A PHASE 3 STUDY (COSMIC-313) OF CABOZANTINIB IN COMBINATION WITH NIVOLUMAB AND IPILIMUMAB IN PATIENTS WITH PREVIOUSLY UNTREATED 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 (NCT03937219).

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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**Background** Antitumor activity with pembrolizumab + enzalutamide was observed in cohort C of the phase 1b/2 KEYNOTE-365 (NCT02861573) study of abiraterone acetate-pretreated patients with mCRPC and in a phase 2 study (NCT02312357) of patients with mCRPC who experienced progression with enzalutamide alone. In KEYNOTE-365 cohort C, prostate-specific antigen (PSA) response rate was 22%, objective response rate (ORR) was 20%, and 12-month PFS and OS rates were 24.6% and 72.8%, respectively. Safety and tolerability of the combination was consistent with individual profiles of each agent. In the phase 2 study of enzalutamide-pretreated patients, 5 of 28 patients (18%) had a PSA decline of ≥50%, and 3 of 12 patients (25%) with measurable disease achieved objective response. KEYNOTE-641 (NCT03834493) is a randomized, phase 3 trial to assess efficacy and safety of pembrolizumab + enzalutamide versus placebo + enzalutamide in patients with mCRPC.

**Methods** Enrolled patients have biochemical or radiographic progression with androgen deprivation therapy/aft bilateral orchiectomy within 6 months of screening, ECOG PS 0/1, ongoing androgen deprivation with serum testosterone <50 ng/dL, and tumor tissue availability for biomarker analysis. The study continues to enroll those who previously had abiraterone acetate therapy; the abiraterone-naive cohort is filled. Exclusion criteria are prior chemotherapy for mCRPC, checkpoint inhibition, or any treatment with a second-generation androgen receptor inhibitor. Treatment stratification factors are prior abiraterone acetate treatment (yes or no), metastases location (bone only or liver or other), and prior docetaxel treatment for metastatic hormone-sensitive prostate cancer (yes or no). Response and progression will be determined by imaging (CT/MRI/bone) per PCWG3-modified RECIST v1.1 on visits Q9W during the first year and Q12W thereafter. Approximately 1200 adults will be randomly assigned 1:1 in a double-blind fashion to receive enzalutamide 160 mg orally once daily + pembrolizumab 200 mg IV Q3W or enzalutamide 160 mg orally once daily + placebo for a maximum of 35 cycles or until disease progression, unacceptable toxicity, or consent withdrawal. Coprimary end points are radiographic PFS per PCWG3-modified RECIST v1.1, as assessed by blinded independent central review, and OS. The key secondary end point is time to subsequent anticancer therapy or death. Other secondary end points include PSA response rate, time to PSA progression, ORR, DOR, time to radiographic soft tissue progression, time to radiographic bone progression, and safety. KEYNOTE-921 is ongoing or planned in 22 countries across Asia, Australia, Europe, and North and South America.

**Results** N/A

**Conclusions** N/A