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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 tumors[1]. Interleukin-1 (IL-1) is a major "alarm" inflammatory cytokine upstream in the cytokine cascade and there is a robust body of evidence supporting that IL-1 signaling is involved in cancer progression[2]. The relevance of targeting IL-1 has recently been highlighted by an exploratory analysis of the CANTOS study where patients treated with canakinumab in the highest dose arm had a significantly reduced incidence of lung cancer (HR 0.33, p<0.0001) and lung cancer specific mortality (HR 0.23, p=0.0002)[3]. Interleukin-1 receptor associated protein (IL1RAP) is a co-receptor of the IL-1 receptor (IL1R1) and is required for IL-1 signaling (Fig 1). IL1RAP is expressed in multiple hematological and solid tumor indications. Non-small cell lung cancer (NSCLC) and pancreatic cancer (PDAC) represent key indications due to high expression of IL1RAP (NSCLC 80% and PDAC 70%), high unmet medical need and evidence supporting that IL-1 signaling is of relevance in these indications, not least as a resistance mechanism to chemotherapy[3-14].

CAN04 is a fully humanized antibody directed against IL1RAP that in pre-clinical models potently inhibits IL-1α and IL-1β and also triggers antibody dependent cytotoxicity (ADCC) (Fig 2). The current ongoing CANFOUR phase I/IIa study (**NCT03267316**) is designed to assess safety/tolerability of CAN04.

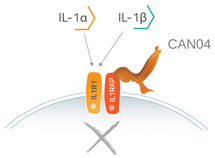


Fig 1. IL1RAP is a co-receptor for the IL-1 receptor and is required for both IL-1α and IL-1β signaling. CAN04 binds to IL1RAP, inhibits signaling and induces ADCC

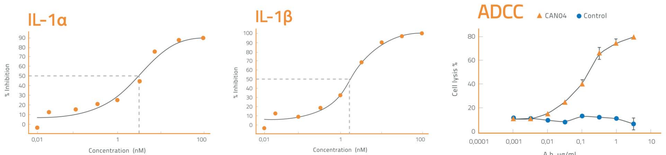
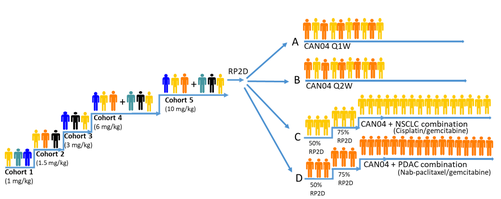


Fig 2. Preclinical data supporting inhibition of IL-1α and IL-1β signaling (assessed in HEK-Blue IL-33/IL-1b-cells) and induction of ADCC (SK-MEL-5 melanoma cells as target cells and NK cells as effector cells)

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, pancreatic ductal adenocarcinoma, breast (TNBC) or colorectal (CRC) cancer were included in the initial part of the trial using a 3+3 dose escalation design. Key eligibility criteria were ECOG ≤1, normal organ function and no bleeding disorder or coagulopathy. Tumor responses were evaluated according to irRC every 8 weeks. Serum samples were obtained for pharmacokinetic evaluation and for assessment of circulatory biomarkers of relevance for the mechanism of action (e. g. IL-6, CRP).

Study design



Patient population

Key inclusion criteria:

- Age ≥ 18 year.
- Measurable disease in accordance to immune related Response Criteria (irRC) by computed tomography (CT) or magnetic resonance imaging (MRI) scan, no more than 6 weeks prior to screening.
- At least 4 weeks since the last dose of chemotherapy, radiation therapy, immunotherapy, or surgery; at least 6 weeks for therapy which is known to have delayed toxicity; at least 4 weeks since treatment with biologic/targeted therapies.
- Eastern Cooperative Oncology Group (ECOG) performance status ≤1.
- Histologically or cytologically confirmed, locally advanced, metastatic NSCLC, PDAC, CRC or TNBC tumor, relapsed or refractory to standard therapy or for which there is no standard therapy. CRC and TNBC are not allowed in second part of the trial.

Key exclusion criteria:

- Subjects receiving any other investigational agents during or just prior to (within 28 days of first study drug administration) participation in this study.
- Clinical evidence of an active second malignancy.
- Subjects with a life expectancy <12 weeks.
- Uncontrolled or significant cardiovascular disease defined as New York Heart Association Classification III, or IV.
- Immunocompromised subject currently receiving systemic therapy.
- Other medical conditions that in the opinion of the investigator disqualify the subject for inclusion.

RESULTS

Patient population

Key characteristics of the patient population are summarized in Table 1. Sixteen subjects were enrolled and there were 9 screen failures across the four initial cohorts (1-6 mg/kg). Patients were heavily pre-treated with a mean of 3.9 prior lines of therapy (range 1-11).

Table 1: Baseline characteristics

Characteristics	Total (n=16)	Characteristics	Total (n=16)
Mean age, years (range)	63 (39-81)	ECOG PS, n (%) 0 1	 12 (75) 4 (25)
Male, n (%)	11 (69)		
Female, n (%)	5 (31)	HB (mmol/L), Median (range)	7.6 (6.0-10.0)
Indication, n (%) • Colorectal cancer • Non-small cell lung cancer • Pancreatic ductal adenocarcinoma • Triple-negative breast cancer	 9 (56) 3 (19) 4 (25) 0	LDH (U/L), Median (range)	217 (162-475)
Lines of prior therapy*, n (%) • ≤2 • 3-5 • ≥6	 5 (31) 9 (56) 2 (12)	ALB (g/L), Median (range)	41 (29-45)

* adjuvant/neo-adjuvant therapy was included as a line of therapy

Safety

CAN04 has generally been well tolerated (Table 2 and 3). The most common AE was infusion related reaction (IRR) (in 44% of all patients) and associated events, with the infusion reaction in the first dose and resolving within a few hours. To reduce the risk of IRR, a priming dose, premedication with antihistamines, paracetamol and corticosteroids and prolonged duration of infusion have been implemented for the first dose. A single patient experienced an infusion reaction on the second dose, otherwise no infusion related reactions have been seen at later doses. A dose limiting toxicity (leucopenia/neutropenia) that was reversible was seen in 1/7 patients at 6 mg/kg. Cohort 5 has recently been initiated at 10 mg/kg. A maximum tolerated dose has not yet been reached.

Table 2: Safety summary

Parameter, n (of total)	1.0 mg/kg (n=3)	1.5 mg/kg (n=3)	3.0 mg/kg (n=3)	6.0 mg/kg (n=7)	Total (n=16)
All causality AEs	58 (3/3)	42 (3/3)	33 (3/3)	52 (7/7)	185 (16/16)
Treatment related AEs	27 (3/3)	6 (2/3)	9 (2/3)	26 (6/7)	68 (13/16)
Treatment related grade 3 AEs	0	0	1 (1/3)	3 (2/7)	4 (3/16)
Treatment related grade 4/5 AEs	0	0	0	0	0
All causality serious AEs	2 (1/3)	2 (1/3)	4 (2/3)	8 (4/7)	16 (8/16)
Treatment related serious AEs	0	0	1 (1/3)	5 (3/7)	6 (4/16)

Table 3: Most common treatment-related AEs
(Any grade incidence ≥ 2 patients). With the exception of one patient, infusion related reactions were only seen at the initial dose. Some AEs (e g nausea, chills, pyrexia) are reported both as symptoms relating to infusion reaction and as separate AE in the table.
Grade 3: One patient with infusion related reaction in cohort 3, one patient with hypokalemia in cohort 4, low white blood cells count and neutropenia, both in the same patient in cohort 4.
There were no treatment-related grade 4/5 AEs

Treatment related AEs	Any toxicity n (of total)	Grade 3 n (of total)
Any	68 (13/16)	4 (3/16)
Nausea	8 (5/16)	0
Fatigue	7 (5/16)	0
Infusion related reaction	7 (7/16)	1 (1/16)
Pyrexia	6 (6/16)	0
Chills	4 (4/16)	0
Vomiting	4 (4/16)	0
Diarrhoea	3 (3/16)	0
Hypotension	2 (2/16)	0
Pruritus	2 (2/16)	0

Biomarkers

An extensive biomarker analysis will be performed at the end of the study. Interim analysis of a select set of parameters of relevance in serum showed a decrease versus baseline in IL-6 in 11 of 14 patients with a strong trend (p=0.06) and a decrease in CRP in 9 of 11 patients (p=0.04) after two doses of CAN04, consistent with the CAN04 mode of action and supporting target engagement.

Clinical efficacy data

Of the patients that had received at least one (1) dose of CAN04, 13 patients had available pre- and post-treatment assessment by imaging at the time of data cut off (Oct 5th). Five (5) patients (38%) had stable disease (SD) by irRC at 8 weeks follow up: NSCLC (1), CRC (3), and PDAC (1). Eight (8) patients had progressive disease (PD). One patient with NSCLC had SD at 6 months.

Pharmacokinetics

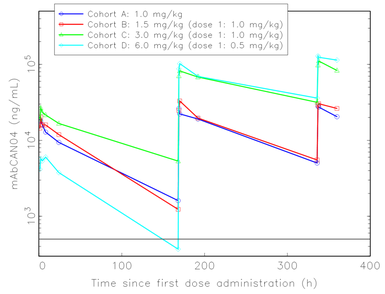


Fig. 3. The serum profiles of CAN04 from an initial priming dose followed by repeated dose administrations indicates higher exposures and slower elimination with increasing doses although the truncated curves does not yet allow for any reliable calculation of PK parameters

CONCLUSIONS

- CAN04 has generally been well tolerated, the most common treatment related AE is an infusion related reaction during the first infusion and resolving 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 target engagement already after two doses of CAN04.
- In a heavily pre-treated patient population, 5 of 13 patients (38%) that had received at least 1 dose of CAN04 had SD by irRC at 8 weeks follow up. One patient with NSCLC had SD for 6 months.
- The next step after the recommended phase II dose has been established will be to evaluate CAN04 in a dose expansion phase as monotherapy as well as in combination with standard of care therapy in the target indications NSCLC (1st and 2nd line) and PDAC (1st line) in separate treatment arms

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