

IL1RAP as a therapeutic target

Göran Forsberg, CEO



Cantargia

- Specialized in antibody therapy/immunology, with initial focus on oncology
- Lead antibody CAN04 (nidanilimab) in clinical development
- Listed on Nasdaq Stockholm, approximately 5000 shareholders
- Based in Lund, Sweden at Medicon Village Science park
- Virtual company, with strong academic and corporate collaborations





IL-1 blockade - recent intriguing clinical data

CANTOS trial (>10000 pat)

- Canakinumab (anti-IL-1β)
- Reduced lung cancer incidence by 67 % and death by 77 %.





Canakinumab NSCLC phase 3 trials

Adjuvant NSCLC

After surgery, no mets, placebo control 1500 patients, recruitment ongoing Completion 2021/22

First line (CANOPY-1)

Untreated locally advanced/metastatic Combination Pembro/Platinum doublet 627 patients, start Dec 2018 Completion 2021/22

Second line metastatic (CANOPY-2)

Previously treated loc adv/metastatic Combination Docetaxel 240 patients, start Dec 2018 Completion 2021



CANTOS additional findings (from Canakinumab)

CANCER decreased risk of death with treatment (high dose)							
Lung cancer	77 %	P=0.0002					
Non-lung cancer	37 %	P=0.06					
Decreased incidence of inflammatory disease (all doses)							
Arthritis	32%	p<0.0001					
Ostheoartritis	28%	P=0.0005					
Gout	53%	p<0.0001					
Cardiovascular	12%	P=0.02					
Biomarker levels (reduction)							
CRP	26-41%	P<0.0001					
IL-6	25-43%	P<0.001					



IL-1 is a "broad-spectrum" cytokine implicated in a number of inflammatory diseases

- IL-1 is released by tissues or the innate immune system to induce inflammation, IL-1 has highly proinflammatory properties and affect a large number of cells
- IL-1 is involved in several autoimmune diseases and is the dominant cytokine in autoinflammatory diseases
- Blocking drugs are on the market (anakinra, rilonacept, canakinumab)

Approved IL-1 inhibiting drugs, IL1RaccP = IL1RAP



Doherty et al., J Leukoc Biol 90(1):37-47 2011



Next step in IL-1 blockade?

- IL-1 blockade can be used to treat disease
- Approved for autoimmune/inflammatory disease
- Promising clinical data for cancer treatment/prevention
- Is IL-1β the optimal target?
- Advantages of receptor targeting?
- Antibodies against IL1RAP.



IL1RAP – IL-1 Receptor Accessory Protein



Annu. Rev. Immunol. 27:519–50



Low expression of IL1RAP on normal cells

- Low reactivity on monocytes and lymphocytes
- No significant tissue reactivity seen on normal tissue (frozen tissues FDA/EMA panel)
- Low-to-moderate expression on monocytes
- The highest expression is found on cancer cells



IL1RAP

- Three different systems signal through IL1RAP
- These systems contribute to various inflammatory diseases
- Can be blocked by antibodies against IL1RAP





The IL-33 and IL-36 signaling pathways - novel targets for several diseases

- IL-33 and IL-36 are barrier-associated cytokines highly expressed in skin and mucosal tissues.
- IL-33 is involved in allergic inflammation and Th2-responses
- IL-36 is heavily upregulated in inflamed skin and mediates *e.g.* certain psoriatic conditions
- No approved product on the market but several projects in preclinical or clinical phase
 - Allergy
 - Asthma
 - Atopic Dermatitis
 - Rhinosinusitis
 - Pustular psoriasis
 - Palmo-Plantar Pustulosis
 - Ulcerative Colitis
 - Crohn's Disease



Unique binding properties of IL-1 and IL-33





Günther et al, Immunity 2017, 47, 510-523



Cantargia pipeline





CAN04 and CAN03 both inhibit IL-1 β and IL-33 signaling but with different properties



CAN03

Less potent, but the binding mode allows full inhibition of IL1 β and IL33 signaling



CANO4 and CANO3 bind different domains of IL1RAP

Measurement of binding affinities to IL1RAP by SPR

Antibody	ka (1/M•s)	kd (1/s)	KD (M)
CAN03	2.26E+05	7.25E-05	3.21E-10
CAN04	4.27E+05	4.72E-05	1.10E-10



Wang et al., 2010, Nature Immunology, 11, 905-912.



Epitope mapping in collaboration with Eric Sundberg, University Maryland

IL1RAP as a target in cancer



The original finding: IL1RAP - a novel target on cancer cells



Leukemic cells from patients

Production of a polyclonal

anti-IL1RAP antibody (KMT1)



Genomics & Bioinformatics



Selective killing of leukemia stem cells using antibodies



IL1RAP identified as upregulated on CML leukemia stem cells

PNA



Isolation of CML leukemia stem Cells based on IL1RAP expression

Isolation and killing of candidate chronic myeloid leukemia stem cells by antibody targeting of IL-1 receptor accessory protein

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Edited by Janet D. Rowley, University of Chicago, Chicago, IL, and approved August 10, 2010 (received for review April 02, 2010)

Chronic myeloid leukemia (CML) is genetically characterized by the identified in this disorder that would allow prospective separa-Philadelphia (Ph) chromosome, formed through a reciprocal translocation between chromosomes 9 and 22 and giving rise to the in the rare CD34+CD38- cell population (13, 14). Identification constitutively active tyrosine kinase P210 BCR/ABL1. Therapeutic of such a marker would not only be instrumental in characterstrategies aiming for a cure of CML will require full eradication of izing CML stem cells but could also be used for the development



IL1RAP expressed in several tumor forms



Size of each indication corresponds to annual deaths in USA



Tumor inflammation – key to cancer progression





Hanahan D & Weinberg RA, The Hallmarks of Cancer, Cell 2000; Hanahan D & Weinberg RA, Hallmarks of Cancer: The Next Generation, Cell 2011

CAN04 phase I clinical data at ESMO (Oct 2018)

1172P

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

BACKGROUND

Inflammation has been acknowledged as an important part of the development of tumors¹, interleukin-1 (L-1) is a major "alarm" inflammatory cynchine upstream in the cynchine cascade and there is a robust body of elvidence supporting that it a signaling is involved in concer progression? The relenance of targeting II: 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 independent of the Concession Mary Memory and the procession of the manuscription of the Concession of expressed in multiple hematological and solid tumor indications. Non-small cell lung cancer (NSCIC) and pancreatic cancer (PDAC) represent key indications due to high expression of ILIBAP (NSCLC 80% and PDAC 70%), high unmet medical need and vidence supporting that II.1 signaling is of relevance in these indic

chemotherapy³⁻¹⁸. CANO4 is a fully humanized antibody directed against IL1RAP that in pre clinical models potently inhibits II 1g and IL-1β and also triggers antibody dependent cytotoxicity (ADCC) [Fig 2]. The current ongoing CANFOUR phase I/Ia study (NCT03267316) is designed



IL-10) IL-18)



METHODS

The primary objective was to assess safety (CTCAE v4.03) and tolerability of weekly administration of CANO4 in order to define the Maximum tolerated Dose/Recommended Phase 2 Dose. Patients with relapsed or refractory non-small cell lung cancer, ncreatic ductal adenocarcinoma, breast (INBC) 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 s1, 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,

Study design



Patient population

Cey inclusion criteria: Age > 18 year. Measurable disease in accordance to imr Measurable diseane is accordance to immune related Response Citeria (RHG) by compared transgraphy (CT or magnetic measure (RMG) scare, moreom than 6 weeks prior to according. At least 4 weeks along the start of the start isometry to the start of the start isometry to the start of the start isometry to the start of t

therapy or for which there is no standard therapy. CRC and INBC are not allowed in sec

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 inclusio

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 ms/sc). Patients were heavily one-treated with a mean of 3.9 prior lines of therapy (range 1-11).



Safety

CANDH has generally been well tolerated (Table 2 and 3). The most common AE was infrainen related reaction (IBBI (in 49% of all patients) and associated events, with the infoldom cancels in the first fixed and movoling within a low hours. To reduce the risk of 188, a prinning dose, prenedication with ambitistamines, paravatanum and environment and patient generative and individe have been implemented for the first dose. A single patient exercise call in individe next term on the second dose, dherwise no individence individe matter have been sense at the second dose, otherwise no individence individence individence in the second dose, otherwise no individence individence in the been sense at the second dose. ns door, otherwise no influsion related reactions have been oven at A dose limiting toxicity (becopenta/neutropenta) that was revenible 1/7 patients at 6 mg/kg. Cohort 5 has recently been initiated at 10 teimum tolerated dose (MID) has not yet been reached.

maller A to maller & down Red Total
 Adv mg/mg
 Adv mg/mg
 Normg/mg
 Normg/mg

Biomarkers

An extensive biomarker analysis will be performed at the end of the study. Interim analysis of a select set of param showed a decrease versus baseline in 1L-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 CANO4, consistent with the CANO4 mode of action and supporting target engagement

Clinical efficacy data

Of the patients that had received at least one (1) dose of CAND4, 13 patients had available pre- and post-trea time of data cut off (Oct 5¹⁴). Five (5) patients (38%) had stable disease (50) 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 50 at 6 months.

Pharmacokinetics



CONCLUSIONS

· CAND4 has generally been well tolerated, the most common treatment related AF 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. MID 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 2 doses of CANO4.

In a heavily pre-treated patient population, 5 of 13 patients (38%) that had received at least 1 dose of CAN04 had SD by inRC at 8 weeks follow up. One patient with NSCLC had 50 for 6 months. The next step 3 fort for 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 (1" and 2

line) and PDAC (1st line) in separate treatment arms

References

Wang et al. Cancer Rep 203 Volgt C et al. Proc Natl Aca

ura at al. Mcl Res 20

Hanahan Diet al. Cell 20



O antargia

- CAN04 has generally been well tolerated
- 6 mg/kg is safe.
- **Biomarker results (IL-6 and CRP)** support target engagement already after two doses of **CAN04**.
- In a heavily pre-treated patient ۲ population, 5 of 13 patients (38%) had SD. One patient with NSCLC had SD for 6 months.
- Recently 10 mg/kg was shown to be safe (Dec 2018)



CAN04 – CANFOUR clinical trial

Phase I/IIa trial - NSCLC and pancreatic cancer

- Norway, Denmark, Netherlands and Belgium
- 22 patients treated, good safety
 - NSCLC, pancreatic cancer, colon cancer, triple negative breast cancer
- Phase IIa: focused on NSCLC and pancreatic cancer (appr 20 centres)
 - Monotherapy
 - Combination with standard therapy
 - NSCLC Cisplatin/Gemcitabine
 - Pancreatic cancer Gemcitabine/nabpaclitaxel



Details on www.clinicaltrials.gov

Receptor blockade vs IL-1ß blockade



CAN04 - immuno-oncology mechanism with antitumor effect



- Antitumor effects in NSCLC PDX models
- CAN04 stimulates immune cells to infiltrate tumor
- (CAN04 not cross reactive with mIL1RAP)



Activity in AML

Blocking proliferation ex vivo



Treating AML (PDX) in vivo





Inflammation and metastasis

- Cancer cells (seeds) needs a good soil to form a metastasis
- The IL-1 system (inflammation) can provide such environment (soil)





A tumor can create its own "seed and soil"



CAN04 attacks several cell types in the tumor



IL-1 and resistance to therapy

Interleukin-1 blockade overcomes erlotinib resistance in head and neck squamous cell carcinoma

Aditya Stanam^{1,2}, Katherine N. Gibson-Corley^{2,5,6}, Laurie Love-Homan², Nnamdi Ihejirika³, Andrean L. Simons^{1,2,4,5,6}

[CANCER RESEARCH 62, 910-916, February 1, 2002]

Autocrine Production of Interleukin 1B Confers Constitutive Nuclear Factor KB Activity and Chemoresistance i A Novel Role for the Interleukin-1 Receptor Axis in **Resistance to Anti-EGFR Therapy**

Alexander Arlt,² Jens Vorndamm,² Susanne Heiner Schäfer

Serum levels of IL-6 and IL-1 β can predict the efficacy of gemcitabine in patients with advanced pancreatic cancer

S Mitsunaga^{*,1,2}, M Ikeda¹, S Shimizu¹, I Ohno¹, J Furuse³, M Inagaki⁴, S Higashi⁵, H Kato⁵, K Terao⁶ and A Ochiai²

Valerio Gelfo ^{1,2,†}, Martina Mazzeschi ^{1,†}, Giada Grilli ¹, Moshit Lindze Chemotherapy-triggered cathepsin B release in Gabriele D'Uva 60, Balázs Győrffy ^{7,8}, Andrea Ardizzoni ¹, Yosef Yarden myeloid-derived suppressor cells activates the Nlrp3 IRAK1 is a therapeutic target that drives breast

cancer Neutrophil-Derived IL-1 β Impairs the Efficacy Zhen Ning Wee of NF-κB Inhibitors against Lung Cancer Puay Leng Lee¹

Dave S.B. Hoon Allyson G. McLoed,¹ Taylor P. Sherrill,² Dong-Sheng Cheng,² Wei Han,² Jamie A. Saxon,¹ Linda A. Gleaves,² Pingsheng Wu,³ Vasiliy V. Polosukhin,² Michael Karin,⁴ Fiona E. Yull,^{1,5} Georgios T. Stathopoulos,^{2,6,7} Constitutive Vassilis Georgoulias,⁸ Rinat Zaynagetdinov,^{2,11,*} and Timothy S. Blackwell^{1,2,5,9,10,11}

Prognosis and Chemoresistance in Pancreatic Ductal Adenocarcinoma 🕫

Daoxiang Zhang¹, Lin Li¹, Hongmei Jiang¹, Brett L. Knolhoff¹, Albert C. Lockhart¹, Andrea Wang-Gillam¹, David G. DeNardo¹, Marianna B. Ruzinova², and Kian-Huat Lim¹ Mélanie Bruchard^{1,2,8}, Grégoire Mignot^{1,2,8}, Valentin Derangère^{1,2}, Fanny Chalmin^{1,2}, Angélique Chevriaux¹⁻³, an^{1,2}, Wilfrid Boireau⁴, Benoit Simon⁴, Bernhard Ryffel⁵, Jean Louis Connat⁶, los⁷, François Martin^{1,2}, Cédric Rébé¹⁻³, Lionel Apetoh^{1-3,8} & François Ghiringhelli^{1-3,8}

ory cytokines defines resistance of inhibitors

, Maria Teresa Rodia^{1,*}, Michela Pucci¹, Massimiliano Dall'Ora¹, ^{5,4}, Rossella Solmi¹, Lee Roth⁵, Moshit Lindzen⁵, Massimiliano a Bertotti⁶, Elisabetta Caramelli¹, Pier-Luigi Lollini¹, Livio Trusolino⁶, Jabriele D'Uva^{7,**}, Mattia Lauriola^{1,2,**}



NSCLC CAN04/Cisplatin combination



	Control	CAN04	Cisplatin	Combination
Animals withdrawn	20 % (Tumor)	0 %	50 % (Toxicity)	20 % (Toxicity)
Tumor reduction	N/A	14%	18%	52 %
Comment	Highest tumor burden	Best safety	Highest toxicity	Superior efficacy and reduced toxicity

Combination CAN04/Cisplatin superior to individual agents

- Reduction in severe toxicity
- Increased efficacy



Cantargia pipeline







- Three different systems signal through IL1RAP
- These systems contribute to various inflammatory diseases
- Can be blocked by antibodies against IL1RAP



Cantargia partnership with Panorama Res Inc (Sunnyvale, CA)



IL1RAP summary

- IL1RAP is a novel target for antibody therapy
- IL-1, IL-33 and IL-36 use IL1RAP for signaling
- IL-1 and IL-33 function through distinct binding
- Generating antibodies blocking various function of these cytokines
- CAN04 is entering phase IIa clinical trials in NSCLC and pancreatic cancer

