A Phase I/IIa study to evaluate the safety and efficacy of CCS1477, a first in clinic inhibitor of p300/CBP, as monotherapy in patients with selected molecular alterations

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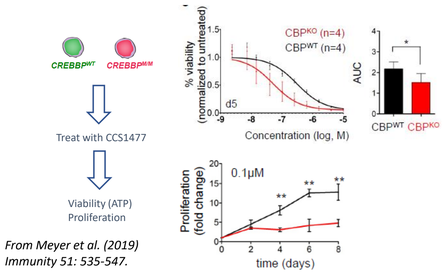
Background

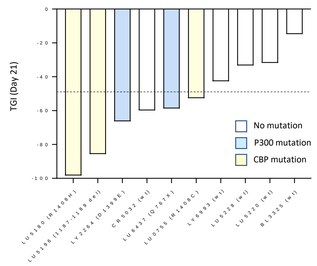
- CCS1477 is a potent, selective and orally bioavailable inhibitor of the bromodomain of p300 and CBP. Pre-clinical studies show that tumours with certain molecular alterations are more sensitive to CCS1477.
- **Three leading hypotheses.**
  1. **P300/CBP synthetic lethality.** Tumours with loss of function mutations in either p300 or CBP become dependent on the corresponding non-mutated paralogue (twin) protein.

CBP-mutant cells are preferentially sensitive to CCS1477 *in vitro*



From Meyer et al. (2019) Immunity 51: 535-547.

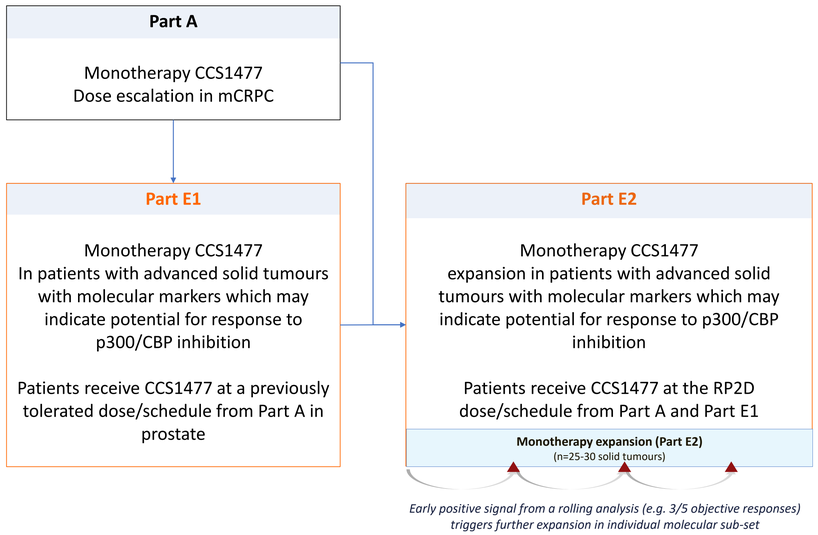
PDX models with loss of function mutations in CBP or P300 are more sensitive to CCS1477 *in vivo*



  2. **ARID1A mutated tumours are more sensitive to p300/CBP inhibition.** Wilson *et al* (2020). ARID1A mutations promote p300-dependent endometrial invasion through super-enhancer hyperacetylation. Cell Reports 33, 18366.
  3. **Tumours that are dependent on AR and Myc are more sensitive to CCS1477.** (Pegg *et al* 2018). Novel small molecule inhibitor of p300/CP down-regulates androgen receptor and C-Myc for the treatment of prostate cancer and beyond. AACR Annual Meeting Abstract # 3991.

Study design

- This first in human Phase I/II study (sponsored by CellCentric Ltd) is modular in design. Described here are Parts E1 and E2, which specifically evaluate the clinical activity of CCS1477 in patients with advanced solid tumours harbouring molecular alterations that indicate potential enhanced sensitivity to p300/CBP inhibition. Dose selection for Parts E1/2 is guided by Part A, which is a monotherapy dose-escalation in patients with mCRPC.



Early positive signal from a rolling analysis (e.g. 3/5 objective responses) triggers further expansion in individual molecular sub-set

Response assessments

- Anti-tumour activity determined by standard imaging according to RECIST guidelines
- Paired tumour biopsies for biomarker assessment are collected with ctDNA and Paxgene blood collection for exploratory biomarker analysis

Patient criteria/Molecular testing

- Histological or cytological confirmation of solid malignancy that is advanced and not considered to be appropriate for further approved/standard of care treatment
- Potential sensitivity biomarkers are identified by local testing using next generation sequencing or equivalent, in archival or fresh tumour biopsies or in cell free DNA from a pre-treatment blood sample.
- Sensitivity markers include loss of function mutations in p300, CBP or ARID1A as well as MYC and AR gene amplification or protein over-expression
- IHC and or FISH may be used to determine over-expression and/or gene amplification for AR or MYC
- Patients with cancers where there is a strong molecular rationale for a response to CCS1477 (e.g. MYC amplification in small cell lung cancer and radiation induced breast angiosarcoma) may be entered without molecular testing

Current Status

- 8 patients enrolled, 1 SCLC, 1 with a p300 mutation, 1 with a CBP mutation, 3 with ARID1A mutations and 2 with Myc alterations. The trial is currently open in the UK and US and soon in the EU (Spain, The Netherlands, France and Sweden)

Conflict of interests: Simon Crabb has no conflicts of interest to declare.

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