A Phase 1 first-in-human trial to evaluate the safety and tolerability of CCT3833, an oral panRAF inhibitor, in patients with advanced solid tumours, including metastatic melanoma

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BACKGROUND

- Over 70,000 patients are diagnosed with malignant melanoma in the USA alone every year[1]
- Treatments targeting the mitogen activated protein kinase (MAPK) signal transduction pathway, including BRAF inhibitors, have improved survival for patients with BRAF mutated melanoma[2] (Figure 1)
- However, utility of these inhibitors is impeded by intrinsic and acquired resistance through diverse mechanisms[3,4]. Patients with a RAS mutated melanoma also represent a current unmet need[5]
- CCT3833/BAL3833 is a potent inhibitor of mutant BRAF, CRAF and SRC family kinases
- Preclinical data using CCT3833/BAL3833 in a range of mutant RAF or RAS human cell lines in vitro and in xenograft models demonstrated activity, including melanoma patient-derived xenografts with intrinsic or acquired resistance to selective BRAF inhibitors
- This ongoing Phase 1, first-in-human trial evaluates the safety and tolerability of CCT3833, also known as BAL3833, in patients with advanced solid tumours, including metastatic melanoma (NCT02437227)

OBJECTIVES

Primary
- MTD and RP2D of CCT3833 (Part A)
- Safety / tolerability profile of CCT3833 (A & B)

Secondary
- PK parameters of CCT3833 (A)
- Radiological/clinical response (A & B)
- Correlation between PK and tolerability (A)

Exploratory
- Measurement of PD biomarkers (A & B)
- Magnitude and duration of effect (PD [A & B])

METHODS

Study schema

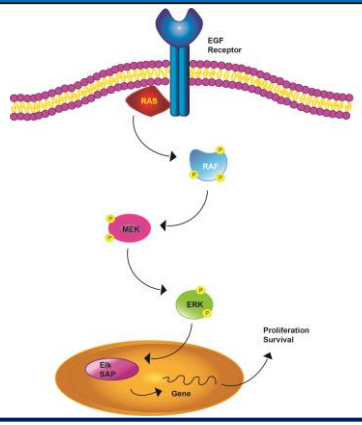
PART A – DOSE ESCALATION PHASE
Patients with advanced solid malignancies including metastatic melanoma receive escalating doses of CCT3833 in cohorts of 3 or 6 to determine the Maximum Tolerated Dose (MTD) and Recommended Phase 2 dose (RP2D)

PART B – EXPANSION PHASE
Patients with locally advanced or metastatic malignant melanoma receive RP2D of CCT3833 in 3 patient cohorts

- **BRAF mutant & BRAF inhibitor treatment naïve**
- **BRAF mutant & progressed on licensed BRAF inhibitor**
- **RAS mutant**

Continue until disease progression or toxicity

Figure 1.



Treatment
- A single dose of CCT3833 will be given between Days -7 and -3 for clinical safety and PK analyses (starting dose 20 mg/day)
- Study drug will then be taken once daily continuously in a 28 day cycle

Assessments
- Patients will be clinically reviewed on a weekly basis (± 1 day) starting from Cycle 1, Day 1 (C1D1)
- Patients are regularly assessed for adverse events, concomitant medications, tumour serum markers, ECOG performance status, physical examination, weight, vital signs, laboratory tests, ECG and echocardiogram
- All patients are radiologically assessed every 8 weeks (2 cycles) using RECIST 1.1 criteria

Pharmacokinetic analyses
- To include; peak plasma concentration (Cmax), time to Cmax (Tmax), elimination half-life ($T_{1/2}$), AUC from zero to last quantifiable concentration (AUC0-t)
- Comparison between single and multi-dose parameters will assess steady-state accumulation
- Correlation between PK parameters and DLT/non-DLT toxicity will be assessed at each dose level

Pharmacodynamics (exploratory)
- Samples analysed for biomarkers to include; total ERK, phospho-ERK, cyclin D1, Ki67, phospho-SRC, total SRC, CD34

Trial Status
- Four cohorts of the dose escalation have completed enrolment without dose-limiting toxicity

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