A first-in-class, first-in-human phase I/IIa trial of CAN04, targeting Interleukin-1 Receptor Accessory Protein (IL1RAP), in patients with solid tumors

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BACKGROUND
Inflammation has been acknowledged as an important part of the development of tumors1. Interleukin-1 (IL-1) is a major T-helper inflammatory cytokine expressed in the epidermal and mammary tissue, and is a crucial body of evidence supporting that IL-1 signaling is involved in cancer progression2. The relevance of targeting IL-1 has recently been highlighted by an exploratory analysis of the CAN04-005 study where patients treated with canakinumab in the highest dose arm showed a significantly reduced incidence of CRC (HR 0.13, p<0.001) and lung cancer specific mortality (HR 0.21, p<0.001)2. Interleukin-1 receptor associated protein (IL1RAP) is a co-receptor of the IL-1 receptor (IL1R) and is required for IL-1 signaling (Fig 1). IL1RAP is expressed in multiple hematological and solid tumor indications. Small cell lung cancer (NSCLC) and pancreatic cancer (PDAC) represent key indications due to high expression of IL1RAP (NSCLC 82% and PDAC 70%). High tumor medical need and evidence supporting that IL-1 signaling is of relevance in these indications, not least as a resistance mechanism to chemotherapy3-5. CAN04 is a fully humanized antibody directed against IL1RAP that in pre-clinical models potently inhibits IL-1a and IL-1b and also triggers antibody dependent cytotoxicity (ADCC) (Fig 2). The current ongoing CAN04/IIa phase I/IIa study (NCT03789746) is designed to assess safety/tolerability of CAN04.

Study design

Fig.1. Preclinical activity supporting inhibition of IL-1a and IL-1b signaling leading to ADCC (left: IL-1b; right: IL-1a) and inhibition of IL1RAP (right).

Table 1: Indication, n (%).

Study design

METHODS
The primary objective was to assess safety (CTCAE v4.03) and tolerability of weekly administration of CAN04 in order to define the Maximum Tolerated Dose (MTD)/Recommended Phase 2 Dose (RP2D). Patients with relapsed or refractory non-small cell lung cancer (NSCLC), recurrent glioblastoma (GBM), or pancreatic ductal adenocarcinoma (PDAC) cancer were included in the initial part of the trial using a 3+3 dose escalation design. Key eligibility criteria were: GOG-C2, normal organ function and no bleeding disorder or local active infection. The CAN04 dosing regimen was started on day 1 at 1 mg/kg and was increased every 3 weeks by a 50% dose increase until MTD was reached. Toxicity profiles were observed for pharmacokinetic evaluation and for assessment of circulatory biomarkers of relevance for the mechanism of action (i.e. IL-6, CRP).

RESULTS

Patient population

Key inclusion criteria:

• Age ≥ 18 years
• Measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) or radiographic imaging (CT/ MRI) scan, no more than 6 weeks prior to inclusion.
• At least 6 weeks since the last dose of chemotherapy, radiation therapy, immunotherapy, or surgery; at least 6 weeks for therapy which is known to be desensitizing therapy; and at least 4 weeks since treatment with biological/immunotherapeutic agents.
• No previous treatment with IL1RAP antibody

Key exclusion criteria:

• Subjects receiving any investigational agents during or just prior to (within 28 days of first dose drug administration) participation in this study.
• Clinical evidence of an active infection requiring hospitalization.
• Subjects with a history of ≥ Grade 2 infusion reaction in any prior trial.
• IL1RAP positive patients or patients with preexisting autoimmune disease.
• Any medical condition that in the opinion of the investigator disqualified the subject for inclusion.

Patients received 3.5 mg/kg, and with 3 (4/16) being re-evaluated as refractory. CAN04 at 1 mg/kg was found to be safe and well-tolerated at this dose, and a phase IIa dose of 3.5 mg/kg was selected for further clinical evaluation.

Safety

Table 2: Safety summary.

Fig. 2. A schematic diagram illustrating the binding of CAN04 to IL1RAP, showing the neutralization of IL1RA signaling and the ADCC activity.

CONCLUSIONS

• CAN04 has generally been well-tolerated, the most common treatment related AE is an infusion related reaction during the first infusion and lasting within a few hours, a side effect often observed with antibody therapy.
• 6 mg/kg is safe and tolerable. MTD has not been reached and the study is now enrolling patients in cohort 5 at 10 mg/kg.
• Biomarker results support stronger engagement of IL-1, including IL-1b and IL-1a.
• A trend to lower tumor burden has been observed in the patients treated with CAN04 at 1 mg/kg or 3.5 mg/kg.
• The most after the recommended phase dose has been established it will be evaluated CAN04 in a dose expansion phase as monotherapy as well as in combination with standard of care therapy in the targeted indications NSCLC (1st and 2nd line) and PDAC (1st line) in separate treatment arms.

REFERENCES

1. National CAN 2017
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