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 after enzalutamide or abiraterone acetate therapy.

• Pembrolizumab, a humanized monoclonal antibody that binds to PD-1 and prevents interaction with its ligands, is currently being studied in the treatment of mCRPC.

• Pembrolizumab plus docetaxel and prednisone/prednisolone has shown activity in patients with previously treated, PD-L1-positive advanced prostate cancer.

• KEYNOTE-921 is a randomized, global, parallel-group, 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.

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.

• Patients receiving continued androgen deprivation therapy will be randomly assigned 1:1 to receive 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/m² will be administered IV Q3W; prednisone/prednisolone 5 mg will be administered orally twice daily.

• Pembrolizumab 200 mg will be administered every 3 weeks until disease progression or death.

Study Population
• Eligible patients had prostate cancer that progressed on an NHA and had no prior chemotherapy or patients who were being treated with luteinizing hormone–releasing hormone agonists or antagonists (patients who had not undergone orchiectomy) that had been initiated at least 4 weeks before randomization and must continue the therapy throughout the study.

• Pembrolizumab and pembrolizumab + docetaxel and prednisone/prednisolone were previously treated with abiraterone acetate or enzalutamide for mCRPC, warranting further evaluation.

• Patients whose disease spread is limited to regional pelvic lymph nodes are not eligible.

• 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.

• Patients with metastatic bone-only, liver, or other metastases only will be enrolled.

• Tissue for biomarker analysis will be collected from patients with radiographic disease progression who meet the following criteria: patients with only bone or only liver or other metastases.

• Patients with previously treated, PD-L1-positive or PD-L2-positive advanced prostate cancer will be enrolled.

• Prior treatment with only 1 NHA (eg, abiraterone acetate, enzalutamide, apalutamide, or darolutamide) for mCRPC and/or other.

• Progression at study entry defined as 1 of the following:

  • PSA progression based on PCWG3 criteria

  • Radiographic disease progression in soft tissue per RECIST v1.1

  • Radiographic disease progression in bone per PCWG3 criteria

  • Progression in either arm will continue with radiographic disease progression, unacceptable toxicity, or another therapy; targeted small molecule or another therapeutic agent or with an agent directed toward the T-cell receptor

  • Progression after 8 weeks of treatment for soft tissue and 16 weeks for bone

  • Ineligibility to the drug after 48 weeks of treatment

  • Ongoing or continued enzalutamide treatment with severe tolerability (≥30 mg)

• Adequate organ function

• Tissue for biomarker analysis

Efficacy End Points
• Time to first symptomatic skeletal-related event

• Time to pain progression based on IITD 3.2 of the Brief Pain Inventory (Short Form) and on opioid analgesic use based on the analgesic quantification algorithm score

• Safety and tolerability

Figure 1. Pembrolizumab and the PD-1 Pathway

Figure 2. Study Design

Figure 3. End Points

Figure 4. Flow Chart of Patients

Figure 5. Kaplan-Meier Curve for Progression-Free Survival

Figure 6. Kaplan-Meier Curve for Overall Survival

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