic pathways and/or due to very short half-life. Therefore, several new approaches have been taken to develop multivalent receptor DR5 agonists to enhance tumor cell apoptosis. We have taken the approach to efficiently cluster DR5 with multivalent IgM antibodies that contain 10 to 12 binding sites to DR5. First, we converted five agonistic IgG antibodies into the IgM antibody format and evaluated them using *in vitro* cell killing assays with colorectal cancer cell line Colo205 and compared them to IgG antibodies with the same binding domains. In all cases, we found the DR5 IgM antibodies significantly enhanced cellular cytotoxicity, resulting in at least 5,000 fold increased potency compared to IgGs. We have further developed a pentameric IgM antibody, IGM-8444, which has 10 binding sites specific for DR5 and efficiently triggers tumor cell apoptosis. *In vitro* tumor cell cytotoxicity screening identified IGM-8444 sensitive cell lines across 17 solid and hematologic cancer indications. IGM-8444 was efficacious as a monotherapy in both CDX and PDX preclinical mouse tumor xenograft models with complete and durable tumor regressions observed in a gastric PDX that expressed moderate levels of DR5 by immunohistochemistry. The combination of IGM-8444 with chemotherapeutic agents enhanced the cytotoxicity in several IGM-8444 resistant cell lines *in vitro*. IGM-8444 also combined well with standard-of-care therapies (e.g. irinotecan) *in vivo*, leading to enhanced efficacy. A significant challenge to the clinical development of multivalent DR5 agonists has been on-target liver toxicity. However, IGM-8444 had a favorable *in vitro* safety profile, with little/no *in vitro* cytotoxicity observed using primary human hepatocytes at concentrations >10,000 fold above the cytotoxicity EC_{50} observed in Colo205 cytotoxicity assays. Taken together, these data support

the clinical development of IGM-8444 for the potential treatment of both solid and hematologic malignancies and an IND is projected to be filed in 2020.