An open-label Phase I/IIa study to evaluate the safety and efficacy of CCS1477 as monotherapy and in combination, in patients with advanced solid/metastatic tumours.

Published: 10-06-2021
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Primary objective To investigate the safety and tolerability of CCS1477 as monotherapy and in combination.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metastases
Study type	Interventional

Summary

ID

NL-OMON51947

Source
ToetsingOnline

Brief title
Phase I/IIa study to evaluate CCS1477 in advanced tumours

Condition

- Metastases

Synonym
Solid/metastatic tumour

Research involving
Human

Sponsors and support

Primary sponsor: CellCentric Ltd
Source(s) of monetary or material Support: Industry

Intervention

Keyword: advanced solid tumours, Phase 1

Outcome measures

Primary outcome

Primary objective

To investigate the safety and tolerability of CCS1477 as monotherapy and in combination.

Secondary outcome

Secondary objectives

- To obtain a preliminary assessment of the anti-tumour activity of CCS1477

- To characterize the pharmacokinetics (PK) of combination agents when dosed in combination with CCS1477 to investigate any drug-drug interactions.

Exploratory objectives

- To explore the relationship between PK, safety, efficacy and blood borne and tissue biomarkers, if appropriate.

- To collect and store blood and tumour samples for exploratory biomarker analysis

- To investigate the presence, and/or identity of drug metabolites of CCS1477 and, if appropriate, characterise their PK.

Study description

Background summary

BACKGROUND
Prostate cancer is the most common form of malignancy in men and is the second leading cause of male cancer-related death, with approximately 47,000 new cases and 11,000 deaths annually in the UK alone1. It is the 2nd commonest cancer overall (behind breast cancer) and the 3rd leading cause of cancer death in U.S. men behind lung and colorectal cancer. At diagnosis approximately 79% of patients have localised disease (confined to the prostate gland) while approximately 12% have regional disease (spread beyond the prostate to local lymph nodes) and 4% have distant metastatic disease (spread to distant anatomical sites). The 5-year survival for localised, regional and metastatic disease are 100%, 100% and 29.8% respectively.
The choice of treatment for patients with mCRPC largely depends on the presence or absence of symptoms and the extent and location of metastases. These treatment options include
-Abiraterone (androgen biosynthesis inhibitor), enzalutamide (androgen receptor inhibitor) for patients with asymptomatic or mildly asymptomatic disease.
- Sipuleucel-T (autologous cellular immunotherapy targeted against prostatic acid phosphatase) for patients with asymptomatic or mildly asymptomatic disease
- Radium-223 (targeted alpha emitter that selectively binds to areas of increased bone turnover in bone metastases) in patients with symptomatic and predominantly bone metastases
- Docetaxel (chemotherapy) in patients with significantly symptomatic disease (including visceral metastases)
- Patients previously treated with docetaxel may be treated with any treatments which they have not previously received (abiraterone, enzalutamide, radium-233, and cabazitaxel (2nd generation taxane chemotherapy)
There is now a substantial body of evidence demonstrating that disease progression after ADT is dependent on ongoing signalling through the AR via a number of different but related mechanisms. These include:
- An increase in the expression of AR through genomic AR amplification, which can sensitise prostate cells to low levels of androgen
- AR activating mutations that cause AR antagonists to behave as agonists or the AR to respond to alternative ligands
- Alternative splicing of AR to produce constitutively active forms of AR that lack the ligand binding domain
- Increased expression of AR co-regulators
- Increased androgen generation within prostate tumours

Understanding of the central role of the AR in prostate cancer has led to the development of second generation anti-androgen drugs, notably abiraterone and enzalutamide. Both drugs are approved for the treatment of patients with

mCRPC, based on an improvement in overall survival. However, these therapies are not curative and further resistance occurs, again mediated by restored AR pathway activation.
When tumours are exposed to AR antagonists, mutations can arise in the ligand-binding domain of the AR that are specific to the anti-androgen therapy that the patients have been receiving. These mutations result in the anti-androgen acting to promote rather than block AR signalling. Expression of constitutively active splice variant forms of the androgen-receptor (AR-SV) is another important mechanism of resistance to drug treatment. AR-V7 is the best-characterised of the many different AR-SV forms, all of which lack the ligand-binding domain (LBD), but retain the deoxyribonucleic acid (DNA)-binding domain of the receptor8. Treatments that target the LBD, including anti-androgens such as enzalutamide, are ineffective on AR-SVs. Thus, whilst focusing in on the AR is key, there is a clear need to develop new approaches beyond specifically targeting the LBD with capability to inhibit the major mechanisms of resistance at the same time.

One such approach is to target key co-regulators of AR structure and function. P300 and CBP are two closely related histone acetyltransferase (HAT) proteins that are critical transcriptional co-regulators of the AR. Both are believed to be oncogenic in prostate cancer and are up-regulated during disease progression. P300/CBP have two main functions:
- to acetylate key client proteins such as the AR, and
- to act as part of a complex of proteins including the AR, which enhances transcription of AR target genes

Inhibiting p300/CBP would be expected to inhibit both the expression and function of AR. Importantly, because the mode of action does not involve interaction with the LBD of the AR, inhibition of p300/CBP should be effective against tumours with amplified AR, AR-mutations and AR splice variants.
In addition to the critical role that p300/CBP plays in co-regulating the AR, it is also becoming increasingly evident that certain other tumours may be particularly sensitive to p300/CBP inhibition. Tumours that harbour loss of function mutations in either p300 or CBP become dependent on the corresponding non-mutated paralogue (twin) protein for their continued growth. When the non-mutated twin is inhibited, this drives synthetic lethality leading to apoptosis/cell death. In lung cancer, genetic analysis reveals that up to 15% of both non-small cell and small cell tumours have these loss of function mutations. Similar mutations are also found in up to 25% of bladder cancers, as well as in a number of haematological malignancies. It has been shown that CCS1477 has selective anti-proliferative activity in a range of cancer cell lines which have loss of function mutations in either p300 or CBP.

Other cancer cell lines also demonstrate sensitivity to CCS1477; the underlying molecular determinants of this have yet to be determined, but may include over-expression of c-Myc and expression of AR in tumours other than prostate such as breast. Thus, beyond CRPC, CSS1477 has the potential to benefit

patients with a range of malignancies.

Study objective

Primary objective
To investigate the safety and tolerability of CCS1477 as monotherapy and in combination.

Study design

This is a phase I/IIa open-label, multicentre study of CCS1477 administered as monotherapy or in combination with abiraterone or enzalutamide in patients with mCRPC, and as monotherapy in patients with advanced solid tumours with molecular markers which may indicate potential for response to p300/CBP inhibition.

There are multiple parts to this study.

Monotherapy Dose Escalation

Part A - CCS1477 monotherapy dose escalation in patients with mCRPC to determine the maximum tolerated dose (MTD) or the recommended dose and schedule of CCS1477 monotherapy (RP2D-M).

Initially dose escalation will involve a single patient cohort design (until a related toxicity >= CTCAE Grade 2 is observed) to minimise the number of patients exposed to potentially sub-therapeutic doses. The study will then switch to a modified rolling 6 design in which 3-6 patients will be enrolled into each cohort.

• Parts B1 and B2 - CCS1477 monotherapy expansion cohorts in patients with mCRPC, 2 different doses and/or schedules may be tested.

• Part C has two parts, conducted in sequence:
Part C1 - CCS1477 in combination with abiraterone in patients with mCRPC (combination dose finding), intended to establish the recommended phase II dose and schedule for CCS1477 in combination with abiraterone (RP2D-Cabi)
Part C2 - combination therapy expansion cohort

• Part D has two parts, conducted in sequence:
Part D1- CCS1477 in combination with enzalutamide in patients with mCRPC (combination dose finding), intended to establish the recommended phase II dose and schedule for CCS1477 in combination with enzalutamide (RP2D-Cenz), which may be the same as RP2D-Cabi
Part D2 - combination therapy expansion cohort

• Part E has 2 parts:
Part E1 - Monotherapy CCS1477 in patients with advanced solid tumours with molecular markers which may indicate potential for response to p300/CBP inhibition. Patients can be entered into Part E1 during the dose escalation phase of the study and will receive CCS1477 at a dose and schedule which has been previously declared tolerated during the ongoing Part A dose escalation phase.
Part E2 - Monotherapy CCS1477 exploratory expansion in patients with advanced solid tumours with molecular markers which may indicate potential for response to p300/CBP inhibition. Patients will be entered into Part E2 following the completion of Part A using data from Part A and Part E1 to establish the best dose for Part E2.

•Part F has 2 parts:
Part F1 will establish the recommended dose and schedule of CCS1477 in combination with darolutamide in patients with mCRPC who have previously received abiraterone and/or enzalutamide (or equivalent anti-androgen) treatment and have received, or are ineligible for, treatment with a taxane, will be assessed.
Part F2 is an expansion phase which will recruit approximately 25 mCRPC patients to investigate the clinical activity of the RP2D of CCS1477 in combination with darolutamide

• Part G has 3 parts:
Part G1 will establish the recommended dose and schedule of CCS1477 in combination with olaparib in patients with either mCRPC or locally advanced or metastatic breast cancer.
Part G2 is an expansion phase which will recruit approximately 25 mCRPC patients to investigate the clinical activity of the combination of the RP2D of CCS1477 in combination with olaparib (mCRPC patients from Part G1 may be included in this number).
Part G3 is an expansion phase which will recruit approximately 25 metastatic breast cancer patients to investigate the clinical activity of the combination of the RP2D of CCS1477 in combination with olaparib

• Part has 2 parts:
Part H1 will establish the recommended dose and schedule of CCS1477 in combination with atezolizumab in patients with locally advanced or metastatic NSCLC after prior chemotherapy
Part H2 is an expansion phase which will recruit approximately 25 patients with locally advanced or metastatic NSCLC after prior chemotherapy to investigate the clinical activity of the combination of the RP2D of CCS1477 in combination with atezolizumab

There will be no randomisation in this study.

Intervention

Open label study. Each part of the study will have treatment with CCS1477.

Part A: Monotherapy CCS1477 Dose Escalation -> completed as of 14April 2021
Part B: Monotherapy CCS1477 Expansion
Part C1 and C2: CCS1477 in combination with abiraterone
Part D1 and D2: CCS1477 in combination with enzalutamide
Part E: Monotherapy CCS1477 Expansion
Part F1 and F2: CCS1477 in combination with darolutamide
Part G1: CCS1477 in combination with olaparib in patients with either mCRPC or locally advanced or metastatic breast cancer.
Part G2: Expansion CCS1477 in combination with olaparib (mCRPC patients)
Part G3: Expansion CCS1477 in combination with olaparib (metastatic breast cancer)
Part H1: CCS1477 in combination with atezolizumab in patients with locally advanced or metastatic NSCLC
Part H2: Expansion CCS1477 in combination with atezolizumab in patients with locally advanced or metastatic NSCLC

Study burden and risks

CCS1477 has the potential to provide clinical benefit to patients who have progressed after treatment with 2nd generation anti-androgen therapies such as abiraterone or enzalutamide. The mechanisms by which tumours become resistant to 2nd generation anti-androgen therapies include the generation of activating mutations and splice variant forms of the AR, which drive disease progression. CCS1477 works by down-regulating the expression and function of all forms of the AR, including mutated and splice variant AR and has anti-tumour activity in models of CRPC, where abiraterone or enzalutamide are ineffective.

Preliminary signals of activity have been seen in some patients in dose escalation cohorts.

CCS1477 in combination with abiraterone or enzalutamide has the potential to provide superior clinical benefit to patients compared with either anti-androgen therapy given alone. CCS1477 and abiraterone or enzalutamide, target independent but complimentary mechanisms that regulate AR expression and function and would therefore be expected to give enhanced anti-tumour activity when combined by more effectively supressing the AR pathway. Anti-tumour activity is greater in CRPC models that are responsive to enzalutamide when CCS1477 is combined with enzalutamide vs enzalutamide given alone.

CCS1477 has the potential to provide clinical benefit to patients with advanced solid tumours with molecular markers which may indicate potential for response to p300/CBP inhibition. CCS1477 is active in certain cell lines that have

mutations in p300/CBP compared with cell lines without the mutations or in cell lines that over-express AR or are c-Myc dependent. .

Potential risks
The preclinical and emerging safety profile has not identified any risks that would preclude investigation of CCS1477 in the advanced cancer setting.

P300/CBP is known to play a role in haematopoiesis. Impact on haematological parameters, including a reduction in platelets with corresponding pathological changes in lymphoid tissues including the bone marrow, was observed in both rats and dogs dosed with CCS1477. In the pre-clinical studies the reduction in platelets emerges after several days of treatment in some animals, with the nadir being observed after 14 days of continuous dosing in the rats. Interruption of CCS1477 led to recovery in platelet numbers and re-treatment with CCS1477 did not lead to a worsening of effect. Based on the preclinical studies, other haematological abnormalities may be observed including possibly anaemia and lymphopenia. Patients will have regular planned haematology assessment (including platelet count estimation) and will be informed and asked to report any symptoms or signs of bleeding (easy bruising, petechiae etc). Appropriate treatment will be administered as needed (CCS1477 dose interruption and platelet transfusions).

P300/CBP is known to cause an effect on the AR. Atrophy of androgen-dependent tissues, including lymphoid tissues and reproductive organs, were observed in both the rat and the dog after dosing CCS1477. These changes are considered to be a direct consequence of on-target pharmacology. Atrophic changes may also be seen in male reproductive organs associated with symptoms and signs of androgen deprivation. Although part of the desired mechanism of action for patients with CRPC, such changes may be unwanted in males with other tumours enrolled in the study. Serum luteinizing hormone (LH), follicular stimulating hormone (FSH) and testosterone (male patients only) will be measured at screening and on study treatment, and CCS1477-related symptoms or signs consistent with androgen deprivation (including but not limited to decreased libido, erectile dysfunction, gynaecomastia, fatigue, depression, osteopenia/osteoporosis and anaemia) will be monitored during the study.

Changes in electrolytes (slight increase in plasma potassium, sodium and calcium concentrations) were observed after 28 days dosing in the rat. As a result of prolonged changes in electrolyte concentrations, minimal vacuolation and degeneration in the kidney was observed at the highest dose level in the rat. Electrolyte concentrations in patients will be monitored, with appropriate action taken if needed.

The current emerging clinical safety profile is generally in line with the pre-clinical safety, with haematological toxicity (predominantly thrombocytopenia) and electrolyte disturbances (mainly hyponatremia), which are reversible with treatment interruption and/or intervention. Important potential

risks consistent with preclinical data continue to be carefully monitored in clinical data and one new potential risk (gastrointestinal toxicity) has been identified during the reporting*period*based on*clinical*data and literature report for another investigational compound inhibiting p300/CBP.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Written informed consent;
2. willing and and able to comply with study protocol procedures
3. >= 18 years
4. ECOG performance status 0-1 with no deterioration over previous 2 weeks and minimum life expectancy of 12 weeks
5. Adequate organ functions:
• AST/ALT <=3 x ULN or AST/ALT <=5 x ULN

• Total bilirubin <=1.5 x ULN (or <3 UNL if bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin, or due to underlying liver involvement).
• Calculated creatinine clearance by Cockcroft-Gault formula >=30 ml/min²
• ANC >=1.5 x 109/L
• Platelets >=100 x 109/L
• Haemoglobin >=9g/dL. (maintained without transfusion within 14 days of starting CCS1477)
• Normal sodium level (patients with borderline sodium decrease below normal level may be eligible following discussion with medical monitor).
• Serum albumin >2.5 g/dL
• LDH within normal level (patients with borderline LDH results may be eligible following discussion with medical monitor)
6. For duration of the study and 1 week after the last study administration, sexually active male patients must be willing to use barrier contraception with all sexual partners. Where the sexual partner is a *woman of child-bearing potential* who is not using effective contraception, men must use a condom and another form of contraception during the study and for 6 months after the last dose of study medication.
7. Females must agree to use highly effective contraceptive measures, must not be breast feeding and must have a negative serum pregnancy test prior to start of dosing if of child-bearing potential, or must have evidence of non-child-bearing potential at screening per one of:
• Post menopausal defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments
• Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation
• Amenorrhoeic for 12 months and serum FSH, LH and plasma oestradiol levels in the postmenopausal range for institution
8. Patients must have assessable disease (by CT, MRI, bone scan or X-ray) but are not required to have measurable disease

Additional inclusion criteria for mCRPC patients (Parts A, B, C, D and F only)
9. Patients must have previously received standard available therapy including (but not limited to):
• abiraterone and/or enzalutamide (or equivalent anti-androgen), and
• a taxane (unless ineligible)
10. Progressive disease documented by one or more of:
• Biochemical progression defined as at least 2 stepwise increases in a series of any 3 PSA values collected while the patient has castrate levels of testosterone. The 3 PSA values selected do not need to be consecutive, and do not need to include the most recent PSA collected at, or prior to, study enrolment, but must meet the following criteria:
a. PSA progression defined by minimum of 3 rising PSA levels with an interval of >=1 week between each determination
b. Each of the 3 PSA values must be collected while the patient is under medical castration or is surgically castrated
c. Ideally all 3 should be done after anti-androgen withdrawal (if applicable),

but they can be done during the withdrawal period
• Progression as defined by RECIST v1.1 guideline for assessment of malignant soft tissue disease or modified RECIST v1.1 criteria as defined by PCWG-3 for progression of nodes
• Progression defined as 2 or more new metastatic bone lesions confirmed on bone scan from a previous assessment
11. PSA at screening must be >=2 µg/L (2 ng/mL)
12. Serum testosterone concentration <=50 ng/dL sustained by medical or surgical castration
13. Serum albumin >2.5 g/dL

Additional Part C inclusion criteria (CCS1477 plus abiraterone)
14. Patients must have previously progressed on abiraterone treatment
15. Patients whose last dose of abiraterone is >6 months prior to start of study treatment will receive a 4-week run-in treatment with abiraterone to confirm refractoriness to abiraterone treatment

Additional Part D inclusion criteria (CCS1477 plus enzalutamide)
16. Patients must have previously progressed on enzalutamide treatment
17. Patients whose last dose of enzalutamide is >6 months prior to start of study treatment will receive a 4-week run-in treatment with enzalutamide to confirm refractoriness to enzalutamide treatment. All patients in drug-drug interaction (DDI) arm will receive enzalutamide monotherapy during Cycle 0

Additional Part E inclusion criteria (non-prostate only)
18. Histological or cytological confirmation of malignancy that is advanced. Patients must be refractory to, or intolerant of available therapies known to provide clinical benefit for their condition
19. Identification of markers which may indicate potential for response to p300/CBP inhibition will be determined by local testing and will include, but not be limited to, loss of function mutations in either p300 or CBP and/or Myc amplification or over-expression, determined by next generation sequencing in tumour biopsies/cell free DNA extracted from a pre-treatment blood sample. IHC may also be used, as appropriate, to determine over expression of proteins such as myc or AR. Patients with certain cancers where molecular testing has not been performed may be eligible upon discussion with medical monitor.

Additional inclusion criteria for patients in CCS1477 plus olaparib arm (Part G)
20. Patients receiving olaparib as standard of care (as per the local label). Patients should not be responding sufficiently to treatment (in the opinion of the investigator) within approximately 3 months of starting olaparib.
21. Patients should be tolerating treatment with olaparib and should be continuing treatment with olaparib. Patients who have had a transient interruption of treatment may be eligible following discussion with the medical monitor.

Additional inclusion criteria for patients in CCS1477 plus atezolizumab arm

(Part H)
22. Patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR mutant or ALK-positive NSCLC should also have received targeted therapies.

Exclusion criteria

All Patients:
1. Intervention with any of the following
• Any chemotherapy, investigational agents or other anti-cancer drugs within 14 days or 5 half-lives (whichever is longer of these two) of the first dose of study treatment (excludes treatment with immunotherapy agents which must be assessed on a case by case basis). This does not apply to prior treatment with abiraterone for patients in Part C1 or C2 or prior treatment with enzalutamide for patients in Part D1 (except patients in the DDI arm who must have a 4 week washout of enzalutamide prior to starting the study) and D2.
• Radiotherapy with a wide field of radiation or to more than 30% of the bone marrow within 4 weeks of the first dose of study treatment
• Major surgical procedure or significant traumatic injury as judged by the investigator, within 4 weeks of the first dose of study treatment, or have an anticipated need for major surgery during the study
• Strong inducers of CYP3A4 (See Appendix E) taken within 4 weeks of the first dose of study treatment or while on study treatment (excluding enzalutamide in Part D1 and D2 which does not require a 4 week wash-out prior to the first dose of study treatment, except for patients in the DDI arm).
• Strong inhibitors of CYP3A4 or CYP2C8 or CYP3A4 sensitive substrates (See Appendix E) taken within 2 weeks of the first dose of study treatment or while on study treatment.
• Washout periods may be reduced for specific medications (eg. statins) following discussion with the medical monitor.
• Herbal medications cannot be taken within 7 days of the first dose of study treatment (4 weeks for St John*s wort) or while on study treatment
• Statins; patients may receive fluvastatin or pravastatin (with monitoring for potential toxicities), or atorvastatin or simvastatin at 10mg daily dose only.
Patients
• Systemic cancer treatment should not be initiated for at least 30 days after the last administration of Radium-223 (Ra-223, Xofigo)
2. Any unresolved reversible toxicities from prior therapy greater than Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 at the time of starting study treatment with the exception of alopecia and neuropathy
3. Female patients who are pregnant or breast-feeding at study entry. Breast feeding is contraindicated during study treatment and for 1 month after study drug is discontinued.
4. Any evidence of severe or uncontrolled systemic diseases, including for example diabetes, uncontrolled hypertension and active bleeding diatheses,

which in the investigator*s opinion makes it undesirable for the patient to participate in the study or which would jeopardise compliance with the protocol, or active infection* including hepatitis B, hepatitis C and human immunodeficiency virus (HIV). *Active viral infection is defined as requiring antiviral therapy. Screening for chronic conditions is not required
5. Patients with any known uncontrolled inter-current illness including ongoing or active clinically significant infections, symptomatic congestive heart failure, hypertension, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements. Refractory nausea and vomiting, chronic gastrointestinal diseases or previous significant bowel resection, with clinically significant sequelae that would preclude adequate absorption of study treatments
6. Repeatable QTcF prolongation (>480 msec)
7. Prior malignancy that could affect compliance with the protocol or interpretation of results. Patients with a history of non-melanoma skin cancers or carcinoma in situ treated with curative intent, are generally eligible
8. Primary brain tumours or known or suspected brain metastases. Patients with brain metastases could be eligible if treated and stable within 28 days of the first dose of study treatment (after discussion and agreement with the CellCentric medical advisor).
9. Patients with any known severe allergies to any active or inactive ingredients in the study medications

Additional exclusion criteria for patients in CCS1477 plus abiraterone combination arm (Part C)
10. Patients with clinically significant cardiac abnormalities or contraindications to abiraterone such as:
Severe hepatic impairment (Child-Pugh class C)
11. Clinically significant cardiac abnormalities as assessed by the treating physician that may include (but not be limited to) recent myocardial infarction (<=6 months) or unstable angina (<=3 months), New York Heart association (NYHA) class III or IV heart failure except if LVEF is >=50%, clinically significant uncontrolled rhythm disturbances, and patients with uncontrolled hypertension
Note: Abiraterone is contraindicated in combination with Radium-223

Additional exclusion criteria for patients in CCS1477 plus enzalutamide combination arm (Part D)
12. History of seizures or other predisposing factors including, but not limited to, underlying brain injury, stroke, primary brain tumours, brain metastases and leptomeningeal disease, or alcoholism
13. Use of substrates with a narrow therapeutic index metabolised by CYP2C9 or CYP2C19 within 2 weeks of the first dose of study treatment
14. Patients with clinically significant cardiac abnormalities as assessed by the treating physician that may include (but not be limited to) recent myocardial infarction (<=6 months) or unstable angina (<=3 months), New York Heart association (NYHA) class III or IV heart failure except if LVEF is >=50%, clinically significant uncontrolled rhythm disturbances, and patients with

uncontrolled hypertension

Additional exclusion criteria for patients in CCS1477 plus darolutamide combination (Part F)
15. The use of moderate CYP3A4 inducers taken within 4 weeks of the first dose of study treatment or while on study treatment
16. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption
Additional exclusion criteria for patients in CCS1477 plus olaparib combination (Part G)
17. Severe hepatic impairment (Child-Pugh class C)
18. The use of moderate inhibitors of CYP3A4 taken within 2 weeks of the first dose of study treatment or while on study treatment
19. Evidence of MDS/AML on peripheral blood smear
Additional exclusion criteria for patients in CCS1477 plus atezolizumab combination (Part H)
20. History of autoimmune disease, including, but not limited to myasthenia gravis, myositis, pneumonitis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis or glomerulonephritis. Subjects with diabetes mellitus type I, hypothyroidism only requiring hormone replacement or controlled hyperthyroidism, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enrol.
21. Patients administered a live, attenuated vaccine within 28 days prior to first dose; systemic immunostimulatory agents within 4 weeks or 5 half lives (whichever is longer), or systemic immunosuppressive medicinal products within 2 weeks prior to first dose of study treatment.
22. Active tuberculosis
23. Severe infection within 4 weeks, or IV antibiotics treatment within 2 weeks of the first dose of study treatment
24. Prior allogeneic bone marrow or solid organ transplant
25. Treatment with systemic corticosteroids (>10mg daily of prednisolone or equivalent) within 1 week of the first dose of study treatment

Study design

Design

Study phase:	2
Study type:	Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-03-2022
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	abiraterone acetate
Generic name:	abiraterone acetate
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	CCS1477
Generic name:	CCS1477
Product type:	Medicine
Brand name:	Darolutamide
Generic name:	Darolutamide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Enzalutamide
Generic name:	Enzalutamide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Olaparib
Generic name:	Olaparib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	10-06-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-08-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-09-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-11-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-05-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-08-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-09-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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
EudraCT	EUCTR2018-000285-10-NL
ClinicalTrials.gov	NCT03568656
CCMO	NL77469.056.21