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A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF MEVROMETOSTAT (PF-06821497) WITH ENZALUTAMIDE IN METASTATIC CASTRATION-SENSITIVE PROSTATE CANCER (MEVPRO-3)

Study Intervention Number:	PF-06821497
Study Intervention Name:	Mevrometostat
US IND Number:	134135
EU CT Number:	2024-519369-24-00
ClinicalTrials.gov ID:	Not Available
Pediatric Investigational Plan Number	Not available
Protocol Number:	C2321008
Phase:	3
Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001 United States

Brief Title:

A Study to Learn About the Investigational Medicine Called Mevrometostat (PF-06821497) in Men With Metastatic Castration-Sensitive Prostate Cancer Who Have Not Tried Novel Hormonal Therapy or Chemotherapy for Metastatic Prostate Cancer (MEVPRO-3)

5.1. Inclusion Criteria

Participants are eligible to be included in this study only if all of the following criteria apply:

Age and Sex:

1. Male participants aged 18 years of age or older (or the minimum age of consent in accordance with local regulations) at screening.

Refer to Appendix 4 for reproductive criteria (Section 10.4.1).

Disease Characteristics:

2. Histologically or cytologically confirmed adenocarcinoma of the prostate without small cell features (neuroendocrine differentiation and other histologic components are permitted if adenocarcinoma is the primary histology). For participants without a prior histological diagnosis, a baseline de novo biopsy must be used to confirm the diagnosis.

3. Metastatic prostate cancer documented by positive bone scan (for bone disease) or metastatic lesion(s) on CT or MRI scan (for soft tissue/visceral disease).

    a. Measurable soft tissue/visceral disease (per RECIST v1.1) is required if there is not an evaluable bone lesion (per PCWG3 criteria).

    b. For participants with measurable soft tissue disease only, regional lymph node disease (eg, below aortic bifurcation) alone does not qualify the participant for the study.

    c. PET and SPECT are not evaluable imaging modalities for this study.

    d. A bone scan showing intense symmetric activity in the bones (referred to as a superscan) is not considered evaluable.

4. Resolution of acute effects of any prior therapy to either baseline severity or CTCAE Grade ≤1 (except for AEs which do not constitute a safety risk in the investigator's judgement).

Allowed Prior Treatments:

5. Participants cannot have received any cytotoxic chemotherapy, ARPIs (eg, enzalutamide, apalutamide, abiraterone acetate, or darolutamide), any other systemic anticancer therapies for mCSPC, with the following exceptions:

    a. ADT (chemical or surgical) must be started prior to randomization and must continue throughout the study. Prior therapy with up to 3 months of ADT (with or without antiandrogens) is allowed with no radiographic evidence of disease progression or rising PSA levels indicative of disease progression prior to Day 1.

b. Treatment with estrogens, cyproterone acetate or first-generation antiandrogens is allowed until randomization, but must be discontinued prior to randomization.

c. Participants may have received 1 course of palliative radiation or surgery for symptomatic control secondary to prostate cancer, which should be completed at least 2 weeks prior to randomization.

Note: Radical prostatectomy or definitive radiotherapy (including concurrent radiotherapy) to the primary prostate tumor for mCSPC with curative intent is not permitted.

Other Inclusion criteria:

6. Participants must have ECOG PS 0 or 1 (Appendix 11).

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Any medical or psychiatric condition including any active suicidal ideation in the past year or suicidal behavior in the past 5 years or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

    a. HIV/HBV/HCV testing is not required unless mandated by local health authorities.

    b. Participants with known HIV or AIDS-related illness, or active hepatitis B or C are excluded.

    Active HBV is defined as any of the following:

    - HBsAg reactive or detectable [qualitative] HBV DNA

    Note: Participants who are HBsAg(-), HBcAb(+) are eligible and should be monitored/treated as per local standard of care.

    Active HCV is defined as:

    - Detectable [qualitative] HCV RNA

    c. Participants with a known history of chronic liver diseases including alcoholic liver disease, primary biliary cirrhosis, primary sclerosing cholangitis autoimmune hepatitis, Wilson's disease, hemochromatosis, alpha-1 antitrypsin deficiency, or other chronic liver disease are excluded.

d. Participants with a known history of active inflammatory gastrointestinal disease, chronic diarrhea, or previous gastric resection or lap-band surgery are excluded.

2. Clinically significant cardiovascular disease, defined as:

   a. Any of the following in the previous 6 months: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (New York Heart Association Class III or IV), cerebrovascular accident, or symptomatic pulmonary embolism or other clinically significant episode of thromboembolic disease, congenital long QT syndrome, Torsade de Pointes, clinically important arrhythmias, left anterior hemiblock (bifascicular block), ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, or other clinically significant cardiovascular disease as assessed by the investigator. If a participant has a cardiac rhythm device/pacemaker placed and QTcF >470 ms, the participant may be considered eligible. QTcF >480 ms on screening ECG.

3. CNS pathology/neurological findings:

   a. Known or suspected brain metastasis or active leptomeningeal disease.

   b. Symptomatic or impending spinal cord compression or cauda equina syndrome.

   c. Participants with epidural disease, canal disease and prior cord involvement are NOT excluded if those areas have been treated, are stable and not neurologically impaired.

   d. Clinically significant history of seizure or any condition that may predispose to seizure (eg, prior cortical stroke, significant brain trauma). Also history of unexplained loss of consciousness or transient ischemic attack within 12 months of randomization.

4. Any history of myelodysplastic syndrome, acute myeloid leukemia, or any other prior malignancy except for any of the following:

   a. Carcinoma in situ or nonmelanoma skin cancer.

   b. Any prior malignancies ≥3 years before randomization with no subsequent evidence of recurrence or progression regardless of the stage.

   c. Stage 0 or Stage 1 cancer <3 years before randomization that has a remote probability of recurrence or progression in the opinion of the investigator.

5. In the opinion of the investigator, any clinically significant gastrointestinal disorder affecting absorption.

Prior/Concomitant Therapy:

6. Current use of any prohibited concomitant medication(s) or unwillingness or inability to use a required concomitant medication(s). Refer to Section 6.9.

    a. Current use or anticipated need for drugs that are known strong CYP3A4/5 inhibitors and inducers (with the exception of enzalutamide as part of this study) outlined in Section 6.9.1 and Section 6.9.2, including their administration within 10 days or 5 half-lives, whichever is longer prior to randomization.

    b. Current use of prednisone >10 mg/day (or equivalents) is prohibited within 28 days prior to randomization.

    c. Current use of 5-alpha reductase inhibitors is prohibited within 28 days prior to randomization.

7. Prior treatment with:

    a. ADT in the adjuvant/neoadjuvant setting, where the completion of ADT was <12 months prior to randomization and the total duration of ADT was >36 months.

    b. ARPI's such as abiraterone, apalutamide, darolutamide, enzalutamide or other investigational ARPI's.

    c. Cytochrome P17 enzyme inhibitors such as oral ketoconazole as anticancer treatments for prostate cancer.

    d. Chemotherapy including docetaxel or immunotherapy for prostate cancer.

    e. Radiopharmaceuticals (ie, 177Lu-PSMA-617, radium-223)

    f. CDK4/6 inhibitors

    g. Any other anticancer treatment for metastatic prostate cancer, excluding palliative radiotherapy/surgery and ADT as discussed above.

Prior/Concurrent Clinical Study Experience:

8. Previous administration of an investigational product (drug or vaccine) which does not meet exclusion criterion 7 within 30 days or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer). Participation in studies of other investigational products (drug or vaccine) at any time during participation in this study.

Diagnostic Assessments:

9. Inadequate renal function defined by an eGFR <45 mL/min/1.73 m^2. Based upon participant age at screening, eGFR is calculated using the recommended formulas in Appendix 7 Section 10.7.1 to determine eligibility and to provide a baseline to quantify any subsequent kidney safety events. For eligibility assessment based upon estimated renal function, the higher of the screening and baseline eGFR values may be used.

10. Hepatic dysfunction defined as having any 1 of the following, which may be confirmed by a single repeat test, if necessary:

    a. Total bilirubin ≥1.5 x ULN (≥3 x ULN for participants with documented Gilbert's syndrome, direct bilirubin >ULN is exclusionary)

    b. AST >2.5 x ULN

    c. ALT >2.5 x ULN

11. Hematologic abnormalities defined as having any 1 of the following, which may be confirmed by a single repeat test, if necessary:

    a. ANC <1500/mm^3

    b. Platelets <100,000/mm^3, independent of transfusion within 14 days of randomization

    c. Hemoglobin <9 g/dL, independent of transfusion within 14 days of randomization

Other Exclusion Criteria:

12. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

13. Inability to swallow oral medications.

14. Major surgery (as defined by investigator) from which the participant has not fully recovered at least 28 days prior to randomization.