Phase 1 study of CB-103, a novel first-in-class inhibitor of the CSL-NICD gene transcription factor complex in human cancer

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INTRODUCTION

- CB-103 selectively inhibits the CSL-NICD interaction leading to down-regulation of CSL-NICD mediated oncogenic pathway activation downstream of NICD/NFκB signaling.
- The discovery of a novel Mode of Action to control oncogenic activation of NOTCH-related signaling at the level of gene transcription has allowed to overcome dose limiting toxicities (DLT) observed in preclinical models of leukemias and solid tumors with targeted/chemotherapies.

BACKGROUND

- CB-103 has shown potent antitumor activity as single agent and in combination with targeted/chemotherapies in preclinical models of leukemias and solid tumors.
- The aim of this dose escalation/expansion phase 1/2a study is to assess safety, baseline demographics and treatment history.

METHOD

- Adult patients aged 18 years with advanced solid tumors unselected for NOTCH aberrations. Tumor tissue, where available, and liquid biopsies were retrospectively tested for NOTCH pathway alterations; surrogate tissue were evaluated for gene expression of related target genes.
- CB-103 is a breakthrough in targeting Notch: CB-103 is the first drug controlling oncogenic CSL-NICD gene transcription factor (GTF) complex.
- CB-103 is well tolerated in patients with advanced tumors and without the typical toxicities associated with Notch targeting GSIs or mAbs.

RESULTS

- Preliminary efficacy shows promising response and disease control in ACC patients with Notch-activated disease. Preliminary efficacy is expected to be prospectively assessed in dose expansion.
- No signal of cardiotoxicity and no QTc or other ECG abnormalities were observed. There seemed to be a trend of higher incidence in dose groups receiving 250mg or higher doses.
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CASE 1: ACC patient with Notch mutation

Woman (48y) with metastatic ACC, multiple metastases in liver, pleura and large lesion in the lung.

Prior to study participation, patient had received 1 prior line of combination chemotherapy before. Preliminary efficacy was maintained after 3 cycles because of toxicity and further disease progression.

CB-103 (170mg OD) achieved sustained long-term disease control with radiologically confirmed stable disease for nearly 6 months.

- Different responses of metastases suggests heterogeneous disease.
- Liver metastasis in the liver decreased by 67%.
- Plaque metastasis, after initial growth, stopped growing after cycle 4
- Two lung metastases resolved only after modulo and gradual growth.
- Progression of 8 months was due to lesions growth and progression of existing lesions.

Case 2: ACC patient with Notch1 mutation

41-year-old woman with metastatic ACC, multiple metastases in the liver, lung, and bone.

Prior therapy consisted of radiation to the bone; systemic treatment was started 3 months after the first dose due to toxicity.

- During treatment with CB-103, tumor growth significantly slowed down and patient had radiologically confirmed stable disease for 7 months.
- After 7 months on treatment, some of the metastases grew again.

CONCLUSIONS

CB-103 is a breakthrough in targeting Notch: CB-103 is the first drug developing oncogenic CSL-NICD mediated pathway activation safety and potently through a novel mechanism of action targeting gene transcription.

CB-103 is the first drug in clinical testing to effectively control the CSL complex.

CB-103 is well tolerated in patients with advanced tumors and without the typical toxicities associated with Notch targeting GSIs or mAbs.

Preliminary efficacy show strong and long-term disease control in patients with Notch-activated tumors with a good prognosis and rapid disease progression.

The RP2D has been established for advancing clinical development into Phase 2