EDISON

Onxeo

Company update

Expanding AsiDNA R&D programme

Pharma & biotech

Currently, Onxeo is running a triple combination Phase Ib study (n=6; AsiDNA plus carboplatin plus paclitaxel). Top line results should be available by end-2020, subject to the COVID-19 pandemic impact. A major expansion of the R&D programme is the new Phase Ib/II REVOCAN trial. This new study will evaluate AsiDNA's potentially unique ability to reverse tumour resistance to the PARP inhibitor, niraparib. First data are expected by the end of 2020 or early-2021. The outcomes of these studies will define AsiDNA's mid- to late-stage development, so they represent substantial catalysts for the share price. Newly released preclinical data suggest that AsiDNA could also abrogate resistance to tyrosine kinase inhibitors (TKIs), which could significantly broaden its applications. Our valuation is €134m or €2.00 per share.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/18	6.1	(4.2)	0.05	0.0	N/A	N/A
12/19	4.3	(11.5)	(0.15)	0.0	N/A	N/A
12/20e	9.6	(4.8)	(0.07)	0.0	N/A	N/A
12/21e	3.5	(11.1)	(0.17)	0.0	N/A	N/A

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

Phase Ib DRIIV combination study ongoing

The ongoing Phase Ib DRIIV combination study is the first study testing AsiDNA in combination with carboplatin alone (first cohort) and carboplatin plus paclitaxel (second cohort). In September 2019, Onxeo released encouraging initial results from the first cohort of patients (n=3). In the second cohort (n=6), patients with various solid tumours will receive AsiDNA with carboplatin and paclitaxel (the standard of care in many solid tumours). As of January 2020, three of six patients have been enrolled in the second cohort with preliminary results expected by end-2020 (the exact timing is subject to any impact from COVID-19).

New Phase Ib/II REVOCAN study

In its preclinical studies, Onxeo previously identified another possible use of AsiDNA, which is a potentially unique ability to abrogate acquired resistance to PARP inhibitors. This strategy will be explored for the first time in a clinical setting in the upcoming Phase Ib/II study, REVOCAN, where AsiDNA will be used to abrogate the resistance to PARP inhibitor niraparib. So far, Onxeo has presented a preliminary design for the study. The trial will enrol up to 26 platinum-sensitive relapsed ovarian cancer patients in six French centres with the first patient expected to be recruited in early-H220. Depending on the impact of the COVID-19 pandemic, preliminary results are expected by the end of 2020 or early-2021.

Valuation: €134m or €2.00 per share

We value Onxeo at €134m or €2.00 per share vs €129m or €2.30 per share previously after rolling the model forward. Onxeo reported a cash position of €5.7m at end-2019. Together with an equity financing line in place and the licensing payment from Acrotech (€6m), the company estimates cash reach to Q221.

27 May 2020

Price	**€0.49**
Market cap	**€33m**
Net cash (€m) at end 2019	5.7
Shares in issue	67.8m
Free float	80%
Code	ONXEO
Primary exchange	Euronext Paris
Secondary exchange	OMX Copenhagen

Share price performance

%	1m	3m	12m
Abs	8.0	(5.9)	(38.7)
Rel (local)	2.4	16.2	(29.6)
52-week high/low		€0.83	€0.33

Business description

Onxeo is focused on cancer indications, specialising in novel DNA damage response inhibitors. AsiDNA, a novel DNA break repair inhibitor from Onxeo's platON platform, is in a Phase Ib trial with preliminary results expected in Q419. AsiDNA has a broad potential and can be combined with various anticancer treatments.

Next events

Phase Ib/II REVOCAN trial start	Mid-2020
OX401 preclinical development update	2020
Results from Phase Ib DRIIV triple combination cohort	End-2020

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Edison profile page

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Expected impact of the COVID-19 pandemic

Onxeo has provided an update on the expected impact of the COVID-19 pandemic. The company introduced preventive measures as required by the authorities. Presuming the situation improves in Q320 Onxeo expects the impact on its operating activities will be limited, although it is too early to predict with certainty. While some delays are expected with the ongoing Phase Ib study, the new key Phase Ib/II study, REVOCAN, is still in planning stages. A significant part of the preclinical development is performed internally and Onxeo is able to carry out most of the work.

Belinostat fully out-licensed to Acrotech Biopharma

The most significant recent development was the licensing deal announced on 6 April 2020 with Acrotech Biopharma, a wholly-owned subsidiary of Aurobindo Pharma. The deal extends Acrotech's rights to belinostat, the HDAC inhibitor developed by Onxeo, to all territories not previously covered and also transferred certain related intangibles (IP and know-how). Onxeo will receive a one-time payment of $6.6m (no royalties).

Belinostat is currently marketed in the US under the name Beleodaq (injectable belinostat) in the second-line treatment of peripheral T-cell lymphoma. Originally, Onxeo out-licensed the US rights to Spectrum Pharmaceuticals. Acrotech acquired these rights in March 2019. The new licensing agreement grants Acrotech the rights to all remaining regions.

In June 2018, Onxeo effectively sold royalties from belinostat to SWK Holdings in exchange for an immediate payment of $7.5m. The SWK agreement is unaffected by the licensing deal with Acrotech ie Onxeo will continue booking belinostat royalties as revenues in the P&L, which will be allocated to the reimbursement of the bonds owned by SWK (which is entitled to receive US$13.5m). In our reports since Onxeo and SWK's agreement, we have completely excluded any potential residual value of belinostat from our rNPV valuation, so the $6.6m payment from Acrotech for the updated licensing deal comes as a positive surprise for us.

Following this transaction, Onxeo is now solely focused on its DDR platform and the cash runway is extended into Q221 (company's guidance).

Triple combo Phase Ib study ongoing

The ongoing Phase Ib DRIIV combination study is the first study testing AsiDNA in combination with carboplatin alone in the first cohort and carboplatin plus paclitaxel in the second cohort. It is an extension of the Phase I dose escalation trial, which showed that intravenous administration of AsiDNA had no serious drug-related side effects and had a positive effect on activity biomarkers (increased levels of γH2AX and pHSP90) at the optimal dose of 600mg.

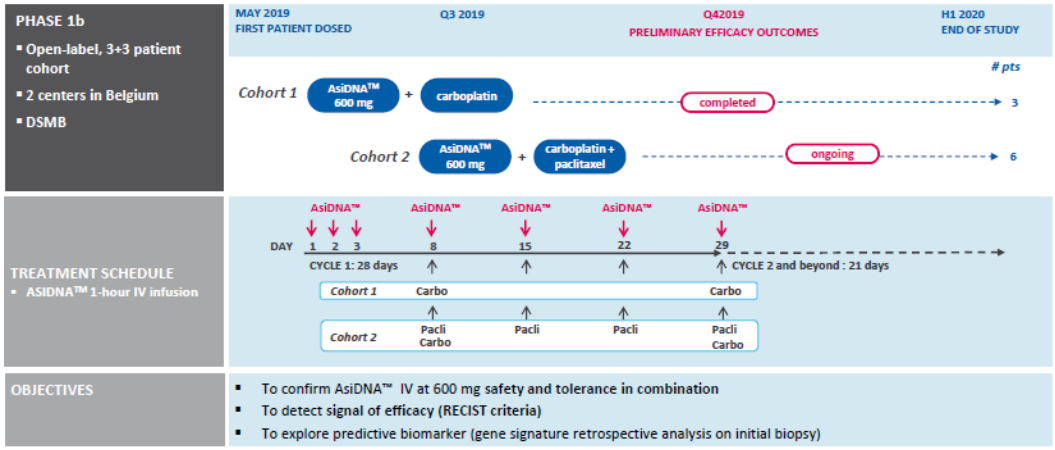
In September 2019, Onxeo released initial results from the first cohort of patients (n=3) in the DRIIV Ib study. The three patients had progressive metastatic cancer (non-small cell lung cancer, triple negative breast cancer, gastric cancer) and were treated with AsiDNA plus carboplatin:

- Two of the three patients have shown stable disease (RECIST) since the start of the treatment. All three patients had metastatic-progressing cancer at the time of inclusion.
- Onxeo also noted that the duration of the disease stabilisation was longer than that following the prior anticancer treatments these two patients (third-line NSCLC and sixth-line TNBC) had received.

- No dose-limiting toxicity was observed.

While it is too early to draw any conclusions on efficacy, stable disease status in two out of the three patients and a good safety profile are the first encouraging signs of the combination therapy. In the second cohort (n=6), patients with various solid tumours will receive a combination of AsiDNA plus carboplatin and paclitaxel (standard of care in many solid tumours). Results are expected by end-2020.

Exhibit 1: Study design for Phase Ib DRIIV combination



Source: Onxeo

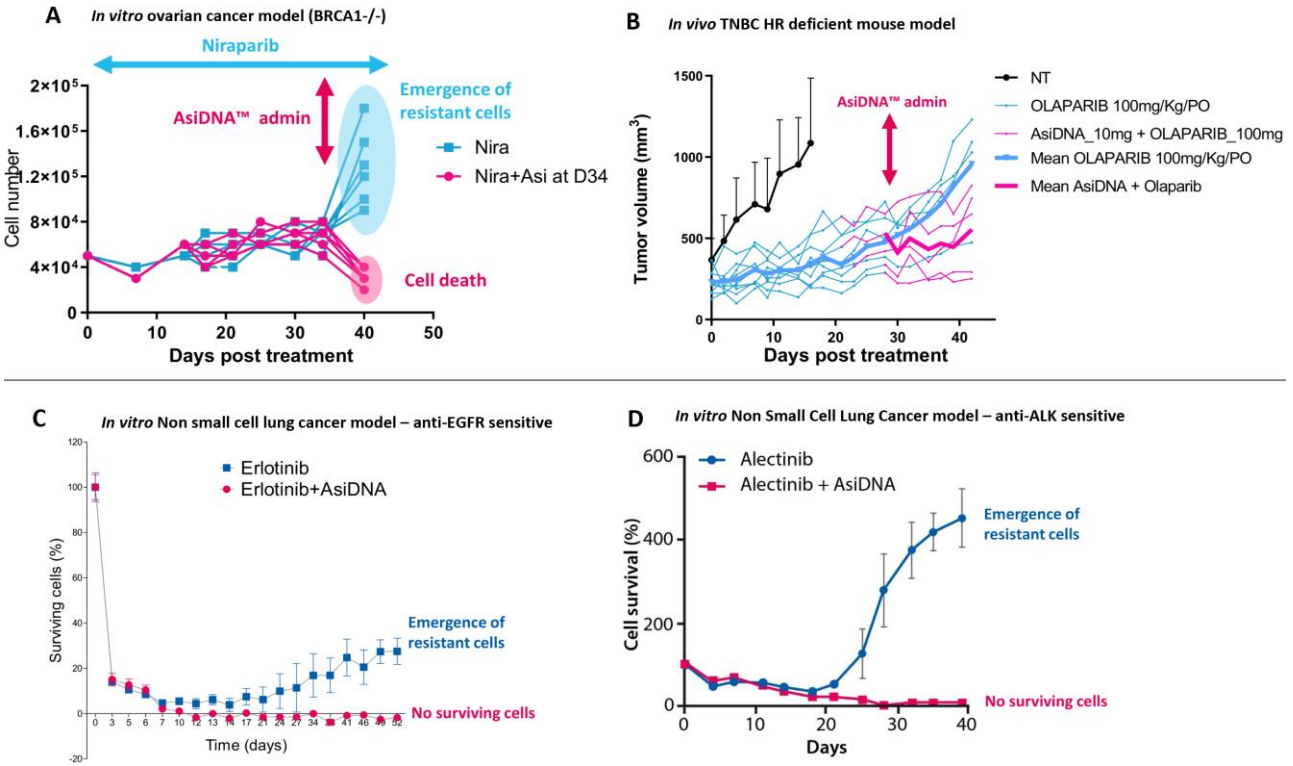
AsiDNA belongs to the DNA damage repair inhibitor class, like PARP inhibitors, but has a unique mechanism of action. It is the only oligonucleotide decoy agonist in development that disrupts and exhausts the tumour DNA damage response mechanism. The combination of AsiDNA with DNA-damaging chemotherapies, such as platinum-based anticancer drugs, is expected to produce synergies.

New Phase Ib/II REVOCAN study: AsiDNA and abrogation of resistance to anticancer treatments

In its preclinical studies, Onxeo previously identified another possible use of AsiDNA, which is a potentially unique ability to abrogate acquired resistance to PARP inhibitors. Some of the accumulated proof-of-concept preclinical data were presented at the American Association for Cancer Research Annual Meeting in April 2019. More recently, Onxeo released a fresh set of in vitro and in vivo data, where AsiDNA allowed resistance to PARP inhibitors to be overcome even when it was introduced after the resistance had emerged (Exhibit 2A and B). This strategy will be explored for the first time in a clinical setting in the upcoming Phase Ib/II study, REVOCAN (REVersion of resistance in Ovarian Cancer with AsiDNA and Niraparib). In this study AsiDNA will be used to abrogate the resistance to PARP inhibitor niraparib (details below).

The preclinical data also suggest AsiDNA could have a similar ability to abrogate resistance to TKIs. In the in vitro models of non-small cell lung cancer, AsiDNA prevented the emergence of resistance to two different TKIs, erlotinib (anti-EGFR) and alectinib (anti-ALK) (Exhibit 2C and D). This is the first time Onxeo has reported proof-of-concept data showing that such a mechanism of action is not limited to PARP inhibitors, but also includes TKIs. If confirmed, this could substantially broaden AsiDNA's potential use in combination anticancer treatments. The data are still early, but Onxeo may start another clinical trial, likely Phase Ib/II also, where AsiDNA could be used to abrogate resistance to an EGFR inhibitor or another targeted therapy in NSCLC.

Exhibit 2: AsiDNA abrogates acquired resistance to PARP inhibitors and TKIs in preclinical models



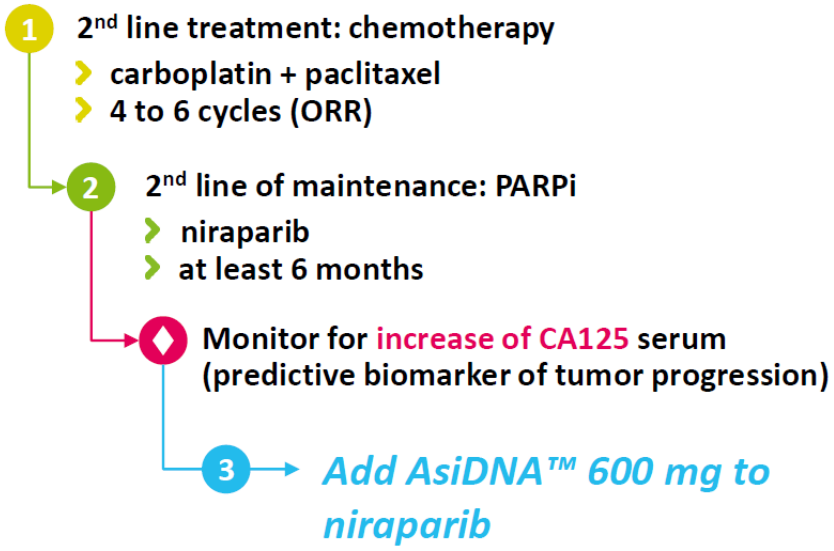
Source: Onxeo corporate presentation

Preliminary design of Phase Ib/II REVOCAN study

In this trial Onxeo will explore AsiDNA's potential to abrogate tumour resistance to the PARP inhibitor, niraparib (Tesaro/GSK; consensus sales forecast of $1.3bn in 2024; EvaluatePharma). To date, there are four approved PARP inhibitors and, while commercially successful drugs, they still suffer from the rapid development of resistance. If the ability to abrogate resistance can be proven, AsiDNA could be a good partner drug because of its benign safety profile.

So far, Onxeo has presented a preliminary design for the study (Exhibit 1). The company plans to enrol up to 26 platinum-sensitive relapsed ovarian cancer patients in up to six French centres; the first patient is expected to be recruited in mid-H120. AsiDNA will be given to the patients once the serum biomarker (CA125) for tumour progression start to rise. The **primary endpoints** are safety/tolerability and a decrease in CA125. The **secondary endpoints** are progression-free survival and overall survival. Preliminary results are expected before the end of 2020 or early 2021.

Exhibit 3: Preliminary design of the Phase Ib/II REVOCAN study (n = up to 26)



Source: Onxeo

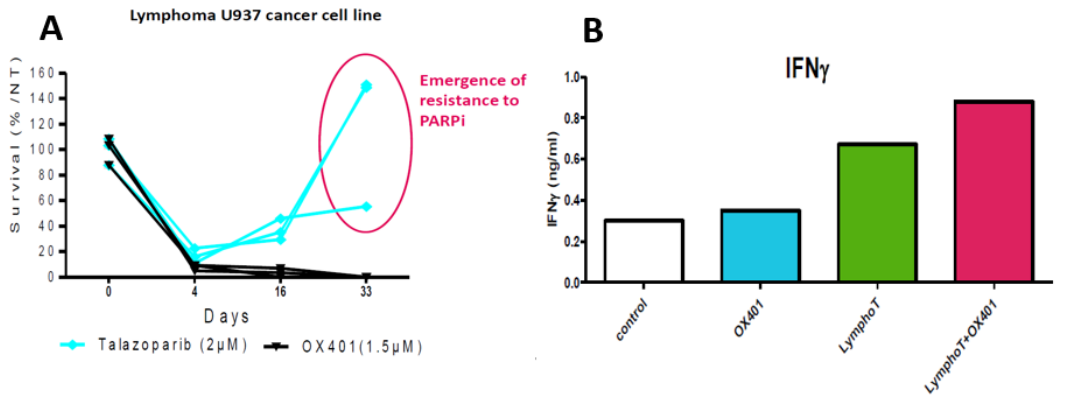
OX401: New generation asset from platON

The second asset that Onxeo has chosen to progress from its platON platform is OX401. Like AsiDNA, OX401 is comprised of double strand oligonucleotides, a linker (coupling agent) and a cellular uptake facilitator (cholesterol). Oligonucleotide is composed of 16 DNA base pairs and is optimised to bind and activate PARP signalling enzymes. This is the main difference to AsiDNA which is composed of 32 DNA base pairs and has a broader effect (hyperactivates PARP and DNA-PK). Like AsiDNA, OX401 acts as decoy agonist; it binds PARP protein specifically and then hyperactivates it, thus distracting it from its role in cancer cells. In addition, preclinical data show that OX402 is able to activate the STING pathway.

Recently, Onxeo presented first detailed preclinical data with OX401 at the PARP & DDR Inhibitors Summit in Boston, MA, 29–30January 2020. Although the data are still early, the findings suggest that:

- Unlike PARP inhibitors, cancer cells do not develop resistance to OX401 (Exhibit 4A).
- PARP inhibitor efficacy is dependent on the presence of BRCA gene mutation, the so called 'synthetic lethality' principle (described in detail in our outlook report). Onxeo's data show that OX401 is active even in BRCA non-mutated cancers.
- Early data suggest that OX401 could be used as a single agent in certain genetically defined cancer subgroups.
- In addition to PARP hyperactivation, OX401 was able to activate the STING pathway (Exhibit 4B). This could present opportunities to combine OX401 with immune checkpoint inhibitors and other cancer immunotherapies.

Exhibit 4: Selected preclinical OX401 data



Source: Onxeo

A STING receptor is a known mediator of the immune system that when activated induces expression of interferon and other T-cell recruitment factors. This results in the activation of dendritic cells, which act as antigen-presenting cells. The ultimate outcome is a tumour-specific immune response with 'trained' CD8+ T-cells attacking the cancer. The strategic opportunity for STING activating therapies could be patients not responding to checkpoint inhibitors (CPI), but there is also potential for use in combination with CPIs, as a single agent or in combination with targeted anticancer therapies. The strong rationale for combinations is based on the fact that CPIs act late in the immunity cycle (they make the tumour 'visible' to T-cells), while the STING pathway appears to prime the production of cancer-specific T-cells, so both technologies are potentially synergistic.

Although early, the first preclinical data indicate the next generation asset from Onxeo's platON platform has several interesting features and seems to be clearly differentiated from AsiDNA. The finding that it activates STING means that Onxeo will be able to explore its potential in combinations with cancer immunotherapies in clinical trials.

Financials

Onxeo booked revenues of €4.3m in 2019, of which recurring revenues of €3.5m came in from the sales of Beleodaq. Following the royalty sale agreement with SWK and the updated licensing deal with Acrotech, Beleodaq-related sales growth is no longer a value driver for Onxeo.

Total operating expenses amounted €14.2m in 2019, in line with 2018. Onxeo also booked €24.5m in one-off costs (impairment charges related to belinostat, SpeBio shares and a €6m provision relating to future payments due by Onxeo to SpePharm as per the settlement with SpePharm). Our total operating spending estimates for 2019 and 2020 are largely unchanged at €14.0m and €14.2m respectively.

Onxeo reported a cash position of €5.7m at the end of 2019. The company has an equity financing line with Nice & Green, which Onxeo used to raise €4.9m in 2019. Onxeo also reported that on 31 March 2020 the cash position was €7.3m. This, the licensing payment from Acrotech (€6m) and the remaining balance of the equity line, provides funding until Q221.

Valuation

We value Onxeo at €134m or €2.00 per share vs €129m or €2.00 per share previously after rolling the model forward and updating the total number of shares (from the equity financing line). We

presented our valuation approach in detail in our recent outlook report. We include AsiDNA in two indications, although there is potential to expand beyond that. For example, with its 2019 results Onxeo presented a rationale for AsiDNA in non-small cell lung cancer. We do not yet include OX401 in our rNPV model due to the early stage of the project, but we will re-evaluate it once more data are released.

Exhibit 5: Onxeo rNPV valuation

Product	Indication	Launch	Peak sales (US$m)	NPV (€m)	Probability (%)	rNPV (€m)	NPV/share (€/share)
AsiDNA	Ovarian cancer	2026	1,850	359.9	15%	62.7	0.93
AsiDNA	TNBC and metastatic, HER2-, BRCA-mutated breast cancer	2026	4,060	718.3	15%	116.5	1.74
Validive milestones				48.3	25%	12.1	0.18
Net cash (last reported)				5.7	100%	5.7	0.09
Valuation				**772.3**		**134.3**	**2.00**

Source: Edison Investment Research. Note: TNBC = triple negative breast cancer.

Exhibit 6: Financial summary

€000s	2018	2019	2020e	2021e
Year end 31 December	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS				
Revenue	6,127	4,288	9,565	3,455
Cost of Sales	(215)	(350)	(350)	(350)
Gross Profit	5,912	3,938	9,215	3,105
EBITDA	(3,435)	(9,124)	(4,087)	(10,450)
Operating Profit (before amort. and except.)	(19,189)	(3,527)	(3,527)	(9,795)
Intangible Amortisation	0	0	0	0
Exceptionals	(12,117)	(24,543)	0	0
Operating Profit	(15,644)	(34,338)	(4,758)	(11,121)
Other	5,176	(39)	0	1
Net Interest	(690)	(1,677)	(3)	(3)
Profit Before Tax (norm)	(4,217)	(11,472)	(4,761)	(11,124)
Profit Before Tax (reported)	(11,158)	(36,054)	(4,761)	(11,123)
Tax	1,760	2,324	0	0
Profit After Tax (norm)	2,719	(9,187)	(4,761)	(11,124)
Profit After Tax (reported)	(9,398)	(33,730)	(4,761)	(11,123)
Average Number of Shares Outstanding (m)	53.4	61.3	67.1	67.2
EPS - normalised (€)	0.05	(0.15)	(0.07)	(0.17)
EPS - normalised fully diluted (€)	0.05	(0.15)	(0.07)	(0.17)
EPS - (reported) (€)	(0.18)	(0.55)	(0.07)	(0.17)
Dividend per share (€)	0.0	0.0	0.0	0.0
Gross Margin (%)	93.3	96.5	93.5	93.5
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	42,874	26,346	26,346	26,346
Intangible Assets	38,573	23,358	23,358	23,358
Tangible Assets	296	109	109	109
Investments	4,005	2,879	2,879	2,879
Current Assets	20,376	11,284	8,848	5,576
Stocks	47	64	64	64
Debtors	1,479	3,353	3,353	3,353
Cash	11,253	5,708	3,272	0
Other	7,597	2,159	2,159	2,159
Current Liabilities	(8,393)	(6,200)	(6,200)	(6,200)
Creditors	(7,943)	(5,030)	(5,030)	(5,030)
Short term borrowings	(450)	(1,170)	(1,170)	(1,170)
Long Term Liabilities	(9,454)	(14,233)	(14,233)	(23,759)
Long term borrowings	0	0	0	(9,526)
Other long term liabilities	(9,454)	(14,233)	(14,233)	(14,233)
Net Assets	45,403	17,197	14,761	1,963
CASH FLOW				
Operating Cash Flow	(10,191)	(6,413)	(6,435)	(12,798)
Net Interest	6,148	(1,077)	(1)	0
Tax	(1,764)	(2,324)	0	0
Capex	(45)	(26)	0	0
Acquisitions/disposals	0	0	0	0
Financing	2,508	4,745	4,000	0
Dividends	0	0	0	0
Net Cash Flow	(3,344)	(5,095)	(2,436)	(12,798)
Opening net debt/(cash)	(14,147)	(10,803)	(4,538)	(2,102)
HP finance leases initiated	0	0	0	0
Other	(0)	0	0	0
Closing net debt/(cash)	(10,803)	(5,708)	(2,102)	10,696

Source: Onxeo accounts, Edison Investment Research

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