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 in patients with advanced haematological malignancies

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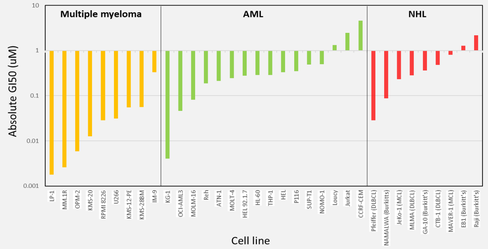
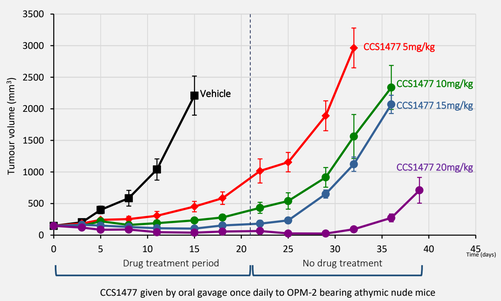
Background

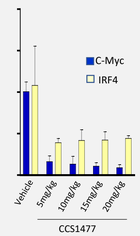
- CCS1477 is a potent, selective and orally bioavailable inhibitor of the bromodomains of p300 and CBP, two closely related histone acetyl transferases with oncogenic roles in haematological malignancies
- CCS1477 is a potent inhibitor of proliferation in a panel of multiple myeloma, AML and NHL cell lines *in vitro*



- CCS1477 monotherapy causes tumour regression in an OPM-2 xenograft model of multiple myeloma and is accompanied by a significant decrease in c-Myc and IRF4 gene expression

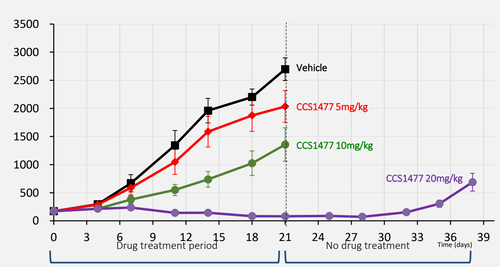


CCS1477 given by oral gavage once daily to OPM-2 bearing athymic nude mice

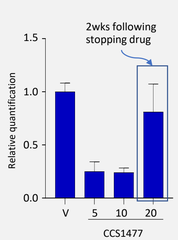


Tumour c-Myc and IRF4 gene expression by qPCR at day 6 of treatment

- Tumour regression after CCS1477 treatment in a xenograft model of AML (MOLM-16): continued growth inhibition following drug withdrawal

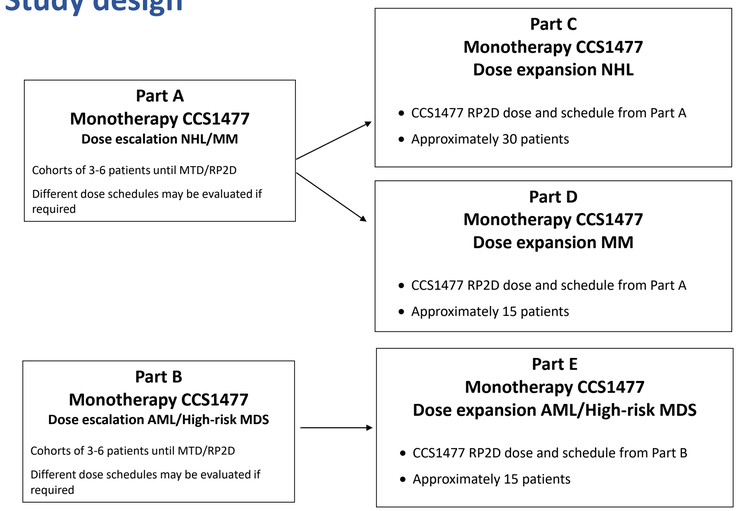


CCS1477 given by oral gavage once daily to MOLM-16 bearing athymic nude mice.



Impact on c-Myc gene expression at d21 of treatment (5 & 10mg/kg) and at d38 following drug withdrawal at 20mg/kg

Study design



Primary objective

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

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 in patients with relapsed or refractory haematological malignancies

Patient criteria

- Aims to enrol 90 patients with confirmed, per standard disease specific diagnostic criteria, relapsed or refractory haematological malignancies (AML, MM and NHL)
- Patients must have received standard therapy

Response assessments

- AML responses will be assessed according to the 2017 ELN recommendation criteria (Döhner *et al* 2017. Blood. 129: 424-447) in bone marrow and blood samples
- Myeloma responses will be evaluated as described in the 2016 IMWG Response Criteria (Kumar *et al* 2016. The Lancet Oncology. 17: e328-346) based on changes in M protein in blood and/or urine, changes in serum free light chains if measurable, and changes on imaging and/or bone marrow if applicable
- In NHL patients, tumour assessments will be done for measurable disease, non-measurable disease, and new lesions on CT (or magnetic resonance imaging [MRI]) and/or combined with visual assessment of [18F]2-fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET) with clinical parameters and bone marrow if applicable, per recent 2017 IWG consensus criteria (RECIL; Younes *et al* 2017. Ann Oncol. 28: 1436-1447). Specific standardised response criteria for selected NHL subtype will be used, where applicable

Exploratory biomarkers

- Blood samples along with bone marrow biopsies and aspirates will be collected for exploratory biomarker analysis to understand mechanisms of response to treatment or disease progression
- This will include the analysis of tumour-specific and circulating biomarkers, such as tumour DNA, mRNA, proteins or metabolites
- In NHL patients, analysis of CBP (and p300) mutations will be undertaken for retrospective correlation with tumour response and to determine if loss of function mutations in the genes for either proteins can be utilised as response predictive biomarkers in future studies

Status

- Dose escalation is continuing in both Part A (MM/NHL) and Part B (AML/MDS)

Conflict of interests: Karen Clegg, Nigel Brooks, Fay Ashby, Neil Pegg and Will West are employees and stockholders in CellCentric. Tomasz Knurowski is consultant to CellCentric. Steven Knapper has financial relationships with Novartis, Tolero, Jazz, Daiichi Sankyo and Pfizer. There are no relationships to disclose for Harriet Walter, Tim Somervaille or Andrew Davies.