A Phase 2/3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate Plus Prednisone with or without Abemaciclib in Patients with Metastatic Castration-Resistant Prostate Cancer

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This study has been transitioned to CTIS with ID 2023-506777-36-00 check the CTIS register for the current data. Main objective:Part 1: To determine the RP2D of abemaciclib that may be safely administered to patients with mCRPC in combination with...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Renal and urinary tract neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON54799

Source
ToetsingOnline

Brief title
I3Y-MC-JPCM

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
Metastatic Castration-Resistant Prostate Cancer, Prostate Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Eli Lilly
Source(s) of monetary or material Support: Eli Lilly and Company

Intervention

Keyword: Abemaciclib, CDK4/6 inhibition, mCRPC, Prostate cancer

Outcome measures

Primary outcome

Primary endpoint part 1:

Determine the recommended Phase 2 dose (RP2D) of abemaciclib in combination

with abiraterone acetate and prednisone

Primary endpoints part 2:

Radiographic progression-free survival (rPFS)

Secondary outcome

Secondary endpoint:

The safety endpoints evaluated will include but are not limited to the

following: AEs, TEAEs, SAEs, clinical laboratory tests, ECGs, vital signs,

and physical examinations.

• ORR and DoR

• OS

• Time to PSA progression

• (If Part 3 is opened) rPFS by blinded, independent, central review (BICR)

Time from randomization to any of the following (whichever occurs earlier):

- Symptomatic Skeletal Event SSE: symptomatic fracture, surgery or radiation to bone, or spinal cord compression

- Pain progression or worsening of disease-related symptoms requiring initiation of a new systemic anti-cancer therapy

- Development of clinically significant symptoms due to loco-regional tumor progression requiring surgical intervention or radiation therapy Abemaciclib and abiraterone acetate steady state plasma concentrations. Time to worst pain progression, using the Worst Pain NRS score and the WHO-AL.

Study description

Background summary

Prostate cancer (PCa) is a leading cause of mortality and morbidity globally, with more than 1 million cases diagnosed and more than 300,000 deaths annually. Advanced or metastatic PCa is an androgen-dependent disease and PCa cells are primarily dependent on AR activity for proliferation and survival. The key element in the control of prostate tumor growth is androgen-deprivation therapy (ADT), which consists of initiating a luteinizing hormone-releasing hormone (LHRH) agonist/antagonist (medical castration) or, less commonly, bilateral orchiectomy (surgical castration) with or without concurrent anti-androgens.*

Based on the recent findings from the CHAARTED (NCT00309985), STAMPEDE (NCT00268476), and LATITUDE (NCT01715285) trials, all showing significant improvement in overall survival (OS), a combination approach of docetaxel, or abiraterone acetate plus prednisone, with ADT is now also considered a treatment option for men with high-risk forms of metastatic hormone-sensitive prostate cancer*. Although most patients with advanced metastatic disease initially respond to conventional ADT with or without docetaxel or abiraterone acetate, inevitably and despite effective suppression of serum testosterone, disease progresses to Metastatic castration-resistant prostate cancer (mCRPC)*. Despite the recent advances in the therapy for mCRPC, median OS remains approximately 18 to 36 months. In addition, the optimal treatment sequencing pathway remains unknown. In practice, sequencing decisions are made in the light of the distribution, extent, and pace of disease, co-morbidities, patient preferences, and drug availability*. As treating metastatic PCa is becoming increasingly complex, the current focus must be to continue improving outcomes

for patients with aggressive disease and explore innovative combinations capable of controlling and delaying tumor progression.

Abemaciclib is an oral, selective, and potent adenosine triphosphate (ATP)-competitive inhibitor of CDK4 and CDK6. In cancer cells, continuous exposure to abemaciclib inhibited Rb phosphorylation and blocked progression from G1 into S phase of the cell cycle, resulting in senescence and apoptosis.

In hormone-dependent and CRPC cell models, abemaciclib has demonstrated in vitro activity, as single agent and in combination with anti-hormonal agents, with regard to limiting cellular proliferation (data on file). Targeting aberrant cell cycling with abemaciclib and the AR pathway in patients with PCa is expected to inhibit the proliferation of prostate tumor cells and delay progression of anti-androgen-resistant disease.

Also, two large, randomized, double-blind, placebo-controlled Phase 3 clinical trials have demonstrated the effectiveness of abemaciclib when combined with endocrine therapy forHR+/HER2* metastatic breast cancer.

This Phase 2/3 study will be conducted in up to 3 parts and is designed to determine the recommended Phase 2 dose and assess the safety and efficacy of abemaciclib in combination with abiraterone acetate plus prednisone for the first-line treatment of patients with mCRPC.

*For references, please refer to the clinical protocol.

Study objective

This study has been transitioned to CTIS with ID 2023-506777-36-00 check the CTIS register for the current data.

Main objective:
Part 1: To determine the RP2D of abemaciclib that may be safely administered to patients with mCRPC in combination with abiaterone acetate and prednisone.

Part 1&2&3:
To compare the rPFS of patients receiving abiraterone acetate plus prednisone with or without abemaciclib.

Secondary objective:
To characterize further the safety profile of the combination of abemaciclib and abiraterone acetate plus prednisone.
To compare the efficacy in patients receiving abiraterone acetate plus prednisone with or without abemaciclib.
Time to Symptomatic Progression
To characterize the PK of abemaciclib and abiraterone acetate when administered in combination

To assess patient reported pain

Study design

Study JPCM is a Phase 2/3, multicenter, multinational, randomized, double-blind, placebo-controlled study designed to assess the safety and efficacy of abemaciclib when given in combination with abiraterone acetate plus prednisone as first-line therapy for patients with mCRPC.

Part 1 is a double-blind placebo-controlled safety lead-in portion that will randomize approximately 30 patients in a 2:2:1:1 ratio to explore 2 doses of abemaciclib (150 mg and 200 mg, twice daily or matching placebo) when given in combination with abiraterone acetate 1000 mg once daily plus prednisone 5 mg twice daily. Part 1 is designed to determine the RP2D of abemaciclib.

Part 2 is a double-blind placebo-controlled portion that will randomize approximately 150 patients in a 1:1 ratio between abiraterone acetate 1000 mg once daily plus prednisone 5 mg twice daily and abemaciclib given at the RP2D or matching placebo.

Part 3 may be opened if the prespecified expansion criteria in an adaptive interim analysis are
met and will randomize approximately 170 additional patients.

Intervention

Study treatment is defined as blinded study drug (abemaciclib or placebo) and/or abiraterone acetate plus prednisone. Abemaciclib, abiraterone acetate, and prednisone are administered orally on Days 1 through 28 of a 28-day cycle.

Part 1:
- Experimental Arm A1: Abemaciclib (3 tablets/capsules) orally twice daily
- Experimental Arm A2: Abemaciclib (4 tablets/capsules) orally twice daily
- Control Arm B1: Placebo (3 tablets/capsules) orally twice daily
- Control Arm B2: Placebo (4 tablets/capsules) orally twice daily
- All arms: Abiraterone acetate orally once daily plus prednisone orally twice daily

Part 2 and Part 3:
- Experimental Arm A: Abemaciclib at RP2D orally twice daily
- Control Arm B: Placebo (matching number of tablets/capsules) orally twice daily
- Arms A and B: Abiraterone acetate 1000 mg orally once daily plus 5 mg prednisone orally twice daily

Study burden and risks

Risks:
Unwanted events of abemaciclib. The unwanted events that were determined related to abemaciclib given alone, are listed in section E9. The study procedures, including blood draws, also come with certain risks. The risks are described in more detail in the subject information sheet and the Investigator's Brochure. Abemaciclib, prednisone, abiraterone, the study procedures and a combination thereof may include other, unknown risks.

Burden:
Patients will receive treatment until their disease progresses, they cannot tolerate the treatment, or if they or the investigator want to stop treatment. After study treatment has stopped, they will be asked to return for follow-up visits.

Patients may experience a return or worsening of their symptoms at any time during this study. They may be advised to take supportive medication or receive radiation therapy to treat symptoms that may arise during the study.

Diary entries: patients will be asked to complete a patient diary to help track actual doses of study treatment taken.

Blood draws: patients will have blood drawn during each visit (minimum 11 and maximum 46 ml per visit).

ECG: patients will have ECGs recorded during some visits (every 8 weeks for the first 6 months, then every 12 weeks).

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

[1] Male patients, 18 years of age or greater; willing and able to provide written informed consent., [2] Histologically confirmed adenocarcinoma of the prostate. Well-differentiated neuroendocrine carcinoma, small cell or large cell neuroendocrine carcinoma, sarcomatoid, and carcinoid tumors are excluded., [3] Metastatic prostate cancer documented by positive bone scan and/or measurable soft tissue metastatic lesions by computed tomography (CT) or magnetic resonance imaging (MRI). If lymph node metastasis is the only evidence of metastasis, it must be >=1.5cm in the short axis. Visceral metastasis, including to liver, is allowed., [4] Serum testosterone level <= 1.73 nmol/L (50 ng/dL) at the Screening visit. Patients who have not undergone orchiectomy are required to continue androgen-deprivation therapy (LHRH agonists/antagonists) throughout the study., [5] Progressive disease at study entry demonstrated during continuous androgen deprivation therapy (ADT)/post orchiectomy defined as one or more of the following criteria:, •Sequence of at least 2 rising PSA values at a minimum of 1-week intervals with the last result being at least 1.0 ng/ml if confirmed rise is the only indication of progression. Patients who received an anti-androgen must have PSA progression after withdrawal (>= 4 weeks since last flutamide or >= 6 weeks since last bicalutamide or nilutamide)., •Radiographic progression per RECIST1.1 for soft tissue and/or per PCWG3 for bone, (i.e., appearance of >=2 new bone lesions), with or without PSA progression., [6] Patient must have discontinued all previous treatments for cancer (except androgen-deprivation therapy and bone loss prevention treatment), must have recovered from of all acute toxic effects of prior therapy or surgical procedure to Grade <= 1 or baseline (as per Common Terminology Criteria for Adverse Events 5.0) prior to randomization, with the exception of alopecia or peripheral neuropathy AND have a washout period from last dose of prior systemic or radiation therapy as follows:
- Patients must discontinue flutamide at least 4 weeks, bicalutamide and nilutamide at least 6 weeks, prior to randomization.

- At least 4 weeks must have elapsed from the use of 5-α reductase inhibitors (eg,
dutasteride, finasteride), estrogens, and cyproterone to randomization.
- At least 4 weeks must have elapsed from the use of chemotherapy (ie, docetaxel,
for mHSPC) to randomization.
- At least 4 weeks must have elapsed from major surgery or radiation therapy prior
to randomization., [7] Able and willing to undergo tumor biopsy of at least one metastatic site (mandatory for part 1 and 2, optional for part 3), which should be collected following determination of eligibility and before initiating study treatment. [8] Have adequate organ function. [9] Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1. [10] Willing to comply with study procedures, able to swallow large capsules. Patients with reproductive potential must agree to use effective contraception and to not donate sperm during the study and for at least 3 months following the last dose of study treatment.

Exclusion criteria

[11] Prior therapy with CYP17 inhibitors (including abiraterone acetate, TAK-700, TOK-001 and ketoconazole), [12] Prior treatment with abemaciclib or any CDK4 & 6 inhibitors, [13] Known or suspected contraindications or hypersensitivity to abiraterone acetate, prednisone or abemaciclib or to any of the excipients. , [14] Prior cytotoxic chemotherapy for metastatic castration resistant prostate cancer (patients treated with docetaxel in the mHSPC are eligible), Prior radiopharmaceuticals for prostate cancer, or prior enzalutamide, apalutamide, sipuleucel-T. Patients who had prior radiation or surgery to all target lesions., [15] Are currently enrolled in a clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study. Have participated in clinical trial for which treatment assignment is still blinded. If patient has participated in a clinical study involving an investigational product, 3 months or 5 half-lives (whichever is shorter) should have passed. If a patient is currently enrolled in a clinical trial involving non-approved use of a device, then agreement with the investigator and Lilly Clinical Research Physician/ Clinical Research Scientist (CRP/CRS) is required to establish eligibility., [16] Gastrointestinal disorder affecting absorption or inability to swallow large pills, [17] Have prior malignancies or active concurrent malignancy (with the exception of non-melanomatous skin cancer). Patients with carcinoma in situ of any origin and patients with prior malignancies who are in remission and whose likelihood of recurrence is very low per Investigator's judgement are eligible for this study. The Lilly CRP/CRS will approve enrollment of patients with prior malignancies in remission before these patients are enrolled., [18] The patient has serious

preexisting medical condition(s) that, in the judgment of the investigator, would preclude participation in this study (for example, interstitial lung disease, severe dyspnea at rest or requiring oxygen therapy, history of major surgical resection involving the stomach or small bowel, or preexisting Crohn*s disease or ulcerative colitis or a preexisting chronic condition resulting in baseline Grade 2 or higher diarrhea)., [19] The patient has an history of any of the following conditions: syncope of cardiovascular etiology, ventricular arrhythmia of pathological origin (including, but not limited to, ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest. Atrial Fibrillation, or other cardiac arrhythmia requiring medical therapy., [20] Clinically significant heart disease as evidenced by myocardial infarction, arterial thrombotic events in the past 6 months, severe or unstable angina, or New York Heart Association (NYHA) Class II-IV heart failure or cardiac ejection fraction measurement of < 50% at baseline., [21] Patients with clinically active or chronic liver disease, moderate/severe hepatic impairment (Child-Pugh Class B and C), ascites or bleeding disorders secondary to hepatic dysfunction., [22] History of adrenal dysfunction, [23] The patient has active systemic infections (for example, bacterial infection requiring intravenous [IV] antibiotics at time of initiating study treatment, fungal infection, or detectable viral infection requiring systemic therapy) or viral load (such as known human immunodeficiency virus positivity or with known active hepatitis B or C [for example, hepatitis B surface antigen positive]). Screening is not required for enrollment., [24] Known or suspected CNS metastatic disease (Baseline screening for CNS metastases is not required unless presence of signs and/or symptoms of involvement)., [25] Uncontrolled hypertension (systolic BP >= 160 mmHg or diastolic BP >= 95 mmHg). Patients with a history of hypertension are allowed provided blood pressure is controlled by anti-hypertensive treatment, [26] Life expectancy < 6 months, [27] Patient treated with drugs known to be strong inhibitors or strong or moderate inducers of cytochrome P450 3A4 (CYP3A4), and the treatment cannot be discontinued or switched to a different medication at least five half-lives prior to starting study drug. , [28] Have received recent (within 4 weeks prior to randomization) live vaccination. Seasonal flu vaccines that do not contain a live virus are permitted., [29] Untreated spinal cord compression or evidence of spinal metastases with risk of spinal compression. Structurally unstable bone lesions suggesting impending fracture.

Study design

Design

Study phase:	3
Study type:	Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-11-2018
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	VERZENIO
Generic name:	abemaciclib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	30-10-2018
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-12-2018
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-02-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-03-2019

Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-05-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-08-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-09-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-09-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-05-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-05-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-07-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-07-2020

Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-12-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-12-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-06-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-07-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-01-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-03-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-04-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-04-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-03-2023

Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-04-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-04-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-09-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-10-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-506777-36-00
EudraCT	EUCTR2016-004276-21-NL
ClinicalTrials.gov	NCT03706365
CCMO	NL67029.028.18