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 indi-
cative of macrophage polarization, IFNγ-signaling, and T cell
inflammation. To identify predictive biomarkers of pharma-
dynamic 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 can-
cer samples of matched pharmacodynamic responders com-
pared 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.

Further information can be found in the online abstract.

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

Hyeonseok Yoo*, Jeong Kook Kim, Ji Yea Choi, Sun Kwang Song, Jihyun Park, Ara Jeon, Ji
Hye Lee, Sook Kyung Chang, Yun Song. ImmunOnCia Therapeutics, Seongnam-si, Moldova,
Republic of

**Background** Immunotherapy with immune checkpoint inhibi-
tors 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 can-
cer 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 param-
eters and toxicity profiles were assessed in mice and cynomol-
gus monkeys.

**Results** IMC-002 strongly bound to CD47 ligand and to vari-
ous 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 macro-
phages and strongly suppressed tumor growth in a dose-
dependent manner in xenograft animal models. Treating IMC-
002 with tumor antigen targeting IgG1 type therapeutics
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. Consis-
tent with the in vitro data, IMC-002 was well tolerated in
cynomolgus monkeys with no adverse effects including hema-
tologic 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 tol-
erability 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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Further information can be found in the online abstract.

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

Ahmad Tarhini*, David McDermott, Apoorva Ambavane, Agnes Benedict, Cho-Han
Lee, Corey Ritchings, Brian Stavely, Meredith Regan, Michael Atkins. Moffit
Comprehensive Cancer Center and Research Institute, Tampa, FL, USA; *Harvard Medical
School; Beth Israel Deaconess Medical Center, Boston, MA, USA; ‡Evidra, London, MD,
UK; †Bristol Myers Squibb, Princeton, NJ, USA; ‡Harvard Medical School and Dana-Farber
Cancer Institute, Boston, MA, USA; ‡Georgetown Lombardi Comprehensive Cancer Center,
Washington, DC, USA

**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 match-
ing-adjusted indirect comparison (MAIC) was conducted for
IO vs. BRAF+MEK inhibitors, using the longest follow-up
available in the published literature. Multivariate risk equations