EDISON

Cantargia

Company update

Excellent end to the year

Pharma & biotech

Over the past several weeks Cantargia has reported positive interim data from the ongoing Phase IIa trial with lead asset CAN04, an anti-IL1RAP antibody targeting the IL-1 pathway, announced the first clinical trial in the US and introduced CAN10, a preclinical project in inflammation uniquely targeting three interleukin pathways, IL-1, IL-33 and IL-36. Two days after the introduction of CAN10, J&J's Janssen announced the acquisition of bermekimab from the US-based XBiotech for an impressive $750m upfront and $600m in potential milestones. The mechanism of action of bermekimab, which is in mid-stage clinical trials as an anti-inflammatory anti-IL-1-alpha antibody, partially overlaps with that of CAN10. Our Cantargia valuation is SEK2.94bn or SEK40.4/share (virtually unchanged).

Year end	Revenue (SEKm)	PBT* (SEKm)	EPS* (SEK)	DPS (SEK)	P/E (x)	Yield (%)
12/17	0.0	(60.3)	(1.86)	0.0	N/A	N/A
12/18	0.0	(91.2)	(1.38)	0.0	N/A	N/A
12/19e	0.0	(100.7)	(1.45)	0.0	N/A	N/A
12/20e	0.0	(114.1)	(1.57)	0.0	N/A	N/A

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

Phase IIa CANFOUR data

On 2 December 2019, Cantargia reported interim data from the ongoing open-label, three-arm Phase IIa study with CAN04 in combination with first-line, standard of care (SoC) chemotherapy in non-small cell lung cancer (NSCLC) and metastatic pancreatic cancer (pancreatic ductal adenocarcinoma, PDAC). Four of seven evaluable patients with PDAC achieved partial response (PR) and two out of three evaluable patients with NSCLC achieved an objective response (OR); there was one complete response (CR) and one PR. Although the data are early, the results compare favourably to response rates to standalone chemotherapy regimens used in the CANFOUR trial (23% in PDAC; 22–28% in first-line NSCLC). These results support the hypothesis that CAN04 is synergistic with the SoC chemotherapy.

US study to test CAN04 combo with CPIs

The recruitment to the PDAC and NSCLC arms is expected to be completed in early Q220 and Q320, respectively, with key survival results due in 2021. The somewhat slower than expected enrolment to the NSCLC arm was addressed by opening additional centres. Cantargia recently announced a major expansion of its clinical programme with plans to initiate a Phase Ib study in the US. The company will file for an investigational new drug (IND) application in January and the trial could start in H120. The trial design is yet to be confirmed, but the goal is to explore the potential of CAN04 combination with checkpoint inhibitors (CPIs) in three indications (NSCLC, head and neck cancer and bladder cancer).

Valuation: SEK2.94bn or SEK40.4/share

Our valuation of Cantargia is virtually unchanged at SEK2.94bn or SEK40.4/share versus SEK2.65bn or SEK36.4/share previously. Updates on recruitment progress for the Phase IIa CANFOUR trial and the initiation of the US study are the most visible R&D events in the near term.

17 December 2019

Price	**SEK19.9**
Market cap	**SEK1.45bn**

Net cash (SEKm) at end-Q319 (includes short-term investments)	194.5
Shares in issue	72.8m
Free float	90%
Code	CANT
Primary exchange	Nasdaq Stockholm
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	30.1	24.1	24.4
Rel (local)	26.8	14.5	(0.2)
52-week high/low	SEK21.6	SEK12.8	

Business description

Cantargia is a clinical-stage biotechnology company based in Sweden, established in 2009 and listed on the Nasdaq Stockholm main market. It is developing two assets against IL1RAP, CAN04 and CAN10. CAN04 is being studied in a Phase IIa clinical trial, CANFOUR, in solid tumours focusing on NSCLC and pancreatic cancer. Cantargia is preparing to file an IND and initiate a trial in the US next year.

Next events

Initiate new US study with CAN04 in combination with CPIs	H120
Phase IIa CANFOUR updates	2020
CAN10 preclinical development updates	2020

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Edison profile page

Interim data from the Phase IIa CANFOUR trial

On 2 December 2019, Cantargia reported interim data from the ongoing open-label, three-arm Phase IIa study with CAN04 in NSCLC and PC as monotherapy and in combination with first-line chemotherapies (Exhibit 2). The CANFOUR trial consists of two parts – Phase I and Phase IIa. The full Phase I data were presented at ASCO on 2 June 2019, which showed that CAN04 was generally safe and well tolerated. The ongoing Phase IIa study includes initial efficacy endpoints among others. The first results include:

- No major new side effects were reported.
- Two out of three evaluable patients with metastatic NSCLC achieved ORs (there was one CR and one PR).
- Four out of seven evaluable patients with metastatic pancreatic cancer (PDAC) achieved PR:
  - Of these four patients, three had more than a 90% decrease in CA19-9, which is a biomarker for pancreatic cancer tumour burden.
  - The remaining three patients had a progressive disease; however, one of those three patients showed pseudoprogression and a pronounced decrease in the CA19-9 biomarker.

The results showed the addition of CAN04 increased the response to treatment rates compared to historical efficacy rates of the same standard of care chemotherapy regimens. Reported historical response rates with the chemotherapy regimens used in the CANFOUR trial are 23% (PDAC; Von Hoff et al, 2013), 22–28% in first-line NSCLC (Schiller et al, 2002; Scagliotti et al, 2008). Also, the historical data showed more than a 90% reduction of CA19-9 was reported in 31% of PDAC patients after standard gemcitabine/abraxane therapy (Von Hoff et al, 2013).

Moreover, the pseudoprogression case is particularly interesting because it is a known phenomenon when treating patients with immunotherapies. It is defined as ‘a response to treatment after initial increase in volume of cancer lesions, due to the infiltration of tumoral tissue by immune cells’. Although the patient was still considered to have progressive disease during the last check, the pseudoprogression phenomenon after the administration of CAN04 would imply the immune system was activated. This is supportive to the expected mechanism of action of CAN04. In addition to direct cell killing via antibody-dependent cellular cytotoxicity, by inhibiting IL1RAP CAN04 blocks the IL-1 signalling pathway, which the tumour exploits as a defence strategy against immune system attack.

Overall, although the data are still at an early stage, the large margin in achieved ORs compared to historical controls provides some confidence in the hypothesis that CAN04 is synergistic with the SoC chemotherapy.

Next steps

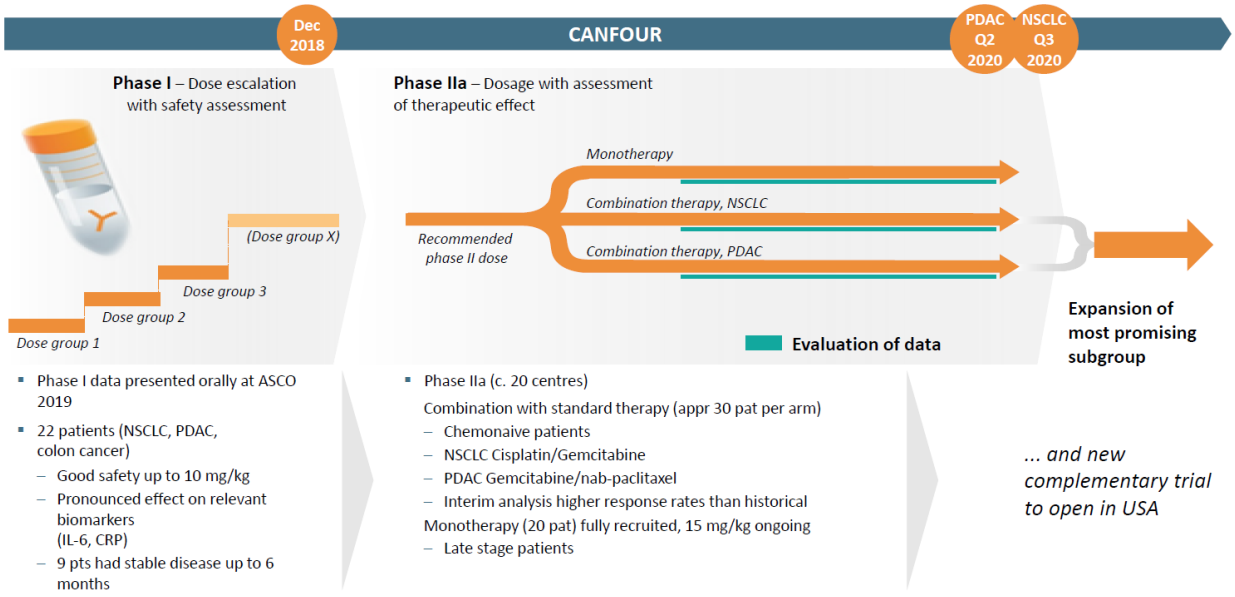
The recruitment to the PDAC arm is expected to be completed in early Q220. Cantargia reported somewhat slower than expected enrolment to the NSCLC arm. To address that, the company opened additional centres and recruitment is expected to be completed in early Q320. More response, biomarker and safety data will likely be released in 2020. In addition to the chemotherapy combination, the Phase IIa CANFOUR trial includes a monotherapy arm primarily analysing safety and biomarkers in patients with late-stage disease with results from different dose levels expected in H120. The key readouts (progression free survival and overall survival) from the combination arms are likely in 2021.

Exhibit 1: Phase IIa CANFOUR trial interim data

	Initiated	On therapy	Evaluable	CR/PR	SD	PD
PDAC	10	7	7	4		3[2)]
Historical				23%	27%	20%
NSCLC	4	3	3	2	1	
Historical				22-28%	18%	40%

Source: Cantargia

Exhibit 2: Phase IIa CANFOUR trial design



Source: Cantargia

Clinical development expansion in the US

On 15 November 2019, Cantargia announced it is proceeding with plans to initiate a clinical trial in the US, which followed a positive pre-IND meeting with the FDA. Cantargia plans to file for the IND application in January 2020. The rationale to test CAN04 in combination with CPIs is based on several observations:

- Myeloid suppressive cells, such as tumour associated macrophages or myeloid derived suppressor cells, express IL1RAP and play a substantial role in PD-1 resistance.
- IL-1 upregulates PD-L1 on macrophages and induces downstream factors, such as IL-6, which add to immunosuppression in the tumour microenvironment.
- IL-1beta blockade has been shown to reverse the tolerance to anti-PD-1 in an in vivo setting.

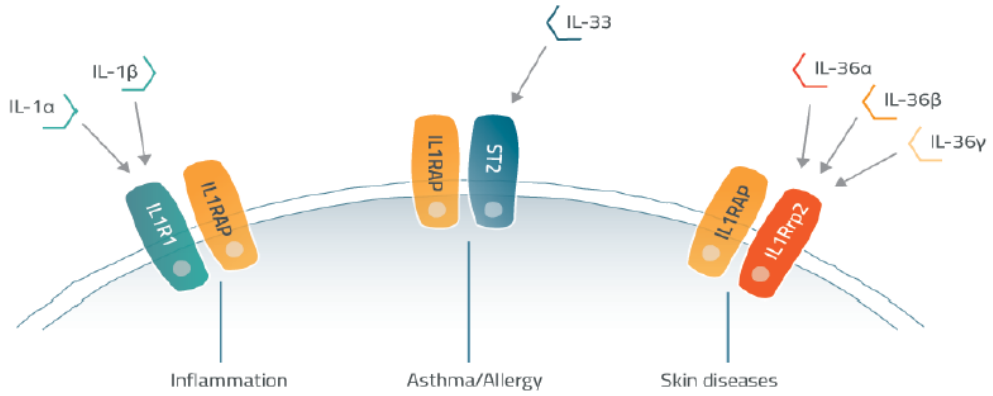
The trial design has not yet been confirmed, but preliminary to this will be a Phase Ib trial with CAN04 in combination with checkpoint inhibitors in three indications: NSCLC, head and neck squamous cancer (HNSC) and bladder cancer. These indications were selected because the

tumours express IL1RAP and are relatively immunogenic, therefore suitable for treatment with CPIs. In addition, checkpoint inhibitor (Keytruda) is a standard therapy in these indications. The patients in the trial will be eligible if they have progressed on prior PD1/PDL-1 antibody therapy. (second-line positioning). Up to 18 patients are planned to be included in the trial. Endpoints will include typical safety evaluation, as well as exploratory biomarkers and initial efficacy. The trial could start in Q220.

CAN10: New preclinical project introduced

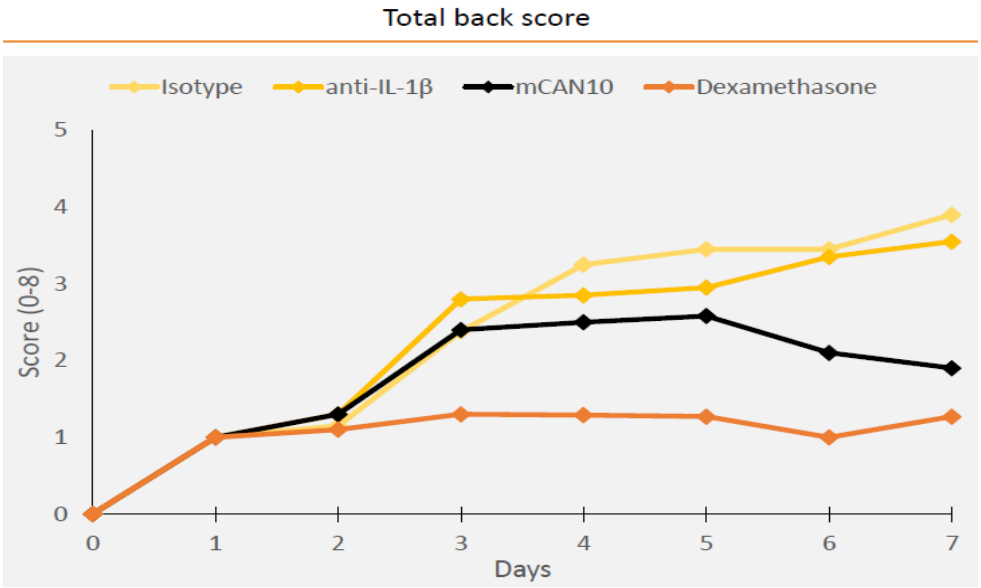
In addition to its lead project CAN04, Cantargia and its collaborator Panorama Research worked together on the preclinical programme CANxx. CANxx is focused on the discovery of an antibody against IL1RAP that has the potential to treat autoimmune and inflammatory diseases with the involvement of three interleukin pathways (IL-1, IL-33 and IL-36). On 5 December 2019, Cantargia announced it had selected CAN10 for preclinical development. The project includes two different antibodies that show potential in targeting all three pathways. Cantargia expects to name the drug candidate later and, in case of favourable results, the Phase I trial could start in 2021.

Exhibit 3: CAN10 simultaneously targets IL-1, IL-33 and IL-36 pathways



Source: Cantargia

Exhibit 4: CAN10 reduces inflammation in animal disease model



Source: Cantargia

Based on an extensive literature review Cantargia selected two indications on which to focus: systemic sclerosis and myocarditis. The rationale for selecting these indications is that all three interleukin pathways are involved. Both conditions can be described as orphan indications, so Cantargia could develop these projects on its own. In contrast, CAN10's mechanism of action makes it a unique asset and we do not know of any other R&D projects in development that simultaneously target the three interleukins. From the perspective of competition, this makes it a potentially attractive in-licensing target for pharma companies in the anti-inflammatory drug development field.

To this end, US-based XBiotech announced on 7 December 2019 that Janssen (Johnson & Johnson) acquired its anti-IL-1alpha antibody bermekimab for $750m upfront and $600m in potential milestones payments. Initially, XBiotech tested bermekimab in oncology; however, results from Phase III trials in colorectal cancer were mixed and ultimately the antibody was repositioned for inflammatory diseases. XBiotech is running two mid-stage clinical trials with bermekimab for hidradenitis suppurativa and atopic dermatitis, but the company will be prohibited (for anti-competitive reasons) from entering dermatology again with new antibodies, presumably the area of interest for Janssen. Although it is still not clear what Janssen's plans with bermekimab are, the deal terms suggest its interest in this pathway is very high.

Given its troubled past in oncology, the comeback that XBiotech has made in dermatology is remarkable. With CAN04 Cantargia does not target inflammatory diseases, but CAN10's mechanism of action does overlap that of bermekimab. Theoretically, as we described in our initiation report, anti-IL1RAP antibodies (CAN10 and CAN04) would have a more profound downstream effect as they block the signalling via both IL-1alpha and IL-1beta receptors, as opposed to inhibiting only IL-1alpha (eg bermekimab) or IL-1beta (eg canakinumab, Novartis).

Another deal involving interleukin-based assets was announced on 9 December 2019, when Sanofi agreed to pay $2.5bn for Synthorx, a biotech company in California, US. Synthorx's lead compound is THOR-707, a variant of IL-2. To our knowledge, there is no significant overlap between the downstream effects of IL-2 and the three interleukin pathways Cantargia is targeting (IL-1, IL-33 and IL-36). Therefore, this deal is not directly comparable. However, when taken together the XBiotech and Synthorx deals demonstrate pharma's interest in immunotherapies exploiting interleukin pathways.

Financials and valuation

With its Q319 results, Cantargia reported an operating loss of SEK26.3m versus SEK21.4m in Q318. R&D costs in Q219 were SEK23.2m versus SEK16.7m in Q318, an increase due to the initiation of the larger Part 2 (Phase IIa) of the CANFOUR trial. We have adjusted our operating loss slightly to SEK101.1m and SEK114.1m for 2019 and 2020, from SEK94.9m and SEK117.8m, respectively. The reported cash position at end Q319 was SEK194.5m (including short-term investments).

Our updated valuation of Cantargia is higher at SEK2.94bn or SEK40.4/share versus SEK2.65bn or SEK36.4/share previously, as we slightly increased the success probability for CAN04 to reach the market to 18% from 15% to reflect the early positive interim data. The modest revision of our estimates and rolling our model forward were offset by the lower cash position. Potential catalysts for Cantargia's share price in the near term include:

- The initiation of the US trial with CAN04 in combinations with checkpoint inhibitors (likely Q220);
- Phase IIa CANFOUR trial combination results in PDAC and NSCLC:
  - more response, biomarker and safety data in 2020;

  - progression free survival and overall survival in 2021;
- Phase IIa CANFOUR trial monotherapy biomarker/biopsy results (2020); and
- CAN10 preclinical development update.

Exhibit 5: 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	3,100	6,518.6	89.5	18.0%	1,186.6	16.3
CAN04 – pancreatic cancer	2024	2,100	6,614.9	90.9	18.0%	1,587.9	21.8
Net cash/short-term investments, FY19e			165.3	2.3	100%	165.3	2.3
Valuation			**13,298.8**	**182.7**		**2,939.8**	**40.4**

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

Exhibit 6: Financial summary

SEK000s	2017	2018	2019e	2020e
Year end 31 December	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS				
Revenue	0	0	0	0
Cost of Sales	0	0	0	0
Gross Profit	0	0	0	0
Research and development	(52,419)	(76,951)	(86,951)	(99,602)
EBITDA	(60,010)	(93,306)	(101,074)	(114,149)
Operating Profit (before amort. and except.)	(60,010)	(93,306)	(101,074)	(114,149)
Intangible Amortisation	0	0	0	0
Exceptionals	0	0	0	0
Other	0	0	0	0
Operating Profit	(60,010)	(93,306)	(101,074)	(114,149)
Net Interest	(243)	2,145	360	0
Profit Before Tax (norm)	(60,253)	(91,161)	(100,715)	(114,149)
Profit Before Tax (reported)	(60,253)	(91,161)	(100,715)	(114,149)
Tax	0	0	0	0
Profit After Tax (norm)	(60,253)	(91,161)	(100,715)	(114,149)
Profit After Tax (reported)	(60,253)	(91,161)	(100,715)	(114,149)
Average Number of Shares Outstanding (m)	32.4	66.2	69.5	72.8
EPS - normalised (SEK)	(1.86)	(1.38)	(1.45)	(1.57)
Dividend per share (SEK)	0.0	0.0	0.0	0.0
Gross Margin (%)	N/A	N/A	N/A	N/A
EBITDA Margin (%)	N/A	N/A	N/A	N/A
Operating Margin (before GW and except.) (%)	N/A	N/A	N/A	N/A
BALANCE SHEET				
Fixed Assets	2,957	2,957	2,957	2,957
Intangible Assets	0	0	0	0
Tangible Assets	0	0	0	0
Investments	2,957	2,957	2,957	2,957
Current Assets	271,496	168,486	184,426	70,277
Stocks	0	0	0	0
Debtors	0	0	0	0
Cash	149,781	76,528	25,283	51,134
Other*	121,715	91,958	159,143	19,143
Current Liabilities	(28,334)	(16,398)	(35,014)	(35,014)
Creditors	(28,334)	(16,398)	(35,014)	(35,014)
Short term borrowings	0	0	0	0
Long Term Liabilities	0	0	0	0
Long term borrowings	0	0	0	0
Other long term liabilities	0	0	0	0
Net Assets	246,119	155,045	152,369	38,220
CASH FLOW				
Operating Cash Flow	(40,860)	(105,165)	(99,962)	(114,149)
Net Interest	(243)	478	360	0
Tax	0	0	0	0
Capex	0	0	0	0
Acquisitions/disposals	0	0	0	0
Financing	304,479	0	98,037	0
Other*	(139,499)	31,434	(49,680)	140,000
Dividends	0	0	0	0
Net Cash Flow	123,877	(73,253)	(51,245)	25,851
Opening net debt/(cash)	(25,904)	(149,781)	(76,528)	(25,283)
HP finance leases initiated	0	0	0	0
Other	0	0	0	(0)
Closing net debt/(cash)	(149,781)	(76,528)	(25,283)	(51,134)

Source: Cantargia accounts, Edison Investment Research. Note: *Mainly short-term investments.

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