An open-label Phase I/IIa study to evaluate the safety and efficacy of CCS1477, a first in clinic inhibitor of the p300/CBP bromodomains, as monotherapy and in combination, in patients with advanced haematological malignancies

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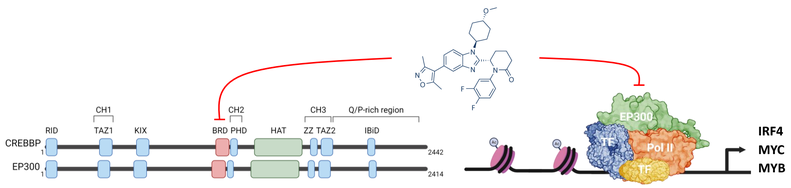
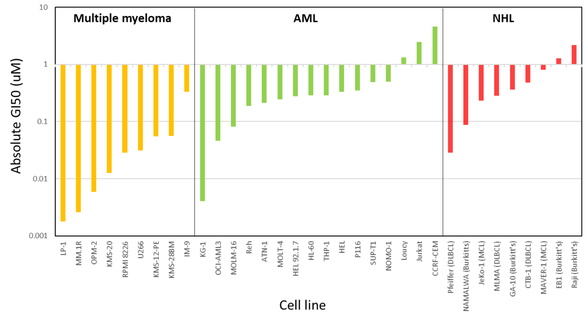
Background

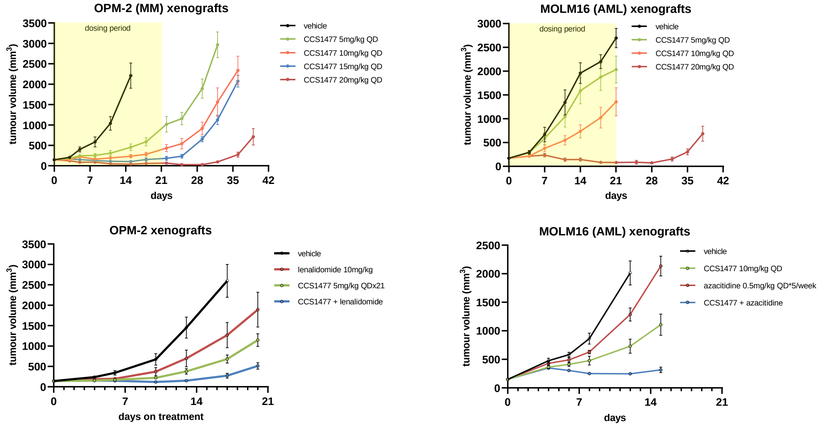
- CCS1477 (inobrodib) is a potent, selective and orally bioavailable inhibitor of the bromodomains of p300 and CBP, two closely related histone acetyl transferases with oncogenic roles in haematological malignancies. Their inhibition impacts IRF4, MYC, MYB.



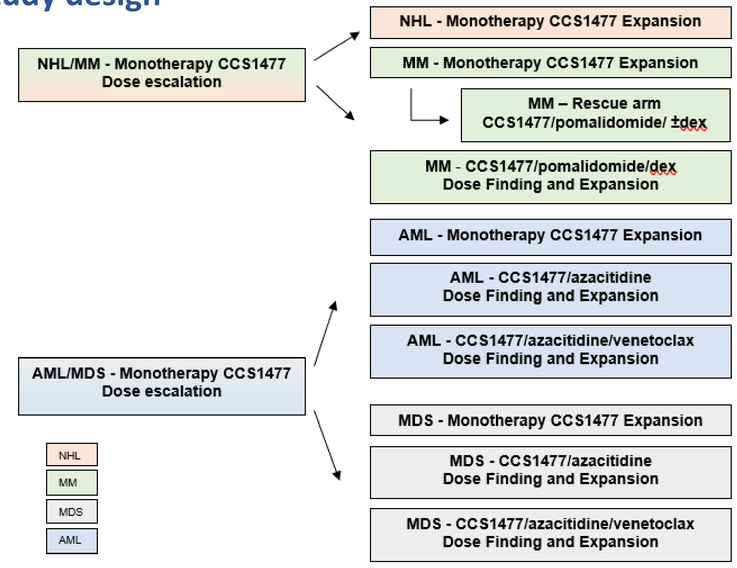
- CCS1477 exhibits robust anti-cancer potential against multiple haematological cancer cell lines



- CCS1477 has dose-dependent anti-tumour efficacy and combines well with standard of care therapies. Tumour suppression persists beyond exposure to the drug.



Study design



Primary objective

- Assess the safety and explore the recommended Phase 2 dose (RP2D) and/or the maximum tolerated dose (MTD) of CCS1477 as monotherapy, or in combination, in patients with relapsed or refractory haematological malignancies; multiple myeloma (MM), Non Hodgkin lymphoma (NHL), acute myeloid leukaemia (AML) and higher risk myelodysplastic syndrome (MDS)
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Secondary objectives

- Characterise the pharmacokinetics (PK) of CCS1477, following a single dose and at steady state after multiple dosing
- Assess preliminary tumour response/activity of CCS1477 as monotherapy, or in combination, in patients with relapsed or refractory haematological malignancies

Patient criteria

- Aim to enrol 250 patients with confirmed (per standard disease specific diagnostic criteria), relapsed or refractory haematological malignancies MM, NHL, (AML, and higher risk)
- Patients must have received standard therapy

Response assessments

- AML responses are assessed according to the 2017 ELN recommendation criteria (Döhner *et al* 2017; Blood) in bone marrow and blood samples
- MDS responses are assessed according to the 2006 IWG guidelines (Cheson *et al* 2006; Blood) with modification/clarifications as proposed in the revised IWG guidelines (Platzbecker *et al* 2019; Blood)
- Myeloma responses are evaluated as described in the 2016 IMWG Response Criteria (Kumar *et al* 2016; The Lancet Oncology) based on changes in; M protein in blood and/or urine; serum free light chains if measurable, and; imaging and/or bone marrow if applicable
- In NHL patients, tumours are assessed for measurable disease, non-measurable disease, and new lesions on CT (or MRI) and/or combined with visual assessment of FDG-PET with clinical parameters and bone marrow if applicable, per recent 2017 IWG consensus criteria (RECIL; Younes *et al* 2017; Ann Oncol). Specific standardised response criteria for selected NHL subtype are used, where applicable

Exploratory biomarkers

- Blood samples along with bone marrow biopsies and aspirates are collected for exploratory biomarker analysis to understand mechanisms of response to treatment or disease progression
- This includes the analysis of tumour-specific and circulating biomarkers, such as tumour DNA, mRNA, proteins or metabolites
- In NHL patients, retrospective analysis of EP300/CREBBP mutations will be undertaken to determine if loss of function mutations in these genes can be utilised as response predictive biomarkers in future studies

Status

- The monotherapy RP2D has been established. Recruitment is ongoing in monotherapy expansion arms and combination dose finding arms

Conflict of interests: Tomasz Knurowski, Karen Clegg, Neil Pegg, Debbie Haynes, Kristopher Frese and Will West are employees and stockholders in CellCentric. Tim Somervaille received research funding from CellCentric. There are no relationships to disclose for Emma Searle.