control antibody for 24 hrs in the histoculture system. RNA was isolated from tumors prior to any treatment as well as from JTX-8064 and isotype control treated samples. Gene expression was analyzed using the NanoString nCounter® and qPCR assays. Additional IHC analyses were performed on baseline untreated tumor samples.

**Results** JTX-8064 was shown to induce pharmacodynamic responses to treatment significantly above isotype control indicating of macrophage polarization, IFN-g-signaling, and T cell inflammation. To identify predictive biomarkers of pharmacodynamic response to JTX-8064, matched untreated samples were characterized by gene expression analysis and by IHC (CD8, CD163, and HLA-G proteins). Numerous LILRB2 pathway-related molecules (e.g. HLA-A, HLA-B, CD163, LILRB2) and gene signatures were found to be statistically significantly higher in the untreated kidney, head and neck, and lung cancer samples of matched pharmacodynamic responders compared to non-responders. Further bioinformatics analysis revealed additional cancer subtypes where these biomarkers are enriched.

**Conclusions** These data will inform indication selection and combination strategies for JTX-8064 to maximize potential therapeutic benefit for patients with solid tumor malignancies.

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**A PRECLINICAL STUDY OF IMC-002, A FULLY HUMAN THERAPEUTIC ANTIBODY SAFELY TARGETING CD47 IN CANCER**


**Background** Immunotherapy with immune checkpoint inhibitors such as PD-(L)1 and CTLA-4 blocker has become an important part of cancer treatment. For the cancers resistant to these drugs, however, many other therapeutic targets are being tested to modulate the tumor microenvironment (TME) toward anti-cancer immunity. Due to the functional flexibility, macrophages play an essential role in orchestrating tissue immunity including TME. CD47 is one of the key targets that modulate macrophages, which is often overexpressed on cancer cells. When it binds to its receptor, SIRPα, it gives a ‘don’t-eat-me’ signal and inhibits phagocytosis of cancer cells by macrophages. IMC-002 is a fully human IgG4 monoclonal antibody targeting human CD47, which has been engineered to possess optimal efficacy and safety profile. IMC-002 does not induce hemagglutination and contains a hinge stabilizing S228P mutation to prevent Fab arm exchange.

**Methods** A series of in vitro functional assays including ligand binding, cell surface binding and phagocytosis assays were performed. Putative epitopes for IMC-002 were identified using synthetic peptide libraries. In vivo efficacy of IMC-002 was tested in human breast cancer models. Pharmacokinetic parameters and toxicity profiles were assessed in mice and cynomolgus monkeys.

**Results** IMC-002 strongly bound to CD47 ligand and to various types of CD47-expressing cancer cells including solid and hematological cancers. IMC-002 also bound to human CD4 T cells and, to a lesser degree, to CD8 T cells, but not to NK or B cells. Interestingly, IMC-002 showed no binding to RBCs which highly express CD47 and thus, did not induce RBC agglutination in vitro. IMC-002 induced phagocytosis of cancer cells by human blood CD14+ monocyte-derived macrophages and strongly suppressed tumor growth in a dose-dependent manner in xenograft animal models. Treating IMC-002 with tumor antigen targeting IgG1 type therapeutic antibodies increased phagocytosis compared to single treatment. Epitope mapping analysis revealed that compared to RBC-binding anti-CD47 antibody and a natural ligand, SIRPα-Fc, IMC-002 bound to distinct parts of CD47 antigen, which may be responsible for the cell-selective binding of IMC-002. Consistent with the in vitro data, IMC-002 was well tolerated in cynomolgus monkeys with no adverse effects including hematologic toxicity at doses up to 100 mg/kg. IMC-002 showed a typical pharmacokinetic profile of therapeutic antibody with a half-life of 5–10 days. Given its differential binding profile toward tumor cells vs normal cells such as RBC, preclinical data was thoroughly analyzed to simulate human PK and to come up with the optimal first-in-human dose.

**Conclusions** Preclinical efficacy and safety profiles of IMC-002 provide a strong rationale for assessing therapeutic potential in clinical studies. Particularly, IMC-002 is expected to be beneficial for hematologic cancer patients because it has been engineered to minimize hematological toxicities such as anemia which is a class effect of the CD47-targeting antibodies. The first-in-human (FIH) study of IMC-002 is ongoing in the US sites. The purpose of the study is to assess the safety and tolerability of IMC-002 and determine the recommended Phase 2 dose (RP2D) of IMC-002 in subjects with metastatic or locally advanced solid tumors and relapsed or refractory lymphomas.

**Ethics Approval** All experimental procedures were performed according to the guidelines of the Institutional Animal Care and Use Committee (IACUC) of the contract research organizations.

**REFERENCES**


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**LONG-TERM CLINICAL OUTCOMES ASSOCIATED WITH SEQUENTIAL TREATMENT OF BRAF MUTANT ADVANCED MELANOMA PATIENTS**

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**Background** Patients with BRAF mutant advanced melanoma can be treated sequentially with immunotherapies (IO) and BRAF+MEK inhibitors. We evaluated the clinical outcomes associated with various treatment sequences for BRAF mutant advanced melanoma based on the 5-year follow-up data from clinical trials.

**Methods** In the absence of head-to-head trial data, a matching-adjusted indirect comparison (MAIC) was conducted for IO vs. BRAF+MEK inhibitors, using the longest follow-up available in the published literature. Multivariable risk equations were performed to estimate the incremental benefit at 5 years of follow-up.