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 after 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 secondary end point is time to subsequent antiancer 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

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

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Abstracts

PHASE 3 TRIAL OF PEMBROLIZUMAB AND ENZALUTAMIDE VERSUS ENZALUTAMIDE IN PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (MCRPC) (KEYNOTE-641)

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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 after 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 secondary end point is time to subsequent antiancer therapy or death. Other secondary end points are ORR, DOR, PSA response rate, PSA undetectable rate, time to PSA progression, time to pain progression, time to symptomatic skeletal-related event, time to soft tissue progression, and safety. KEYNOTE-641 is ongoing or planned in 21 countries across Asia, Australia, Europe, and North and South America.

Results N/A

Conclusions N/A

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

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PHASE 3 STUDY OF COMBINATION PEMBROLIZUMAB + OLAPARIB THERAPY VERSUS ENZALUTAMIDE/ABIRATERONE IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (MCRPC) AFTER PROGRESSION ON CHEMOTHERAPY (KEYLYNK-010)

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Background Cohort A of the phase 1b/2 KEYNOTE-365 study (NCT02861573) demonstrated promising antitumor activity with pembrolizumab + olaparib in patients with mCRPC unselected for homologous recombination deficiency. The prostate-specific antigen (PSA) and objective response rates (ORR) were both 9%, progression-free survival (PFS) was 4.3 months, overall survival (OS) was 14.4 months, and 12-month PFS and OS rates were 23.3% and 58.2%, respectively. The safety profile of the combination therapy was also aligned with the individual profiles of each agent. KEYLYNK-010 (NCT03834519) is a phase 3 trial to evaluate efficacy and safety of pembrolizumab + olaparib in molecularly unselected enzalutamide- or abiraterone-pretreated patients with mCRPC who progressed with docetaxel chemotherapy.

Methods Eligibility criteria include histologically confirmed mCRPC unselected for homologous recombination repair (HRR) gene mutation, progression on docetaxel chemotherapy, progression on androgen deprivation therapy within 6 months before screening, received either abiraterone for metastatic castration-sensitive prostate cancer/mCRPC or enzalutamide for mCRPC (but not both) for ≥8 weeks (≥14 weeks with bone progression), and Eastern Cooperative Oncology Group performance status of 0 or 1. Patients will also be required to provide tumor tissue for biomarker analysis. Approximately 780 adults will be randomized in a 2:1 ratio to pembrolizumab 200 mg IV Q3W (maximum 35 cycles) + olaparib 300 mg PO QD or abiraterone 1000 mg PO QD + prednisone or prednisolone 5 mg PO BID (enzalutamide-pretreated patients) or enzalutamide 160 mg PO QD (abiraterone-pretreated patients). Randomization will be stratified by prior treatment (abiraterone or enzalutamide) and measurable disease (yes/no). Treatment for all patients will continue until disease progression, unacceptable toxicity, or withdrawal. Response will be assessed by imaging (CT/MRI/bone) per Prostate Cancer