EDISON

Onxeo

Company outlook

Introducing platON; AsiDNA approaches Phase I

Pharma & biotech

Onxeo has experienced a volatile 2017 mainly due to Livatag's Phase III ReLive not meeting its primary endpoint. The out-licensing of Validive, fresh data from several preclinical studies with core assets – AsiDNA and belinostat combinations – were more positive recent developments. Although the share price halved after the disappointing ReLive data, the asset portfolio has been radically reshaped to focus on DNA break repair inhibition and epigenetics and Onxeo has cash reach until 2020. Our updated valuation is €218m (vs €350m) or €4.3/share.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/15	3.5	(20.0)	(0.44)	0.0	N/A	N/A
12/16	4.4	(20.4)	(0.45)	0.0	N/A	N/A
12/17e	10.2	(15.7)	(0.24)	0.0	N/A	N/A
12/18e	2.6	(14.0)	(0.28)	0.0	N/A	N/A

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

ReLive did not meet primary endpoint

As announced in September 2017, the Phase III ReLive trial with Livatag (proprietary doxorubicin-loaded nanoparticles) in advanced hepatocellular carcinoma (HCC) did not meet its primary endpoint of improving survival as a second line therapy in HCC patients over the comparison standard of care arm. Unexpected high survival in the comparison arm was the main reason given by the company. Onxeo noted that Livatag tended to show a similar efficacy as recently approved regorafenib in a subpopulation of HCC patients with well-preserved liver function (inter-trial comparison). The unmet need is significant in HCC; therefore, while Onxeo has discontinued internal development for Livatag, it plans to explore all options for licensing. However, we do not expect rapid progress in this area.

Introducing platON – DNA-targeting platform

Onxeo announced a major R&D expansion in October 2017 by introducing a proprietary, novel platform – platON – based on decoy oligonucleotides. Decoy oligonucleotides are based on three components: double strand oligonucleotides, a linker, and a cellular uptake facilitator. Each component can be modified resulting in new products while the main mechanism of action is to act as a decoy for key tumour DNA regulation mechanisms. The first product, AsiDNA has already generated supportive data from a Phase I trial with melanoma patients using intratumoural administration. Onxeo has done preclinical work to expand the use of AsiDNA via systemic administration and now plans to initiate a Phase I trial in 2018.

Valuation: €218m or €4.3/share

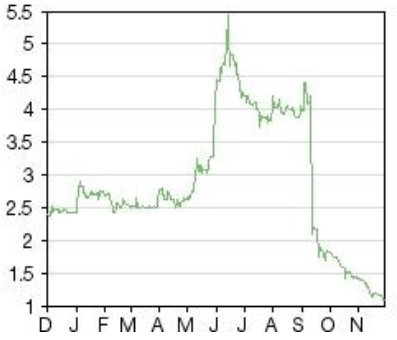
Our significantly revised model indicates a value for Onxeo of €218m (previously €350m) or €4.3/share, including net cash of €27.3m as at Q317e. Following the setback with Livatag, the main value drivers now are AsiDNA (and potential other drug candidates from platON) and belinostat, Onxeo's HDAC inhibitor. Belinostat is marketed by Spectrum Pharmaceuticals as Beleodaq in PTCL in the US, while Onxeo is developing an oral formulation to allow for more flexible combination treatments including with AsiDNA.

29 November 2017

Price	**€1.09**
Market cap	**€55m**

Net cash (€m) at end Q317e	27.3
Shares in issue	50.7m
Free float	80%
Code	ONXEO
Primary exchange	Euronext Paris
Secondary exchange	OMX Copenhagen

Share price performance



%	1m	3m	12m
Abs	(24.3)	(71.9)	(54.4)
Rel (local)	(23.0)	(73.4)	(62.1)
52-week high/low		€5.4	€1.1

Business description

Onxeo is focused on orphan cancer indications specialising in epigenetics and DNA break repair inhibition. Beleodaq, a HDAC inhibitor, is approved for PTCL in the US and partnered with Spectrum Pharmaceuticals. AsiDNA, a novel DNA break repair inhibitor from Onxeo's platON platform, is expected to enter Phase I in 2018.

Next events

AsiDNA Phase I trial start	2018
Preclinical data from oral belinostat formulation	2018

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Edison profile page

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Investment summary

Description: Focusing on epigenetics and DNA repair inhibition

Onxeo is a French biotechnology company, which following the reorganisation of its portfolio now focuses on epigenetics and DNA break repair inhibition technology. Both these technologies are novel, indicating that the company has moved away from R&D strategies such as reformulation of existing drugs (Livatag is an example). Onxeo is now a pure drug developer with lead technologies in epigenetics (Beleodaq, belinostat, an HDAC inhibitor) and DNA break repair inhibition (AsiDNA). Beleodaq is approved and partnered with Spectrum Pharmaceuticals in the US for rare blood cancer peripheral T-cell lymphoma (PTCL). Onxeo plans to explore belinostat (oral or intravenous form) in combination with AsiDNA, which is from Onxeo's newly introduced platON platform. Both compounds have synergistic potential with belinostat inducing DNA breaks, while AsiDNA prevents their repair. Onxeo has done extensive preclinical work to expand the use of AsiDNA via systemic administration and now plans to initiate clinical development in 2018.

Valuation: €218m or €4.3/share

We significantly revised our model to reflect the recent portfolio changes and our updated Onxeo valuation is €218m (vs €350m previously) or €4.3/share. This includes estimated net cash of €27.3m at Q317 (cash of €27.5m at Q317 less €155k in debt at H117). The main changes to our model include the divestment of Loramyc/Sitavig, out-licensing of Validive, increased peak sales assumption for AsiDNA and substantially reduced probability of success for Livatag. We keep the indications for AsiDNA and belinostat unchanged. However, as Onxeo progresses its R&D, there is a potential to add more indications for AsiDNA standalone or in combination with oral belinostat.

Financials: Reduced cash burn

Following the Q317 business update released in September 2017, we increased FY17e revenues from €7.9m to €10.2m mainly due to upfront payments following the divestment of Loramyc/Sitavig and the out-licensing of Validive. We have reduced FY18e revenues to reflect the removal of Loramyc/Sitavig. We have decreased our forecast R&D costs related to Livatag programme as well as personnel costs as Onxeo stated that the workforce involved with the Livatag project could be reduced by 20%. Onxeo reported a cash position of €27.5m at end-Q317. The lower cash burn means that our forecast cash reach is now until early 2020, although this is dependent on the outcome of the litigation case against SpeBio/SpePharm, as described in the Sensitivities section.

Sensitivities: Typical biotech risks apply; litigation uncertainty

Onxeo is subject to the usual drug development risks, including clinical development delays or failures, regulatory risks, competitor successes, partnering setbacks, financing and commercial risks. The main sensitivities in both the near- and mid-term relate to the lead assets: 1) AsiDNA progressing into clinical development; 2) Beleodaq US sales progression in PTCL in addition to initiation of the required Phase III trial and successful development of an oral formulation of belinostat. Beleodaq is approved in the US for PTCL, with partner Spectrum responsible for commercialisation. A further study is required to satisfy the FDA conditional approval requirements and to secure approval in Europe. Onxeo announced in October 2017 that the court's decision in the litigation case was unfavourable and the company was ordered to pay €8.6m and other smaller charges to SpePharm/SpeBio. Onxeo had a distribution agreement with SpePharm/SpeBio for Loramyc, which was terminated in 2009. Onxeo indicated that it will seek all legal options to appeal the decision. Furthermore, as Onxeo owns a 50% stake in SpeBio, a joint venture with SpePharm, the net impact is not clear at the moment should Onxeo be required to make the payment.

Outlook: Innovative drug developer

Onxeo's portfolio now focuses on its novel DNA-targeting platON platform, from which AsiDNA is the first product expected to move into clinical testing in 2018 (Exhibit 1). Belinostat is also in the core portfolio, which is approved for PTCL in the US. Onxeo is working on an oral administration formulation, which will allow for several clinical development pathways going forward: standalone oral formulation or in combination with other anti-cancer drugs, including AsiDNA. This sharp focus on epigenetics and DNA break repair inhibition follows a volatile period when the Phase III trial with Livatag did not meet the primary endpoint. More positive recent developments include Validive out-licensing to Monopar Therapeutics and divestment of non-core products Sitavig/Loramyc to Vectans Pharma. Exhibit 1 summarises Onxeo's assets and current status.

Exhibit 1: Onxeo assets

Product	Indication	Status	Comments
CORE ASSETS			
AsiDNA - DNA-targeting - *DNA break repair inhibitor*	Solid tumours, including breast cancer	Phase I/II via iv administration route planned for 2018	Phase I will establish safety and tolerability of an intravenous formulation of AsiDNA as monotherapy. Future Phase II trials will likely be in combination therapy in various solid tumours. Large potential for combinations, eg PARPi, and HDACi, including belinostat (see below).
Belinostat, (Beleodaq brand), - *injectable HDAC inhibitor*	r/r PTCL	US: approved EU: Phase III planned	US: approved and partnered with Spectrum (also in India; Onxeo receives royalties). Pint Pharma is conducting regulatory registration work in South America. EU: According to plans, the next Phase III study could address both the FDA requirement to conduct one more clinical trial after the conditional approval and will allow Onxeo to file for approval in Europe.
Belinostat, - *oral administration of HDAC inhibitor*	tbd	Preclinical	Onxeo is conducting preclinical work to develop belinostat in oral formulation. Subsequent R&D programme yet to be developed. One intention already supported by preclinical data is to explore AsiDNA and belinostat in combination treatment in various cancers.
OTHER ASSETS			
Livatag - *proprietary doxorubicin-loaded nanoparticles*	Liver cancer	Phase III	As reported in September 2017, the Phase III trial did not meet its primary endpoint, although in subgroup analysis there were signals of non-inferiority compared to other new treatments for liver cancer. Onxeo is now considering all options.
Validive - *mucoadhesive buccal clonidine*	Prevention of oral mucositis in cancer patients post radiation or chemotherapy	Out-licensed (Phase III ready)	Exclusive worldwide rights out-licensed to Monopar Therapeutics for a total deal value of $108m, including a $1m upfront payment, and up to double-digit royalties. The deal was in line with Onxeo's strategy not to initiate the Phase III trial on its own, but seek a partnership deal. Validive has 'fast track' designation from the US FDA and has been awarded orphan drug status in Europe.
Sitavig - *mucoadhesive buccal acyclovir* Loramyc - *mucoadhesive buccal miconazole*	- Recurrent *H. labialis* - Oropharyngeal candidiasis	Divested (marketed)	Onxeo divested these non-core assets in July 2017 to Vectans Pharma for €4m and potential earn-outs.

Source: Edison Investment Research; Onxeo. Note: r/r PTCL – relapsed or refractory peripheral T-cell lymphoma

Setback with Livatag

Livatag (proprietary doxorubicin-loaded nanoparticles) was being explored in the Phase III ReLive trial in advanced hepatocellular carcinoma (HCC) patients who are refractory or intolerant to sorafenib (Nexavar). As announced in September 2017, the ReLive trial did not meet its primary endpoint of improving survival as a second line or more advanced therapy in HCC patients over the comparison arm, where patients received the best standard of care (BSC). Unexpected high survival in the comparison arm was the main reason given by the company for Livatag not meeting the primary endpoint. Onxeo noted that Livatag tended to show a similar level of efficacy as recently approved (April 2017) regorafenib in second line treatment of a subpopulation of HCC patients with well-preserved liver function (inter-trial comparison, not head-to-head data).

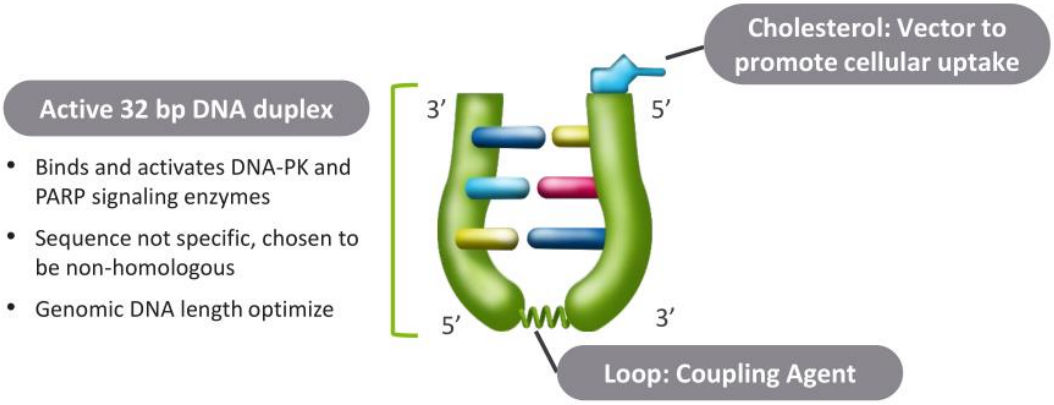
HCC is the fifth most diagnosed cancer globally and the third leading cause of death. Two thirds of patients are usually diagnosed at an advanced stage and so far only two innovative tyrosine kinase

inhibitors (sorafenib and regorafenib) have been approved. The unmet need is still significant in this indication; therefore, while Onxeo discontinued internal development for Livatag, it expects to explore all options for licensing including potential development in combinations, regions where expensive branded therapies are not available (eg parts of Asia) or other indications. However, we do not expect rapid progress in this area.

platON: New platform with AsiDNA first to Phase I

In October 2017, Onxeo announced a major R&D expansion by introducing a proprietary platform – platON – based on decoy oligonucleotides. Decoy oligonucleotides are based on three components: double strand oligonucleotides, a linker (coupling agent), and a cellular uptake facilitator (Exhibit 2). Each of these compounds can be modified resulting in different products, which main mechanism of action is to act as a decoy and target the mechanisms of tumour DNA function regulation. The first product – AsiDNA, a DNA break repair inhibitor – is expected to advance into clinical testing in 2018 using an intravenous administration route.

Exhibit 2: AsiDNA – first product from platON platform



Source: Onxeo. Note: DNA-PK = DNA-dependent protein kinase; PARP = poly(ADP ribose) polymerase.

Synthetic lethality and rationale for AsiDNA

DNA repair inhibition is experiencing a surge in interest after the three lead drugs in the area, all PARP inhibitors (Lynparza, Rubraca and Zejula) have been approved by the FDA over the past three years. Regardless of the type of DNA lesion (endogenous like replication errors or exogenous like chemotherapy and radiation) cells initiate a highly coordinated cascade of events known as DNA damage response (DDR), which leads to the initiation of the damage repair mechanism specific to the type of the lesion (Exhibit 3). There are at least four main, partly overlapping DNA repair pathways in mammals: base excision repair (BER), mismatch repair (MMR), nucleotide excision repair (NER) and double-strand break repair via two different pathways – homologous recombination (HR) and non-homologous end joining (NHEJ)[1] (Exhibit 3):

- Single strand breaks are repaired by BER. Among other enzymes involved in BER are poly(ADP ribose) polymerase 1 and 2 (PARP1 and PARP2), which act as sensors and signal transducers[1]. PARP inhibition therefore affects this pathway specifically.
- Double strand breaks are the most serious lesions (one unrepaired double strand break could trigger cell death), which are primarily repaired via two pathways, HR and NHEJ. The stage of

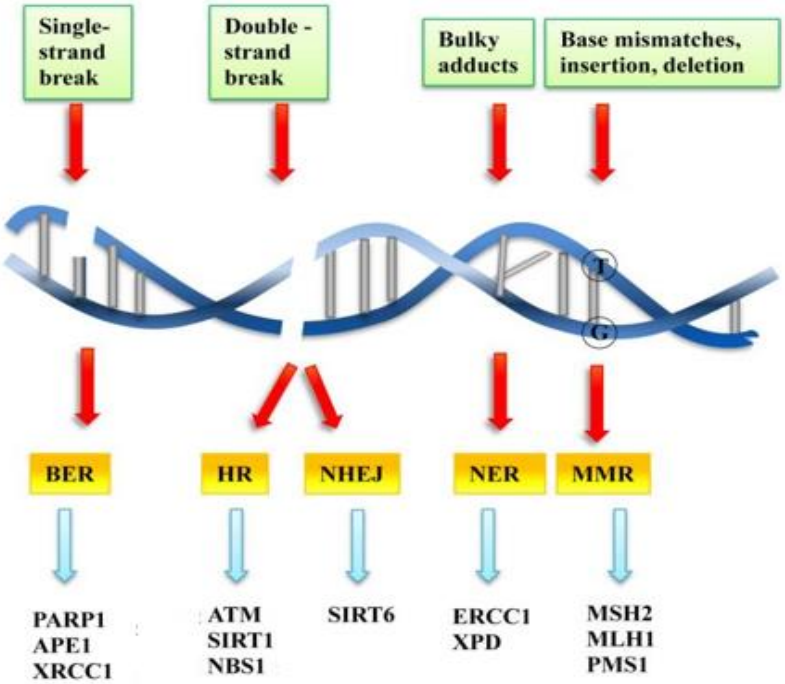
[1] T. Cervelli et al. DNA Damage and Repair in Atherosclerosis: Current Insights and Future Perspectives *Int J Mol Sci.* 2012; 13(12): 16929–16944.

cell cycle influences which mechanism is used. Among the important proteins involved in this pathway are BRCA1 and BRCA2.

- NER pathway repairs a wide class of helix-distorting lesions that interfere with base pairing and obstruct transcription and normal replication.
- MMR pathway repairs base mismatches that occur during cell DNA replication.

The aforementioned PARP inhibitors, the most advanced drugs in DNA repair inhibition field, inhibit BER pathway resulting in the accumulation of single strand DNA breaks, which eventually leads to double strand breaks[2]. This could cause cell death, but in healthy cells double strand breaks are repaired via HR or NHEJ pathways. Therefore, otherwise healthy cells are not sensitive to PARP inhibition alone. In a special case of mutated BRCA1/2 genes, the HR pathway is dysfunctional and these cells have been shown to be 100- to 1,000-fold more sensitive to PARP inhibition[2]. BRCA1/2 mutations are found in around 15% of all ovarian cancer, which is the indication all approved PARP inhibitors were developed for. A biological defect such as mutated BRCA (dysfunctional HR) complemented by a drug leading to cell death, a PARP inhibitor in this case (blocks BER), is known as synthetic lethality.

Exhibit 3: DNA damage, DDR pathways and various enzymes involved in each pathway



Source: T. Cervelli et al. Note: DDR = DNA damage response.

The rationale for using AsiDNA standalone and in combos

PARP inhibitors have shown promising efficacy and safety in clinical trials, but the main drawbacks were the necessity of a dysfunctional HR pathway and a rapid emergence of resistance[2]. First-in-class AsiDNA is based on signal-interfering DNA technology, which if introduced into a cell acts as a signal mimicking the damage of the cell's own DNA. AsiDNA molecules are short double-strand DNA that mimic double-strand breaks in the cell's DNA and are recognised as "damaged DNA" by repair and signalling proteins. Namely, AsiDNA hyper-activates PARP1 and the DNA-dependent protein kinase (DNA-PK) leading to a cascade of repair proteins being recruited to "repair the

[2] W. Jdey et al. Drug-Driven Synthetic Lethality: Bypassing Tumor Cell Genetics with a Combination of AsiDNA and PARP Inhibitors. Clinical Cancer Research, 2017

damage", as a result of which the actual damage of a cell's DNA remains unrepaired. This action renders the HR and NHEJ pathways dysfunctional.

Since HR and NHEJ are responsible for repairing double strand breaks, AsiDNA's ability to disrupt these pathways was initially explored in combination with DNA-damaging therapies, such as radiotherapy and chemotherapy. Due to its independent mechanism of action there is also strong rationale to use AsiDNA in combination with PARP inhibitors to potentiate their effect in BRACA-mutated tumours. In addition, AsiDNA could potentially be used to sensitise BRCA non-mutated tumours to PARP inhibitors, which in turn would expand their use substantially.

AsiDNA: A differentiated DNR repair inhibitor

The initial preclinical efficacy of AsiDNA technology was observed in combination with irradiation, ie sensitising tumours to radiation therapy. However, due to AsiDNA acting as a non-specific decoy activating a false DNA damage signal, other treatment modalities that produce DNA damage were also found to be possible for use in combination with AsiDNA, such as chemotherapy (with alkylating agents, antimetabolites, topoisomerase inhibitor) and radio-ablation therapy (hyperthermia). Existing preclinical data from several tumour models with different DNA damage therapies and with PARP inhibitors using different AsiDNA administration routes show that AsiDNA is a very versatile technology (Exhibit 4).

Exhibit 4: AsiDNA efficacy was demonstrated in several preclinical models

Tumour model	Treatment in combination	Route of administration
Glioblastoma	AsiDNA + Radiotherapy	Intratumoural
Cutaneous melanoma	AsiDNA + Radiotherapy	Subcutaneous/peritumoural
Cutaneous melanoma	AsiDNA + Radiotherapy	Intratumoural+subcutaneous/peritumoural
Colorectal cancer	AsiDNA + RFA* (hyperthermia)	Intratumoural+subcutaneous
Colorectal Liver metastasis	AsiDNA + chemotherapy**	Intraperitoneal
Breast cancer (TNBC)	AsiDNA standalone or with chemotherapy	Systemic
Breast cancer	AsiDNA + olaparib (PARPi)	Intratumoural

Source: Edison Investment Research, Onxeo. Note: *RFA: Radio Frequency Ablation. **5FU+oxaliplatin.

Clinical data support further development

AsiDNA (formerly DT01) has already been tested in a clinical trial with skin melanoma patients by the original developer DNA Therapeutics, which was acquired by Onxeo in February 2016. In the Phase I DRIIM study the drug was injected intratumourally or peritumourally in conjunction with the radiation therapy. DRIIM was an open-label, non-randomised, multicentre, dose escalation study. In total, 23 patients received a full course of treatment and were evaluated for safety and pharmacokinetics, while 21 patients with a total of 76 skin melanoma lesions were evaluated for initial efficacy. Key headline results were presented at ASCO in May 2015 and published later on[3]:

- AsiDNA was well tolerated and did not induce additional toxicity when combined with radiotherapy. Most frequent adverse events were reversible grade 1 and 2 injection site reactions, while the maximum tolerated dose was not reached.
- AsiDNA did not cause innate immune response, which would imply that the drug is less likely to be neutralised by the immune system or cause unwanted significant local inflammation.
- AsiDNA subcutaneous injections led to systemic exposure, which provided additional insights: lesions that were not injected with AsiDNA demonstrated a response as well, indicating AsiDNA's ability to circulate and advocating for a systemic effect. This, and a good safety profile allowed for testing systemic delivery of AsiDNA.

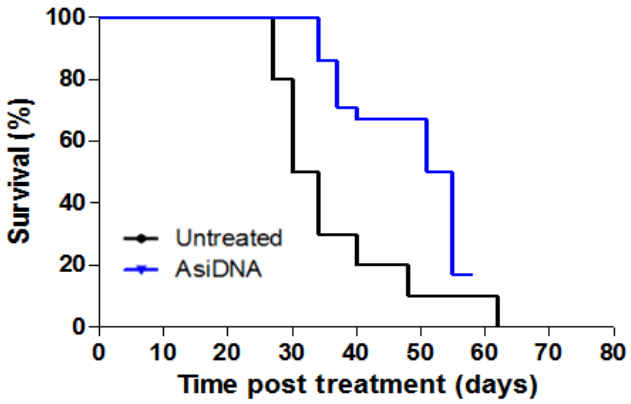
[3] C. Le Tourneau et al. First-in-human phase I study of the DNA-repair inhibitor DT01 in combination with radiotherapy in patients with skin metastases from melanoma. British Journal of Cancer (2016), 1–7.

- In the 21 patients that were evaluated for efficacy, a total of 76 tumour lesions were treated, of which 41 lesions were injected with AsiDNA.
- Objective response rate of all lesions was 59%, complete response was 30% and partial response was 29%. For comparison, similar radiation therapy schemes were reported to have complete response rate of 9%[3].
- The overall response rate of the 41 lesions injected with AsiDNA was 68% whereas in the 35 non-injected lesions it was 49% (P=0.103). This lack of significant difference could at least partially be explained by an abscopal effect through immunogenicity (ie the immune system was trained to attack the injected tumours and then non-injected as well) and systemic exposure to AsiDNA after it was absorbed from the local injection site.

Systemic administration opens many possibilities

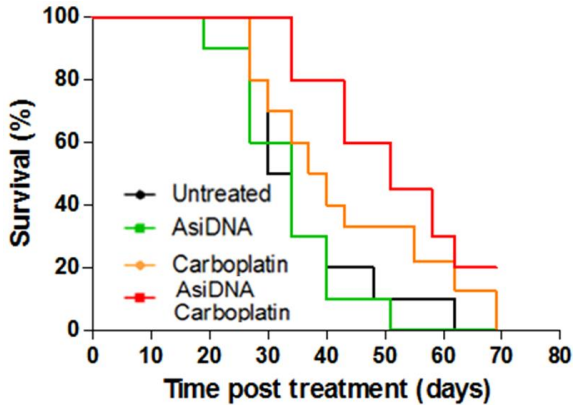
Based on preclinical data and insights from the DRIIM trial, Onxeo believed that AsiDNA's systemic administration was feasible in humans, which could open potential to explore many more indications than with local administration. The company has conducted preclinical studies and, in July 2017, announced its first preclinical proof-of-concept data with AsiDNA demonstrating the potential for intravenous administration. AsiDNA standalone significantly decreased tumour growth in a triple negative breast cancer (TNBC) model and improved survival (Exhibit 5). Onxeo also tested the drug in combination with the classic neoadjuvant chemotherapy (ie given before surgery), carboplatin. Despite AsiDNA being administered in lower doses than in the standalone trial, the combination with carboplatin outperformed other arms (untreated, low dose AsiDNA alone or carboplatin alone; Exhibit 6).

Exhibit 5: AsiDNA standalone, systemic administration



Source: Onxeo

Exhibit 6: AsiDNA in combination with carboplatin



Source: Onxeo

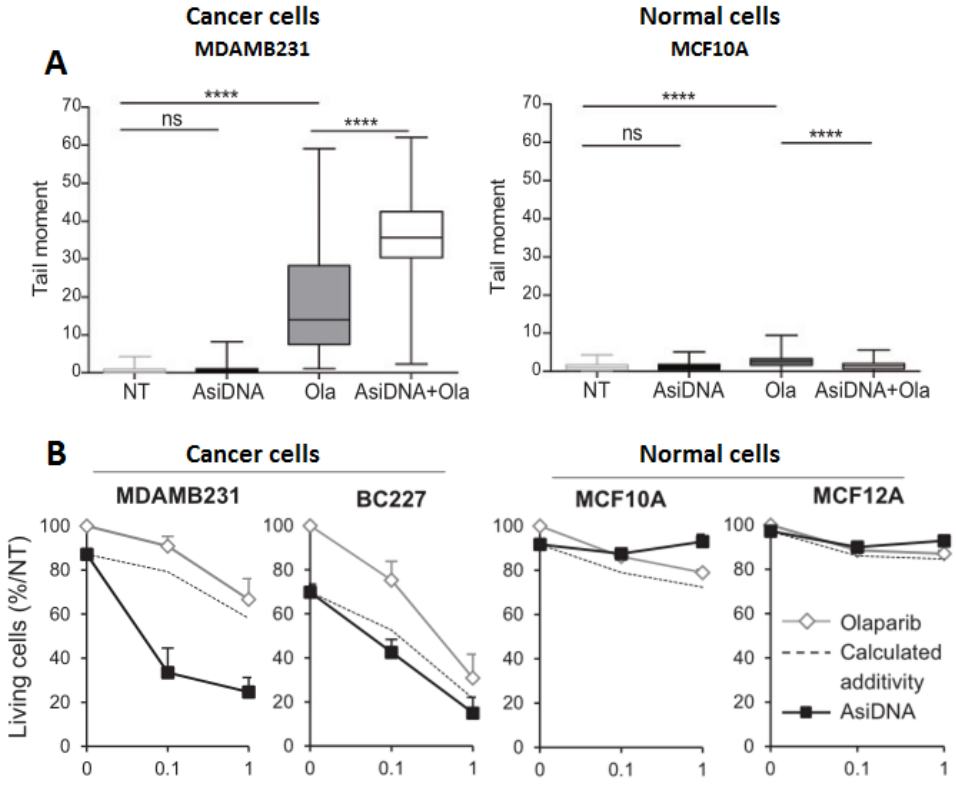
Combination with PARP inhibitors

Jdey et al explored *in vitro* the synergistic potential of the combination treatment of PARP inhibitors and AsiDNA[2]. The researchers studied AsiDNA with PARP inhibitor or standalone in 21 cancer cell lines in total with different BRCA status and three non-tumour cell lines. The most detailed comparison has been made between AsiDNA and PARP inhibitor olaparib using a breast cancer model. BRCA mutations were observed in 8.8% of all new breast cancer cases, which increased to 30% in the difficult to treat triple-negative (ER-, PR-, HER2-) breast cancer subgroup. The main conclusions were:

- AsiDNA in combination with olaparib demonstrated a synergistic effect in all cell lines regardless of the BRCA status (Exhibit 7A and 7B), which could open new indications for PARP inhibitors ie the presence of BRCA mutation would not be necessary for the use of a PARP inhibitor.

- Standalone AsiDNA did not induce damage to DNA by itself and did not show any toxicity in non-tumour cells.
- The combination of AsiDNA with other PARP inhibitors (veliparib, niraparib, iniparib, talazoparib and rucaparib) was shown to be effective as well.
- Different molecular mechanisms were observed underlying the effects of AsiDNA or olaparib, which suggests that resistance to one drug will increase sensitivity to the other drug making a double resistance very unlikely.

Exhibit 7: Effects of AsiDNA in combination with olaparib on cancer and normal cell lines



Source: Jdey et al. Note: Charts A and B show that the treatment with AsiDNA and olaparib accumulates DNA damage in cancer cells, but not healthy cells, as evaluated with comet assay (tail moment indicates DNA damage); MDAMB231 = BRCA-proficient breast cancer cells; BC227 = BRCA-deficient breast cancer cells; MCF10A and MCF12A = normal cells.

AsiDNA development strategy

Currently Onxeo is conducting preclinical studies in other tumour models and also in combination with PARP inhibitors. Onxeo indicated that it aims to file the investigational new drug application by end-2017, which will likely allow initiation of Phase I in H118, in our view. The Phase I trial will be in a variety of tumours, which will allow the selection of the best indication to progress forward.

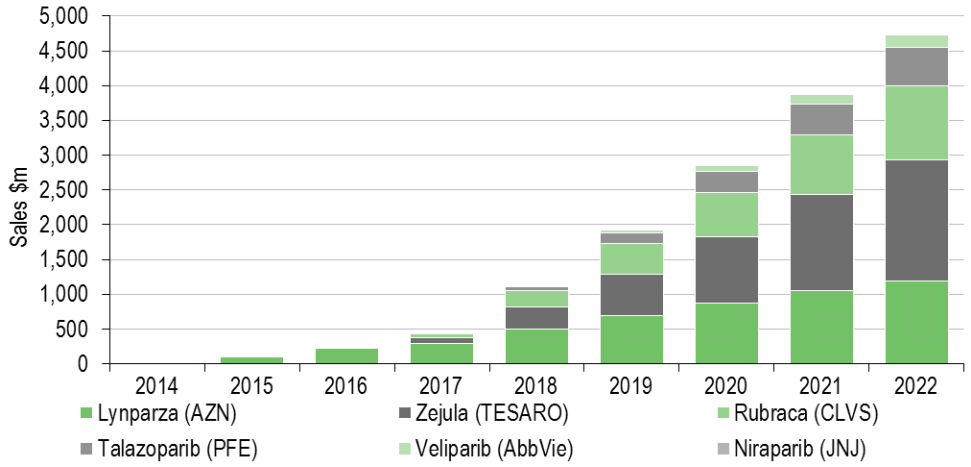
Following the acquisition of DNA Therapeutics in March 2016 we revised our valuation and included triple negative breast cancer (TNBC) indication to reflect the potential value of AsiDNA. Onxeo mentioned that while this was one of the potential directions, it was open to explore other cancers, such as platinum-resistant ovarian cancer and non-small cell lung cancer. By pathological definition, TNBC lacks an expression of oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). This type of cancer is typically more aggressive when compared to other types of breast cancer and is unresponsive to hormonal and monoclonal antibody therapies (eg trastuzumab). The standard initial treatment options are anthracycline and taxane-based combinations (eg doxorubicin, cyclophosphamide, docetaxel), but patients have a poorer prognosis and overall survival than in other types of breast cancer. A variety of new targeted

therapies are in investigation, including PARP inhibitors, with AstraZeneca also exploring its olaparib in Phase III in metastatic breast cancer with BRCA1/2 mutations and HER2 negative disease.

PARP inhibitors on the market and in development

Currently, there are three PARP inhibitors approved by the FDA and all for ovarian cancer: Lynparza (olaparib, AstraZeneca), Rubraca (rucaparib, Clovis Oncology) and Zejula (niraparib, Tesaro). PARP inhibitors piqued the market's interest after the first drug Lynparza (olaparib, AstraZeneca) was launched in late 2014 and brought $218m in sales in 2016. Initially Lynparza was approved for the treatment for ovarian cancer patients with BRCA mutant tumours no longer responsive to three or more prior therapies. However, in March 2017 AstraZeneca published new data showing that Lynparza delayed the recurrence of ovarian cancer by more than two years compared to a placebo in women with relapsed or recurrent BRCA-mutated ovarian cancer. This will likely allow expanding Lynparza's marketing label in the US to include maintenance therapy for ovarian cancer. AstraZeneca is currently evaluating olaparib in several other indications such as breast and prostate cancer. Pfizer's talazoparib and Abbvie's veliparib are two other PARP inhibitors in Phase III, both for breast cancer indication. EvaluatePharma estimates sales of all PARP inhibitors will total $4.8bn by 2022 (Exhibit 8).

Exhibit 8: PAPR inhibitor sales forecast



Source: EvaluatePharma

Overall, AsiDNA is clearly differentiated from PARP inhibitors, as it acts more upstream; it is not a specific enzyme inhibitor, but activates PARP among other repair proteins (ie it distracts, when olaparib inhibits). Therefore, it represents a new treatment approach by itself or in combination with PARP inhibitors, which could not only potentiate them, but also expand their use beyond BRCA mutated tumours. For example, while the recent Lynparza data are impressive, prolonging the survival by two years versus placebo, all the women selected in the trial had BRCA mutation and only around 15% of all ovarian cancers have this specific mutation. Onxeo will continue discussions with PARPi manufacturers to explore opportunities to combine AsiDNA with PARPi in the treatment of certain gynaecological (ovarian) and pulmonary (NSCL) cancers, in particular for tumours without genetic mutation involved in HR (HR wild type).

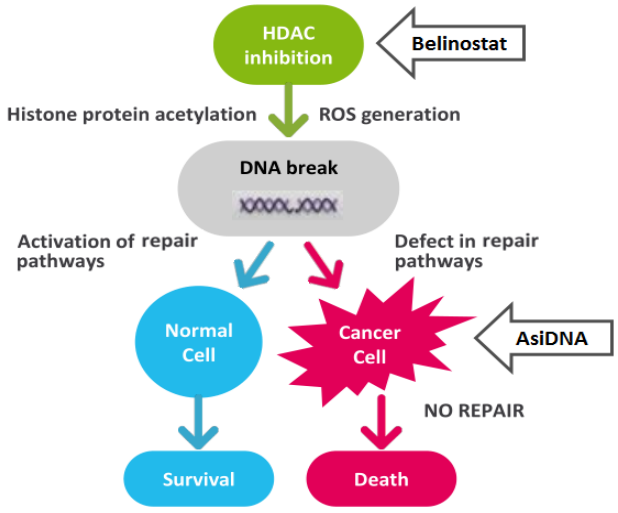
Beleodaq: Expanding commercial potential with oral belinostat formulation

Beleodaq is marketed in the US under a conditional FDA approval granted in July 2014 for relapsed or refractory peripheral T-cell lymphoma (r/r PTCL) by partner Spectrum. We continue to expect initiation in coming months of the Phase III trial in first-line PTCL comparing belinostat in combination with CHOP (cyclophosphamide, hydroxydaunorubicin, Oncovin, prednisone) therapy, compared to CHOP therapy alone. A Phase III controlled trial was a condition of the July 2014 FDA's accelerated approval based on the US Phase II BELIEF study in relapsed/refractory PTCL (n = 120). Beleodaq's approval in Europe for PTCL is also subject to the completion of a Phase III trial. As outlined previously, Onxeo and partner Spectrum plan to address both the FDA and European requirements with a single further Phase III controlled trial in first-line PTCL combining belinostat with CHOP (BelCHOP) compared to CHOP alone (ie expanding to frontline therapy and also into a new geography). The timing of the initiation of the new study, however, has not been announced by Spectrum. As per the co-development terms of the deal with Spectrum, costs will be shared, with Onxeo contributing 30%.

Onxeo is also focusing on developing an oral formulation of belinostat, which could provide a competitive advantage over the intravenous formulations of other HDAC inhibitors, allowing more flexibility not only in PTCL, but also other indications, including combination treatments. The oral formulation would also extend belinostat patent protection until 2038. Preliminary data demonstrated good bioavailability, which can be a hurdle in the development of orally available drugs. The bioavailability was 28% when using the new formulation technology, an amorphous spray dried dispersion, compared to 7% when using a conventional capsule formulation with active pharmaceutical ingredient. Onxeo expects that the first clinical trial could be conducted in 2018, which would allow it to accumulate PK/PD data. The company indicated that there is a rationale to combine oral belinostat with DNA repair inhibitors including Onxeo's AsiDNA (Exhibit 9).

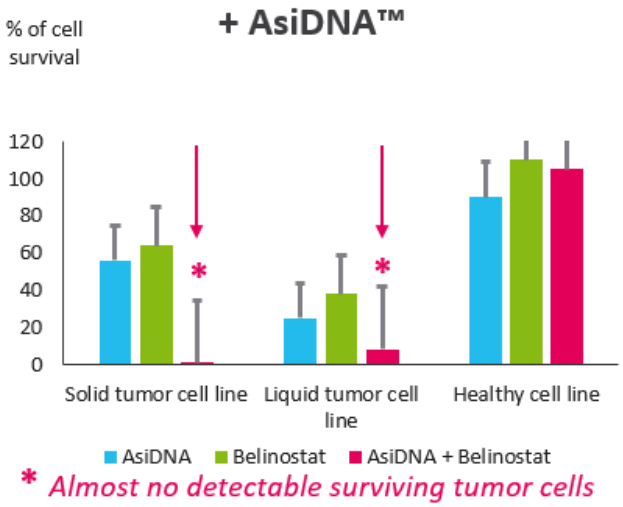
In September 2017, Onxeo reported new data from preclinical studies combining belinostat and various DNA break repair inhibitors including AsiDNA. There was a clear synergistic effect on malignant cells when compared to monotherapy of either of the drugs. Notably, the effect on healthy cells was minimal (Exhibit 10). Onxeo has started *in vivo* studies to confirm the *in vitro* data and expects peer-reviewed publications in H118.

Exhibit 9: Rationale for combining HDACi with DNA break repair inhibitors



Source: Onxeo

Exhibit 10: Belinostat in combination with AsiDNA in various tumours cell lines



Source: Onxeo data

HDAC inhibitors are attracting renewed interest. Belinostat is a strong inducer of DNA breaks, therefore the combination with AsiDNA, a DNA break repair inhibitor, could potentially be synergistic. Since Onxeo owns both technologies, the company is in a unique position to explore the synergistic potential and the best way to market.

Sensitivities

Onxeo is subject to the usual drug development risks, including clinical development delays or failures, regulatory risks, competitor successes, partnering setbacks, financing and commercial risks. The main sensitivities in both the near- and mid-term relate to the lead assets: 1) AsiDNA progressing into clinical development; and 2) Beleodaq US sales progression in PTCL in addition to initiation of the required Phase III trial. Furthermore, as preclinical progress is made with an oral formulation of belinostat, it could become more critical to the investment case. Beleodaq is approved in the US for PTCL, with partner Spectrum responsible for commercialisation. Sales momentum in the US is a driver for the share price performance. A further study is required to satisfy the FDA conditional approval requirements and to secure approval in Europe. For both AsiDNA and Beleodaq, Onxeo is pursuing a comprehensive preclinical strategy to explore the potential of these assets in other cancers and in combination with other therapies. Future clinical development would likely lead to an increase in R&D spending and require additional investment, but could also provide considerable upside to our forecasts if the projects are successful.

Onxeo announced in October 2017 that the court's decision in the litigation case was unfavourable and the company was ordered to pay €8.6m to SpeBio and other smaller charges to SpePharm/SpeBio for costs incurred to market Loramyc in Europe. The litigation started in 2009 after Onxeo (formerly BioAlliance Pharma, ie before the merger with Topotarget) terminated a distribution agreement with SpePharm/SpeBio. Onxeo believed that SpePharm/SpeBio breached contractual obligations resulting in a delayed marketing of Loramyc. Onxeo indicated that it will seek all legal options to appeal the decision. Onxeo owns a 50% stake in SpeBio, which is a joint venture with SpePharm, therefore the net impact is not clear at the moment should Onxeo be required to make the payment.

Valuation

Following the changes to our R&D model and rolling our model forward our updated Onxeo valuation is €218m (vs €350m previously) or €4.3/share, which includes FY17e net cash of €27.9m. Our indications for AsiDNA and belinostat (described above) are unchanged. However, as Onxeo progresses its preclinical development, there is a potential to add more indications for AsiDNA standalone or in combination with oral belinostat. The main changes to our model include:

- **Loramyc/Sitavig divestment**. Onxeo divested its two non-core assets Sitavig and Loramyc to Vectans Pharma. In return Onxeo received an upfront payment of €4m and potential earn-outs depending on the performance of the products in the market. The company also indicated that it will receive most of the expected milestone payments over the next three years from existing partners that distribute the products. While only the upfront payment has been disclosed, earn outs could also represent significant value for Onxeo. According to the company's 2016 annual report the two assets were partnered with a number of different distributors in various geographies. The total value of milestone/upfront payments received from the partnerships was €15m by end-2016 and the total value of payments still due (if milestones are met) was €80m. Although the assets are in the hands of Vectans Pharma, to reflect the potential future value for Onxeo we spread the contract value of milestones over a period of 10 years, risk adjust the

milestones using a conservative 30% probability and apply a discount rate of 12.5% (Exhibit 11).

- **Validive out-licensed**. As Onxeo announced in September 2017, global rights to its Phase III ready Validive have been out-licensed to Monopar Therapeutics. This was in line with the company's strategy not to initiate a Phase III study before finding a partner. Onxeo will receive a $1m upfront payment, while future milestones could reach up to $108m (of which $15.5m is related to R&D and regulatory milestones) and up to double digit royalty rates. We leave most of our assumptions unchanged, but now include the deal with Monopar with the royalty rate increasing to 10% and risk-adjusted milestones triggered with total peak sales reaching €225m by 2029.
- **Increased peak sales of AsiDNA**. We have increased market penetration for AsiDNA from 15% to 30% with a subsequent increase in peak sales to €2.2bn from €1.1m. This was based on the successful performance of the first PARP inhibitor in terms of increasing market share, but also potentially expanding in other indications. We leave our other assumptions for this asset unchanged.
- **Reduced probability for Livatag**. After the Phase III trial did not meet its primary endpoint Onxeo stated that the internal development for this asset will be discontinued, but the company will look for opportunities to find a partner. We reduce the success probability from 40% to 5%.
- So far, Spectrum Pharmaceuticals, in charge as the market authorization holder in the US, has not specifically indicated when the **Phase III trial with Beleodaq** could start. We have therefore postponed the initiation of the study by one year to 2019 allowing time for a two-year study and a launch in 2022.

Exhibit 11: Onxeo rNPV valuation

Product	Indication	Launch	Peak sales (€m)	NPV (€m)	Probability (%)	rNPV (€m)	NPV/share (€/share)
CORE ASSETS							
AsiDNA	TNBC	2024	2,170	355.5	15%	67.0	1.3
Beleodaq (US)	PTCL	2014	80	34.5	100%	34.5	0.7
Beleodaq (EU + US)	PTCL	2022	60	56.3	70%	39.4	0.8
OTHER ASSETS							
Livatag			250	211.0	5%	10.5	0.2
Validive			70	52.1	50%	26.1	0.5
Est. earn-outs associated with Loramyc/Sitavig				43.3	30%	13.0	0.3
Net cash, FY17e				27.9	100%	27.9	0.6
Valuation				**780.6**		**218.3**	**4.3**

Source: Edison Investment Research. Note: Specialty products shaded. PTCL = peripheral T-cell lymphoma, TNBC = triple negative breast cancer.

Financials

Following the Q317 business update released in September 2017, we upped our FY17 revenue estimate from €7.9m to €10.2m mainly due to the upfront payments following the divestment of Loramyc/Sitavig and the out-licensing of Validive. We have reduced our 2018 revenue forecast to reflect the removal of Loramyc/Sitavig. We have also reduced the R&D costs related to the Livatag programme and estimated personnel costs as Onxeo has stated that the workforce involved with the Livatag project could be reduced by 20%.

Onxeo reported a cash position of €27.5m at end-Q317 while we forecast cash of €27.9m at end-2017, as the company indicated earlier in the year that it is due to receive €4m in research tax credit in 2017. The lower cash burn means that our forecast cash reach is until early 2020. However, significant financial risk is related to the litigation case against SpeBio/SpePharm, as described in Sensitivities section. In addition, due to the lack of visibility on timing and the value of

payments, at present we do not include any milestones from different partnerships in our financial estimates. A summary of the main changes to our financial forecasts is shown in Exhibit 12.

Exhibit 12: Key changes to our financial forecasts

€m	2016	2017e			2018e
	Actual	Old	New	Change	
Revenue	4.423	7.850	10.248	+31%	2.623
Operating profit (reported)	(23.211)	(19.529)	(17.160)	-12%	(15.672)
Profit before tax (normalised)	(20.435)	(17.541)	(15.692)	-11%	(14.020)
Profit after tax (normalised)	(21.001)	(17.541)	(11.692)	-33%	(14.020)
EPS (norm, €)	(0.45)	(0.37)	(0.24)	-35%	(0.28)

Source: Onxeo accounts, Edison Investment Research

Exhibit 13: Financial summary

€000s	2011	2012	2013	2014	2015	2016	2017e	2018e
Year end December	IFRS	IFRS	IFRS	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS								
Revenue	3,231	4,028	1,467	22,081	3,482	4,423	10,248	2,623
Cost of Sales	(750)	(375)	(264)	(249)	(337)	(655)	(789)	(689)
Gross Profit	2,481	3,653	1,202	21,832	3,145	3,768	9,459	1,934
EBITDA	(14,429)	(11,300)	(15,189)	(4,505)	(20,355)	(21,304)	(15,121)	(13,620)
Operating Profit (before amort. and except.)	(14,841)	(11,506)	(15,412)	184	(20,574)	(21,542)	(15,505)	(14,017)
Intangible Amortisation	(97)	(9)	(10)	(800)	(1,600)	(1,626)	(1,654)	(1,654)
Exceptionals	0	0	0	(4,861)	(160)	(43)	0	0
Operating Profit	(14,938)	(11,515)	(15,422)	(5,477)	(22,334)	(23,211)	(17,160)	(15,672)
Other	0	0	(29)	(77)	(29)	0	0	0
Net Interest	316	(33)	126	5	602	1,107	(187)	(3)
Profit Before Tax (norm)	(14,525)	(11,539)	(15,286)	189	(19,972)	(20,435)	(15,692)	(14,020)
Profit Before Tax (reported)	(14,622)	(11,548)	(15,325)	(5,549)	(21,761)	(22,104)	(17,346)	(15,675)
Tax	0	0	0	(2,150)	2,353	(566)	4,000	0
Profit After Tax (norm)	(14,525)	(11,539)	(15,315)	(2,038)	(17,648)	(21,001)	(11,692)	(14,020)
Profit After Tax (reported)	(14,622)	(11,548)	(15,325)	(7,699)	(19,408)	(22,670)	(13,346)	(15,675)
Average Number of Shares Outstanding (m)	17.7	17.7	20.7	40.5	40.5	47.0	48.7	50.5
EPS - normalised (€)	(0.82)	(0.65)	(0.74)	(0.05)	(0.44)	(0.45)	(0.24)	(0.28)
EPS - normalised and fully diluted (€)	(0.82)	(0.65)	(0.74)	(0.05)	(0.44)	(0.45)	(0.24)	(0.28)
EPS - (reported) (€)	(0.83)	(0.65)	(0.74)	(0.19)	(0.48)	(0.48)	(0.27)	(0.31)
Dividend per share (€)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Gross Margin (%)	76.8	90.7	82.0	98.9	90.3	85.2	92.3	73.7
EBITDA Margin (%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Operating Margin (before GW and except.) (%)	N/A	N/A	N/A	0.8	N/A	N/A	N/A	N/A
BALANCE SHEET								
Fixed Assets	1,793	1,540	1,300	89,052	87,539	88,232	86,785	84,799
Intangible Assets	27	33	23	87,932	86,367	87,213	85,558	83,904
Tangible Assets	1,401	1,086	908	711	841	713	921	589
Investments	366	422	369	409	331	306	306	306
Current Assets	32,288	20,581	16,432	62,946	41,697	36,868	37,743	22,058
Stocks	1	3	3	65	106	184	222	193
Debtors	456	2,089	338	582	1,036	1,548	3,587	918
Cash	28,666	14,503	11,329	57,227	33,793	29,243	28,042	15,053
Other	3,164	3,986	4,762	5,073	6,762	5,893	5,893	5,893
Current Liabilities	(7,051)	(6,147)	(6,357)	(12,919)	(10,606)	(12,417)	(12,098)	(9,619)
Creditors	(6,881)	(6,090)	(6,266)	(11,290)	(10,537)	(12,311)	(11,943)	(9,464)
Short term borrowings	(170)	(57)	(91)	(1,630)	(69)	(106)	(155)	(155)
Long Term Liabilities	(4,128)	(4,231)	(3,487)	(17,108)	(15,831)	(18,594)	(16,806)	(16,806)
Long term borrowings	(2,237)	(511)	(303)	(138)	0	0	0	0
Other long term liabilities	(1,891)	(3,720)	(3,185)	(16,970)	(15,831)	(18,594)	(16,806)	(16,806)
Net Assets	22,902	11,742	7,888	121,971	102,799	94,089	95,625	80,432
CASH FLOW								
Operating Cash Flow	(11,614)	(14,076)	(14,020)	(7,733)	(20,067)	(16,838)	(18,197)	(13,920)
Net Interest	(1,106)	1,837	333	843	579	(1,560)	201	(3)
Tax	0	0	0	0	(2,448)	538	2,859	1,000
Capex	(148)	(39)	(119)	(2)	(410)	(316)	(512)	(66)
Acquisitions/disposals	0	0	0	14,208	0	0	0	0
Financing	19,367	(46)	10,807	37,207	611	13,589	14,400	0
Dividends	0	0	0	0	0	0	0	0
Net Cash Flow	6,499	(12,324)	(3,000)	44,524	(21,735)	(4,587)	(1,250)	(12,988)
Opening net debt/(cash)	(19,760)	(26,259)	(13,935)	(10,935)	(55,459)	(33,724)	(29,137)	(27,887)
HP finance leases initiated	0	0	0	0	0	0	0	0
Other	0	0	(0)	0	0	0	0	0
Closing net debt/(cash)	(26,259)	(13,935)	(10,935)	(55,459)	(33,724)	(29,137)	(27,887)	(14,898)

Source: Onxeo accounts, Edison Investment Research

Contact details	Revenue by geography
49 boulevard du Général Martial Valin 75015 Paris France +33 1 45 58 76 00 www.onxeo.com	N/A

Management team

CEO: Judith Greciet	CFO: Nicolas Fellmann
Judith Greciet became CEO in 2011. From 2007 to 2010, she was president of Eisai France, focusing on Alzheimer's disease. She has held operational and strategic managerial positions at Wyeth France (now Pfizer), LFB Group, Zeneca and Pharmacia. She is a pharmacist and has headed up oncology and hospital departments.	Nicolas Fellmann became CFO in November 2006. From 1996 to 2006, he held various finance positions at Pfizer France and was notably director of treasury tax and audit from 1999. From 1992 to 1995, he was a financial auditor at Ernst & Young. He has an MBA from EM Lyon Business School.
CMO: Olivier de Beaumont	**Executive VP – US Operations and corporate development: Philippe Maitre**
Olivier de Beaumont spent more than 10 years at Stallergenes Greer, most recently as senior vice president, head of global clinical development, pharmacovigilance and medical affairs. Prior to that, he led various clinical development programmes and strategic marketing activities at Quintiles and Aventis, addressing a wide range of therapeutic areas and leading teams, notably in oncology. He is a medical doctor and also holds a MBA from ESCP Business School and a master's degree in public health & health economics.	Philippe Maitre joined Onxeo in March 2016. He has over 35 years of experience in the pharma and biotech industries, including 15 years in corporate management within US public companies. This includes co-founder and CEO of mAbRx, CEO of Anosys and CFO of PPD Inc and Oscient Pharmaceuticals. He has a master's in finance from the HEC Business School in Paris.
CSO: Françoise Bono	
Françoise Bono spent over 25 years at Sanofi and Evotec, including as executive vice president at Evotec, Oncology, until late 2016. She has brought several innovative compounds from preclinical development through to IND filing and Phase I trials. She has led over 20 major projects, notably in the field of immune-oncology, and developed extensive experience in translational and development strategy in oncology. She received her PhD in cellular biology from Toulouse University.	

Principal shareholders	(%)
Financière de la Montagne	13.0

Companies named in this report

Spectrum Pharmaceuticals (SPPI.US), Monopar Therapeutics, Vectans Pharma