Cancer Research Consortium of West Michigan
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Fast Facts

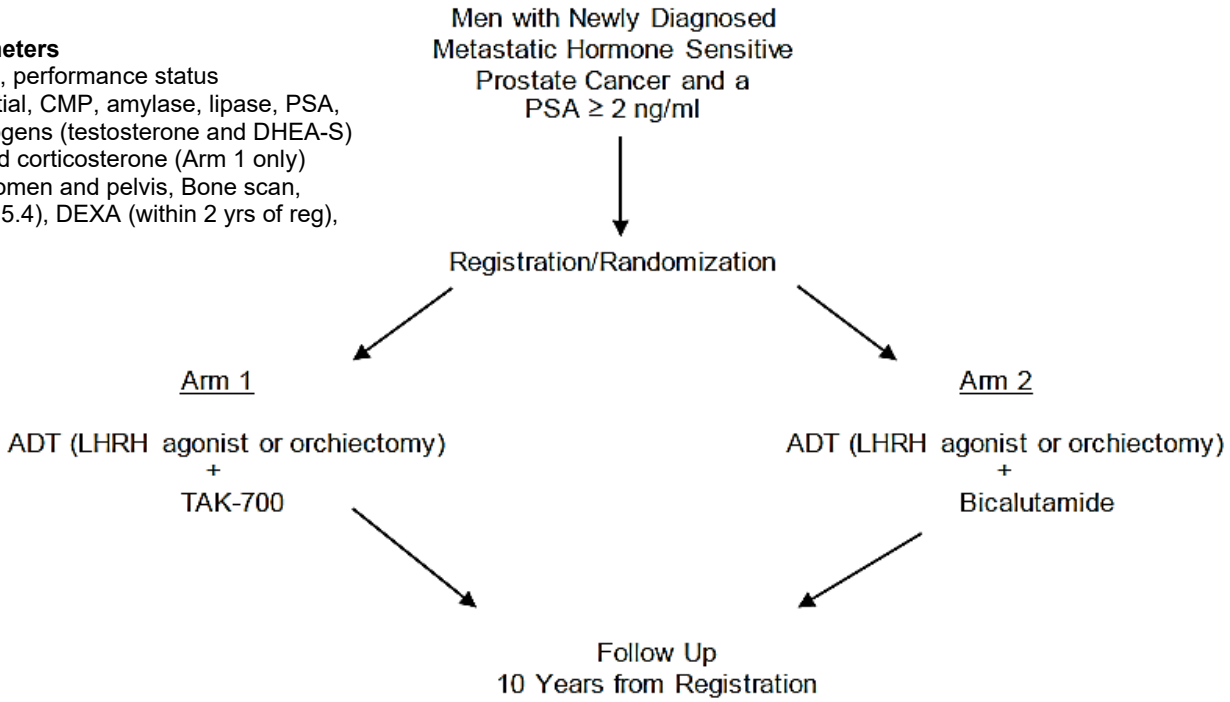
S1216: A Phase III Randomized Trial Comparing Androgen Deprivation Therapy + TAK-700 with Androgen Deprivation Therapy + Bicalutamide in Patients with Newly Diagnosed Metastatic Hormone Sensitive Prostate Cancer

There are two patient populations eligible for the study: those who have not started any therapy with LHRH agonist or antagonist (or orchiectomy) (Early Induction Group) and those who have already started therapy with LHRH agonist or antagonist (or orchiectomy) within the 30 days prior to registration (Late Induction Group). Patients must be registered within 30 days of first injection of the LHRH agonist or antagonist (or orchiectomy).

Provided Drug: TAK-700
Bicalutamide and the LHRH agonist (goserelin acetate or leuprolide acetate) are commercially available;

SCHEMA

Pre-Study Parameters
History & physical, performance status
CBC with differential, CMP, amylase, lipase, PSA, lipid profile, Androgens (testosterone and DHEA-S)
ACTH, cortisol and corticosterone (Arm 1 only)
CT or MRI of abdomen and pelvis, Bone scan, Brain CT (section 5.4), DEXA (within 2 yrs of reg), ECG / ECHO



ELIGIBILITY

a. All patients must have a histologically or cytologically proven diagnosis of adenocarcinoma of the prostate. All patients must have metastatic disease as evidenced by soft tissue and/or bony metastases prior to initiation of androgen deprivation therapy.
b. Patients who have not yet started androgen deprivation therapy (LHRH agonist/antagonist or orchiectomy) and will not have an LHRH agonist injection until after randomization (early induction group) must have radiographic assessments of all disease including bone scan (or PET scan) within 42 days prior to registration. In a late induction patient, if any of the required scans have not been obtained prior to starting LHRH agonist/antagonist or orchiectomy, those scans will need to be obtained prior to registration. All disease must be assessed and documented on the Baseline Tumor Assessment Form. NOTE: Androgen deprivation therapy does not include treatment with anti-androgens such as bicalutamide or flutamide or five alpha reductase inhibitors such as finasteride or dutasteride.

c. Patients with known brain metastases are not eligible. Brain imaging studies are not required for eligibility if the patient has no neurologic signs or symptoms suggestive of brain metastasis. But, if brain imaging studies are performed, they must be negative for disease.
d. Patients who are deemed to have high-risk or extensive metastatic, hormone sensitive prostate cancer (mHSPC) per "clinical judgment" of the treating physician are eligible for enrollment if they are unsuitable candidates for docetaxel or if they have declined docetaxel therapy.

PRIOR THERAPY CRITERIA

a. Patients may have received prior androgen deprivation therapy (ADT) - neoadjuvant and/or adjuvant setting only - but it must not have lasted for more than 36 months (note that this is NOT the same as "late induction" as described in Section 5.1b above). Single or combination therapy allowed. At least 6 months must have elapsed since completion of androgen deprivation therapy in the neoadjuvant and/or adjuvant setting, and serum testosterone must be > 50 ng/dL (non-castrate levels) within 28 days prior to registration for early induction patients. Note: Serum testosterone assessment is required for eligibility for only those early induction patients with prior treatment with neoadjuvant or adjuvant ADT. Late induction patients with prior neoadjuvant or adjuvant ADT do not need serum testosterone assessment.
b. Patients must not have received prior and/or must not have any plans for receiving concomitant therapy with ketoconazole, aminoglutethimide or abiraterone acetate, or enzalutamide (MDV3100). Concurrent megestrol for hot flashes is allowed.
c. Patients must not have received any prior cytotoxic chemotherapy for metastatic prostate cancer. Prior cytotoxic chemotherapy with curative intent in the neoadjuvant or adjuvant setting is allowed. At least 2 years must have elapsed since completion of cytotoxic chemotherapy in the neoadjuvant and/or adjuvant setting.
d. Patients may have received prior surgery. For all major surgeries, at least 14 days must have elapsed since completion and patient must have recovered from all major side effects of surgery per investigator's assessment.
e. Patients may have received or plan to receive concurrent bone targeting agents that do not have an effect on PSA (e.g. denosumab or bisphosphonate).
f. Patients must have no plans to receive any other experimental therapy while on the protocol treatment. Previous experimental therapy must have been completed within 28 days prior to registration.
g. In the late induction group, patients must have had no more than 30 days of prior castration (medical or surgical) for metastatic prostate cancer prior to registration. The start date of medical castration is considered the day the patient first received an injection of a LHRH agonist/antagonist (or orchiectomy), not an oral antiandrogen.
   If the method of castration was luteinizing hormone releasing hormone (LHRH) agonists (i.e., leuprolide or goserelin), the patient must be willing to continue the use of LHRH agonist and add bicalutamide or TAK-700 (according to randomization) during protocol treatment.
   If the patient was on an antiandrogen (e.g. bicalutamide, flutamide), the patient must be willing to switch over to bicalutamide or TAK-700 (according to randomization). There is no limit on how many days a patient may have been on an antiandrogen (e.g. bicalutamide, flutamide) or a five alpha reductase inhibitor (e.g. finasteride or dutasteride) prior to going on study and no washout is required.
   If the method of castration was LHRH antagonists (i.e. Degarelix), the patient must be willing to switch to an LHRH agonist during protocol treatment.

CLINICAL/LABORATORY CRITERIA

a. Patients must have a complete physical examination and medical history within 28 days prior to registration.
b. Patients must have a PSA ≥ 2 ng/mL obtained within 90 days prior registration.
c. A DEXA scan must be obtained within 2 years prior to registration.
d. Patients must not have New York Heart Association Class III or IV heart failure (see section 18.4) at the time of screening. Patients must not have any thromboembolic event, unstable angina pectoris,

myocardial infarction, or serious uncontrolled cardiac arrhythmia within 6 months prior to registration. (Note: Androgen deprivation therapy may prolong the QT/QTc interval. Patients with congenital long AT syndrome, congestive heart failure, frequent electrolyte abnormalities, and patients taking drugs known to prolong the QT interval may be at increased risk.)

e. Patients must have a QTc interval < 461 msec on the 12 lead ECG within 42 days prior to registration. Patients with asymptomatic or incidental bundle branch blocks may have QTc measured by a cardiologist or standard formulas such as Bazett's or Fridericia's to adjust for pre-existing blocks.
f. Patients must have a left ventricular ejection fraction (LVEF) ≥ 50% by echocardiogram or multiple gated acquisition (MUGA) scan within 42 days prior to registration.
g. Patients must have blood pressure measured within 28 days prior to registration. Patients must not have uncontrolled hypertension (defined as blood pressure > 160 mmHg systolic and > 90 mmHg diastolic at 2 separate measurements no more than 60 minutes apart) despite appropriate medical therapy. Note: Patients may be rescreened after adjustments of antihypertensive medications. See ACCF/AHA.AMA-PCPI joint statement.
h. Patients must have adequate hepatic function as evidenced by bilirubin ≤ 2 x institutional upper limit of normal (ULN), SGOT (AST) and SGPT (ALT) ≤ 3 x institutional ULN, or ≤ 5 x institutional ULN if liver metastases are present. These results must be obtained within 28 days prior to registration.
i. Patients must have adequate renal function as evidenced by calculated creatinine clearance ≥ 40 mL/min using a serum creatinine or by 24-hour urine creatinine obtained within 28 days prior to registration.

$$\text{Calculated creatinine clearance} = \frac{(140 - \text{age}) \times \text{wt (kg)}}{72 \times \text{creatinine (mg/dl)}}$$

j. Patients must have adequate hematologic function as evidenced by leukocytes ≥ 3,000/mcL, absolute neutrophil count (ANC) ≥ 1,500/mcL, hemoglobin ≥ 9 g/dL, and platelets ≥ 100,000/mcL. These results must be obtained within 28 days prior to registration.
k. Patients must not be known to have human immunodeficiency virus (HIV) infection, active chronic hepatitis B or C, life-threatening illness unrelated to cancer, or any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with participation in this study. Patients will be tested for hepatitis B or C or HIV infection during screening if they are considered by the investigator to be at higher risk for these infections and have not been previously tested.
l. Patients with a known history of primary and secondary adrenal insufficiency are not eligible.
m. Patients must not be known to have hypersensitivity to TAK-700, to TAK-700 metabolites, to bicalutamide, or to LHRH agonist.
n. Patients must not have known gastrointestinal (GI) disease or GI procedure that could interfere with the GI absorption or tolerance of TAK-700, including difficulty swallowing oral medications per investigator's clinical judgement.
o. Patients must have a Zubrod performance status of 0 - 2 (see Section 10.4). Zubrod performance status 3 will be allowed if from bone pain only.
p. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease-free for 5 years.
q. Patients must be ≥ 18 years of age.
r. Men of reproduction potential and those who are surgically sterilized (i.e., post-vasectomy) must agree to practice effective barrier contraception or agree to abstain from intercourse while receiving treatment on this study and for at least 4 months after protocol treatment ends.

SPECIMEN SUBMISSION CRITERIA

a. Patients must be offered the opportunity to participate in specimen banking for future use to include translational medicine studies outlined in Section 15.0.