and their staff; Cedric Burg PhD and J. MacDougall PhD of BioXcel Therapeutics, Valery Chatikhine MD of Iqvia Biotech and the Iqvia Biotech team for assisting in the conduct of the study.

**Trial Registration** NCT03910660EUDRACT 2018-003734-32

**Ethics Approval** This study was approved by Institution Review Boards or Ethics Committees affiliated with participating institutions.

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**A PHASE 3 STUDY (COSMIC-313) OF CABOZANTINIB IN COMBINATION WITH NIVOLUMAB AND IPILIMUMAB IN PATIENTS WITH PREVIOUSLY UNTRATED ADVANCED RENAL CELL CARCINOMA OF INTERMEDIATE OR POOR RISK**

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**Background** Cabozantinib (C) inhibits tyrosine kinases involved in tumor growth, angiogenesis, and immune regulation, including MET, VEGFR, and TAM kinases (tyro3, AXL, MER), and may promote an immune-permissive tumor environment, resulting in enhanced response to immune checkpoint inhibitors. C has shown preliminary clinical activity and tolerability in combination with the PD-1 inhibitor nivolumab (N) and as part of a triplet combination with N and the CTLA-4 inhibitor ipilimumab (I) in patients (pts) with advanced renal cell carcinoma (aRCC) (Nadal et al. ASCO 2018). C is approved for pts with aRCC, and N+I is approved as a combination therapy in pts with previously untreated aRCC of intermediate or poor risk. We present the study design of a phase 3 trial of C+N+I vs N+I in previously untreated pts with aRCC of IMDC intermediate or poor risk (NCT03937219).

**Methods** This randomized, double-blind, controlled phase 3 study evaluates the efficacy and safety of C+N+I vs N+I in previously untreated pts with IMDC intermediate or poor risk aRCC. Eligible pts are randomized 1:1 to receive C+N+I or N+I in combination with placebo, stratified by IMDC prognostic score and geographic region. Pts receive C (40 mg oral QD) + N (3 mg/kg IV Q3W) x 4 doses + I (1 mg/kg IV Q3W) x 4 doses, followed by C (40 mg oral QD) + N (480 mg IV flat dose Q4W). Control pts receive C-matched placebo and the same treatment regimen for N+I as the experimental arm. N will be administered for a maximum of 2 years. Eligibility criteria include historically confirmed metastatic or aRCC with a clear cell component, intermediate or poor risk RCC per IMDC criteria, measurable disease per RECIST 1.1, KPS ≥70%, adequate organ and marrow function and age ≥18 years. Exclusion criteria include prior systemic therapy for aRCC and uncontrolled significant illnesses. The primary endpoint is PFS per RECIST 1.1 by BICR; the secondary endpoint is OS. Additional endpoints include ORR, safety, correlation of biomarkers with outcomes, and pharmacokinetics of C in combination with N+I. The first patient was enrolled in June 2019 and enrollment is ongoing.

**Results** N/A

**Conclusions** N/A

**Trial Registration** ClinicalTrials.gov: NCT03937219

**Ethics Approval** This study is being conducted in compliance with Good Clinical Practice (GCP), including International Conference on Harmonisation (ICH) Guidelines, the most recent accepted version of the Declaration of Helsinki, and all applicable local laws and regulatory requirements. The appropriate Institutional Review Boards (IRBs) or Ethics Committees (ECs) of participating centers have approved the study protocol. All patients have provided written informed consent.

**Consent** All patients have provided written informed consent.

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**PHASE 3 STUDY OF PEMBROLIZUMAB + DOCTAXEL AND PREDNISONE/PREDNISOLONE FOR METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (mCRPC) PRETREATED WITH NEXT-GENERATION HORMONAL AGENTS (NHAs) (KEYNOTE-921)**

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**Background** Cohort B of the phase 1b/2 KEYNOTE-365 study (NCT02861573) found that docetaxel + pembrolizumab + prednisone demonstrated activity in patients previously treated with abiraterone acetate or enzalutamide for mCRPC. The prostate-specific antigen (PSA) response rate was 28%; objective response rate (ORR) was 18% (7 partial responses); duration of response (DOR) was 6.7 months; progression-free survival (PFS) was 8.3 months; overall survival (OS) was 20.4 months; and the 12-month PFS and OS rates were 24.0% and 75.8%, respectively. The safety and tolerability profile of this combination was consistent with the profiles of each individual agent. The KEYNOTE-921 (NCT03834506) phase 3 trial will evaluate efficacy and safety of pembrolizumab + docetaxel + prednisone/prednisolone in patients with mCRPC after prior treatment with NHA.

**Methods** Eligible patients are adults with histologically or cytologically confirmed mCRPC who experience disease progression with androgen deprivation therapy (or after bilateral orchiectomy) within 6 months of screening and have Eastern Cooperative Oncology Group performance status 0/1. Other eligibility criteria are disease progression or intolerance to NHA in the metastatic hormone-sensitive prostate cancer setting or CRPC setting, no prior treatment with chemotherapy for mCRPC, and tissue available for biomarker analysis. Treatment stratification factors are prior treatment with abiraterone acetate (yes or no) and metastases location (bone only, liver, other). Approximately 1000 patients will be randomly assigned to receive docetaxel 75 mg/m2 IV Q3W + prednisone/prednisolone 5 mg orally BID and pembrolizumab 200 mg IV Q3W or docetaxel 75 mg/m2 IV Q3W + prednisone/prednisolone 5 mg PO BID + placebo IV Q3W (1:1 ratio). Response and progression will be determined using imaging (CT/MRI/bone) according to PCWG3-modified RECIST v1.1 by blinded independent central review (BICR) Q9W during the first year and Q12W thereafter. Treatment maximums are 10 cycles for docetaxel + prednisone/prednisolone and 35 cycles for pembrolizumab or placebo. Treatment discontinuation regardless of therapy received is mandated for disease progression, unacceptable toxicity, or consent withdrawal. The dual primary end points are radiographic PFS per PCWG3-modified...