PHASE 1B/2 KEYNOTE-365 COHORT I: PLATINUM-CONTAINING CHEMOTHERAPY ALONE OR IN COMBINATION WITH PEMBROLIZUMAB FOR TREATMENT-EMERGENT NEUROENDOCRINE PROSTATE CARCINOMA

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Background Treatment-emergent neuroendocrine prostate carcinoma (t-NE) can occur de novo or after diagnosis of prostate adenocarcinoma. Treatment often includes platinum-containing chemotherapy because of t-NE's histologic similarity to small cell lung cancer. The PD-1 inhibitor pembrolizumab has shown promising efficacy and acceptable safety when combined with olaparib, docetaxel, or enzalutamide for treatment of metastatic castration-resistant prostate cancer (mCRPC) in the multicohort phase 1b/2 KEYNOTE-365 study (NCT02861573). Cohort I will be used to compare platinum-containing chemotherapy alone with chemotherapy + pembrolizumab as treatment for t-NE.

Methods Patients who have t-NE ($\geq 1\%$ neuroendocrine cells in a recent biopsy specimen confirmed by central histology review); experienced progression within 6 months of starting a next-generation hormonal agent (NHA) for mCRPC or hormone-sensitive prostate cancer and experienced progression within 6 cycles of docetaxel treatment for mCRPC; and have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 are eligible. Prior therapy with ≤ 2 NHAs and 1 other chemotherapy for mCRPC is permitted. Patients will be randomly assigned 1:1 to receive pembrolizumab 200 mg IV on day 1 of each cycle every 3 weeks + carboplatin AUC of 5 IV on day 1 + etoposide 100 mg/m² IV on days 1, 2, and 3 of each 21-day cycle for 4 cycles (arm 1) or the same chemotherapy regimen without pembrolizumab (arm 2); in each arm 40–100 patients will be enrolled. Pembrolizumab treatment will continue up to 2 years until disease progression, unacceptable toxicity, or withdrawal of consent. Patients will be stratified by ECOG performance status score (0 or 1). Computed tomography or magnetic resonance imaging will be performed every 9 weeks through week 54 and every 12 weeks thereafter. Primary end points are safety and tolerability, prostate-specific antigen (PSA) response rate, and objective response rate (ORR) per RECIST v1.1 by blinded independent central review (BICR). Secondary end points are time to PSA progression; ORR and radiographic progression-free survival (PFS) per PCWG3-modified RECIST v1.1 by BICR; duration of response and disease control rate per RECIST v1.1 by BICR and PCWG3-modified RECIST v1.1 by BICR; and overall survival. End points will be summarized for each arm without formal hypothesis testing.

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Trial Registration ClinicalTrials.gov, NCT02861573

Ethics Approval The study and the protocol were approved by the Institutional Review Board or ethics committee at each site.