EDISON

Cantargia

Initiation of coverage

Tackling tumour promoting inflammation

Pharma & biotech

With its IL1-RAP inhibitor technology, Cantargia tackles tumour-promoting inflammation by targeting IL-1 signalling pathway. Moreover, lead asset CAN04, a fully humanized antibody, causes cancer cell death by an established mechanism ADCC. This dual mechanism action and the potential ability to harness the immunes system to fight cancer makes Cantargia an interesting immunoncology play, in our view. Recent Novartis data publication from its six-year Phase III cardiovascular outcomes study in heart attack patients with canakinumab (direct IL-1 β inhibitor) provides some validation to Cantargia's plans, as it unexpectedly showed that the drug reduced lung cancer incidence and mortality. Our valuation of Cantargia is SEK1.64bn or SEK24.8/share.

Year end	Revenue (SEKm)	PBT* (SEKm)	EPS* (SEK)	DPS (SEK)	P/E (x)	Yield (%)
12/16	0.0	(47.5)	(2.7)	0.0	N/A	N/A
12/17	0.0	(60.3)	(1.9)	0.0	N/A	N/A
12/18e	0.0	(80.2)	(1.4)	0.0	N/A	N/A
12/19e	0.0	(93.5)	(1.4)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding amortisation of acquired intangibles and exceptional items.

Data from the first part of Phase I/II imminent

CAN04 is a fully humanised, dual-action IL1RAP IgG1 antibody with ADCC effect. Cantargia is running a Phase I/IIa trial, known as CANFOUR, testing CAN04 in solid tumour indications, primarily focusing on NSCLC and pancreatic cancer. The CANFOUR trial is divided into two parts. The Phase I part of the study will establish the safety profile of the drug and the dose for the Phase IIa part of the trial. Results from the Phase I part of the study are expected in mid-2018. The second part of the trial (Phase IIa) will look at the efficacy of CAN04 in NSCLC and pancreatic cancer, both as a monotherapy and in combination with standard treatments. Cantargia's second lead asset, CANxx, is in preclinical development for autoimmune diseases.

Differentiated immunoncology play

In our view, Cantargia's investment case has several unique features. The lead asset has a dual mechanism of action via an established ADCC and a novel oncology approach with its IL-1 pathway signalling inhibition. Recently, a large Phase III from Novartis conducted in an unrelated cardiovascular area has surprised with positive findings that directly translate to CAN04 in the oncology setting. With that data in hand, Novartis is now running or planning three Phase III trials in lung cancer. Cantargia has four patent families, all having claims relating to IL1RAP target and antibodies, which further adds the competitive edge.

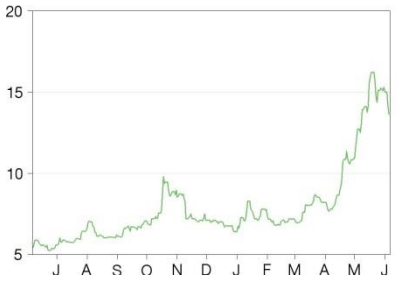
Valuation: SEK1.64bn or SEK24.8/share

We value Cantargia at SEK1.64bn or SEK24.8/share based on an rNPV using a 12.5% discount rate, including SEK200m net cash estimated at end Q218. We include CAN04 in the two lead indications – NSCLC and pancreatic cancer. CAN04 for other indications and second lead asset CANxx are still in preclinical stages and we will revisit the potential once these projects progress. Near-term triggers involve results from the Phase I part of the CANFOUR trial and a listing change in H218.

7 June 2018

Price	**SEK13.65**
Market cap	**SEK903m**
	US$:SEK8.60
Estimated net cash (SEKm) at end Q218	200.0
Shares in issue	66.2m
Free float	90%
Code	CANT
Primary exchange	Nasdaq Stockholm First North
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	7.5	95.0	138.3
Rel (local)	7.4	91.0	144.0
52-week high/low	SEK16.20	SEK5.24	

Business description

Cantargia is a clinical stage biotechnology company based in Sweden, established in 2009 and listed on Nasdaq Stockholm First North in 2015. It is developing two antibodies against IL1RAP, CAN04 and CANxx. CAN04 is being studied in a Phase I/II CANFOUR in solid tumours focusing on NSCLC and pancreatic cancer.

Next events

Results from the Phase I part of the CANFOUR trial	Mid-2018
Up-listing to NASDAQ Stockholm main market	H218
Preclinical CAN04 data	2018

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Edison profile page

Cantargia is a research client of Edison Investment Research Limited

Investment summary

Company description: Differentiated immunoncology play

Cantargia is a clinical-stage biotechnology company based in Lund, Sweden, established in 2009 and listed on Nasdaq Stockholm First North in 2015. The technology is based on research conducted by the company's founders at the Lund University that identified IL1RAP, a molecule essential for signalling through the interleukin-1 receptor (IL-1R), as a target and has since built a patent portfolio around this. Cantargia is developing two antibodies against IL1RAP: CAN04 and CANxx. CAN04 is being studied in a Phase I/II CANFOUR trial in solid tumours with the focus on NSCLC and pancreatic cancer. It has a dual mechanism of action and blocks the IL-1 signalling pathway by shutting down the tumour-promoting inflammation and inducing ADCC. CANxx is in pre-clinical testing for autoimmune and inflammatory diseases. Cantargia successfully raised SEK232m in December 2017, which should be sufficient until 2020. The company is preparing to apply for a listing on the Nasdaq Stockholm Main Market, which is expected in H218.

Valuation: SEK1.64bn or SEK24.8/share

Our Cantargia valuation is SEK1.64bn or SEK24.8/share, which includes CAN04 in the two lead indications – NSCLC and pancreatic cancer. Cantargia also has substantial amount of preclinical data supporting CAN04 use in leukaemia. In addition, the company is diversifying its R&D pipeline and is developing CANxx for the treatment of inflammatory conditions, which is also in preclinical development. We will revisit these preclinical projects once they mature. We have derived our rNPVs based on the assumptions discussed below, such as target population, pricing, R&D costs, patent expiry dates/market exclusivity and calculated peak sales. Cantargia's strategy is to finalise the Phase I/IIa study and then either carry on with the development or establish a partnership. We assume that in the case of positive Phase I/IIa data, the company will be able to out-license CAN04 after the Phase I/IIa.

Financials: Funded until 2020

Cantargia reported an operating loss of SEK60.0m in 2017, compared to SEK47.6m in 2016. Expenses associated with R&D projects were SEK44.8m versus SEK35.5m a year ago. Our total operating expense estimates for 2018 and 2019 grow to SEK80.9m and SEK93.8m, respectively, mainly reflecting increasing R&D costs as Cantargia moves from the Phase I part of the trial to Phase IIa and advances its preclinical projects. Cantargia had cash and short-term investments of SEK270.0m at the end of 2017 compared to SEK34.8m at the beginning of 2017. According to Cantargia, the operations are now financed until 2020, which is in line with our model.

Sensitivities: Typical biotech risks apply

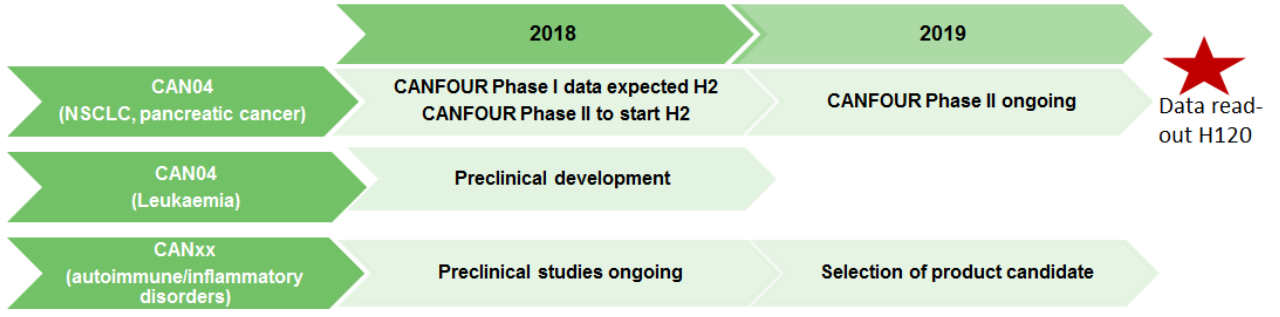
Cantargia is subject to typical biotech company development risks, including the unpredictable outcome of trials, regulatory decisions, success of competitors, financing and commercial risks. The near-term R&D sensitivities are tied to the lead asset CAN04, which is the only clinical-stage product. Any setbacks with this asset will influence Cantargia's share price significantly. Our model assumes that products will be out-licensed; therefore, our valuation is sensitive to potential licensing timing and actual deal terms. Cantargia is mainly an early-stage drug developer, therefore in the foreseeable future the value creation will depend on successful R&D progress and any potential partnering activities. However, as CANxx reaches clinical development, this risk will be diversified.

Cancer immunotherapy with anti-IL-1 and ADCC effect

Cantargia's technology has been built on research at Lund University, which showed that IL1RAP is highly expressed on leukaemia stem cells but rarely seen in healthy tissues. This formed the basis for Cantargia's original focus on leukaemia. The company is developing humanised, monoclonal antibody (CAN04) against IL1RAP, expecting to induce ADCC in the cancer cells. While conducting preclinical studies Cantargia showed that in addition to this direct action on tumour cells, its drug candidate also affects the tumour microenvironment by inhibiting the IL1RAP signalling pathway caused by IL-1. Studies also showed that IL1RAP is expressed in other tumours, for example in about 80% of NSCLC and 70% in pancreatic cancer. Furthermore, other third party research groups also identified IL-1's role in the progression of cancer. As a result, Cantargia shifted its focus on solid tumours (Exhibit 1) that potentially represent a higher unmet need and could better exploit the dual mechanism of action of the company's technology: the anti-inflammatory effect inside the tumours and direct cell killing.

CAN04 is being tested in the first part (Phase I, started in Q317 with the first part of the study to report data shortly) of the planned Phase I/IIa study CANFOUR in four solid tumour indications: NSCLC, pancreatic cancer, breast cancer and colorectal cancer. The second part of the study (Phase IIa) will focus on NSCLC and pancreatic cancer, and CAN04 will be evaluated both individually and in combination with standard treatments in each indication. NSCLC and pancreatic cancer are the primary indications, although Cantargia is also working on other indications and assets in earlier stages, namely, CAN04 for other solid tumours or leukaemia and CANxx for various inflammatory conditions. Given that Cantargia's product blocks the IL-1 signalling, chronic inflammatory conditions are a natural further direction to explore. CANxx is also an antibody against IL1RAP and has the potential to treat autoimmune and inflammatory diseases because of the involvement of IL-1/IL-33/IL-36 signalling in these diseases. Cantargia is evaluating which other indications it will prioritize and carry into the clinic.

Exhibit 1: Cantargia's R&D pipeline



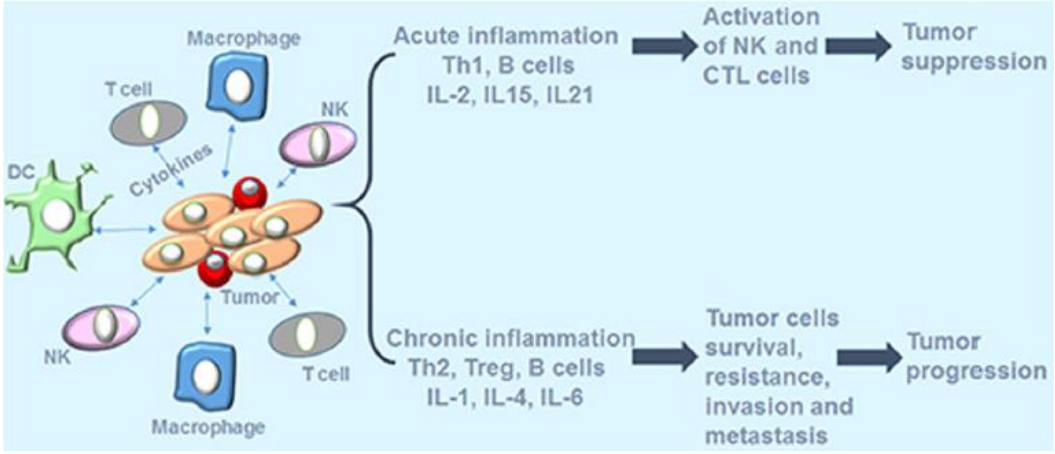
Source: Cantargia, Edison Investment Research

In terms of R&D and commercial strategy, Cantargia is a classic specialist drug developer and aims to accumulate proof-of-concept data and then will seek collaboration agreements or out-licensing deal to carry the products through late-stage development. To this end, Cantargia's technology and R&D strategy received a boost, in our view, when in September 2017 Novartis reported six-year data from its Phase III trial Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS), which explored canakinumab's (an IL-1β inhibitor) efficacy in cardiovascular outcomes study in patients post-myocardial infarction. Surprisingly, Novartis reported that canakinumab significantly reduced the lung cancer incidence and mortality rate (described below). Furthermore, according to *in vivo* data from recent publications in Nature, cytokine release syndrome, which became one of the most concerning and potentially fatal complications of the CAR T cell therapies, can be abated by IL-1 blockade opening interesting possibility for CAN4 to be used in combinations with these novel therapies in the future.

At the intersection of inflammation and oncology

The fact that the immune system reacts to malignant lesions is long established.[1] Historically, such an immune response was thought to reflect the immune system's attempt to clear the malignant tissue. The advent of checkpoint inhibitors put the notion of taking the 'immune system brakes' away from the cancer in the spotlight. However, inflammation can be tumour destructive as well as tumour promoting. The latter came to light around two decades ago; since then, certain inflammatory cells and mediators in the tumour microenvironment have been identified as 'helpers' of tumour growth. These mechanisms are not well understood, but the research field is growing and some have been identified including transcription factors (NF-κB and STAT), inflammatory mediators (including IL-1 and TNF-α) and tumour-associated macrophages (Exhibit 2). With its CAN04 antibody, Cantargia tackles tumour-promoting inflammation by targeting the IL-1 signalling pathway in the tumour microenvironment.

Exhibit 2: Tumour promoting and tumour suppressing factors



Source: S Setrerrahmane and H Xu

Large body of research supporting inhibition of IL-1 signalling in solid tumours treatment

Increasing the understanding of inflammation in malignant process now includes findings that cytokines are not only produced by the immune cells, but also cancer itself could produce certain cytokines and the associated receptors to escape from the immune response.[2] Cytokines represent potentially promising class of targets in cancer management and the most explored molecules with carcinogenic characteristics are IL-1, IL-4 and IL-6.[2]

IL-1 is a proinflammatory cytokine that exists in two forms: IL-1α and IL-1β. IL-1α is found in epithelial cells and the membranes of immune cells and is not secreted. IL-1β is secreted by immune cells such as monocytes and macrophages in response to infection or inflammatory signals.

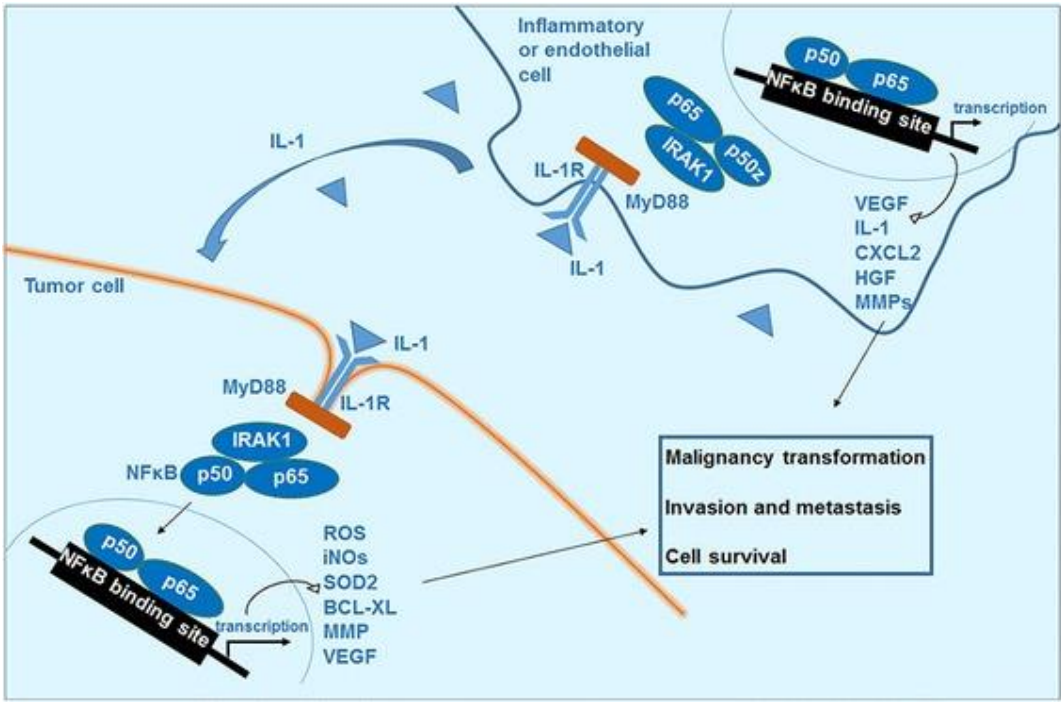
IL-1α and IL-1β are both ligands for IL-1R and through this receptor initiate the same signalling processes inside the cell. There are several types of IL-1R, but IL-1R1 is the most important for IL-1α and IL-1β signalling. In non-tumour tissues and immune cells, IL-1 binds to IL-1R. This results in the activation of NFκB, which in turn activates the expression of certain genes and proteins that are involved in inflammation, proliferation and survival. In the tumour microenvironment, IL-1 is found in

[1] D Hanahan and R Weinberg. Hallmarks of Cancer: The Next Generation. *Cell (2011) 144*

[2] S Setrerrahmane and H Xu. Tumor-related interleukins: old validated targets for new anti-cancer drug development. *Molecular Cancer (2017) 16:153*

high concentrations (the level of expression of the two forms of IL-1 can differ in different forms of cancer). It binds to IL-1R on tumour cells and immune cells and the same downstream signalling occurs, but in this environment the genes and proteins resulting from NFκB activation promote tumour growth and metastasis (Exhibit 3).

Exhibit 3: IL-1 signalling pathway in solid tumours



Source: NCBI

The link between IL-1 and tumour growth and metastasis was discovered in 1990 when a research group in Italy found that IL-1β increased the level of experimental lung metastases in mice.[3] Several studies have pointed to angiogenesis (blood vessel formation) as the mechanism through which IL-1 is tumour promoting, via induction of certain pro-angiogenic factors via NF-κB activation, eg. VEGF.[4,5] Angiogenesis is a key mechanism in tumour progression because tumours require a blood supply to grow and metastasise. Other tumour-promoting mechanisms could be COX2-HIFα pathway activation[6] and induction of the IL-17 pathway.[7]

Some research groups have studied IL-1 inhibition as a potential strategy for cancer treatment. Most of this research is still pre-clinical. A 2016 study found that anakinra, a recombinant form of IL-1R antagonist (marketed as Kineret for several immune disorders), inhibits tumour growth via inhibition of IL-1R and subsequent inhibition of NF-κB in human pancreatic ductal adenocarcinoma cell lines and mouse models.[8] Zhang et al. (2017) discovered that inhibition of IRAK4; a target

[3] Giavazzi et al. Interleukin 1-induced Augmentation of Experimental Metastases from a Human Melanoma in Nude Mice. *Cancer Res (1990) (50) (15) 4771-4775*

[4] Voronov et al. IL-1 is required for tumor invasiveness and angiogenesis. *Proceedings of the National Academy of Sciences (2003) 100 (5) 2645-2650*

[5] Shchors et al. The Myc-dependent angiogenic switch in tumors is mediated by interleukin 1β. *Genes & Development 20.18 (2006): 2527–2538*

[6] Wang et al. IL-1β-Mediated Repression of microRNA-101 Is Crucial for Inflammation-Promoted Lung Tumorigenesis. *Cancer Res (2014) (74) (17) 4720-4730*

[7] Coffelt et al. IL17-producing γδ T cells and neutrophils conspire to promote breast cancer metastasis. *Nature 522.7556 (2015): 345–348.*

[8] Zhuang et al. IL1 Receptor Antagonist Inhibits Pancreatic Cancer Growth by Abrogating NF-κB Activation. *Clin Cancer Res (2016) (22) (6) 1432-1444*

downstream from IL-1R, can also inhibit NF-κB activity in pancreatic ductal adenocarcinoma and thus highlighting the potential for IRAK4 as a target for cancer treatment[9]. Furthermore, combination treatment with gemcitabine was more effective than monotherapy with either rhIL-1R antagonist or gemcitabine. This supports the case for IL-1 pathway inhibitors in combination with standard treatments for solid tumours.

First Phase III trials exploring IL-1 pathway inhibition in cancer

XBiotech, a US biotech company, delivered first Phase III-stage data with Xilonix, an antibody blocking IL-1α in colorectal cancer. The company ran two Phase III trials in Europe and the US. In 2016 the results from the European study (n=333) showed that Xilonix could reverse symptoms in patients with metastatic or unresectable colorectal cancer such as muscle loss, fatigue, appetite loss and pain. 33% of patients in the Xilonix group and 19% patients in the placebo group achieved the primary endpoint, which was statistically significant difference (p=0.0045).

The larger US study was initiated in 2013 and aimed to recruit more than 600 symptomatic colorectal patients with cachexia, and the primary endpoint was overall survival. In June 2017, an Independent Data Monitoring Committee performed a second unblinded interim efficacy analysis (the recommendation after the first analysis was to continue the trial). While no safety concerns were reported, the committee recommended stopping the trial early as the findings were not sufficient to expect that the efficacy endpoint could be reached. XBiotech indicated that it will continue to analyse the data, but the status of Xilonix development in colorectal cancer indication is currently unclear.

XBiotech also tested Xilonix in a Phase I trial in non-small cell lung cancer patients and is currently running a Phase I trial with pancreatic cancer patients with cachexia. While these first large trials provided a glimpse in IL-1 pathway inhibition effect in trials designed specifically for cancer, there are several substantial differences between Xilonix and Cantargia's products. Xilonix targets only IL-1α and not IL-1β. In addition, this target is more upstream of Cantargia's target IL1RAP. Furthermore, Cantargia's CAN04 has a proven mechanism of action of not only modulating inflammation via IL1RAP, but also the ADCC.

Novartis's CANTOS trial a boost for Cantargia's CAN04

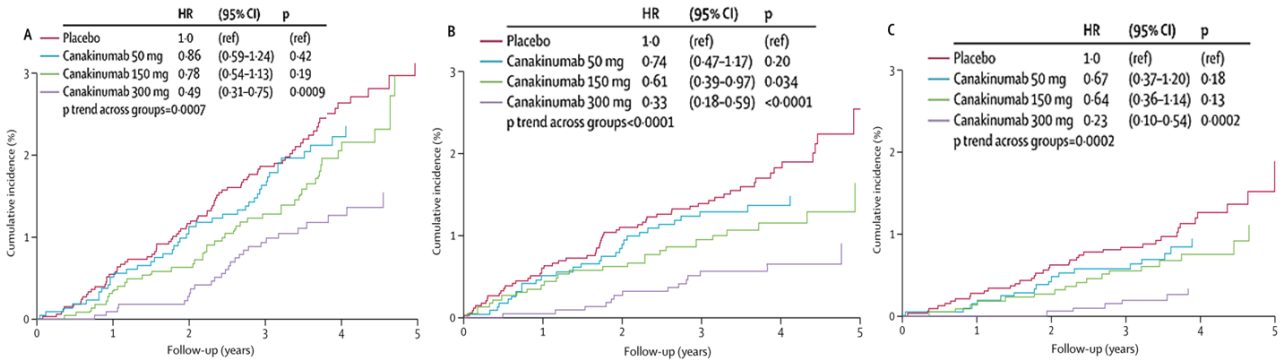
To our knowledge the largest set of data on IL-1 inhibition in cancer were produced by Novartis during the CANTOS trial (NCT01327846) and published in a Lancet paper in August 2017. Canakinumab (Ilaris, Novartis, sales of $402m in 2017, EvaluatePharma) is a fully humanised monoclonal antibody that selectively binds and neutralises IL-1β. It was first approved by the FDA and the EMA in 2009 for cryopyrin-associated periodic syndromes, a group of rare, heterogeneous autoimmune diseases characterised by IL-1β-mediated systemic inflammation.

The six-year CANTOS study was a randomised trial to establish the role of IL-1β inhibition by canakinumab in atherosclerosis carried out in 10,061 patients, who had a medical history of myocardial infarction. By design, all participants had to be free of previously diagnosed cancer, had to be with a persistent proinflammatory response defined by the presence of high-sensitivity C-reactive (hsCRP) concentrations of 2mg/L or higher and were followed up prospectively for three to five years (median 3.7 years). The trial met its primary endpoints, demonstrating that canakinumab in combination with standard-of-care treatment reduced cardiovascular event risk. In addition, surprisingly, additional analysis revealed that IL-1β inhibition might have an effect on cancer incidence. Specifically, the data showed that:

[9] Zhang et al. Constitutive IRAK4 Activation Underlies Poor Prognosis and Chemoresistance in Pancreatic Ductal Adenocarcinoma. *Clin Cancer Res (2017) 23(7)*

- Lung cancer was detected in 129 patients in total. Compared with the placebo arm, canakinumab reduced lung cancer mortality by 77% (Exhibit 4C) and reduced lung cancer incidence by 67% (Exhibit 4B) with a dose of 300mg;
- canakinumab did not significantly affect the incidence of other location cancers other, however, total cancer mortality (including lung) was more than 50% lower in the canakinumab 300mg arm than in the placebo group (p=0·0009);
- as expected, patients with increased concentrations of the inflammatory biomarkers (hsCRP) had the highest risk of developing lung cancer;
- smokers and those who achieved the greatest reductions in hsCRP or IL-6 seemed to gain the most benefit;
- a clear dose response was observed.

Exhibit 4: Cumulative incidence of all fatal cancer (A), lung cancer (B) and fatal lung cancer (C) in CANTOS trial



Source: Paul M Ridker et al. Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis. *The Lancet, 27 August 2017*

In terms of **safety**, canakinumab moderately reduced absolute neutrophil counts and no clinically significant hepatic toxicity was reported. The major toxicity of canakinumab in CANTOS was a significant increase in fatal infection and sepsis versus placebo (p=0.02, 78 events out of n=6,717 versus placebo 23 events out of n=3,344). However, this adverse effect was balanced by the reduction in cancer mortality, therefore no increase in all-cause mortality was noted. Although theoretically there is risk of increased infection rate, given that canakinumab was tested in chronic use, the safety profile for anticancer treatments is likely to be more than sufficient in our view. Furthermore, canakinumab and third-party data show that the inhibition of this pathway could actually be beneficial in chronic inflammatory diseases such as arthritis and gout.

Authors **concluded** that canakinumab is unlikely to have had a direct effect on the development of new lung cancers. A more plausible explanation is that canakinumab reduced the rate of progression, invasiveness and metastatic spread of lung cancers that were undiagnosed at the start of the trial. The findings tie well into existing preclinical data, showing that cytokines such as IL-1β can promote angiogenesis and tumour growth and that IL-1β is essential to tumour invasiveness in existing malignant cells. In addition, the lower incidence of certain cancers such as colorectal carcinoma and lung cancer in persons taking non-steroidal anti-inflammatory drugs such as aspirin is well described. However, while those drugs need to be used for many years to affect cancer incidence, the potential beneficial effects of canakinumab on the incidence of lung cancer and lung cancer mortality were obtained in a much shorter timeframe.

Based on this promising data, Novartis has initiated or planned several clinical studies:

- Initiated an open label Phase Ib study in various in solid cancers in combination with the experimental PD-1 inhibitor PDR001; final results are expected in 2020.

- Initiated a Phase III trial in adjuvant setting (n=1,500). Estimated completion date as per clinicaltrials.gov database is around 2022/23. Primary endpoint is disease-free survival (Exhibit 5).
- Planned two additional Phase III trials exploring canakinumab in, first- and second- line settings.

Exhibit 5: Canakinumab clinical trial design

Trial	Stage	Trial design and upcoming events
Canakinumab	Phase III	■ Study initiated in February 2018, currently recruiting ■ Study design – n=1,500; randomised, double-blind, placebo-controlled, multi-centre trial evaluating efficacy and safety of canakinumab versus placebo as adjuvant therapy in adult subjects with advanced NSCLC ■ Secondary endpoints – OS, LCSS, pharmacokinetic parameters, quality of life questionnaires ■ Estimated primary completion date as per clinicaltrials.gov is March 2022, and estimated study completion date is December 2023

Source: clinicaltrials.gov; Notes: OS = overall survival, LCSS = lung cancer specific survival.

In our view, the findings from the CANTOS trial are supportive of Cantargia's technology and R&D plans. In the case of positive data from the Phase III trials, Novartis is likely to be first to the market with canakinumab in lung cancer. We believe that competition risk to Cantargia is mitigated as CAN04 has a different mechanism of action (different target and dual mode of action). In addition, if canakinumab proves successful in commercial terms, this will only attract attention to CAN04.

Although the Novartis trial did not find statistical significance in other cancers, we note that:

- the trial was designed for other purposes, ie the treatment setting was completely different – chronic prevention rather than acute anticancer therapy;
- patients selected were at higher than in general population risk of developing lung cancer:
  - individuals with increased hsCRP concentrations have increased risk of several inflammatory cancers, most prominently lung cancer;
  - furthermore, patients with atherosclerosis commonly smoke, which is a major risk factor for cancer;
  - the median follow-up time was unlikely to have been adequate to show a reduction in incidence of new cancers;
- CAN04's mechanism of action is not only inflammation modulation via IL1RAP, but also the ADCC;
- canakinumab was administered as a standalone therapy, whereas CAN04 can be positioned as both standalone and in combinations where the modulation of inflammation in tumour microenvironment could be beneficial;
- canakinumab is an IL-1β monoclonal antibody and acts more upstream of Cantargia's target IL1RAP.

CAN04's dual mechanism of action

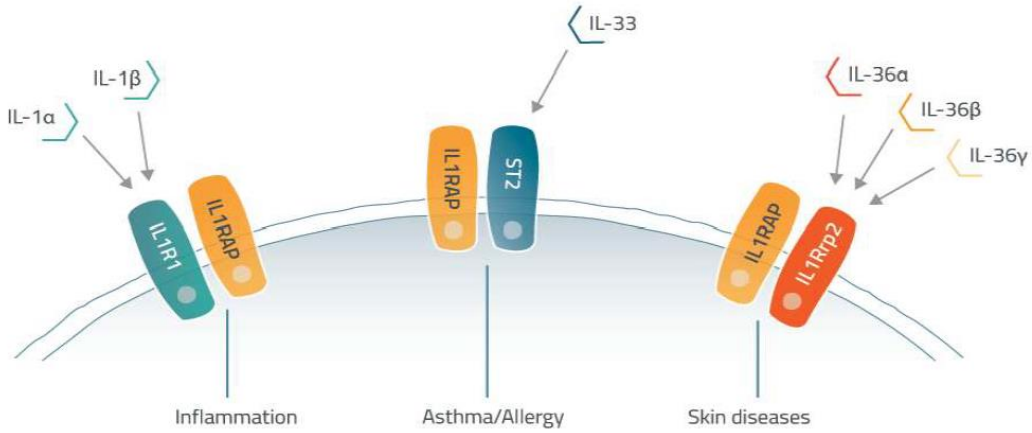
CAN04 is fully humanised IL1RAP IgG1 antibody with enhanced ADCC (licensed from BioWa Potelligent). Therefore, CAN04's mechanism of action consists of two separate effects: ADCC and IL1 signalling pathway inhibition.

CAN04 blocks IL1RAP associated signalling

IL1RAP is associated with IL-1β and IL-1α receptors (IL-1R1, IL-1R2), IL-33 receptor (ST2), IL-36α, IL-36β and IL-36γ receptors (IL1Rrp2) (Exhibit 6). Inhibition of IL1RAP is expected to inhibit the downstream signalling pathways of all these receptors. Cantargia believes inhibition of IL-1 and IL-

33 signalling has beneficial anti-inflammatory and anti-tumour effects, and inhibition of IL-36α, IL-36β and IL-36γ has anti-inflammatory effects (Exhibit 6). CAN04 has been shown to potently inhibit signalling via both IL-1 receptors and approximately 50% via IL-33 receptor. CAN04 data on IL-36 inhibition has not been disclosed. Cantargia's second lead project CANxx is being developed for autoimmune and inflammatory diseases. CANxx is in a preclinical development and a clinical candidate antibody will be selected in 2019, which is when more information is likely to be released on its specific mechanism of action.

Exhibit 6: Normal IL-1, IL-33 and IL-36 signalling in cells requires IL1RAP



Source: Cantargia

- **IL-1 signalling:** IL1RAP was first characterised in 1995 by a research group at Roche[10] and was found to be associated with IL-1 signalling. More recently it was found that IL1RAP is required for IL-1 signalling via the IL-1R.[11] Normally IL-1 acts through its receptor IL-1R together with IL1RAP, which transmits a signal in tumour cells that stimulates inflammation and tumour progression. When CAN04 binds to IL1RAP, IL-1 signalling is blocked. Cantargia has shown this effect can be achieved via inhibition of IL-1-mediated NFkB activation and production of IL-6 and IL-8.[12]
- **IL-33 signalling:** IL1RAP has also been found to be required for IL-33 signalling.[13] IL-33 has been implicated in tumour growth and metastasis[14] and inflammation.[15] As CAN04 has been shown to inhibit approximately 50% of this signalling pathway, it therefore could at least partially inhibit the downstream mechanisms.
- **IL-36 signalling:** IL-36 is mainly implicated in inflammatory skin diseases and, as far as we are aware, not in cancer.

[10] Greenfeder et al. Molecular Cloning and Characterization of a Second Subunit of the Interleukin 1 Receptor Complex. *The Journal of Biological Chemistry (1995) 270, 13757-13765.*

[11] Wesche et al. The Interleukin-1 Receptor Accessory Protein (IL-1RAcP) Is Essential for IL-1-induced Activation of Interleukin-1 Receptor-associated Kinase (IRAK) and Stress-activated Protein Kinases (SAP Kinases). *The Journal of Biological Chemistry (1997) 272, 7727-7731.*

[12] Liberg et al. The CAN04 Antibody Targets IL1RAP and Inhibits Tumor Growth in a PDX Model for NSCLC. *Cantargia Poster Presentation*

[13] Palmer et al. The IL-1 receptor accessory protein (AcP) is required for IL-33 signaling and soluble AcP enhances the ability of soluble ST2 to inhibit IL-33. *Cytokine (2008) 42(3):358-64*

[14] Yang et al. Interleukin-33 enhanced the migration and invasiveness of human lung cancer cells. *Onco Targets Ther. (2018) 11: 843–849*

[15] Liew et al. Disease-associated functions of IL-33: the new kid in the IL-1 family. *Nature Reviews Immunology (2010) volume 10, pages 103–110*

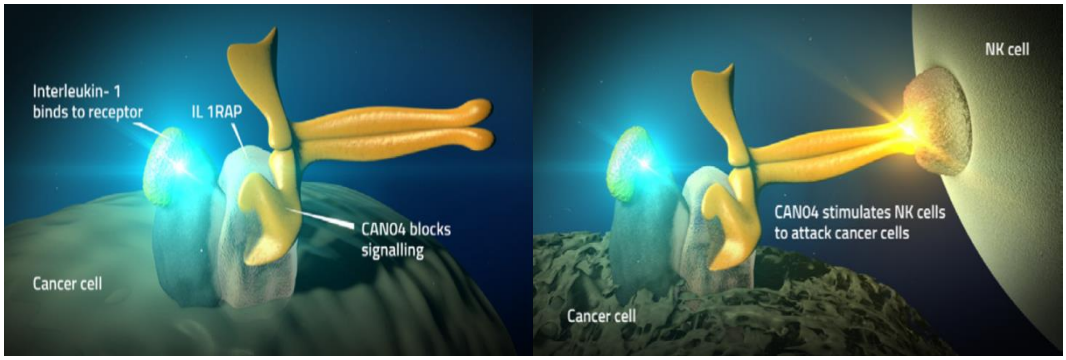
A potential advantage of Cantargia's approach is that CAN04 inhibit both IL-1β and IL-1α signalling, whereas the most advanced clinical products do not: canakinumab (Novartis) only targets IL-1β and Xilonix (XBiotech) only targets IL-1α. For example, inhibition of IL-1β will not prevent all signalling through IL-1R and so the effects on tumour progression could be limited. CAN04 has the potential to inhibit IL-1 signalling to a greater extent because IL1RAP is associated with both IL-1α and β receptors (IL-1R2, IL-1R1). In theory, this could lead to a greater inhibition of the IL-1 pathway and perhaps a greater anti-tumour effect. Anakinra and drugs targeting downstream signalling of IL-1R such as IRAK inhibitors also potentially have this advantage.

CAN04 also activates the patient's natural killer cells

Natural killer (NK) cells are part of the innate immune system. They are present in the bloodstream and can detect and directly kill foreign cells including cancer cells by a process called ADCC. Cantargia believes CAN04 will lead to ADCC of bound tumour cells:

- CAN04 (an antibody) binds to IL1RAP on the tumour cell surface (which leads to downstream intracellular effects, Exhibit 7);
- while bound to the tumour cell, it can be recognised by NK cells via Fc receptors expressed on the surface of the NK cells;
- the bound NK cells become activated and can then destroy the tumour cell by releasing cytotoxic granules and through cell death ligands.

Exhibit 7: CAN04 blocks IL-1 signalling and activates NK cells that directly kill tumour cells



Source: Cantargia Annual Report 2016

ADCC is a well-known and established mechanism in cancer treatment. Many marketed monoclonal antibodies partly attribute their therapeutic effects to ADCC including: nivolumab (antibody against PD-1), rituximab (CD20), obinutuzumab (CD20), dinutuximab (GD2), trastuzumab (HER2) and cetuximab (EGFR).

Existing data and R&D strategy

Cantargia has measured IL1RAP expression in several solid tumour types: melanoma (86%), pancreatic cancer (86%), NSCLC (85%), breast (52%) and colon cancer (27%).[16] More recently, the company released information that liver cancer, oesophageal cancer and head and neck cancer all showed high expression of IL1RAP, with at least 80% of the patients with these cancers overexpressing IL1RAP at moderate to strong levels. The company has decided to focus on NSCLC and a pancreatic cancer as lead indications, based on IL1RAP expression and commercial potential, but believes there may be potential for CAN04 in other IL1RAP-expressing solid tumours

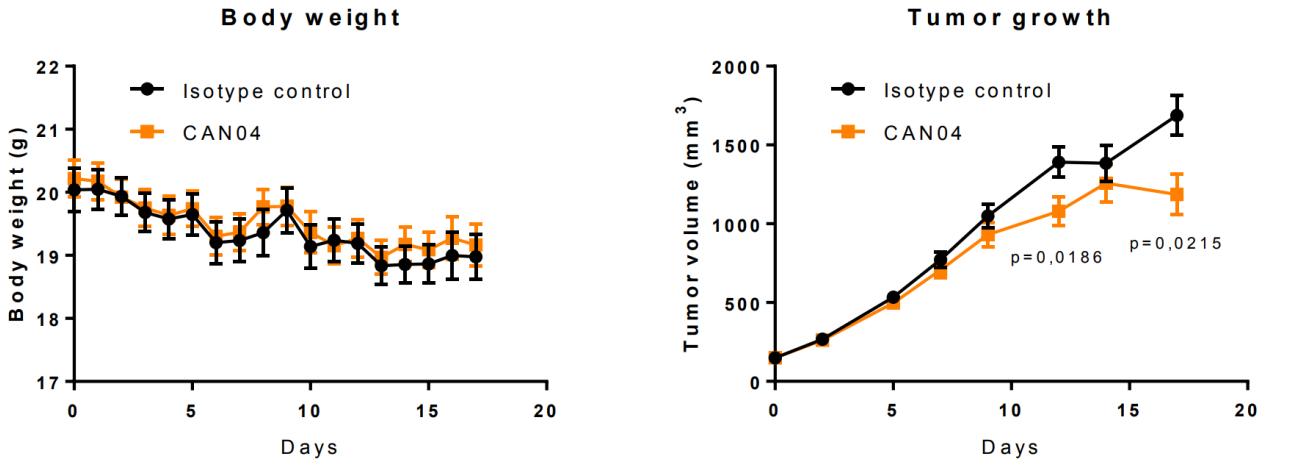
[16] Liberg et al. The CAN04 Antibody Targets IL1RAP and Inhibits Tumor Growth in a PDX Model for NSCLC. *Cantargia Poster Presentation*

as well. So far, the company has gathered pre-clinical data around IL1RAP inhibition in several solid tumours (NSCLC and breast cancer) and haematological malignancies (acute myeloid and chronic myeloid leukaemias).

More recent preclinical data publication is Cantargia's poster presentation in 2016 detailing a preclinical study of CAN04 in a patient-derived xenograft (PDX) mouse model for NSCLC. This was the first in vivo CAN04 data in solid tumours. Cantargia was able to demonstrate that:

- CAN04 inhibits IL-1-induced IL-6 and IL-8 release and stimulates ADCC in IL1RAP+ solid tumour cell lines;
- CAN04 inhibits growth of an IL1RAP+ NSCLC PDX (Exhibit 8);
- CAN04 treatment induces prominent leukocyte infiltration.

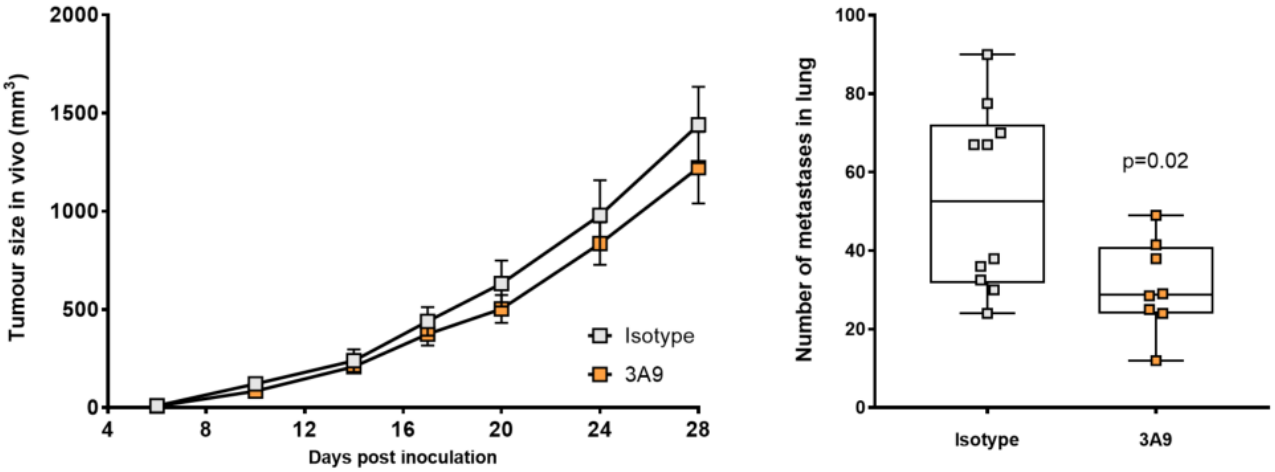
Exhibit 8: CAN04 inhibits growth of an IL1RAP + NSCLC PDX



Source: Liberg et al.

Most recently, Cantargia presented fresh pre-clinical data at the 2018 Annual Meeting of the American Association of Cancer Research. A surrogate antibody (3A9, Exhibit 9) to CAN04 was developed specifically for this study, so that it could be tested in animal studies. The animal model used was mice inoculated with 4T1 breast cancer cells. These cells express low levels of IL1RAP, therefore the antitumour effect of 3A9 could not be attributed to direct IL-1 pathway blockade directly affecting the tumour cells or ADCC. With this model Cantargia was exploring CAN04 effects on tumour microenvironment, primarily targeting myeloid cells (part of the innate immune system), which are known to express IL1RAP and sustain tumour-promoting inflammation. One of the key findings was that the treatment of 4T1 tumour-bearing mice with 3A9 did not reduce primary tumour growth significantly, but reduced both the number of (47% reduction, p=0.02) and size of lung metastases. Given that this was unlikely achieved by IL-1 blockage or ADCC of tumour cells, one potential explanation could be that targeting IL1RAP with an antibody could inhibit the formation of metastases by affecting the tumour microenvironment. The discovery potentially indicates an additional novel mechanism of action for CAN04. Theoretically CAN04 could be used even in cancers where IL1RAP expression in low, but the patient could still benefit by reduced number the metastases.

Exhibit 9: Surrogate antibody to CAN04 blocks metastasis of inoculated 4T1 tumours



Source: Cantargia. 4T1 – syngeneic breast cancer mouse model; 3A9 –surrogate antibody to CAN04.

Design of the Phase I/IIa CANFOUR and next steps

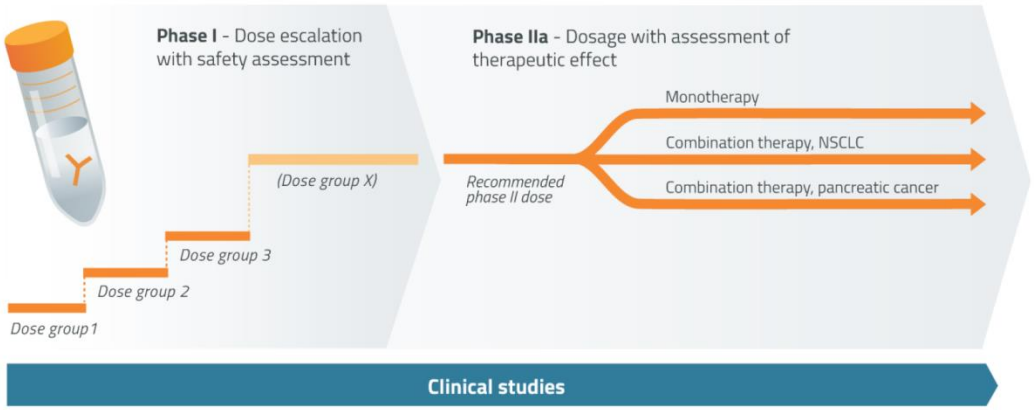
Cantargia recently initiated the Phase I part of a Phase I/II trial, known as CANFOUR, testing CAN04 in four solid tumour indications: NSCLC, pancreatic cancer, breast cancer and colorectal cancer in a small number of patients (Exhibits 10 and 11). This Phase I/IIa trial is divided into two parts. This study will establish the safety profile of the drug and the dose for the Phase IIa part of the trial. Results from the Phase I study are expected in mid-2018. The second part of the trial (Phase IIa) will look at the efficacy of CAN04 in NSCLC and pancreatic cancer both as a monotherapy and in combination with standard treatments (Exhibits 10 and 11). In the case of a positive data readout, Cantargia is open to various pathways for further development including an out-licensing deal.

Exhibit 10: Phase I/IIa design, total n=65

Trial	Stage	Trial status, design and upcoming events
CANFOUR	Phase I	■ Study ongoing (started September 2017)
		■ Patients with relapsed or refractory NSCLC, pancreatic cancer, breast cancer or colorectal cancer
		■ Design – open label, non-randomised, dose escalation followed by dose expansion, safety and tolerability study. Dose escalation: patients will receive intravenous CAN04 once weekly in cohorts of three
		■ **Data from part I (Phase I) study expected summer 2018**
	Phase IIa	■ Patients with advanced NSCLC or pancreatic cancer
		■ Design – open label, non-randomised, three treatment arms: monotherapy; combinations in NSCLC and pancreatic cancer
		■ **Initial data expected to be reported in 2019**
		■ Primary endpoint – treatment related AEs (safety and tolerability)
		■ Secondary endpoints – pharmacokinetic parameters, preliminary signs of efficacy as assessed by tumour response
		■ Study sites in EU (Belgium, Netherlands, Denmark and Norway)

Source: Edison Investment Research, Cantargia, clinicaltrials.gov. Notes: AEs = adverse events; MTD = maximum tolerated dose.

Exhibit 11: Phase I/IIa design



Source: Cantargia year-end Report 2017

CANxx: IL1RAP inhibitor for autoimmune diseases

Cantargia has a preclinical programme exploring the potential of its IL1RAP inhibition technology in autoimmune conditions. It intends to develop and patent a new antibody targeting IL1RAP to treat various autoimmune and inflammatory diseases (Exhibit 12), with the aim to have a product candidate selected in 2019. CANxx is in pre-clinical testing and is being developed in collaboration with Panorama Research Inc, a California-based company. The aim of the collaboration is to generate a lead product candidate that Cantargia can then develop to the point of clinical efficacy. At this point it aims to licence it in the same way as the strategy for CAN04. Panorama Research Inc will contribute its antibody technologies and Cantargia will be responsible for any further development and manufacturing. Cantargia will have to share future profits through royalties or subsequent licensing revenues, but Panorama will receive not more than the amount proportional to its investment in the development prior to partnering with Cantargia. Panorama is a biotech and pharmaceutical incubator based in Sunnyvale, California, and supports the development of both in-house-discovered and in-licensed technologies and offers services including antibody humanisation and production.

NSCLC and pancreatic cancer: Lead indications

NSCLC indication and market

Lung cancer is the leading cause of cancer-related deaths globally (19.4% of total cancer-related deaths); 1.8 million new cases were reported worldwide in 2012. NSCLC is the most common type of lung cancer, accounting for 85-90% of all cases. Five-year survival rates for NSCLC remain poor despite significant investment resources over the last 15 years; only 15% of patients diagnosed with lung cancer survive more than five years. The more recent availability of new treatment options as described below has improved outcomes and survival for patients, but there is still much need for more effective treatments across first-, second- and third-line settings.

NSCLC is not a single entity but a number of pathologies with different molecular abnormalities; subsets of NSCLC can be further defined at the molecular level by identification of 'driver mutation' that occurs across multiple oncogenes. Lung adenocarcinomas are associated with KRAS (30%), EGFR (15%), ALK (5%) and MET (4%) mutations. Common treatable oncogene mutations in NSCLC include the EGFR mutation and ALK translocation. As a result, treatment of NSCLC varies and depends on the type and stage of the tumour and its size and position in the lung; ~10% of

lung cancers are surgically operated on, while the majority are treated with a combination of chemotherapy, radiotherapy and targeted drug therapies. Historically, drug treatment decisions have been based on NSCLC tumour histology and platinum-based chemotherapy has been the cornerstone of treatment; the main limitations of it are low survival rates alongside the troublesome side effects of these cytotoxic agents.

More recently, the treatment paradigm for the management of NSCLC has shifted with the availability of targeted therapies. Current guidelines from the College of American Pathologists and International Association for the Study of Lung Cancer recommend that patients with advanced NSCLC (adenocarcinoma) have the primary tumour or metastasis analysed for EGFR and ALK where feasible. Targeted therapies have improved progression-free survival in patients to 10-12 months versus six months on platinum doublet treatment in a clinical trial setting. In the clinical setting, treatment of NSCLC depends on stage diagnosed and molecular status of the tumour.

Most recent advances are in the field of immunotherapy, specifically immune checkpoint inhibitors (ICIs). This field is dominated by PD-1/PD-L1 immune checkpoint inhibitors. PD-1 inhibitors Opdivo (Bristol Myers Squibb, NSCLC sales $536m in 2017) and Keytruda (Merck, sales $3.8bn in 2017) are approved for the treatment of second-line NSCLC patients who have progressed after platinum-based chemotherapy. Additionally, Keytruda is indicated for first-line patients with metastatic NSCLC whose tumours have high PD-L1 expression (above 50%). Opdivo and Keytruda have demonstrated a significant impact on OS: 12.2 months (vs 9.4 months) and 12.7 months (vs 8.5 months), respectively, versus chemotherapy in their respective clinical trials in second-line NSCLC patients. First-line Keytruda OS was 17.3 months vs 8.2 months for chemotherapy. PD-L1 inhibitor Tecentriq (Roche) was approved in October 2016 for the second-line treatment of NSCLC (NSCLC sales of $495m in 2017).

The NSCLC treatment paradigm will continue to evolve as new resistance mechanisms and further driver mutations are identified. The treatment strategies will move increasingly to a personalised level with genotype testing in all patients as soon as feasible. NSCLC market is already fragmented with novel approved drugs. Furthermore, ongoing combinatorial drug studies are proving that combination therapy is more effective on progression-free survival rates and on challenging the resistance mechanisms. This will further diversify the available treatment options. Due to early stage of CAN04's development precise positioning in clinical setting is premature to model, but given the likelihood that combination treatments are likely to become commonplace, we believe, is Cantargia's CAN04 has a broad potential given its differentiated mechanism of action if synergy is proven. When calculating the target patient population, we therefore take the total lung cancer incidence rates as 223,000 in the US and 315,000 in Europe (defined in Exhibit 15 notes) in 2017, with 85% being NSCLC and 85% expressing IL1RAP (Cantargia's data). This leaves us with 161,000 new patients in the US and 174,000 in Europe.

Pancreatic cancer indication and market

Pancreatic cancer, or pancreatic adenocarcinoma, is responsible for 7% of all cancer-related deaths – the fourth leading cause of cancer deaths and 11th most common cancer diagnosed in the US[17]. Pancreatic cancer is somewhat unique in that there has been very little progress over the past four decades in prolonging survival rates compared to other types of cancer. This challenge has been compounded by the disease usually being diagnosed at a late stage; even if the tumour is resectable, surgery is complicated and dangerous with high recurrence rates, and tumours are relatively resistant to chemotherapy. This means the overall five-year survival is still around 8%.[16]

An estimated 54k new cases were diagnosed in the US in 2017 and we calculate that 64,000 new cases were reported in target European countries. Around 20% of cases are stage I or II at

[17] Cancer Facts & Figures 2017. American Cancer Society. Accessed: July 14, 2017.

diagnosis (Cancer Research UK). Surgery is the primary mode of treatment; however, because around half of patients are diagnosed with a distant disease, often the resection is palliative and chemotherapy follows. For resected pancreatic cancer there is no approved treatment, implying a high unmet need. For non-resectable cancer chemotherapy options include gemcitabine alone or in combinations with several other agents such as capecitabine, erlotinib (Tarceva, Roche) and nab-paclitaxel (Abraxane, Celgene). The non-gemcitabine regimen FOLFIRINOX has been shown to be somewhat more effective than gemcitabine alone in a certain subset of patients. Recently, the standard of care chemotherapy (adjuvant) in resected disease has been changed to gemcitabine plus capecitabine (GemCap). Due to the early stage of the CAN04 development, it is too soon to model precise positioning in a clinical setting; however, because most of the newly diagnosed patients receive chemotherapy, we adjust the incidence number by the rate IL1RAP is expressed (86%) and assume 46,000 as target population for CAN04, growing alongside the population in future years.

Both backbone therapy drugs gemcitabine capecitabine are off patent. Roche's Tarceva revenue was $189m in pancreatic cancer in 2017, second highest to Abraxane with $443m. These two drugs accounted for the majority of the pancreatic cancer market, which was $809m in 2017 (EvaluatePharma). With Tarceva's patent expiring in the next couple of years sales are forecast to decrease; however, the total pancreatic cancer market is projected to grow to $2.2bn due to Abraxane and new entrants, which are still in R&D, but included in the consensus.

Competitive landscape

Due to their well-known pro-inflammatory effects, IL-1 inhibitors have been successful in various immunology indications. Top-selling IL-1 inhibitors are Ilaris (Novartis), with sales of $402m in 2017 and peak sales of $1.5bn by 2024 expected by consensus (EvaluatePharma); and Kineret (Sobi), with sales of $138m in 2017 forecast to reach $215m peak sales by 2024. In contrast, reflecting the relatively new discovery of IL-1 in tumour growth and metastasis, there are only a few IL-1 inhibitors in development for cancer indications.

Cellerant Therapeutics is the only other company developing IL1RAP antibodies. Its product CSC012 is in pre-clinical stage for myelodysplastic syndrome and acute myeloid leukaemia. However, there has been no recent update about the status of CSC012.

Cantargia has four patent families, all having claims relating to IL1RAP target and antibodies in solid tumours and haematological cancers. This will help it to build a control position in this area and cover its lead product CAN04 and any further antibodies it may develop against IL1RAP in these cancer indications. Two of Cantargia's granted European patents had an opposition filed but both remain in force, which suggests the patents are strong and might withstand any further opposition. Cantargia is developing the IP protection around CANxx.

Other drugs in development are targeting other parts of the IL-1 signalling pathway (Exhibit 12). The most advanced IL-1 inhibitor in cancer is Novartis's Ilaris (canakinumab), as discussed previously. Canakinumab is already marketed in several immune indications. Anakinra, marketed as Kineret (Sobi), is being studied in several cancer indications, but these appear to be investigator-led trials with no commercial sponsor involved. IRAK is a downstream target of IL-1 and IL1RAP and is being evaluated as a potential target in cancer as well as inflammatory diseases. Curis has a Phase I IRAK inhibitor for non-Hodgkin lymphoma (Exhibit 12). Large pharma companies also have several early-stage projects in the field.

Other interleukins have also been implicated in tumour growth and metastasis. For example, there is a lot of literature around IL-17 as a tumour-promoting factor.[18] IL-17 has also been found to induce IL-6 and IL-8 production,[19] which have also both been found to be tumour promoting.[20,21] To our knowledge, there are only a few such inhibitors in clinical development (Exhibit 13). No clinical efficacy data have yet been seen from these trials.

Exhibit 12: IL-1 signalling inhibitor landscape cancer indications

Pharmacological class / target	Product (generic name)	Company	Current development status of oncology indications	Notes
Anti-IL-1 beta Mab	Ilaris (canakinumab)	Novartis	Phase III NSCLC, recruiting (NCT03447769)	Already marketed in immune indications: CIAS1 associated periodic syndromes, gout, juvenile idiopathic arthritis, adult-onset Still's disease, familial Mediterranean fever, hyper-IgD syndrome. Filed in myocardial infarction prophylaxis and stroke prophylaxis. Lung cancer data published from CANTOS (NCT01327846).
Anti-IL-1 alpha Mab	Xilonix	XBiotech	Two Phase III trials in colorectal cancer, status unclear (NCT01767857, NCT02138422); Phase I pancreatic cancer patients with cachexia (NCT03207724) Phase I NSCLC (website)	The first Phase III trial (European) trial was positive for the symptomatic progression of the cancer. The second Phase IIII trial (XCITE) was terminated due to lack of efficacy. Current development status in this indication unclear.
Anti- IL1RAP Mab	CAN04	Cantargia	Phase I/II NSCLC, pancreatic cancer (NCT03267316)	No other indications in the Phase IIa part of the trials.
Anti- IRAK 4 small molecule	CA-4948	Curis	Phase I non-Hodgkin lymphoma (NCT03328078); pre-clinical acute myeloid leukaemia	Also in pre-clinical testing for arthritis and myelodysplastic syndrome.
Anti- IL1RAP Mab	CSC012	Cellerant Therapeutics	Pre-clinical acute myeloid leukaemia (website)	No other indications found.

Source: EvaluatePharma, company websites, clinicaltrials.gov. Notes: Ordered by current development status of oncology indication.

Exhibit 13: Other IL inhibitors in development for cancer indications

Pharmacological class/target	Product (generic name)	Company	Current development status of oncology indications	Notes
Anti-IL-6 Mab	Sylvant (siltuximab)	Janssen (Johnson & Johnson)	Phase II multiple myeloma (NCT01484275)	Sylvant is currently marketed for Castleman disease. Phase II studies in prostate cancer and renal cell carcinoma were both stopped early due to lack of efficacy.
Anti-IL8 Mab	HuMax-IL8 / BMS-986253	Bristol-Myers Squibb/ Genmab	Phase I/II advanced cancer in combination with Nivolumab, currently recruiting (NCT03400332)	No other indications listed.
Anti-IL-6 Mab	Actemra (tocilizumab)	Roche	Phase I chronic lymphocytic leukaemia (NCT02336048)	Actemra is already marketed in Castleman disease, rheumatoid arthritis, juvenile idiopathic arthritis, vasculitis and other immune indications. Publication of a Phase I/II study of Tocilizumab+gemcitabine in advanced pancreatic cancer by partner Chugai in 2016. The study was terminated due to 6/15 patient deaths within the first 2 months of the trial. No clinical benefit shown.
IL-17 Mab	Anti-IL-17 Mab	OREGA Biotech	Pre-clinical solid tumour indications	No other indications found.

Source: EvaluatePharma, company websites, clinicaltrials.gov. Notes: Ordered by current development status of oncology indication

[18] Yang et al. The Role of Interleukin 17 in Tumour Proliferation, Angiogenesis, and Metastasis. *Mediators Inflamm. (2014) 2014: 623759*

[19] Hwang et al. IL-17 induces production of IL-6 and IL-8 in rheumatoid arthritis synovial fibroblasts via NF-κB- and PI3-kinase/Akt-dependent pathways. *Arthritis Res Ther (2004) 6:R120-R128*

[20] Nagasaki et al. Interleukin-6 released by colon cancer-associated fibroblasts is critical for tumour angiogenesis: anti-interleukin-6 receptor antibody suppressed angiogenesis and inhibited tumour–stroma interaction. *Br J Cancer. (2014) 110(2): 469–478.*

[21] Srivastava et al. Interleukin-8 is a key mediator of FKBP51-induced melanoma growth, angiogenesis and metastasis. *Br J Cancer. (2015) 112(11): 1772–1781.*

Sensitivities

Cantargia is subject to typical biotech company development risks, including the unpredictable outcome of trials, regulatory decisions, success of competitors, financing and commercial risks. Our model assumes that products will be out-licensed; therefore, our valuation is sensitive to potential licensing timing and actual deal terms. Cantargia is mainly an early-stage drug developer, therefore in the foreseeable future the value creation will depend on successful R&D progress and any potential partnering activities, although typically the timing of licensing deals is difficult to forecast. The near-term R&D sensitivities are tied to the lead asset CAN04, which is the only clinical-stage product. Any setbacks with this asset will influence Cantargia's share price significantly. As CANxx reaches clinical development, this risk will be diversified. Markets in such indications as NSCLC are already rather fragmented with innovative drugs, which means subsequent therapies need to demonstrate added benefit. This is partially mitigated in Cantargia's case, because the underlying rationale of its technology is a potential synergistic effect when using in combinations with current treatment options.

Valuation

We value Cantargia based on risk-adjusted NPV using a 12.5% discount rate, including SEK210m net cash estimated at end-Q218. This results in a value of SEK1.64bn or SEK24.8/share. A relative valuation is not meaningful given cash-losing operations and a technology comparison has been provided above. Exhibits 14, 15 and 16 provide assumptions and our valuation of CAN04 in specific indications. We include CAN04 in the two lead indications, NSCLC and pancreatic cancer. Cantargia has a substantial amount of preclinical data supporting CAN04 use in leukaemia. In addition, the company is diversifying its R&D pipeline and developing CANxx for the treatment of inflammatory conditions. Both CAN04 for leukaemia and CANxx are still in preclinical development; Cantargia will decide which project to prioritize and bring to the market as the CANFOUR trial progresses. We therefore do not include these in our model but will revisit this once the projects advance to clinical development.

We have derived rNPVs based on the assumptions discussed above, such as the target population and pricing, R&D costs, patent expiry dates/market exclusivity (summarized in Exhibit 15) with the calculated peak sales shown in Exhibit 16. Cantargia's **strategy** is to finalise the Phase I/IIa study and then either continue with development or establish a partnership. Given a 'typical' drug development model includes smaller biotech, taking the risk and developing assets until proof-of-concept stage and the initiating partnering discussion, we therefore assume that in the case of positive Phase I/IIa data, the company will be able to **out-license** CAN04 after the Phase I/IIa.

Deal terms are based on relevant benchmarks over the last few years (sourced from EvaluatePharma). There is a lack of directly comparable deals, ie mid-stage, targeting IL-1 pathway for cancer treatment. Therefore, we took the average of deal terms within targeted therapy space (Exhibit 15) and use upfront/milestones of $123/$844m in our model. These values, like R&D costs (Exhibit 14), are split between the NSCLC and pancreatic cancer indications. Licensing deal is adjusted with 70% probability and tiered 11-13% royalty rates used. We excluded deals in the checkpoint inhibitor space due to very high values and a proven mechanism of action. Cantargia's technology also works by harnessing the immune system to fight cancer, therefore if early efficacy signs are positive after the Phase I/IIa trial, we believe there is potential for licensing deal terms closer to the checkpoint inhibitor space shown in Exhibit 15 for comparison.

Target patient populations are discussed above in the relevant indication sections. Target geographies used in the model are the US, top five European countries, Benelux, Scandinavia, Austria and Switzerland. If CAN04 development will be successful, significant upside could come

from other major markets like Japan and China. NSCLC **market penetration** is assumed at 10%, given the market is fragmented. However, because of a differentiated mechanism of action and potential synergies with other drugs, CAN04's potential can be broad. In pancreatic cancer, we assume a higher **marker penetration** at 20% as there is a high unmet need and little innovative treatment in this indication. We assume $80,000 is a **pricing** per year per patient (30% discount in Europe). This is closer to pricing that targeted therapies achieve and is very conservative compared to some checkpoint inhibitors, which can reach c $12,000 a month as with Opdivo and Keytruda. NPV projects for both indications end with eroding sales after 2036 over several years. Until then, CAN04 is protected by **patents** or biological market exclusivity (Exhibit 14).

Exhibit 14: Assumptions for R&D and commercial projects

Product/indication	Comments
CAN04 - NSCLC	■ Target population: c 137k in the US and c 148k in Europe (see notes). Calculated using c 464k lung cancer incidence rate in defined countries, 85% of those are NSCLC, of which estimated 85% express IL1RAP. Assumed that an initial target population will be relapsed/resistant patients, which is around 85%. Assumed lower 10% penetration as the market is fragmented, but given differentiated MoA of CAN04, there is broad potential for its use in combination with various other drugs. ■ Pricing*: $80k per patient per year, 30% discount in Europe. Peak sales in six years.
CAN04 - Pancreatic cancer	■ Target population c 54k in the US and c 64k in Europe. Calculated using pancreatic cancer incidence in the US and defined European countries of c 118k. Assumed 20% penetration as smaller patient population with no effective new treatment options. ■ Pricing*: $80k per patient per year; 30% discount in Europe. Peak sales in six years.
	■ R&D cost: $15m to complete Phase I/IIa, then out-licensed. ■ Licensing deal terms: upfront/milestones of $123/$844m, out-licensed in 2021. Licensing deal is adjusted with 70% probability. Tiered 11-13% royalty rates used. ■ IP rights: proprietary technology; protection until 2035. Biologicals market exclusivity 12 years in the US and 10 years in Europe.

Source: Edison Investment Research. Note: Target geographies used in the model are the US, top five European countries, Benelux, Scandinavia, Austria and Switzerland. *Pricing in US; 30% discount applied in Europe.

Exhibit 15: Comparable Phase I/II oncology deals where a potential indication was pancreatic cancer or NSCLC

Date	Licensor	Licensee	Product	Pharmacological class / Target	Indications included in the deal	Upfront ($m)	Deal value (excl. upfront) ($m)
Targeted antibodies							
10/02/2017	Immunomedics	Seattle Genetics	Govitecan (IMMU-132)	TROP-2	TROP-2 expressing solid tumours (eg. breast, lung, bladder)	300	1,757
15/10/2015	Five Prime Therapeutics	Bristol-Myers Squibb	CSF1R antibody (FPA008) in combination with Opdivo	CSF1R	Six undisclosed solid tumours	350	1,390
03/12/2013	Oncomed Pharmaceuticals	Celgene	Up to six anti-cancer stem cell product candidates (including demcizumab)	DLL4, VEGF	Oncology (including demcizumab for pancreatic cancer)	155	967
06/09/2012	Symphogen	Merck KGaA	SYM004	EGFR (Mab)	All indications (including colorectal and head and neck cancer)	25	614
30/08/2012	Genmab	Johnson & Johnson	Daratumumab, and a second CD38 antibody	CD38	Multiple myeloma	55	1,135
Small molecules							
14/11/2017	Loxo Oncology	Bayer	Larotrectinib and LOXO-195	TRK	TRK fusion cancers (eg. lung)	400	1,350
28/07/2015	Hanmi Pharmaceutical	Boehringer Ingelheim	Olmutinib	EGFR (TKI)	EGFR mutation positive lung cancer	50	730
15/12/2014	Geron	Johnson & Johnson	Imetelstat	Telomerase inhibitor	Oncology including haematological malignancies and other therapeutic uses	35	935
08/12/2011	Pharmacyclics	Johnson & Johnson	PCI-32765	BTK inhibitor	B-cell malignancies, solid tumours, immune disorders	150	975
02/02/2010	Topotarget	Spectrum Pharmaceuticals	Belinostat	HDAC inhibitor	Haematological malignancies, solid tumours	30	350
28/04/2009	Ardea Bioscience	Bayer	RDEA119	MEK inhibitor	Solid tumours	35	407
Anti-PD1 agents							
23/10/2014	CureTech	Medivation	Pidilizumab (CT-011)	PD-1	All indications (including oncology)	5	335

Source: Edison Investment Research, EvaluatePharma, company press releases

Exhibit 16: Sum-of-the-parts Cantargia valuation

Product	Launch	Peak sales ($m)	Unrisked NPV (SEKm)	Unrisked NPV/share (SEK)	Technology probability (%)	rNPV (SEKm)	rNPV/share (SEK)
CAN04 - NSCLC	2026	3,144	5,161.6	78.0	10%	587.4	8.9
CAN04 - pancreatic cancer	2024	2,132	5,220.1	78.9	10%	844.2	12.8
Net cash at end-Q118			210.0	3.2	100%	210.0	3.2
Valuation			**10,591.7**	**160.0**		**1,641.6**	**24.8**

Source: Edison Investment Research. Note: WACC = 12.5% for product valuations.

Financials

Cantargia reported an operating loss of SEK60.0m in 2017, compared to SEK47.6m in 2016. Expenses associated with R&D projects were SEK44.8m versus SEK35.5m a year ago, and personnel expenses came in at SEK8.1m versus SEK6.8m. Cantargia recently switched to IFRS reporting and is now expensing all R&D related costs. Our total operating cost estimates for 2018 and 2019 grow to SEK80.9m and SEK93.8m, respectively, mainly reflecting increasing R&D costs (detailed in Exhibit 15) as Cantargia moves from Phase I of the trial to Phase IIa and advances its preclinical projects. Cantargia had cash and short-term investments of SEK270.0m at the end of 2017 compared to SEK34.8m at the beginning of 2017. The company has received SEK232m gross after a share issue in Q417. According to Cantargia, the operations are now financed until 2020, which is in line with our model. As of end Q118, Cantargia has 85k warrants, which allow holders to subscribe for the same amount of shares (total number of shares outstanding 66.2m at end-Q118).

Exhibit 17: Financial summary

SEK'000s	2014	2015	2016	2017	2018e	2019e
December	GAAP	GAAP	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS						
Revenue	0	0	0	0	0	0
Cost of Sales	0	0	0	0	0	0
Gross Profit	0	0	0	0	0	0
Research and development	(3,495)	(7,045)	(35,493)	(44,819)	(65,219)	(77,699)
EBITDA	(8,115)	(17,018)	(47,557)	(60,010)	(80,866)	(93,815)
Operating Profit (before amort. and except.)	(8,115)	(17,018)	(47,557)	(60,010)	(80,866)	(93,815)
Intangible Amortisation	0	0	0	0	0	0
Exceptionals	0	0	0	0	0	0
Other	(1)	0	0	0	0	0
Operating Profit	(8,116)	(17,018)	(47,557)	(60,010)	(80,866)	(93,815)
Net Interest	(255)	(172)	67	(243)	664	360
Profit Before Tax (norm)	(8,370)	(17,190)	(47,490)	(60,253)	(80,202)	(93,455)
Profit Before Tax (reported)	(8,371)	(17,190)	(47,490)	(60,253)	(80,202)	(93,455)
Tax	0	0	0	0	0	0
Profit After Tax (norm)	(8,371)	(17,190)	(47,490)	(60,253)	(80,202)	(93,455)
Profit After Tax (reported)	(8,371)	(17,190)	(47,490)	(60,253)	(80,202)	(93,455)
Average Number of Shares Outstanding (m)	7.6	13.5	17.5	32.4	56.6	66.2
EPS - normalised (SEK)	(1.10)	(1.27)	(2.72)	(1.86)	(1.42)	(1.41)
EPS - normalised fully diluted (SEK)	(1.10)	(1.27)	(2.72)	(1.86)	(1.42)	(1.41)
EPS - reported (SEK)	(1.10)	(1.27)	(2.72)	(1.86)	(1.42)	(1.41)
Dividend per share (SEK)	0.0	0.0	0.0	0.0	0.0	0.0
Gross Margin (%)	N/A	N/A	N/A	N/A	N/A	N/A
EBITDA Margin (%)	N/A	N/A	N/A	N/A	N/A	N/A
Operating Margin (before GW and except.) (%)	N/A	N/A	N/A	N/A	N/A	N/A
BALANCE SHEET						
Fixed Assets	2,841	6,029	2,662	2,957	2,957	2,957
Intangible Assets	2,447	4,282	0	0	0	0
Tangible Assets	0	0	0	0	0	0
Investments	394	1,747	2,662	2,957	2,957	2,957
Current Assets	17,092	39,636	35,636	271,126	174,835	81,380
Stocks	0	0	0	0	0	0
Debtors	0	14,871	0	0	0	0
Cash	16,660	9,641	25,904	149,781	14,104	80,649
Other	432	15,124	9,732	121,345	160,731	731
Current Liabilities	(16,032)	(3,107)	(9,494)	(27,957)	(18,702)	(18,702)
Creditors	(16,032)	(3,107)	(9,494)	(27,957)	(18,702)	(18,702)
Short term borrowings	0	0	0	0	0	0
Long Term Liabilities	0	0	0	0	0	0
Long term borrowings	0	0	0	0	0	0
Other long term liabilities	0	0	0	0	0	0
Net Assets	3,901	42,558	28,804	246,126	159,090	65,635
CASH FLOW						
Operating Cash Flow	7,154	(30,105)	(42,405)	(40,860)	(96,343)	(93,815)
Net Interest	(255)	(172)	67	(243)	664	360
Tax	0	0	0	0	0	0
Capex	0	0	0	0	0	0
Acquisitions/disposals	0	0	0	0	0	0
Financing	9,500	44,680	56,225	304,479	0	0
Other	(1,235)	(21,422)	2,376	(139,499)	(39,998)	160,000
Dividends	0	0	0	0	0	0
Net Cash Flow	15,164	(7,019)	16,263	123,877	(135,677)	66,545
Opening net debt/(cash)	(1,496)	(16,660)	(9,641)	(25,904)	(149,781)	(14,104)
HP finance leases initiated	0	0	0	0	0	0
Other	(0)	0	0	0	0	0
Closing net debt/(cash)	(16,660)	(9,641)	(25,904)	(149,781)	(14,104)	(80,649)

Source: Cantargia's accounts, Edison Investment Research. Note: *Short-term investments.

Contact details	Revenue by geography
Medicon Village Scheelevägen 2 Lund SE-223 81 Sweden +46(0)46 2756260 http://cantargia.com/en	N/A

Management team

CEO: Göran Forsberg	VP Operations: Liselotte Larsson
Göran Forsberg has a PhD in biochemistry, and is an associate professor and the author of over 40 scientific publications. He has worked for pharmaceutical and biotechnology companies for more than 30 years in various positions, including at KabiGen, Pharmacia, Active Biotech and the University of Adelaide, Australia. Forsberg's most recent position was Chief Business Officer at Active Biotech AB. He has a large amount of drug development experience, with a special focus on oncology.Since 2011, Forsberg is a board member of Isogenica.	Liselotte Larsson has a PhD in biotechnology, and has more than 20 years of experience in various management positions in pharmaceutical and biotechnology companies including BioGaia Fermentation, Novozymes Biopharma and Camurus. Larsson's main fields of expertise are business development, marketing & sales/out licensing, ISO certification, good manufacturing practice (GMP) and overall project management.
VP Clinical Development: Lars Thorsson	**CFO: Bengt Jöndell**
Lars Thorsson graduated with a Ph.D. in clinical pharmacology in 1998. Thorsson has more than 30 years' experience in the pharmaceutical industry, including leading roles in clinical studies and project management in a large number of development phases at AstraZeneca. Thorsson's most recently worked at Novo Nordisk A/S, where he held the role of Senior Clinical Pharmacology Scientist, responsible for preparation and implementation of clinical pharmacological studies in development projects. Thorsson has been responsible for evaluation and documentation of new substances and has the experience of regulatory activities and interactions with health authorities.	Bengt Jöndell has a BSc in Business Aministration and a MSc in Chemical engineering. Jöndell has extensive experience in various executive financial functions such as CFO and Chief Executive Officer at BTJ Group AB, Senior Financial Advisor for BoneSupport, CFO/Administrative manager at Inpac, Business Controller at Pharmacia & Upjohn Consumer Healthcare, Pharmacia, Pharmacia Consumer Pharma and Pharmacia Nicorette. Jöndell´s most recent position was CFO for Enzymatica AB.

Principal shareholders	(%)
Sunstone Life Science Ventures Fund III K/S	9.02
Första AP-fonden	6.87
Försäkringsaktiebolaget, Avanza Pension	6.21
Fjärde AP-fonden	4.63
SEB S.A. Clients Assets Ucits	3.74
Andra AP-fonden	3.32
Tibia Konsult AB	2.10

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