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 indicative of macrophage polarization, IFNg-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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218 A PRECLINICAL STUDY OF IMC-002, A FULLY HUMAN THERAPEUTIC ANTIBODY SAFELY TARGETING CD47 IN CANCER

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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.[1] When it binds to its receptor, SIRPα, it gives a 'don't-eat-me' signal and inhibits phagocytosis of cancer cells by macrophages.[2] 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 therapeutics increased phagocytosis compared to single treatment. Epitope mapping analysis revealed that compared to RBC-binding anti-CD47 antibody and a natural ligand, SIRRα-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.

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219 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. Multivariate risk equations

were developed to predict time-to-event outcomes based on patient-level data from pooled CheckMate-067 &-069 trials. Risk equations were inserted into a discrete event simulation to estimate the average life-years (LYs) and quality-adjusted life-years (QALYs) that can be gained with various treatment sequences over a lifetime horizon. Treatment sequences and corresponding efficacy data sources are presented below (table 1). Utility weights for quality-adjustment of LYs were obtained from published literature.

Results Treatment sequences starting with IO followed by BRAF+MEK were associated with 2.9–4.3 years of additional survival and 2.2–3.3 years of quality-adjusted survival versus sequences starting with BRAF+MEK followed by anti-PD-1. After 1L IO, the time spent in the treatment-free interval (TFI) is 3.3–5.0 years. LYs, QALYs, and time spent in TFI were higher with sequences starting with anti-PD-1+anti-CTLA-4 vs. anti-PD-1 alone.

Abstract 219 Table 1 Clinical outcomes on treatment sequences for BRAF MT melanoma

		Life Years					QALYs
1L therapy:	2L therapy:	1L	TFI	2L	Post 2L	Total	Total
BRAF+MEK[1]	Anti-PD1[2]	1.3	--	0.6	1.9	3.8	3.0
Anti-PD1+Anti-CTLA4[3]	BRAF+MEK[3]	1.5	5.0	0.6	1.0	8.1	6.3
Anti-PD1[3]	BRAF+MEK[3]	1.2	3.3	0.8	1.4	6.7	5.1

[1]COMBI-v & COMBI-d (maximum follow-up 76 months), COLUMBUS (median follow-up 48.8 months)
[2]CheckMate 037 (maximum follow-up 24 months)
[3]CheckMate 067 (minimum follow-up 60 months) & CheckMate 069 (median follow-up 24 months)
BRAF+MEK = dabrafenib+trametinib/encorafenib+binimetinib; Anti-PD-1+Anti-CTLA-4 = nivolumab+ipilimumab; Anti-PD-1 = nivolumab

Conclusions In this sequencing model with 5-year data from randomized clinical trials, initiating 1L treatment with IO provided prolonged survival compared to initiating 1L treatment with BRAF+MEK. Time spent in TFI represents a significant proportion of survival time for patients on IO initiating sequences. Limitations of the study are the reliance on published information for BRAF+MEK, which could lead to biases due to unmeasured differences in the patient populations or trial conduct and the absence of data on 2L combination IO. Anti-PD-1+anti-CTLA-4 as second line option has not been included because of a lack of clinical evidence. Findings from this analysis will require validation in ongoing prospective randomized clinical trials.

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220 REAL-WORLD OUTCOMES OF PATIENTS WITH RESECTED STAGE IIIA MELANOMA TREATED WITH ADJUVANT NIVOLUMAB

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Background Nivolumab is approved in the US and EU for the adjuvant treatment of resected stage III-IV melanoma based on results from the CheckMate-238 clinical trial.[1,2] However, the trial did not enroll any patients with Stage IIIA disease per the American Joint Committee on Cancer (AJCC) 7th edition criteria and included a limited number of patients with stage IIIA disease per the AJCC 8th edition.[3,4,5]Recognizing the need for real-world data to assess outcomes of patients with resected stage IIIA melanoma treated with adjuvant nivolumab, a non-interventional study was conducted to investigate treatment patterns and outcomes among patients receiving adjuvant nivolumab within the US community practice setting.

Methods A retrospective analysis of the US Oncology Network's iKnowMed medical data was conducted to examine patients with resected stage IIIA melanoma treated with adjuvant nivolumab between 01-Jan-2018 and 31-Dec-2019 with a follow-up period through 31-Mar-2020. Patients were followed for up to 27 months after their sentinel lymph node biopsy. Baseline demographic/clinical characteristics and treatment patterns were examined descriptively. Duration of treatment (DOT) and overall survival were analyzed using the Kaplan-Meier method.

Results A total of 58 patients with stage IIIA melanoma treated with adjuvant nivolumab were identified. Median age was 57.8 years (range 21.5–93.5), 62.1% were male, and 75.9% were Caucasian. Among patients with a documented Eastern Cooperative Oncology Group (ECOG) performance status (51.7%), all had an ECOG score of 0 or 1. Median follow-up time was 12.6 months (range 0.3–25.1). Median DOT was 10.6 months (range 6.8–12.0). Overall survival rates at 12 and 24 months were 97.7% (95% CI 84.6–99.7) and 92.2% (95% CI 69.6–98.2), respectively.

Conclusions This real-world analysis of patients with stage IIIA melanoma treated with adjuvant nivolumab showed that a large proportion of patients were alive at the end of the study period, suggesting these patients have a favorable prognosis. Further investigation and follow-up is warranted to assess clinically relevant outcomes among patients with resected stage IIIA melanoma.

Ethics Approval The study was approved by US Oncology Inc's Institutional Review Board, approval number 20-020E-2020-0224-01.

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221 POOR PERFORMANCE STATUS NEGATIVELY AFFECTS SURVIVAL BENEFIT OF IMMUNOTHERAPY IN NON-SMALL CELL LUNG CANCER

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Background Immunotherapy has shown survival benefit as both frontline and subsequent therapy in multiple cancers. However, its efficacy in patients with poor performance status is unknown since they are excluded from the clinical trials. We conducted a retrospective study to investigate the effect of poor performance status (PS) on survival in patients with non-small cell lung cancer (NSCLC) who received immunotherapy as a subsequent line of treatment.