Results from a first-in-man, open label, safety and tolerability trial of CAN04 (nidanilimab), a fully humanized monoclonal antibody against the novel antitumor target, IL1RAP, in patients with solid tumors

Prof. Ahmad Awada, MD, PhD
Institut Jules Bordet, Brussels, Belgium

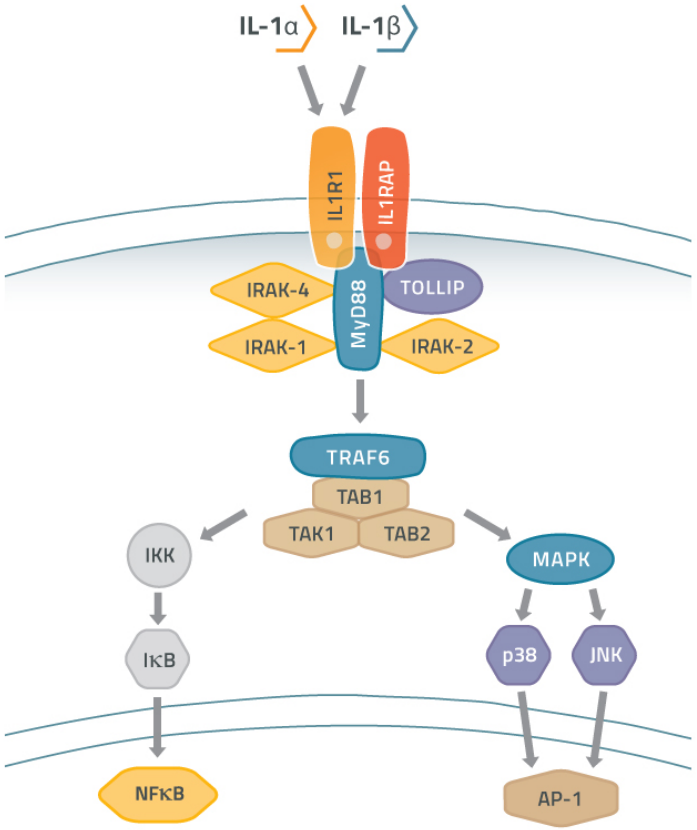
Ferry Eskens, Debbie Robbrecht, Ulrik Niels Lassen, Morten Mau Sørensen, Neeltje Steeghs, Christiane Jungels, Philippe Georges Aftimos, Signe Øien Fretland, Lars Thorsson, Tormod Kyrre Guren

Abstract no: 2504

Slides are the property of the author, permission required for reuse.

IL1RAP – Interleukin-1 Receptor Accessory Protein: A novel target in the IL-1 path

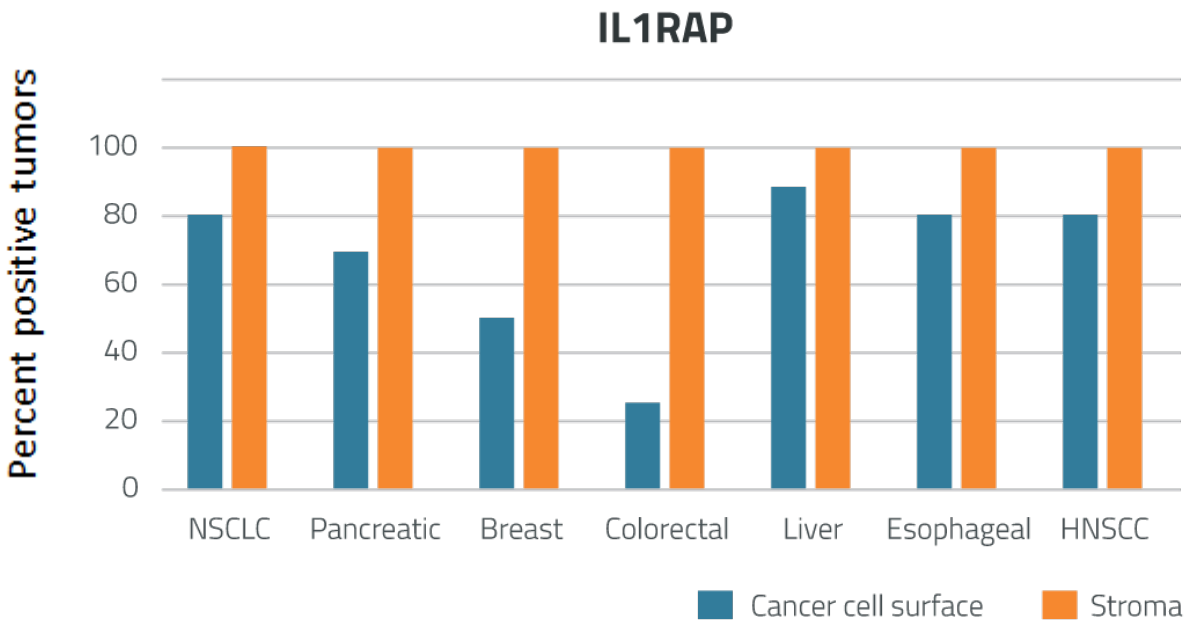
- **Chronic tumor IL-1 signaling is involved in multiple hallmarks of cancer including resistance to therapy, immune evasion and metastases with robust evidence in NSCLC and pancreatic cancer[1-15]**
- **IL1RAP is required in order to activate IL-1 receptor signaling[16]**
- **IL-1β blockade with canakinumab significantly reduced incidence of lung cancer (HR=0.33 for the highest dose cohort) in the CANTOS trial (N=10061)[2]**

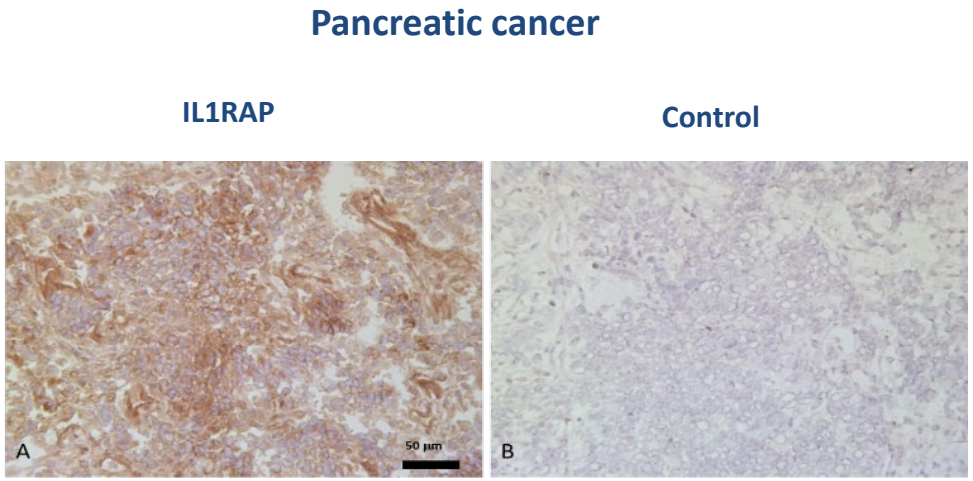


1. Millares et al. Lung Cancer. 2018. 2. Ridker et al. Lancet 2017. 3. Wang et al. Cancer Res 2014. 4. McLoed et al. Cell Report 2016. 5. Tsukamoto H et al. Cancer Res 2018. 6. Nomura et al. Mol Res 2018. 7. Mitsunaga S et al. British Journal of Cancer, 2013. 8. Mace et al. Gut. 2018. 9. Zhuang et al Clin Cancer Res 2016. 10. Schmid et al. Cancer Res 2011. 11. Ling et al Cancer Cell 2012. 12. Maker et al Clin Cancer Res 2011. 13. Melisi et al Mol Cancer Res 2009. 14. Bruchard M et al Nat Med 2013. 15. Zhang et al. Cancer Res 2018. 16.Cunningham et al. J Immunol. 1998

Slides are the property of the author, permission required for reuse.

IL1RAP – expressed in multiple solid malignancies, including NSCLC and PDAC

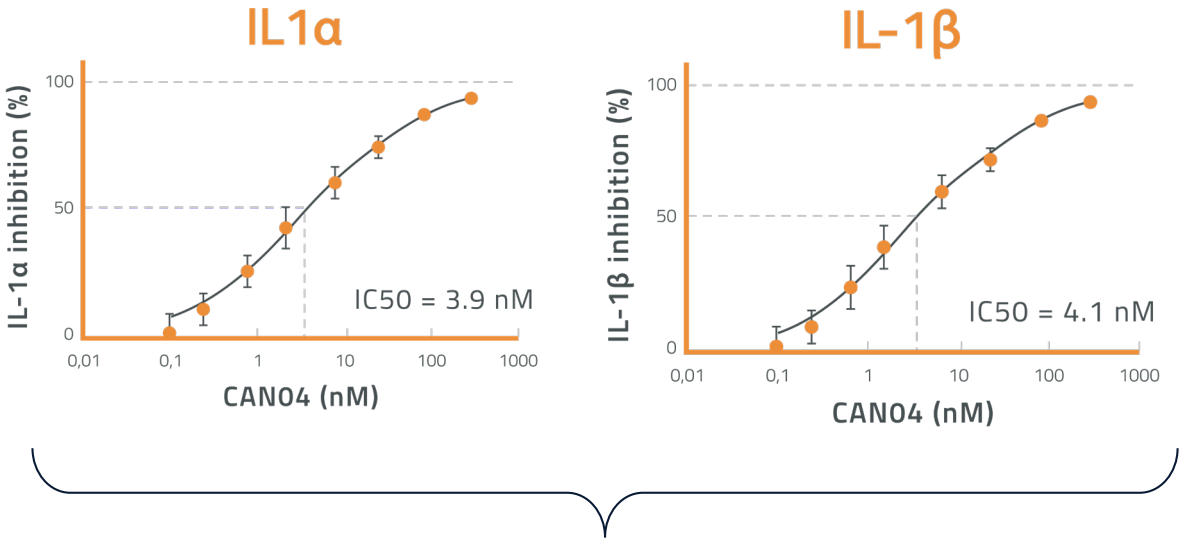


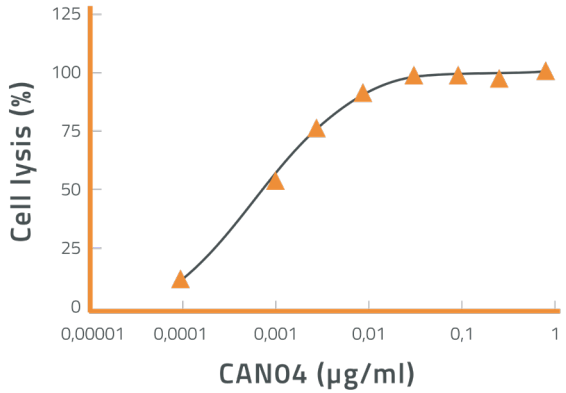


- In majority of cases, homogenous staining - 2+ or higher
- Normal tissue reactivity limited and most pronounced on monocytes and granulocytes

Slides are the property of the author, permission required for reuse.

CAN04 (nidanilimab), a humanized and ADCC-enhanced IgG1 antibody targeting IL1RAP with two modes of action





- **Inhibition of IL-1 signaling: IL-1α and IL-1β (Reporter gene assay)**

- **ADCC enhanced* antibody (ADCC assay against SKMEL-5 cells)**

***CAN04 defucosylated for increased binding to FcγR on e.g. NK cells**

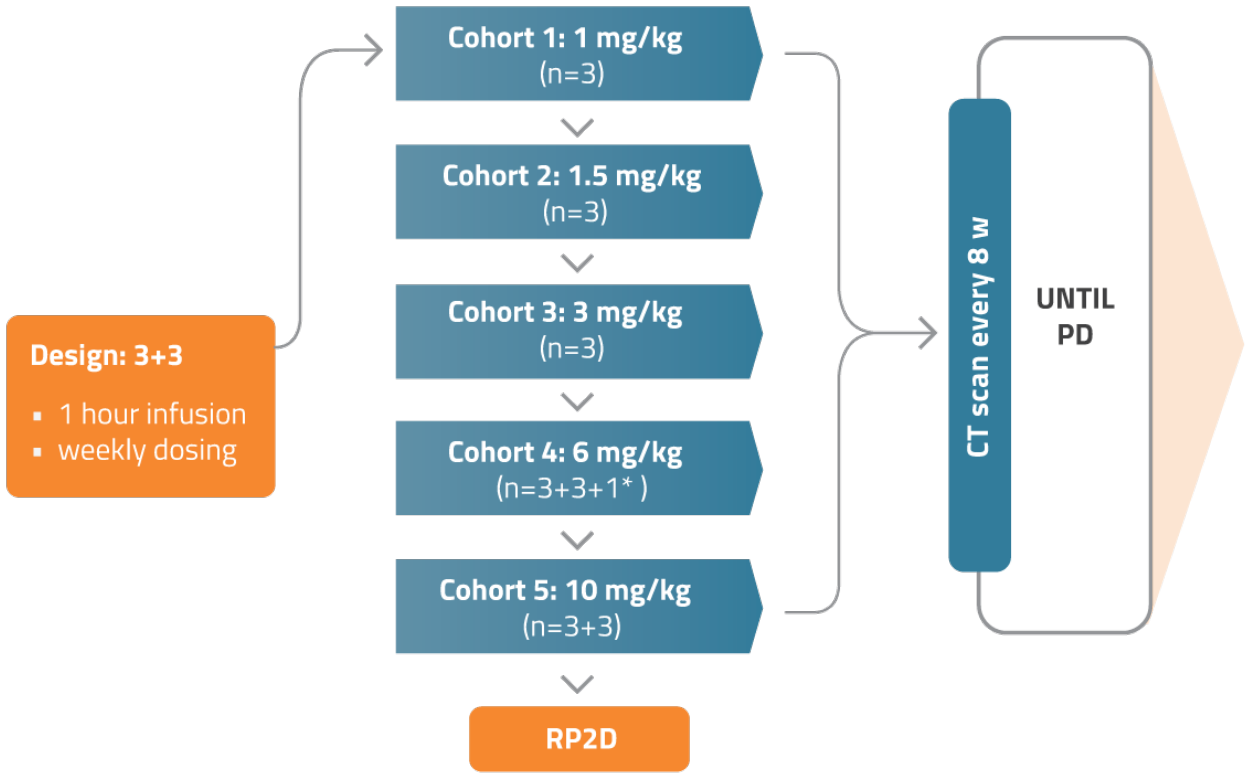
Slides are the property of the author, permission required for reuse.

CANFOUR – Phase I study design

Phase I
n=22

KEY ELIGIBILITY CRITERIA

- NSCLC, PDAC, CRC or TNBC
- Relapsed or refractory to standard therapy or no standard therapy available
- At least 4 weeks since prior systemic therapy, radiation therapy, or surgery
- ECOG PS 0-1



Data cut-off: 28 Mar, 2019
*Replaced

Primary objective:
Safety and Tolerability of CAN04

Primary endpoint:
Incidence of Grade 3 or higher AEs

Key Secondary endpoints:
- **Pharmacokinetics**
- **Biomarkers**
- **ORR (irRC), DoR, PFS, OS**

Slides are the property of the author, permission required for reuse.

Baseline characteristics

Characteristics	Total (n=22)	Characteristics	Total (n=22)
Mean age, years (range)	62 (39-81)	ECOG PS, n (%) 0	15 (68)
		1	7 (32)
Male, n (%)	14 (64)		
Female, n (%)	8 (36)		
		Laboratory values:	
Indication, n (%)		Hb (mmol/L), median (range)	7.60 (6.0-10.0)
▪ Colorectal cancer	12 (55)	LDH (U/L), median (range)	238 (162-475)
▪ Non-small cell lung cancer	4 (18)	ALP (U/L), median (range)	111 (67-468)
▪ Pancreatic ductal adenocarcinoma	6 (27)	AST (U/L), median (range)	27 (13-66)
▪ Triple-negative breast cancer	0	GGT (U/L), median (range)	86 (14-464)
		Bilirubin (µmol/L), median (range)	6.8 (4.0-17.1)
Prior lines of therapy*, n (%)		Albumin (g/L), median (range)	41 (29-45)
▪ ≤2	9 (41)	Lymphocytes (10^9), median (range)	1.19 (0.66-2.30)
▪ 3-5	12 (55)	WBC (10^9), median (range)	6.28 (4.10-13.30)
▪ ≥6	1 (5)	CRP (mg/L), median (range)	14 (1.4-109)

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

Slides are the property of the author, permission required for reuse.

Treatment related AEs

- There were no treatment-related grade 4/5 AEs.
- A total of 55 AEs potentially related to CAN04.
- The most frequent AE was infusion related reactions (IRR), with 10 AEs in 9 patients. The majority of IRRs occurred at the first dose and resolved within a few hours.
- Actions taken only for the first dose to reduce the risk of IRR:
  - Premedication with paracetamol, antihistamines and corticosteroids
  - Priming dose (0.5 – 1.0 mg/kg)
  - Prolonged infusion time (1→2 hrs)
- One reversible dose limiting toxicity (leukopenia/neutropenia) at 6 mg/kg

Treatment related AEs	Any toxicity		Grade 3	
	Events (n)	Frequency	Events (n)	Frequency
Any	55	(16/22)	4	(3/22)
Infusion related reaction	10	(9/22)	1	(1/22)
Fatigue	14	(7/22)	0	-
Constipation	8	(6/22)	0	-
Diarrhoea	8	(6/22)	0	-
Decreased appetite	7	(5/22)	0	-
Nausea	9	(5/22)	0	-
Vomiting	7	(5/22)	0	-
Abdominal pain, upper	10	(4/22)	0	-
Pruritus	5	(4/22)	0	-
Alkaline phosphatase increase	4	(3/22)	0	-
Influenza like illness	3	(3/22)	0	-
Body weight decrease	3	(3/22)	0	-
Cough	3	(3/22)	0	-

Grade 3:

- One patient with infusion related reaction (3 mg/kg)
- One patient with hypokalemia (6 mg/kg)
- One patient (6 mg/kg) with leukopenia and neutropenia

Slides are the property of the author, permission required for reuse.

Serious Adverse Events

- Twenty SAEs reported in 9 subjects
- Five SAEs were considered related to treatment:
  - Leukopenia (grade 3, DLT)
  - Infusion related reactions;
    - grade 3 (1)
    - grade 2 (2)
  - Embolism (grade 2)

	1 mg/kg		1.5 mg/kg		3 mg/kg		6 mg/kg		10 mg/kg		Total	
Treatment related AEs	Events (n)	Frequency	Events (n)	Frequency	Events (n)	Frequency	Events (n)	Frequency	Events (n)	Frequency	Events (n)	Frequency
Any	2	1/3	2	1/3	5	2/3	7	4/7	4	1/6	20	9/22
Infections	2	1/3			1	1/3	1	1/7			4	3/22
Infusion related reactions (IRR)					1*	1/3	2*	2/7			3	3/22
Hepatobiliary disorders			1	1/3	1	1/3	1	1/7			3	2/22
Gastrointestinal disorders			1	1/3					2	1/6	3	2/22
Leucopenia							1*	1/7			1	1/22
Disseminated intravascular coagulation									1	1/6	1	1/22
Thrombocytopenia									1	1/6	1	1/22
Radicular pain							1	1/7			1	1/22
Myocardial infarction					1	1/3					1	1/22
Pulmonary oedema					1	1/3					1	1/22
Peripheral venous emboli							1*	1/7			1	1/22

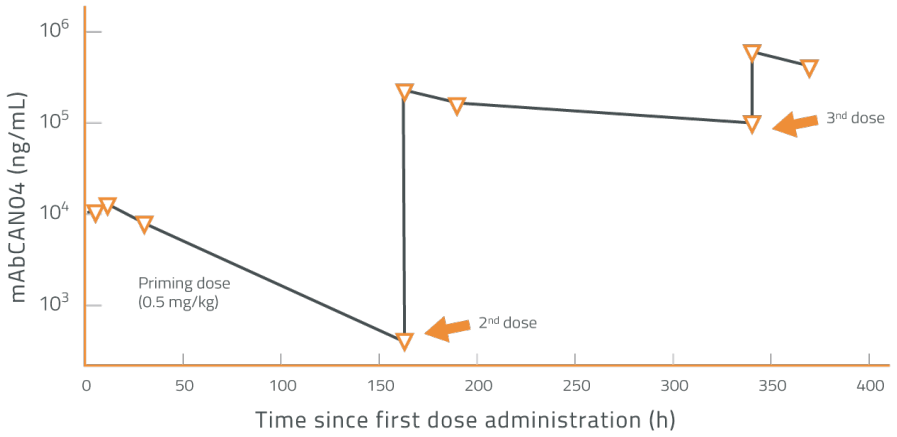
*Treatment related SAE

Slides are the property of the author, permission required for reuse.

Pharmacokinetics:

- There was a linear increase of AUC and C_{max} (1-10 mg/kg)
- Initial data suggests $t_{½}$ being >2 weeks

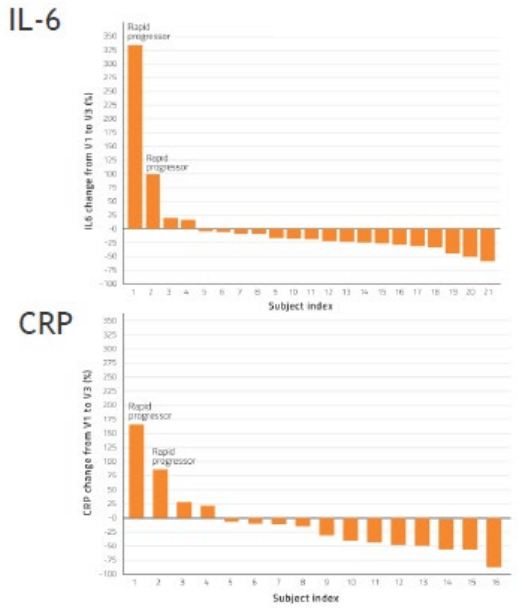
Mean serum concentration of CAN04 at 10 mg/kg (N=6)



Biomarkers (serum):

(taken pre-dose at first and third dose)

- Decrease in IL-6 in 17/21 subjects (median -18.4%, p=0.04)
- Trend in CRP decrease in 13/17 subjects (median -21.6%, p=0.08)
- Decreased levels of IL-6 and CRP consistent with the CAN04 MoA – supporting target engagement



- Rapid increase in IL-6 and CRP in 2 PDAC patients
- Correlated with rapid symptomatic progression and death within 3 weeks

Slides are the property of the author, permission required for reuse.

Clinical efficacy data

- **Twenty-one (21) patients had available pre- and post-treatment assessment by imaging and the following proportion of patients had stable disease (SD) by irRC as best overall response at 2 months :**

Indication		CR/PR	SD	PD
NSCLC	N=4	0	3	1
PDAC	N=6	0	2	4
CRC	N=11	0	4	7
Total	**N=21**	**0**	**9**	**12**

- **One patient with NSCLC had PFS* for 7 months (4 prior lines of therapy, including nivolumab for 8 months)**
- **One patient with PDAC had PFS for 5 months (Prior line of therapy – FOLFIRINOX 7 months)**

***patient received radiation to reduce pain but did not have radiological signs of progression**

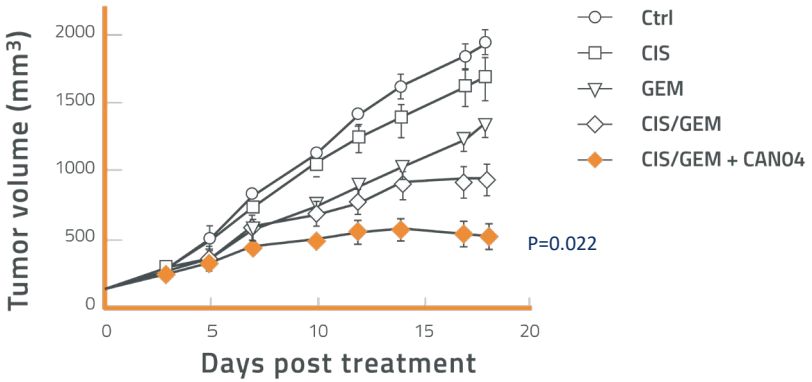
Slides are the property of the author, permission required for reuse.

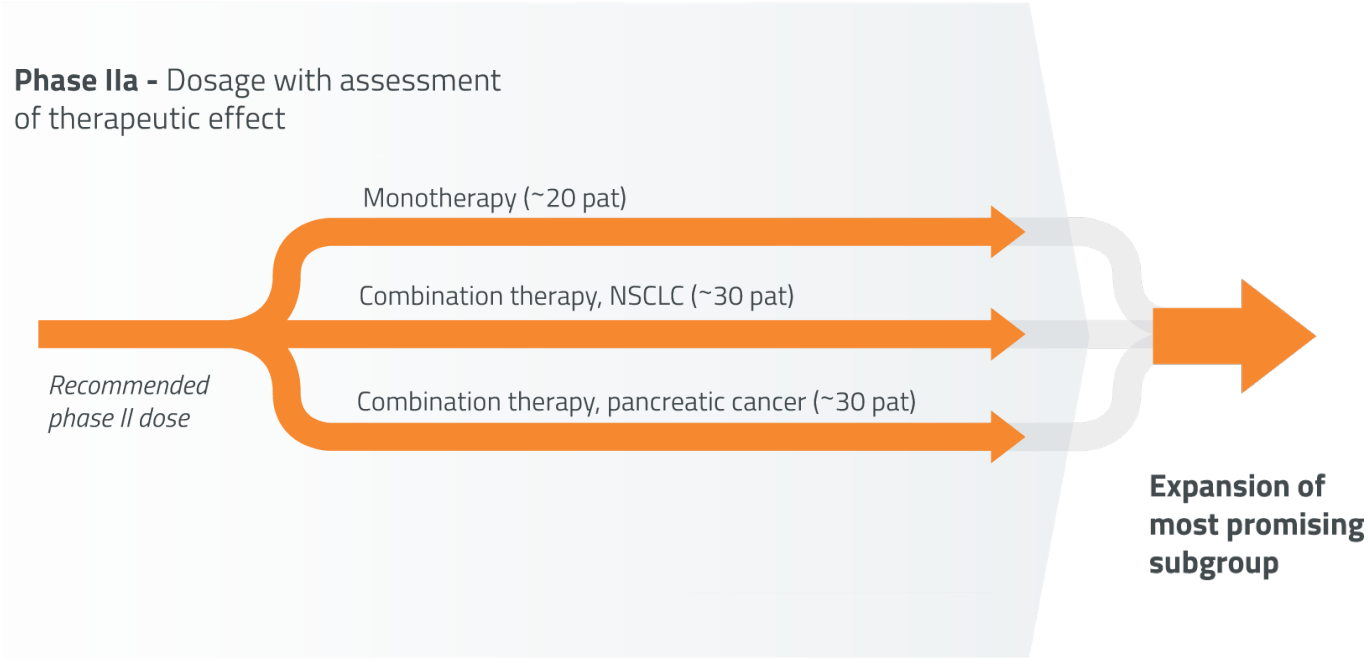
CANFOUR – Phase IIa

Phase IIa: (appr 20 centers)

- FPI Jan 2019
- Monotherapy
- Combination with chemotherapy
  - NSCLC cisplatin/gemcitabine
  - Pancreatic cancer gemcitabine/nab-paclitaxel
- Tumor biopsies pre- and during treatment
- Extensive biomarker analysis

Tumor growth





Preclinical data in NSCLC PDX model show synergistic effects between CAN04 and cisplatin/gemcitabine

- Increased antitumor activity
- Reduced toxicity

Slides are the property of the author, permission required for reuse.

Conclusions (1)

- **CAN04 (nidanilimab) – well tolerated with an IRR as the most common treatment related AE**

- **10 mg/kg selected to be the recommended phase II dose (RP2D) based on:**
  1. **Found to be safe and tolerable with no MTD identified**
  2. **PK properties with exposures above levels showing efficacy in pre-clinical models**
  3. **Early biomarker signals (IL-6; CRP) support target engagement already after 2 doses of CAN04**

Slides are the property of the author, permission required for reuse.

Conclusions (2)

- 9/21 patients (43%) had SD by irRC as best overall response
- One patient with NSCLC and one with PDAC had PFS for 7 and 5 months respectively.
- PhIIa (ongoing)
  - Monotherapy in NSCLC and PDAC
  - Combination with cisplatin/gemcitabine in NSCLC
  - Combination with nab-paclitaxel/gemcitabine in PDAC

Slides are the property of the author, permission required for reuse.

Acknowledgement

- All patients and their families
- Investigators and sites:
  - Institut Jules Bordet, Brussels, Belgium
    PI: Christiane Jungels, MD
  - Rigshospitalet Copenhagen, Denmark
    PI: Morten Mau-Sørensen, MD, PhD
  - Oslo University Hospital, Oslo, Norway
    PI: Tormod Kyrre Guren, MD, PhD
  - Erasmus Medical Centre, Rotterdam, The Netherlands
    PI: Ferry Eskens, MD, PhD
  - Netherlands Cancer Institute, Amsterdam, The Netherlands
    PI: Neeltje Steeghs, MD, PhD
- Cantargia AB: *Lars Thorsson, Christer Svedman, Susanne Magnusson*
- Study sponsored by Cantargia AB
- Study conducted by SMS-oncology BV

Slides are the property of the author, permission required for reuse.