# Pembrolizumab or Placebo Added to Docetaxel and Prednisone/Prednisolone for Metastatic Castration-Resistant Prostate Cancer Previously Treated With Next-Generation Hormonal Agents: KEYNOTE-921 Phase 3 Study

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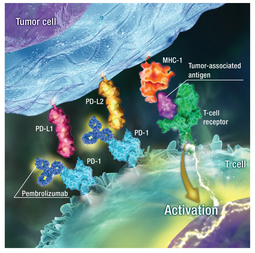
## Background

- Docetaxel was the first systemic therapy that showed improved survival in patients with metastatic castration-resistant prostate cancer (mCRPC), and it is a recommended treatment option after enzalutamide or abiraterone acetate therapy[1-3]
- PD-1 is an immune checkpoint receptor known to play a role in tumor immune evasion (Figure 1)[4]
- Pembrolizumab, a humanized monoclonal antibody that binds to PD-1 and prevents interaction with its ligands PD-L1 and PD-L2, has shown activity as monotherapy in patients with heavily pretreated, PD-L1–positive advanced prostate cancer[5,6]
- In the phase 1b/2 KEYNOTE-365 study, pembrolizumab + docetaxel and prednisone had activity in patients previously treated with abiraterone acetate or enzalutamide for mCRPC, warranting further evaluation of this treatment combination[7]
- KEYNOTE-921 (NCT03834506) is a randomized, global, parallel-group, double-blind, phase 3 trial to compare the efficacy and safety of pembrolizumab + docetaxel and prednisone/prednisolone with that of placebo + docetaxel and prednisone/prednisolone in patients with mCRPC whose disease progressed on a next-generation hormonal agent (NHA) and who have not received chemotherapy

### Figure 1. Pembrolizumab and the PD-1 Pathway




MHC-1, major histocompatibility complex 1.

## Objectives

Dual Primary

- To compare the following for pembrolizumab + docetaxel and prednisone/prednisolone versus placebo + docetaxel and prednisone/prednisolone in patients with mCRPC who have not received chemotherapy and whose disease progressed on an NHA
  - Overall survival (OS)
  - Radiographic progression-free survival (rPFS) per Prostate Cancer Working Group 3 (PCWG3)–modified RECIST v1.1,[8] as assessed by blinded independent central review (BICR)

Secondary

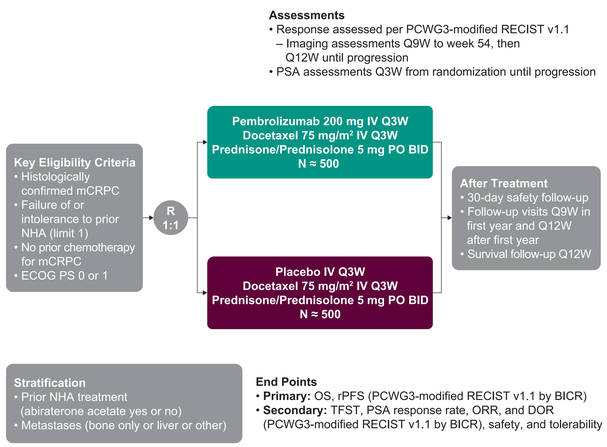
- To compare the following for pembrolizumab + docetaxel and prednisone/prednisolone versus placebo + docetaxel and prednisone/prednisolone in patients with mCRPC who have not received chemotherapy and whose disease progressed on an NHA
  - Time to initiation of the first subsequent anticancer therapy or death (TFST)
  - Confirmed prostate-specific antigen (PSA) response rate
    - Decrease of ≥50% from baseline, measured twice ≥3 weeks apart
  - Objective response rate (ORR) and duration of response (DOR) per PCWG3-modified RECIST v1.1, assessed by BICR
  - Time to PSA progression
  - Time to first symptomatic skeletal-related event
  - Time to pain progression based on item 3 of the Brief Pain Inventory (Short Form) and on opioid analgesic use based on the analgesic quantification algorithm score
  - Safety and tolerability

## Methods

Study Design

- Approximately 1000 patients with histologically or cytologically confirmed prostate cancer who had not received chemotherapy for mCRPC and who experienced disease progression on an NHA for mCRPC will be enrolled (Figure 2)
- Patients receiving continued androgen deprivation therapy will be randomly assigned 1:1 to receive combination treatment with pembrolizumab + docetaxel and prednisone/prednisolone or placebo + docetaxel and prednisone/prednisolone
  - Pembrolizumab 200 mg will be administered intravenously (IV) every 3 weeks (Q3W)
  - Docetaxel 75 mg/m$^2$ will be administered IV Q3W; prednisone/prednisolone 5 mg will be administered orally twice daily
    - Prednisolone used only if prednisone unavailable
- During the study, patients will receive a maximum of 10 cycles of docetaxel + prednisone/prednisolone for either arm; patients can continue to receive pembrolizumab or placebo for up to 35 cycles (approximately 2 years)
- Treatment in either arm will continue until radiographic disease progression, unacceptable toxicity, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the patient, nonadherence to study intervention, withdrawal of consent, or completion of 35 cycles of pembrolizumab or placebo

### Figure 2. Study Design




BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; PO, orally; Q9W, every 9 weeks, Q12W, every 12 weeks; R, randomization.

Patient Eligibility Criteria

| Key Inclusion Criteria | Key Exclusion Criteria |
|---|---|
| • Age ≥18 years<br>• Histologically or cytologically confirmed adenocarcinoma of the prostate without small cell histology<br>• Evidence of metastatic disease documented by bone lesions on bone imaging and/or soft tissue disease by CT/MRI[a]<br>• Progression at study entry defined as 1 of the following<br>– PSA progression based on PCWG3 criteria<br>– Radiographic disease progression in soft tissue per RECIST v1.1<br>– Radiographic disease progression in bone per PCWG3 criteria<br>• Prior treatment with only 1 NHA (eg, abiraterone acetate, enzalutamide, apalutamide, or darolutamide) for mHSPC or CRPC and either<br>– Progression after ≥8 weeks of treatment for soft tissue and ≥14 weeks for bone<br>– Intolerance to the drug after ≥4 weeks of treatment<br>• Ongoing androgen deprivation with serum testosterone <50 ng/dL[b]<br>• Adequate organ function<br>• Tissue for biomarker analysis<br>• ECOG PS 0 or 1 | • Prior treatment with docetaxel or another chemotherapy agent[c]<br>• Prior treatment with radium-223 or another therapeutic radiopharmaceutical agent<br>• Prior therapy with an anti–PD-1, anti–PD-L1, or anti–PD-L2 agent or with an agent directed to another stimulatory or coinhibitory T-cell receptor<br>• Prior systemic anticancer therapy; targeted small molecule therapy or abiraterone acetate, enzalutamide, apalutamide or darolutamide; or 5α reductase inhibitors, estrogen, and/or cyproterone ≤4 weeks from start of treatment<br>• Known active central nervous system metastases and/or carcinomatous meningitis |

CT, computed tomography; mHSPC, metastatic hormone-sensitive prostate cancer; MRI, magnetic resonance imaging.
[a]Patients whose disease spread is limited to regional pelvic lymph nodes are not eligible.
[b]Patients being treated with luteinizing hormone–releasing hormone agonists or antagonists (patients who have not undergone orchiectomy) must have initiated this therapy ≥4 weeks before randomization and must continue the therapy throughout the study.
[c]Patients who received ≥6 cycles of docetaxel for mHSPC and did not experience progression for ≥1 year after the last dose of docetaxel are eligible for enrollment.

Assessments and Follow-Up

- On-study imaging assessments by CT, radionuclide bone imaging, and contrast-enhanced MRI (for abdomen and pelvis) will be performed every 9 weeks from the date of randomization through week 54 and then every 12 weeks thereafter using PCWG3-modified RECIST v1.1 by BICR
- Disease progression in bone lesions will be confirmed by another bone imaging assessment ≥6 weeks after site-assessed first radiologic evidence of progression
- Adverse events (AEs) will be monitored throughout the study and for 30 days during the follow-up period (90 days for serious AEs) and will be graded per the guidelines outlined in the Common Terminology Criteria for Adverse Events, version 4.0

Analyses

Efficacy

- The efficacy analysis population will include all randomly assigned patients (intention to treat)
- OS, rPFS, and TFST will be estimated using the nonparametric Kaplan-Meier method
  - Treatment differences in OS, rPFS, and TFST will be assessed by stratified log-rank test
  - A stratified Cox proportional hazards model with Efron's method of handling ties will be used to assess the magnitude of the treatment difference (ie, hazard ratio)

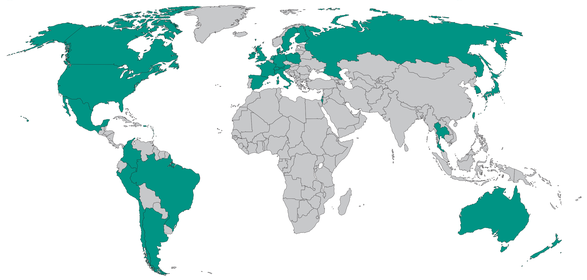
Safety

- The safety analysis population will consist of all randomly assigned patients who received ≥1 dose of study intervention (all patients as treated)
- Safety and tolerability will be evaluated using a tiered approach

## Status

- KEYNOTE-921 is ongoing or planned in 31 countries across Asia, Australia, Europe, and North and South America (Figure 3)

### Figure 3. Countries With Sites of Enrollment for KEYNOTE-921 (in green)



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## Disclosures

D. Petrylak has an consultant/advisory role for Ada Cap (Advanced Accelerator Applications) Amgen, Astellas, AstraZeneca, Bayer, Bicycle Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Clovis Oncology, Eli Lilly, Exelixis, Incyte, Janssen, Mirati, Monopteros, Pfizer, Pharmacyclics, Roche, Seattle Genetics, and Urogen; is a stockholder for Bellicum and Tyme (sold 10/2019); and received research funding (institution) from Ada Cap (Advanced Accelerator Applications), Agensys Inc, *Astellas, AstraZeneca, *Bayer, BioXcel Therapeutics, Bristol Myers Squibb, Clovis Oncology, Eisai, *Eli Lilly, *Endocyte, Genentech, *Innocrin, Medimmune, Medivation, Merck, Mirati, *Novartis, Pfizer, *Progenics, Replimune, Roche, *Sanofi Aventis, and Seattle Genetics (*denotes study trials that have terminated).

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