A Phase III Double-Blind, Randomised, Placebo-Controlled Study Assessing the Efficacy and Safety of Capivasertib + Abiraterone Versus Placebo + Abiraterone as Treatment for Patients with De Novo Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) Characterised by PTEN deficiency (CAPItello-281)

SECONDARY IDENTIFICATION NUMBER
D361BC00001

FDA CLINICAL TRIAL REFERENCE (CTR) NUMBER
2020-CT0557

SCIENTIFIC TITLE
A Phase III Double-Blind, Randomised, Placebo-Controlled Study Assessing the Efficacy and Safety of Capivasertib + Abiraterone Versus Placebo + Abiraterone as Treatment for Patients with De Novo Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) Characterised by PTEN deficiency

PROJECT DESCRIPTION
This Phase III, double-blind, randomised, placebo-controlled, parallel-group, global study is designed to compare the efficacy and safety of capivasertib versus placebo when added to abiraterone (+ prednisone/prednisolone) on a background of ADT in patients with de novo (newly diagnosed, previously untreated) mHSPC characterised by PTEN deficiency. Participants will be recruited globally from approximately 30 countries and approximately 350 study sites in Europe, North America, South America, Australia, and Asia (including China and Japan).

NUHRA DETAILS

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PROJECT DURATION

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PROJECT STATUS

Ongoing

REASON FOR PROJECT PENDING/SUSPENSION/TERMINATION

Unspecified

IMPLEMENTING AGENCY (PRIMARY SPONSOR)

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<td>Private Business</td>
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COOPERATING AGENCY (SECONDARY SPONSOR)

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CONTRACT RESEARCH ORGANIZATION (CRO) INFORMATION

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FUNDING AGENCY (SOURCES OF MONETARY OR MATERIAL SUPPORT)

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CONTACT FOR PUBLIC QUERIES

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<th>Phone Number</th>
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<tr>
<td>Jessa Mae Garcia</td>
<td><a href="mailto:jessamae.garcia@astrazeneca.com">jessamae.garcia@astrazeneca.com</a></td>
<td>0919 091 7164</td>
<td>16th Floor, Inoza Tower, 40th Street, Bonifacio Global City, Taguig, 1634, Philippines</td>
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CONTACT FOR SCIENTIFIC QUERIES

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IMPLEMENTING AGENCY (PRIMARY SPONSOR)

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<thead>
<tr>
<th>Name</th>
<th>Expertise</th>
<th>Affiliation</th>
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<tbody>
<tr>
<td>Jandre Jomar Alipat, MD</td>
<td>Oncology</td>
<td>West Visayas State University Medical Center</td>
</tr>
<tr>
<td>Rubi K. Li, MD</td>
<td>Oncology</td>
<td>St. Luke's Medical Center - Quezon City</td>
</tr>
<tr>
<td>Rudolfo De Guzman, MD</td>
<td>Oncology</td>
<td>National Kidney and Transplant Institute</td>
</tr>
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RESEARCH CLASSIFICATION

Clinical Trial

HEALTH CONDITION(S) OR PROBLEM(S) STUDIED

De Novo Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) Characterised by PTEN deficiency

PRIMARY OUTCOMES

rPFS is defined as the time from randomisation to: 1) radiographic progression, as assessed by the investigator per RECIST version 1.1 (soft tissue) and/or PCWG3 criteria (bone), or 2) death due to any cause.

KEY SECONDARY OUTCOMES

KEY SECONDARY 1. Overall survival is the length of time from randomisation until the date of death due to any cause. 2. TFST is defined as time from randomisation to the earlier of: the start date of the first subsequent anticancer therapy after discontinuation of randomised treatment (capivasertib/placebo), or death due to any cause. 3. SSE-FS is defined as time from randomisation until any of the following: (1) Occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral). Radiologic documentation is required. A pathological fracture, as determined by investigator, is defined as associated with low or no trauma and deemed to have occurred at a site of bone metastasis. (2) Occurrence of spinal cord compression. Radiologic documentation is required. (3) Orthopaedic surgical intervention for bone metastasis. (4) Death due to any cause. 4. TTPP is defined as time from randomisation to clinically meaningful pain progression based on a 2-point increase from baseline in the Brief Pain Inventory-Short Form (BPI-SF) Item 3 “worst pain in 24 hours” score and/or initiation of/increase in opiate analgesic use

RECRUITMENT STATUS

Contact #s.: (+632) 8377534, (+632) 8377537, (+632) 8372071-80 loc. 2117, 2112
Saliksik Building, DOST Compound, Gen. Santos Ave., Bicutan Taguig City 1631 Philippines
COUNTRIES OF RECRUITMENT

Australia, China, Hong Kong, Japan, Philippines, Taiwan

FDA DOCUMENT TRACKING NUMBER

20200611143730

FDA APPROVAL DATE

2020-09-04

ERC APPROVAL DATE

0000-00-00

TARGET SAMPLE SIZE (PHILIPPINES)

69

ACTUAL SAMPLE SIZE (PHILIPPINES)

Unspecified

REASON FOR THE DIFFERENCE BETWEEN TARGET & ACTUAL SAMPLE SIZES

Unspecified

DATE OF FIRST ENROLLMENT

04 Sep 2020

KEY INCLUSION AND EXCLUSION CRITERIA (CT)

INCLUSION

1 *Participant must be ≥ 18 years of age (≥ 20 years of age in Japan), at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2 *Histologically-confirmed de novo (ie, diagnosed within 3 months of randomisation) metastatic hormone-sensitive prostate adenocarcinoma. Note: adenocarcinoma must be the primary histological pattern and patients with small-cell tumours are not eligible.

3 *Consent to provide a FFPE tissue block (preferred) or slides. Details on tissue requirements are specified in the Laboratory Manual. Cytologic or FNA samples are not acceptable. Tumour tissue from bone metastases is not acceptable.

4 *A valid PTEN IHC result indicating PTEN deficiency (centralised testing).

5 Metastatic disease documented prior to randomisation by clear evidence of ≥ 1 bone lesion (defined as 1 lesion with positive uptake on bone scan) and/or ≥ 1 soft tissue lesion (measurable and/or non-measurable) that can be accurately assessed at baseline and is suitable for repeated assessment with CT and/or MRI. Patients with metastatic disease identified by PSMA PET only, will not be eligible. Local lymph node involvement is not considered metastatic disease.

6 Asymptomatic or mildly symptomatic form of prostate cancer based on the investigator’s clinical evaluation.

7 *Candidate for abiraterone and steroid therapy. Previous treatment with abiraterone and/or a steroid for de novo disease is allowed up to a maximum of 3 months prior to randomisation (prior treatment with chemotherapy or other NHAs is not allowed).

8 Ongoing ADT with GnRH analogue (combination with first generation androgen receptor antagonists, eg, bicalutamide is allowed), or LHRH antagonist, or bilateral orchectomy. Duration of ongoing ADT (regardless of method) is from 0 days to a maximum of 3 months prior to randomisation.

9 ECOG/WHO performance status 0 to 1 (see Appendix A) with no deterioration over the previous 2 weeks and minimum life expectancy of 12 weeks.

10 *Able and willing to swallow and retain oral medication.
Participants must complete the 7-day BPI-SF and BFI questionnaires and the analgesic diary during screening (only after PTEN deficiency is confirmed), prior to randomisation. Note: it is required to give participants at least 7 consecutive days to complete the assessments prior to randomisation. If a minimum of 4 assessments is not completed during the 7-day period, participants must be re-screened, a new 7 days of questionnaire/diary entries completed, and any screening tests which are consequently outside of the applicable 28 days prior to randomisation must also be repeated.

Sex

12 *Participants will be male.

Reproduction

13 Agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm:
- Sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
- Participants should use barrier contraception (ie, condoms) from the time of screening until 16 weeks after discontinuation of study drug. It is not known whether the pre-clinical changes seen in the male animal reproductive organs, after treatment with capivasertib, will be fully reversible or will permanently affect the ability to produce healthy sperm following treatment. Therefore, if participants wish to father children, they should be advised to arrange for collection of sperm samples prior to the start of study treatment.

Informed Consent

14 *Capable of giving signed informed consent as described in Appendix B 3, which includes compliance with the requirements and restrictions listed in the ICF and in this CSP.
15 Provision of signed and dated written Optional Genetic Research Information informed consent prior to collection of samples for optional genetic research that supports Genomic Initiative.

EXCLUSION CRITERIA

Medical Conditions

1 Radiotherapy with a wide field of radiation (eg, more than one-third of the skeleton) within 4 weeks before the start of study treatment (capivasertib/placebo).
2 Major surgery (excluding placement of vascular access, transurethral resection of prostate, bilateral orchiectomy, or internal stents) within 4 weeks of the start of study treatment.
3 Brain metastases, or spinal cord compression (unless spinal cord compression is asymptomatic, treated and stable and not requiring steroids for at least 4 weeks prior to start of study treatment).
4 *Past medical history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease.
5 Any of the following cardiac criteria:
- Mean resting corrected QT interval (QTc) > 470 msec obtained from 3 consecutive ECGs.
- Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG (eg, complete left bundle branch block, third-degree heart block).
- Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, potential for torsades de points, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age, or any concomitant medication known to prolong the QT interval (within 5 half-lives of the first dose of study treatment).
- Clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or NYHA or Class II to IV heart failure or cardiac ejection fraction measurement of < 50.
- Experience of any of the following procedures or conditions in the preceding 6 months: coronary artery bypass graft, angioplasty, vascular stent, myocardial infarction, angina pectoris, congestive heart failure NYHA Grade ≥ 2.
- Uncontrolled hypertension – systolic blood pressure (SBP) < 90 mmHg and/or diastolic blood pressure (DBP) < 50 mmHg.
- Cardiac ejection fraction outside institutional range of normal or < 50% (whichever is higher) as measured by echocardiogram (or MUGA scan if an echocardiogram cannot be performed or is inconclusive).
- Uncontrolled hypertension (SBP ≥ 160 mmHg or DBP ≥ 95 mmHg).
- *Clinically significant abnormalities of glucose metabolism as defined by any of the following:
  - Diabetes mellitus type I or diabetes mellitus type II requiring insulin treatment.
  - HbA1c ≥ 8.0% (63.9 mmol/mol).
- Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values:
  - Absolute neutrophil count < 1.5x 10^9/L.
  - Platelet count < 100x 10^9/L.
  - Haemoglobin < 9 g/dL (< 5.59 mmol/L). [Note: any blood transfusion must be > 7 days prior to the determination of a haemoglobin ≥ 9 g/dL (≥ 5.59 mmol/L)].
  - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) > 2.5x upper limit of normal (ULN) if no demonstrable liver metastases or > 5x ULN in the presence of liver metastases. Elevated alkaline phosphatase (ALP) is not exclusionary if due to the presence of bone metastases and
liver function is otherwise considered adequate in the investigator’s judgement.

- Total bilirubin > 1.5x ULN (participants with confirmed Gilbert’s syndrome may be included in the study with a higher value)
- Creatinine > 1.5x ULN concurrent with creatinine clearance < 50 mL/min (measured or calculated by Cockcroft and Gault equation); confirmation of creatinine clearance is only required when creatinine is > 1.5x ULN.

8 *As judged by the investigator, any evidence of severe or uncontrolled systemic diseases, including active bleeding diatheses, or known active infection including hepatitis B, hepatitis C, and HIV. Screening for chronic conditions is not required.

9 Participants who are unevaluable for both bone and soft tissue progression as defined by meeting both of the following criteria:
- A bone scan referred to as a superscan showing an intense symmetric activity in the bones and no or limited technetium excretion by the kidneys, and
- No soft tissue lesion (measurable or non-measurable) that can be assessed by RECIST criteria.

10 *Refractory nausea and vomiting, malabsorption syndrome, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection, or other condition that would preclude adequate absorption of capivasertib.

11 *Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that, in the investigator’s opinion, gives reasonable suspicion of a disease or condition that contra-indicates the use of an investigational drug, may affect the interpretation of the results, render the patient at high risk from treatment complications or interfere with obtaining informed consent.

12 *Evidence of dementia, altered mental status, or any psychiatric condition that would prohibit understanding or rendering of informed consent.

13 *Previous alloimmune bone marrow transplant or solid organ transplant.

14 *Known additional malignancy that has had progression or has required active treatment in the last 3 years. Exceptions include basal cell carcinoma of the skin, and squamous cell carcinoma of the skin that has undergone potentially curative therapy.

Prior/Concomitant Therapy

15 Treatment with any of the following:
- Nitrosourea or mitomycin C within 6 weeks of the first dose of study treatment.
- Any investigational agents or study drugs from a previous clinical study within 30 days or 5 half-lives (whichever is longer) of the first dose of study treatment.
- Any other chemotherapy, immunotherapy, immunosuppressant medication (other than corticosteroids) or anticancer agents within 3 weeks of the first dose of study treatment. A longer washout period may be required for drugs with a long half-life (eg, biologics) as agreed by the sponsor.
- Potent inhibitors or inducers of CYP3A4 within 2 weeks before the start of study treatment (3 weeks for St John’s wort), or sensitive substrates of CYP3A4, CYP2C9 and/or CYP2D6 with a narrow therapeutic window within 1 week before the start of study treatment.
- Drugs known to prolong the QT interval within 5 half-lives of the first dose of study treatment.

Prior/Concurrent Clinical Study Experience

16 Participation in another clinical study with an investigational product administered in the last 30 days or 5 half-lives, whichever is longer.

17 *History of hypersensitivity to active or inactive excipients of capivasertib, abiraterone, or drugs with a similar chemical structure or class.

OTHER EXCLUSIONS

18 *Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

19 *Judgment by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.

20 *Any restriction or contraindication based on the local prescribing information that would prohibit the use of abiraterone.

STUDY TYPE

Interventional

INTERVENTION NAME

Capivasertib + Abiraterone Versus Placebo + Abiraterone

INTERVENTION DESCRIPTION

Capivasertib (AZD5363), a novel pyrrolopyrimidine-derived compound, is a potent, selective inhibitor of the kinase activity of all 3 isoforms of AKT (Davies et al 2012). AstraZeneca is developing capivasertib for use in combination with other anticancer agents for a range of therapeutic indications, including prostate cancer and breast cancer.

AMENDMENT APPROVAL DATE/REASONS

Contact #: (+632) 8377534, (+632) 8377537, (+632) 8372071-80 loc. 2117, 2112
Saliksik Building, DOST Compound, Gen. Santos Ave., Bicutan Taguig City 1631 Philippines

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METHOD OF ALLOCATION

Randomized

MASKING / BLINDING

Double Blind

MASKING DETAILS

Unspecified

ASSIGNMENT

Single

PURPOSE

To compare the effect of capivasertib + abiraterone relative to placebo + abiraterone by assessment of radiographic progression-free survival (rPFS) in patients with PTEN-deficient mHSPC.

PHASE

Phase III

RESEARCH UTILIZATION

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