Target engagement and safety of CB-103, a first-in-class small molecule inhibitor of the NOTCH transcription complex

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Background: CB-103 is an orally active, selective inhibitor of the NOTCH transcription complex, and has shown potent anti-cancer activity in preclinical models.

Method: We designed a dose escalation and expansion phase 1/2a study to assess safety, maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D), preliminary activity, pharmacokinetics and pharmacodynamics of CB-103.

Baseline demographics and treatment history

We analyzed 24 patients. Most common TEAEs regardless of attribution occurring in >10% were transaminase increased (n=8), elevated ALT (n=8), elevated AST (n=7), elevated bilirubin (n=6), lymphopenia (n=5), constipation (n=4), fever (n=3).

Safety

CB-103 was well tolerated in patients with advanced solid tumors at doses leading to a sustained target engagement. MTD of 400mg QD has been declared.

Pharmacokinetics

The elimination half-life is approx. 20 hours and CB-103 is rapidly absorbed after oral administration and reaches Cmax within 1 to 2 hours of dosing. Steady state concentrations are reached within one week of dosing and Cmax is lower at steady state.

Pharmacoconomics

CB-103 is being administered orally once-daily (QD) in 28-days cycles until disease progression or unacceptable toxicity. An adaptive Bayesian logistic regression model (BLRM) is implemented for the dose escalation to guide determination of MTD/RP2D.

Primary endpoint in the dose escalation: number of patients experiencing a DLT during the first 28-days cycle; Secondary endpoints: Incidence of adverse events in each dose group; PK parameters; Tumour response and clinical benefit.

Conclusions

CB-103 is the first drug in clinical testing that can control oncogenic NOTCH pathway activation effectively and safely, in absence of any severe toxicities.

In the dose escalation, 41 patients with advanced metastatic tumors have been treated at doses ranging from 15-400 mg once daily; CB-103 was generally well tolerated.

At doses of 120mg and above, up to 95% down-regulation of NOTCH target genes has been demonstrated, confirming effective and sustained target engagement, in the absence of significant side effects, notably no dose limiting toxicity.

Target engagement coincided with long-term Stable Disease in NOTCH positive ACC patients.

The dose of 800mg QD has been declared as safe dose and further dose escalation is possible; the study is ongoing.