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

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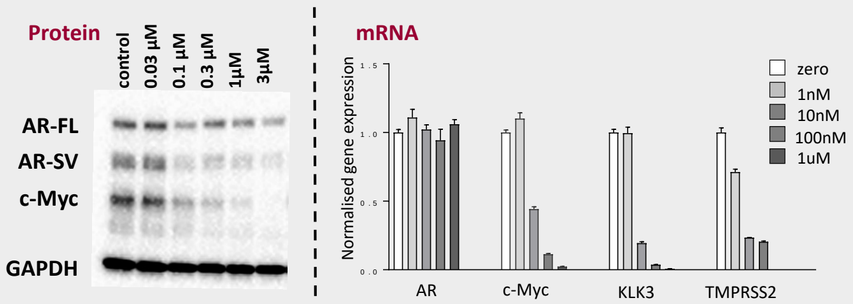
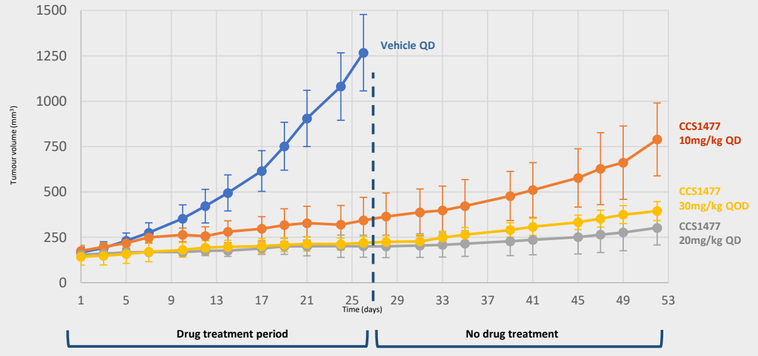
Abstract: TPS5089

Background

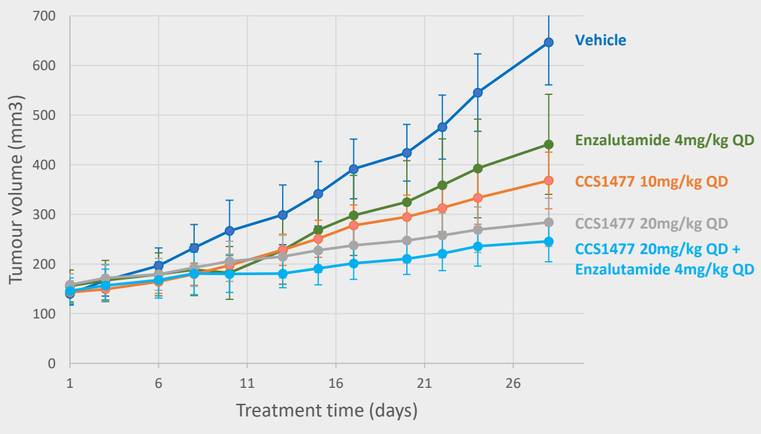
- CCS1477 is a potent, selective and orally bioavailable inhibitor of the bromodomain of p300 and CBP
- CCS1477 inhibits the expression and function of AR-FL, AR-SV and c-Myc



- CCS1477 monotherapy causes complete tumour stasis in a 22Rv1 xenograft model of CRPC, with continued tumour growth block following drug withdrawal



- CCS1477 combines with enzalutamide to inhibit tumour growth in a bicalutamide resistant LNCaP xenograft model



- CCS1477 represents a new therapeutic option for prostate cancer patients who have progressed after failure of, or in combination with, anti-androgens such as enzalutamide or abiraterone

Study Design

Part A: Monotherapy CCS1477 Dose escalation mCRPC
- Single patient cohorts until related ≥CTCAE Grade 2 toxicity
- Cohorts of 3-6 patients until MTD/RP2D-M
- Different dose schedules may be evaluated if required

Part B: Monotherapy CCS1477 Dose expansion mCRPC
- CCS1477 RP2D- M dose and schedule from Part A
- 25 patients

Part C1: Combination CCS1477/ abiraterone Dose Finding mCRPC
- CCS1477 in combination with abiraterone
- Starting dose will be MTD/RP2D-M from Part A
- Different dose/schedules may be evaluated if required

Part C2: Combination CCS1477/ abiraterone Dose Expansion mCRPC
- CCS1477 RP2D-C_{abi} in combination with abiraterone
- 25 patients

Part D1: Combination CCS1477/ enzalutamide Dose Finding mCRPC
- CCS1477 in combination with enzalutamide
- Starting dose will be MTD/RP2D-M from Part A
- Different dose/schedules may be evaluated if required

Part D2: Combination CCS1477/ enzalutamide Dose Expansion mCRPC
- CCS1477 RP2D-C_{enz} in combination with enzalutamide
- 25 patients

Part E: Monotherapy CCS1477 Dose expansion in patients with a p300/CBP mutation
- CCS1477 RP2D-M dose and schedule from Part A
- Advanced solid tumours with confirmed p300/CBP mutation
- 25 patients

Primary objective
- Investigate the safety and tolerability of CCS1477 as monotherapy and in combination with abiraterone or enzalutamide

Secondary objectives
- Obtain a preliminary assessment of the anti-tumour activity of CCS1477 as monotherapy and in combination with abiraterone or enzalutamide in patients with mCRPC by measurement of changes in PSA, CTCs, RECIST and metastatic bone disease status
- Characterise the PK of CCS1477, following a single dose and at steady state after multiple dosing, when given as a single agent or in combination
- Characterise the PK of abiraterone and enzalutamide when dosed in combination with CCS1477
- Obtain a preliminary assessment of the anti-tumour activity of CCS1477 in patients with advanced solid tumours with a confirmed mutation in p300 or CBP

Patient criteria

For patients with mCRPC
- Previous treatment with abiratrone and/or enzalutamide and a taxane (unless ineligible or refused)
- Evidence of disease progression (PCWG-3 guidelines)
- For parts C&D, patients whose last dose of abiraterone or enzalutamide is >6 months prior to start of study will receive a 4-wk run-in treatment to confirm refractoriness to treatment

For patients with a solid tumour p300/CBP mutation
- Histological or cytological confirmation of malignancy that is advanced and not considered to be appropriate for further approved/standard of care treatment
- Advanced solid tumour with a confirmed mutation in p300 or CBP

Status

- Cohort 1 and 2 of dose-escalation (rolling 6 design; 3-6 patients/cohort) has completed
- Currently recruiting to Cohort 3