EDISON

Onxeo

Company outlook

Next generation of DNA damage repair inhibitors

Pharma & biotech

Onxeo is focused on the development of the next generation of DNA damage repair inhibitors from its novel oligonucleotide platON platform. The lead asset, AsiDNA, belongs to the same class of drugs as PARP inhibitors, but has a different mechanism of action. AsiDNA is in a Phase Ib trial in combination with chemotherapy in solid tumours; preliminary results are expected by end-2019, which is within the existing cash reach to Q320. To reflect the progress Onxeo has made with AsiDNA we have included the second indication for this asset in our valuation, but removed some of the legacy projects. Our updated valuation is €129m or €2.3/share.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/17	9.5	(19.7)	(0.24)	0.0	N/A	N/A
12/18	6.1	(4.2)	0.05	0.0	N/A	N/A
12/19e	3.3	(11.9)	(0.22)	0.0	N/A	N/A
12/20e	3.3	(12.2)	(0.22)	0.0	N/A	N/A

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

Targeting already large and fast-growing market

Onxeo's portfolio focuses on its novel platON platform, from which AsiDNA was the first product to enter clinical development. AsiDNA is the only oligonucleotide decoy agonist in development that disrupts and exhausts tumor DNA Damage Response mechanism. To date the only approved similar class drugs are four commercially successful PARP inhibitors (the first one was approved in December 2014). They all are indicated for cancers known to have a high degree of genomic instability, such as breast and ovarian cancers, which are also logical indications for AsiDNA. All four inhibitors are expected to generate total sales of US$1.6bn in 2019. DNA damage repair continues to attract significant attention and Onxeo's acquisition of AsiDNA in early 2016 was well timed as it was before it became apparent how successful PARP inhibitors would become.

AsiDNA finishing Phase I development

Onxeo's R&D plans include finishing the ongoing Phase Ib study with AsiDNA in various solid tumours in combination with chemotherapy (first data end-2019) and initiating a Phase Ib/II in combination with a PARP inhibitor in 2020. Then, depending on results and available funding, the company may continue with Phase II trials in these combinations. The rationale for combinations is the expected synergy with chemotherapy, but also AsiDNA's unique ability to abrogate the resistance to PARP inhibitors seen in preclinical studies. Our base case scenario now includes two cancer indications (breast and ovarian) in various settings and assumes that Onxeo will be able to partner AsiDNA after Phase II.

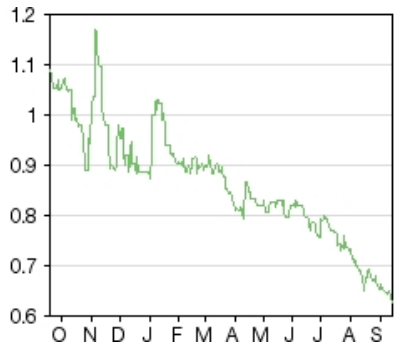
Valuation: €129m or €2.3/share

We have revised our valuation to reflect Onxeo's decision to focus solely on AsiDNA. We have included a second indication for AsiDNA, offset by a review of the Validive out-licensing deal, the removal of the residual rNPV of Beleodaq (the cash was received upfront after the royalty sale) and the removal of the small residual rNPV of Sitavig/Loramyc, two legacy specialty products.

16 September 2019

Price	**€0.62**
Market cap	**€35m**
Net cash (€m) at end of Q219	6.3
Shares in issue	55.9m
Free float	80%
Code	ONXEO
Primary exchange	Euronext Paris
Secondary exchange	OMX Copenhagen

Share price performance



%	1m	3m	12m
Abs	(7.7)	(22.0)	(41.6)
Rel (local)	(12.3)	(25.8)	(44.0)
52-week high/low		€1.17	€0.62

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

Results from Phase Ib with AsiDNA	Q419
OX401 (second platON compound) results from preclinical POC	Q419

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Edison profile page

Investment summary

Company description: Focus on DNA damage repair

Onxeo is a French pure drug developer, which focuses on novel DNA damage repair inhibition technology. The technology came from the acquisition of DNA Therapeutics in March 2016, which brought the lead asset AsiDNA and a broad IP portfolio covering similar oligonucleotides that Onxeo organised into a platform technology called platON. Onxeo has one commercialised product, an HDAC inhibitor, belinostat, branded as Beleodaq in the US. AsiDNA is completing Phase Ib. Unlike similar class PARP inhibitors, AsiDNA is not dependent on specific gene mutations and therefore has broader application areas. In preclinical studies, Onxeo has shown that AsiDNA not only has synergistic potential in combinations with chemotherapeutic drugs that damage DNA (eg carboplatin), but also potentially has a unique feature to abrogate resistance to PARP inhibitors.

Valuation: Risk-adjusted NPV of €129m or €2.3/share

The main revision to our model is the AsiDNA potential. We now include two cancer indications (breast and ovarian cancer). AsiDNA's potential is much broader in various other solid tumours and in combinations with different anticancer treatments including radiotherapy. For valuation purposes, we chose these two cancers, as they are of high priority in Onxeo's near-term R&D plans. We assume Phase II development between 2020-2023, Phase III studies starting in 2023 and launch in 2026. We also assume that Onxeo will be able to partner AsiDNA after Phase II. We factor in R&D costs of €10m per cancer indication (the industry average for Phase II trials in oncology). This implies Onxeo will need to raise more funds, as the current cash reach is to Q320. We have used historical PARP inhibitor licensing deals as benchmark averages for our licensing model: total deal value of US$417m split into $40m upfront payment (roughly 10% of the total value) and the rest into R&D and commercial milestones (50:50) plus tiered 12–15% royalties.

Financials: Cash runway to Q320

Onxeo booked revenues of €6.1m in 2018, of which €2.3m were recurring Beleodaq sales. In June 2018, the company had effectively sold the Beleodaq royalties to SWK Holdings for US$7.5m upfront. Total operating costs were €9.7m in 2018 versus €28.7m in 2017. This fall was mainly due to lower R&D expenditure after the completion of the Phase III ReLive study in September 2017. For 2019 and 2020 we forecast total operating costs of €15.0m and €15.3m, respectively. Onxeo had a cash position of €6.3m at end-Q219. In June 2019, the company announced that it had renewed an equity financing line with Nice & Green, which based on the current share price level, would extend the cash reach to around Q320.

Sensitivities: Biotech risks apply

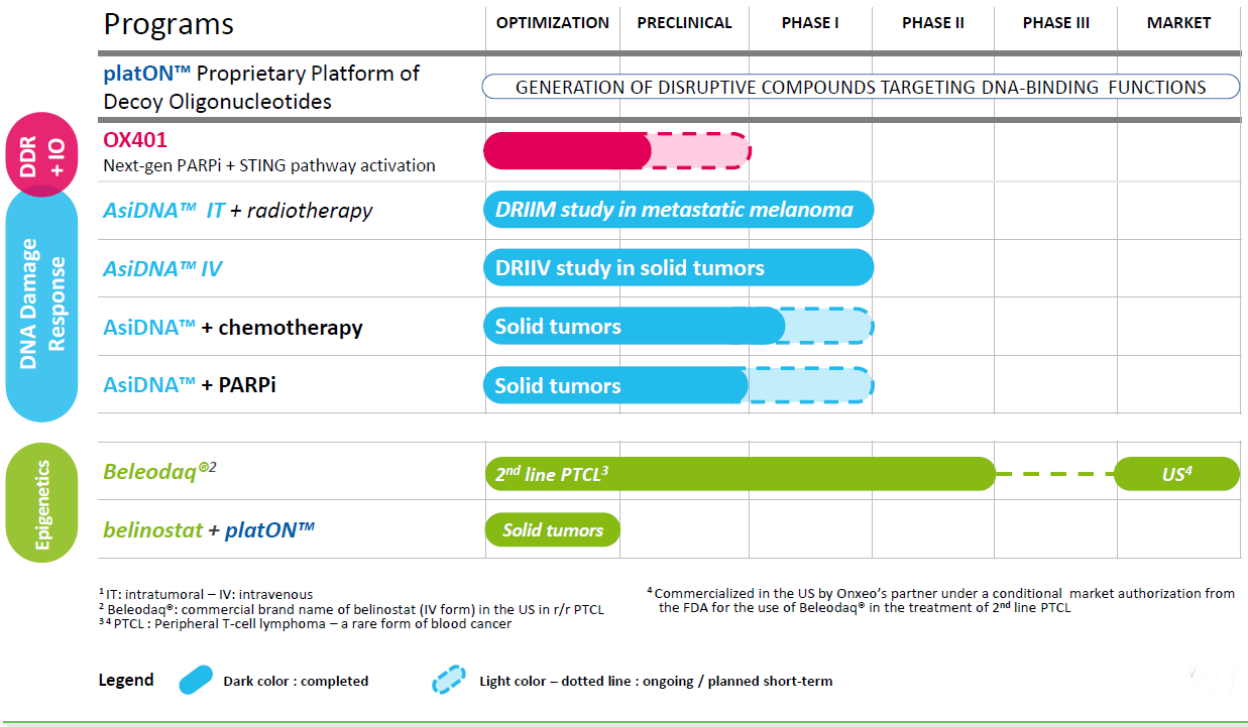
Onxeo is subject to the usual drug development risks, including clinical development delays or failures, regulatory risks, competitor successes, partnering setbacks and financing risks. The main sensitivities relate to the lead asset, AsiDNA. If Onxeo continues the development beyond the ongoing Phase Ib study it will require additional investment. The company aims to accumulate an attractive data package for the potential early out-licensing of AsiDNA (after Phase Ib). However, we believe that the value inflection that clinical trial readouts typically provide could be used to fund the Phase II studies, which would advance AsiDNA to late stage R&D and, presuming a successful clinical trial, would warrant much better licensing deal terms. Onxeo announced in October 2017 that the court's decision in the litigation case was unfavourable and the company was ordered to pay €12m to SpeBio and other smaller charges to SpePharm/SpeBio for costs incurred to market Loramyc in Europe. Onxeo paid the required amount, but it owns a 50% stake in SpeBio, which is a joint venture with SpePharm, therefore the net impact is unclear at present, but Onxeo aims to claim back the proportional payment.

Outlook: Expanding DDR inhibitor R&D portfolio

Onxeo's portfolio focuses on its novel platON platform; in early 2018 AsiDNA was the first product from the platform to enter clinical development (Exhibit 1). The compounds on platON belong to the DDR inhibitor class, which is vital in DNA repair regulation. This area is currently attracting significant attention from both large pharma and biotech. To date, the only approved drugs are commercially successful PARP (poly(ADP ribose) polymerase) inhibitors.

Belinostat, an HDAC inhibitor, is out-licensed and commercialised as Beleodaq for the second line treatment of peripheral T-cell lymphoma. It is approved and marketed in the US following conditional approval and the partner bears the responsibility for any subsequent required studies. As Onxeo's business model focuses on value creation from bringing preclinical assets through to clinical mid-stage, it effectively sold the royalty stream to SWK Holdings for $7.5m upfront in June 2018, raising non-dilutive funds for the development of AsiDNA.

Exhibit 1: Onxeo R&D pipeline



Source: Onxeo

platON: Novel technology platform with AsiDNA first to Phase I

Lead asset AsiDNA – acquisition background

Onxeo gained access to the AsiDNA asset and the IP, around which the platON platform was formed, via the acquisition of DNA Therapeutics in February 2016 (€1.7m upfront, €1m on Phase II initiation: in total up to €25m per approved indication can be paid out). The most advanced asset is AsiDNA (formerly known as DT01), a novel clinical-stage compound. It had already been tested in clinical trials by DNA Therapeutics and showed positive safety/tolerability results and preliminary anti-tumour activity in a Phase I trial with melanoma patients when administered locally. The deal terms appeared attractive and back-loaded for an asset that had Phase I data and could address major cancer indications in broad settings. This was probably due to the following, in our view:

- the timing of the acquisition was very good, as the first approved PARP inhibitor, Lynparza (December 2014) had just finished its first year in the market generating sales of US$218m,

therefore the R&D risk was somewhat lower, but the scale of the commercial success for this class of drugs was still not fully recognised (Lynparza is expected to generate US$1.1bn in sales in 2019 and the four approved (to date) PARP inhibitors are expected to generate total sales of US$1.6bn);

- at the time of the acquisition AsiDNA was being explored only as an intratumourally administered anticancer drug, which limited the number of cancer indications it could target (intratumoural injection may still be explored by Onxeo).

With the commercial success of the PARP inhibitors, there is now significant interest in the area from various players and Onxeo's acquisition timing means that AsiDNA is at the forefront of the next wave entering mid-to-late stage development.

Evolution of platON platform

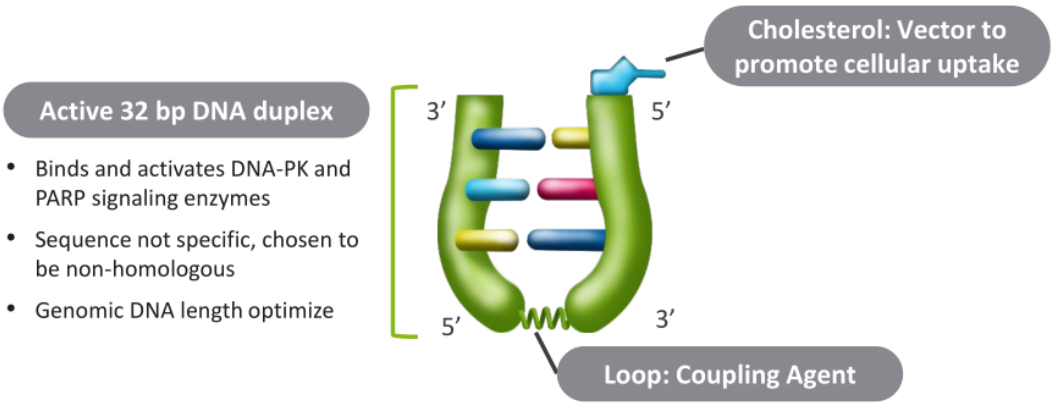
Onxeo recognised that the potential of the technology behind AsiDNA could be increased substantially with systemic administration. Following the acquisition Onxeo completed a preclinical programme and repositioned the asset for systemic use. Onxeo's main focus was on advancing AsiDNA to clinical trials, but based on the preclinical data the company also recognised the potential in other analogue compounds. In October 2017, this was formally introduced as a proprietary platform – platON.

The second platON asset that Onxeo has chosen to progress is OX401, which is now in the proof-of-concept preclinical phase (results expected by Q419). OX401 is also an oligonucleotide decoy agonist targeting PARP proteins and the STING (STimulator of INterferon Genes) pathway. STING is a relatively novel research target in immunoncology, which positions OX401 as a potential combination partner with other immunoncology agents, such as checkpoint inhibitors. In addition to systemic use, Onxeo continues to explore its oligonucleotide decoy technology's potential for intratumoural administration.

AsiDNA –composition

AsiDNA is a decoy oligonucleotide and is comprised of 64 nucleotides in two complementary strands (ie 32 nucleotides in each strand). In tumour cells AsiDNA acts as an agonist and interferes with the repair of tumour DNA by 'distracting' the tumour cell's DNA repair mechanism. 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, and the main mechanism of action is to act as a decoy and target the mechanisms of tumour DNA function regulation.

Exhibit 2: AsiDNA – first product from platON platform



Source: Onxeo. Note: DNA-PK = DNA-dependent protein kinase.

AsiDNA is now being tested in a Phase Ib trial in combination with classic chemotherapy agents (carboplatin + paclitaxel) in various solid tumours. Results are expected in Q419. Depending on available funding, near term development could include:

- Phase Ib/II trial to assess synergy with chemotherapy in selected indications.
- Phase Ib/II trial to assess the abrogation of resistance to PARP inhibitors, likely in maintenance treatment of advanced ovarian cancer.

DNA repair pathways and first breakthrough drugs

In the past five years four PARP inhibitors have been approved by the FDA, prompting a surge in interest in DNA repair inhibition.

- olaparib (**Lynparza**, AstraZeneca); approved in December 2014, expected 2019 sales of US$1.1bn (EvaluatePharma), indicated for relapsed ovarian cancer in maintenance setting (BRCA mutated or non-mutated); and for second line treatment of metastatic breast cancer (BRCA mutated, HER2 negative).
- rucaparib (**Rubraca**, Clovis Oncology); approved in December 2016, expected 2019 sales of US$149m, indicated for relapsed ovarian cancer in maintenance setting (BRCA mutated or non-mutated).
- niraparib (**Zejula**, GSK/Tesaro); approved in March 2016, expected 2019 sales of US$310m, indicated for relapsed ovarian cancer in maintenance setting (BRCA mutated or non-mutated).
- talazoparib (**Talzenna**, Pfizer); approved in October 2018, expected 2019 sales of US$44m, indicated for treatment of BRCA-mutated, HER2 negative metastatic breast cancer.

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, 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]:

- **Single-strand breaks** are repaired by BER. Other enzymes involved in BER are 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). Primarily, these are repaired via two pathways, HR and NHEJ. The stage of 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.

PARP inhibitors, the most advanced drugs in the DNA repair inhibition field, inhibit the BER pathway. This results in the accumulation of single-strand DNA breaks, eventually leading to double-strand breaks[2]. This process could cause cell death, but in healthy cells double-strand breaks are repaired via HR or NHEJ pathways. In a special case of mutated BRCA1/2 genes, the

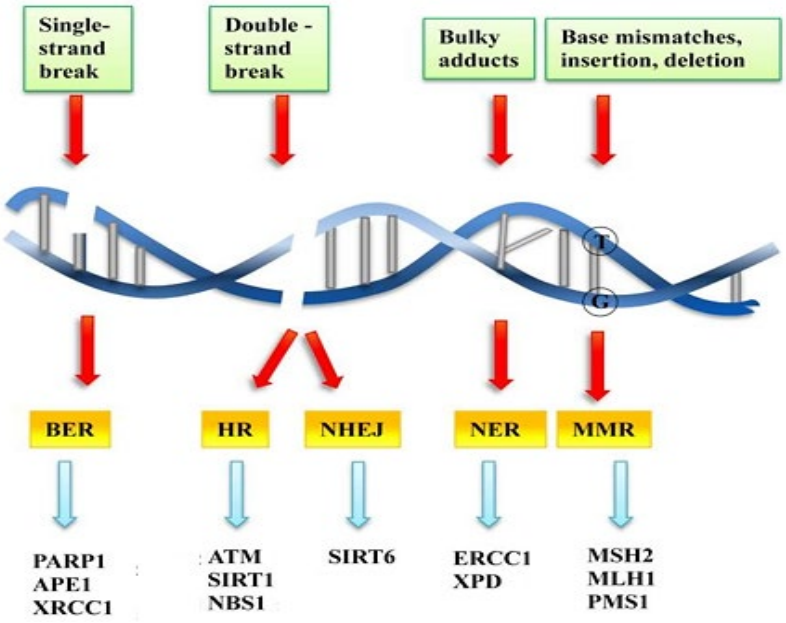
[1] T. Cervelli et al. DNA Damage and Repair in Atherosclerosis: Current Insights and Future Perspectives *Int J Mol Sci*. 2012; 13(12): 16929–16944.

[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

HR pathway is dysfunctional and these cells have been shown to be 100- to 1,000-fold more sensitive to PARP inhibition[2]. 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.

BRCA1/2 mutations are found in around 15% of all cases of ovarian cancer and 5–10% of total breast cancer patients. The first three PARP inhibitors were approved for ovarian cancer. Initially they were explored in BRCA-mutated ovarian cancers, but efficacy has also been shown in BRCA non-mutated ovarian cancer as well. At a later stage, the label of the first PARP inhibitor, Lynparza, was extended to include metastatic breast cancer (BRCA mutated, HER2 negative) and the latest PARP inhibitor, talazoparib, which was approved in October 2018, is indicated for breast cancer only (BRCA-mutated, HER2 negative).

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



Source: T. Cervelli et al

The rationale for using AsiDNA standalone and in combination

PARP inhibitors have shown promising efficacy and safety in clinical trials, but the main drawbacks are 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; if introduced into a cell it acts as a signal mimicking the damage of the cell's own DNA. AsiDNA molecules are short double-strand DNA (32 nucleotides in each strand) 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 DNA-PK leading to a cascade of repair proteins being recruited to 'repair the damage'; as a result the actual damage of a cell's DNA remains unrepaired. This action renders the HR and NHEJ pathways dysfunctional. Therefore, AsiDNA is clearly differentiated from PARP inhibitors, as it acts more upstream; it is not a specific enzyme inhibitor but activates PARP (ie 'distracts', when olaparib inhibits) among other repair proteins. This treatment approach has a broader action than PARP inhibitors, as it targets the entire DNA repair system by hijacking the DNA repair signalling.[3]

Since HR and NHEJ are responsible for repairing double-strand breaks, AsiDNA's ability to disrupt these pathways was initially explored by the original inventors in combination with DNA-damaging

[3] Biau J et al. (2014) A Preclinical Study Combining the DNA Repair Inhibitor Dbait with Radiotherapy for the Treatment of Melanoma. Neoplasia (2014) 16, 835–844.

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 BRCA-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.

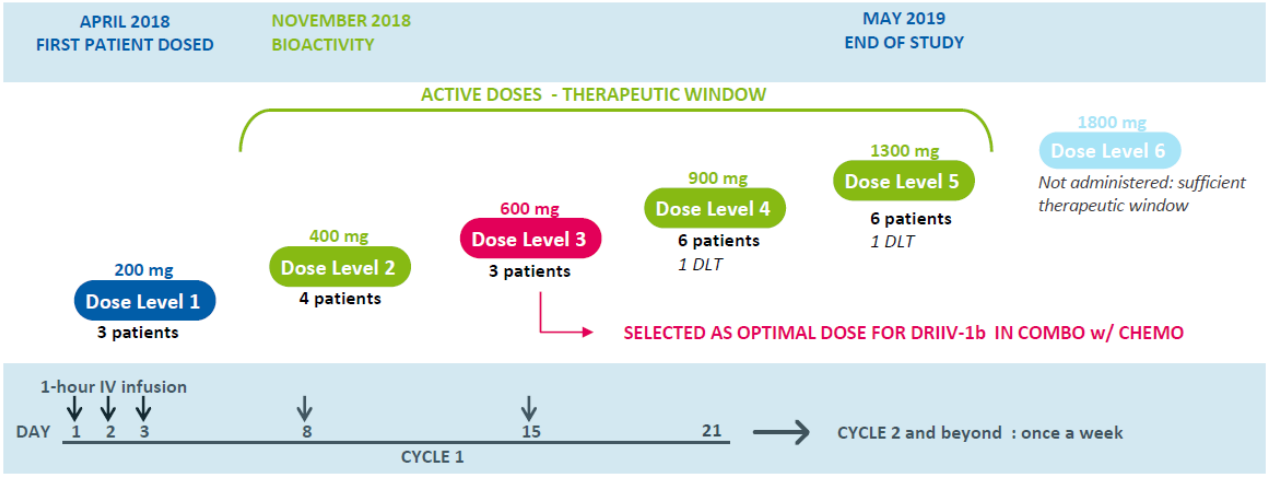
Clinical development of AsiDNA

Phase I DRIIV-1: First trial with systemic AsiDNA administration

This was the first clinical trial Onxeo conducted after acquiring AsiDNA and is the most advanced dataset available at present. The open-label, dose escalation Phase I **D**NA **R**epair **I**nhibitor administered **I**ntra**V**enously (DRIIV) recruited patients (n=22) with various advanced solid tumours, with the first patient treated in April 2018. All patients had metastatic cancers and were failing or progressing after one or more standard treatments with no further therapeutic options. The study aimed to assess:

- The safety/tolerability profile, dose-limiting toxicities (DLTs) and the maximum tolerated dose (MTD), and the recommended dose for subsequent efficacy trials.
- Onxeo also explored various biomarkers that might help to gauge the activity of AsiDNA and stratify patients in later trials.

Exhibit 4: Phase I DRIIV-1 trial design



Source: Onxeo. Note: *Three additional patients if a dose-limiting toxicity is observed.

The final results were announced in May 2019. The findings from a total of 22 patients who received five dose levels of AsiDNA ranging from 200mg to 1300mg include:

- No serious drug-related events and no dose-limiting toxicity at doses 200, 400 and 600mg; first dose-limiting toxicity appeared at 900mg level (1/6).
- Maximum tolerated dose not reached. There was no need to test the highest dose level (1800mg), as the therapeutic window between the optimal dose of 600mg and the highest tested dose of 1,300mg was considered sufficient.
- Biomarker analysis showed that AsiDNA:
  - Increased activity of gH2AX and pHSP90 as early as the second level dose (400mg). γH2AX and pHSP90 are established biomarkers for the activation of DNA-PK, one of the major targets for AsiDNA.
  - Tumour proliferation biomarker Ki67 decreased.
  - The activity was consistent within the therapeutic window.

- At the optimal dose level of 600mg, among the three patients included in the cohort, two patients with relapsed metastatic colorectal cancer were controlled with medical imaging, which showed no further disease progression after the second treatment cycle (the treatment with AsiDNA was continued for three months).

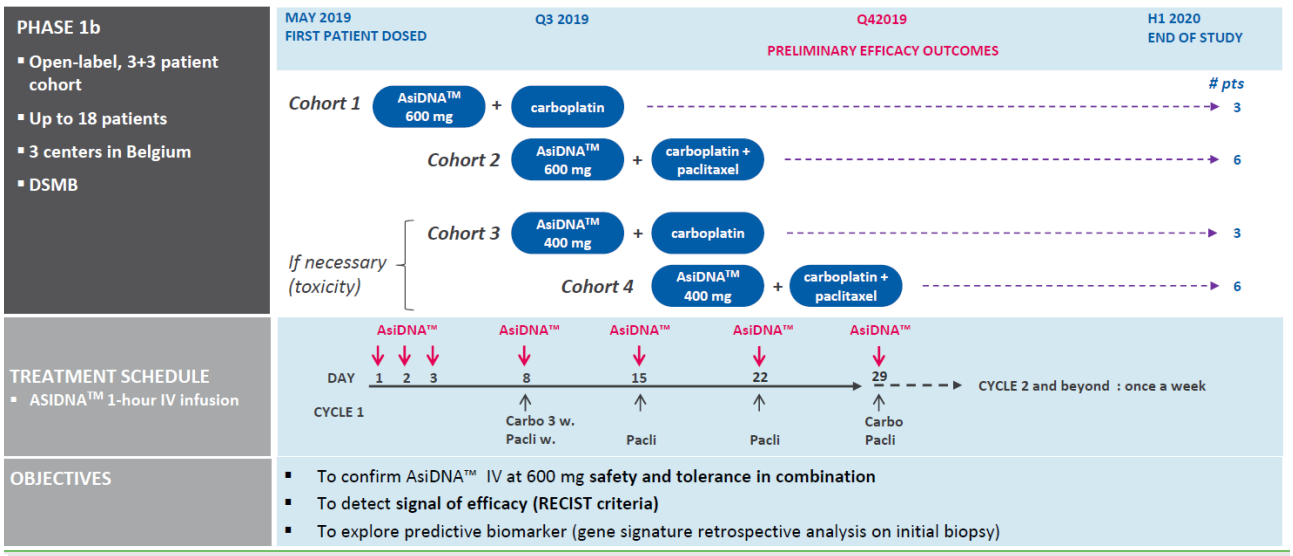
Our view

The rationale for this study was built on previous findings from the Phase I DRIIM, conducted by the inventor company. In that trial AsiDNA was administered intratumourally in melanoma patients. While the data released from the DRIIV-1 trial are still very early and no conclusions about efficacy can be made as yet, we find it reassuring that no serious drug-related side effects emerged with intravenous administration. The consistent pattern of increase in activity biomarkers also demonstrated that the drug reaches its target after intravenous administration. AsiDNA is a unique compound with no close comparators with respect to mechanism of action and therefore there was no visibility on the safety/tolerability profile via a systemic administration before DRIIV-1 results (safety data via local injection in the DRIIM trial was good).

Phase Ib DRIIV-1b (extension) study ongoing

The next step in the development plan for AsiDNA is the extension of the Phase Ib (DRIIV-1b) study, which started enrolling patients in May 2019. This is the first study testing AsiDNA in combination with carboplatin plus paclitaxel, in up to 18 patients (9 + 9 if dose-limiting toxicity is reached; Exhibit 5) with solid tumours eligible for such treatments (such as lung, breast, ovarian or head and neck cancers). The study will evaluate the efficacy of the combination treatment using RECIST criteria (response evaluation criteria in solid tumours) and the initial results are expected in Q419.

Exhibit 5: Design of the Phase Ib DRIIV-1b trial



Source: Onxeo

Future development options for AsiDNA and partnering strategy

As discussed above, the AsiDNA's mechanism of action allows it to be positioned in various combinations with other anticancer therapies. Therefore, near-term R&D plans include studies with AsiDNA in combination with classic chemotherapy drugs and novel PARP inhibitors (Exhibit 6). We note that only the Phase Ib DRIIV-1b study is ongoing; other trials are at the planning stage and the results from the DRIIV-1b trial will help to design other studies. The final decision on which indications to prioritise will be made in the near future, but ovarian and breast cancer seem to be

most likely targets at present. In this regard, we find the Phase Ib/II study with AsiDNA in combination with PARP inhibitors of particular interest. It will explore AsiDNA's potential to abrogate tumour resistance to PARP inhibitors. There is a strong rationale for such a combination and the proof-of-concept was demonstrated in the animal studies (discussed below). To date, the four approved PARP inhibitors have been approved for the treatment of ovarian or breast cancer. While commercially successful drugs, they still suffer from the rapid development of resistance, so AsiDNA's benign safety profile could be a good partner drug because of its ability to abrogate resistance to the drug.

Exhibit 6: Overview of near-term AsiDNA clinical programme

Study	Comments
Phase Ib DRIIV-1b study AsiDNA + carboplatin + paclitaxel	■ Currently ongoing study, enrols patients who are eligible for chemotherapy treatment (cancer such as lung, breast, ovarian or head and neck). ■ Preliminary results are expected later in 2019. ■ **If positive this could lead to Phase IIa in 2020.**
Phase Ib/II study AsiDNA + PARP inhibitor	■ Indications tested likely to be advanced ovarian cancer. ■ Objective is to confirm **AsiDNA's potential to abrogate tumour resistance to PARP inhibitors** and demonstrate synergistic effects. ■ Expected to start in 2020.

Source: Onxeo

When it comes to late-stage development, Onxeo's business strategy implies it will seek to partner or out-license the development of AsiDNA. Central to Onxeo's investment case is its ability to secure a timely out-licensing agreement. The company would consider out-licensing soon after the ongoing Phase Ib trial, which would allow the company to focus on earlier stage products in the platON platform. To be prepared for that outcome Onxeo is accumulating as broad data package as possible. However, as Onxeo employs an early- to mid-stage development biotech business model, the data readouts, if positive, should create value inflection points for the share price, which would allow it to raise the necessary funds for the Phase II development. This option would lead to better deal terms and better returns to investors willing to take on the Phase II development risk.

Our base case scenario

In our model we assume that Onxeo will be able to partner AsiDNA after Phase II and the partner will cover all development and marketing costs from this point. We include two cancer indications (breast and ovarian cancer; detailed below) in our Onxeo rNPV valuation model. We assume the two Phase II studies are initiated in 2020, Phase III studies in 2023 and launch in 2026. The R&D cost for each of the two Phase II trials is €10m (industry average Phase II trials in oncology). This implies Onxeo will need to raise more funds, as the current cash reach is to Q320 (see Financials). Our partnering assumptions include a fairly typical deal structure, including an upfront payment, development and sales-related milestones, in addition to royalties on global sales. We assume that AsiDNA will be out-licensed after the Phase II studies, ie in 2022. We have used historical PARP inhibitor licensing deals as benchmarks for our valuation (Exhibit 17). In our model we include the total deal value of US$417m (average of the values of the three deals). This is split into an upfront payment of US$40m (roughly 10% of the total value) with the rest split into R&D and commercial milestones. These values are equally split between the two indications. We use tiered 12–15% royalty rates. We summarise our other valuation assumptions later in the report.

Phase I DRIIM results (AsiDNA via local administration)

DNA Therapeutics, the original developer, tested AsiDNA (DT01 at that time) in a clinical trial with skin melanoma patients. In the Phase I DRIIM study the drug was injected intratumourally or peritumourally in conjunction with 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[4]:

- AsiDNA was well tolerated and did not induce additional toxicity when combined with radiotherapy. 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.
- 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.
- The 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 a complete response rate of 9%[4].
- 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 in part be explained by systemic exposure to AsiDNA after it was absorbed from the local injection site and an abscopal effect through immunogenicity, ie the immune system was trained to attack both the injected tumours and the non-injected.

These results showed that AsiDNA was well-tolerated and had an effect on lesions when injected locally and that a systemic delivery is also possible. As discussed, we believe that this potential to reposition AsiDNA for systemic delivery was the primary driver for Onxeo's acquisition of DNA Therapeutics in March 2016.

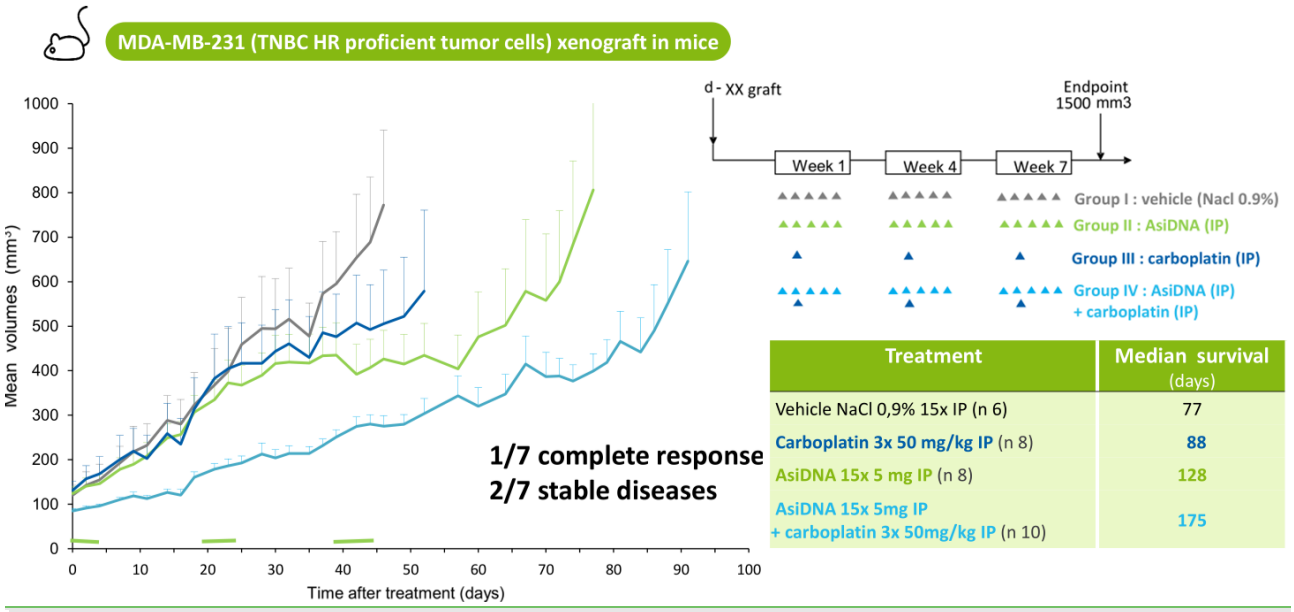
Preclinical data highlights

First proof-of-concept of AsiDNA systemic administration

After Onxeo acquired AsiDNA it completed the required additional preclinical development and the first preclinical proof-of-concept data demonstrating the potential for intravenous administration were released in July 2017. AsiDNA standalone significantly decreased tumour growth in triple negative breast cancer (TNBC) model and improved survival, while a combination with the classic chemotherapy agent carboplatin significantly reduced the growth further and outperformed all other arms (Exhibit 7).

[4] 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.

Exhibit 7: AsiDNA in combination with carboplatin in TNBC *in vivo* model



Treatment	Median survival (days)
Vehicle NaCl 0,9% 15x IP (n 6)	77
Carboplatin 3x 50 mg/kg IP (n 8)	**88**
AsiDNA 15x 5 mg IP (n 8)	128
AsiDNA 15x 5mg IP + carboplatin 3x 50mg/kg IP (n 10)	175

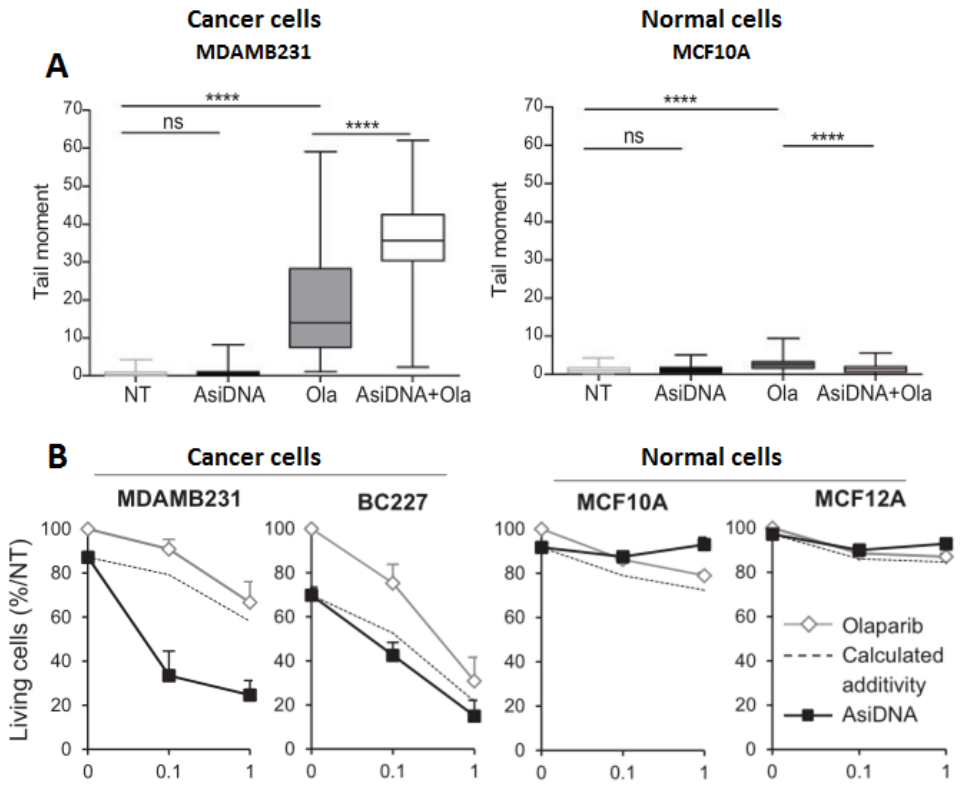
Source: Onxeo

Combination with PARP inhibitors offers synergies

Jdey *et al* (2017) explored in vitro the synergistic potential of the combination treatment of PARP inhibitors and AsiDNA[2]. The researchers studied AsiDNA with PARP inhibitors or standalone in 21 cancer cell lines with different BRCA status and three non-tumour cell lines. The most detailed comparison has been made between AsiDNA and the 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 8A and 9B), which could lead to new indications for PARP inhibitors ie the presence of the 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 also shown to be effective.
- 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 8: Effects of AsiDNA in combination with olaparib on cancer and normal cell lines

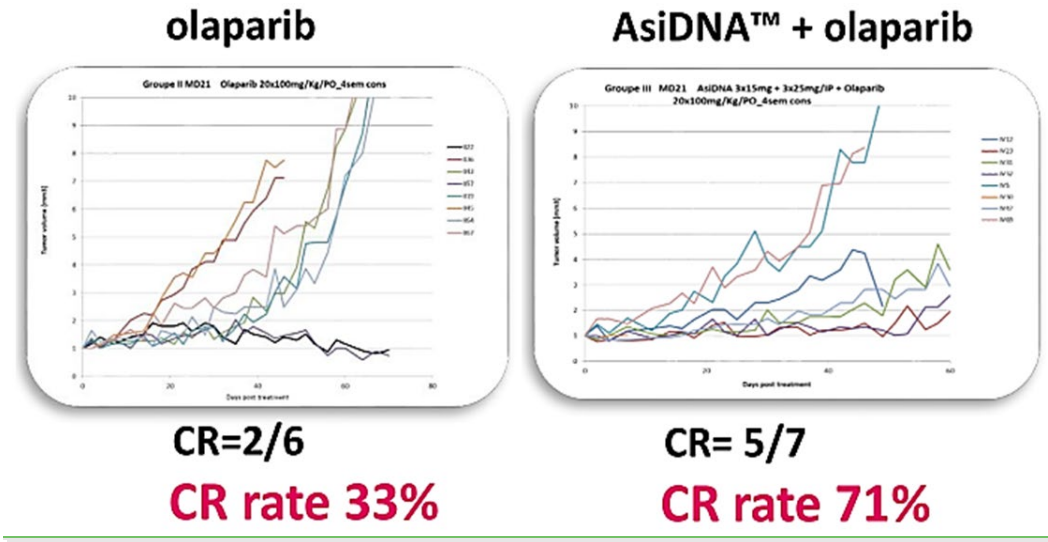


Source: Jdey et al. Note: Charts A and B show that the treatment with AsiDNA and olaparib accumulates DNA damage in cancer cells, but not healthy cells, as evaluated with comet assay (tail moment indicates DNA damage); MDAMB231 = BRCA-proficient breast cancer cells; BC227 = BRCA-deficient breast cancer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

In July 2018, Onxeo announced another set of positive preclinical data with AsiDNA in combination with various PARP inhibitors. AsiDNA was tested with olaparib and talazoparib in in vivo and in vitro models. The findings suggest the following:

- AsiDNA combined with olaparib more than doubled the complete response rate (71% vs 33%) observed with olaparib alone in an in vivo model of TNBC resistant to PARP inhibitors (Exhibit 9).
- AsiDNA combined with olaparib inhibited tumour growth in an in vivo humanised patient-derived xenograft (PDX) mice model of ovarian cancer resistant to olaparib.
- AsiDNA combined with PARP inhibitors prevented the development of resistance and reversed this resistance to PARP inhibitors after repeated exposure in in vitro models of TNBC and small cell lung cancer.

Exhibit 9: Synergistic effect of AsiDNA + olaparib in TNBC model



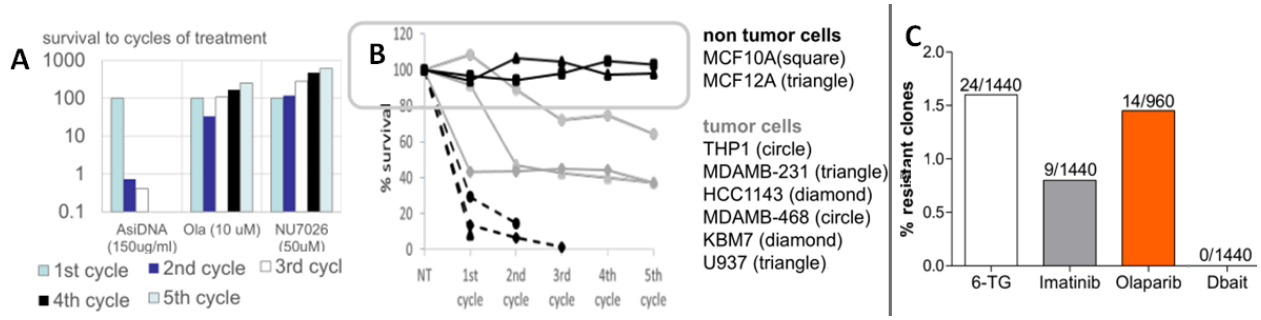
Source: Onxeo

AsiDNA causes tumour cell 'autosensitisation'

One of the more unexpected Onxeo discoveries from the preclinical development was AsiDNA's ability to 'autosensitise' tumour cells. According to this evidence, unlike the majority of drugs in oncology that develop resistance, the tumour cell's sensitivity to AsiDNA could actually increase as the treatment progresses. If confirmed in future studies, it could be the first known drug with such an effect.

The data were first presented at the AACR's annual meeting on 14–18 April 2018 in Chicago, Illinois. In an *in vitro* study AsiDNA's effects were explored in six different tumour cell lines. Cells were treated with AsiDNA and various targeted therapy agents, namely imatinib (original brand Glivec, Novartis), olaparib (Lynparza, AstraZeneca) and 6-thioguanine. The results showed for the first time that long-term treatment with AsiDNA increases the sensitivity of tumour cells to AsiDNA itself. All six cell lines tested became more sensitive to AsiDNA and did not develop resistance. This is a unique feature in oncology, as tumours typically develop resistance to drugs. All tumour cell lines developed some resistance to other targeted therapy agents. In addition, normal cells were not affected by the standalone treatment with AsiDNA.

Exhibit 10: AsiDNA causes 'autosensitisation' (A and B), but no drug resistance (C)



Source: Kozlack et al. Evolution of tumor cells under Dbait (AsiDNA) treatment results in 'autosensitisation'. Poster presentation at AACR, 14-18 April 2018. Note: Dbait – AsiDNA technology

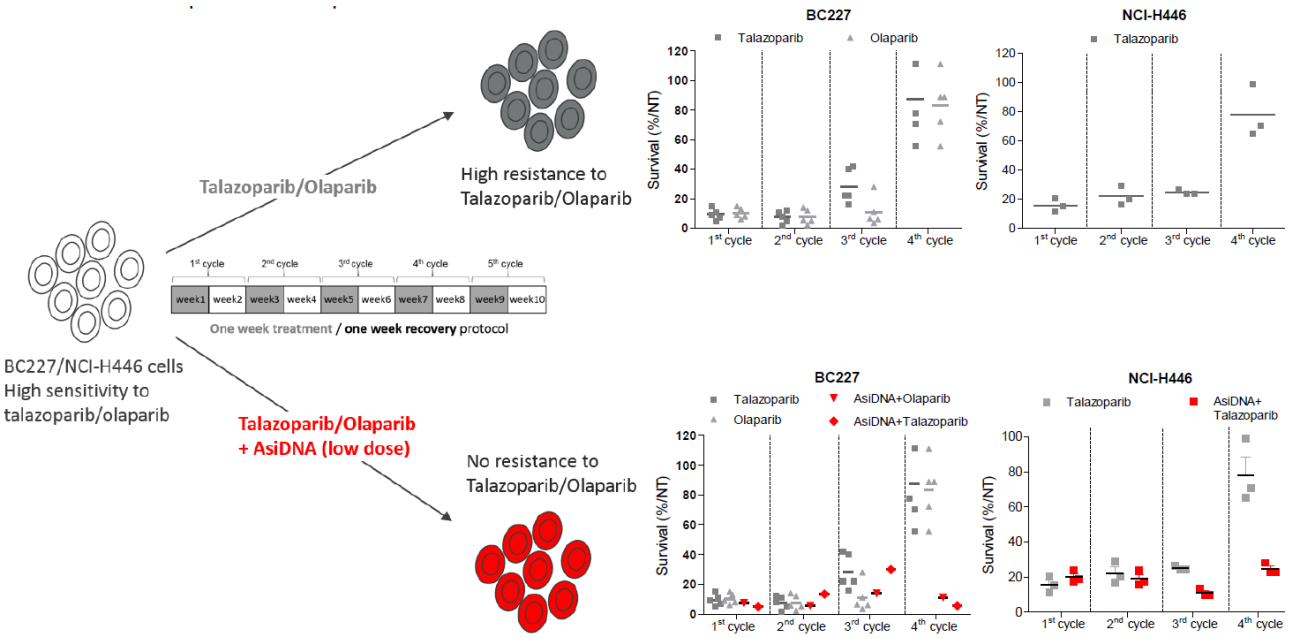
While the new publications describe early in vitro data, in our view, the unique value lies in the identification of a potentially new mechanism of action of AsiDNA, which Onxeo has termed autosensitisation. If the findings are replicated in further trials, AsiDNA could potentially be the first known drug with this effect.

AsiDNA abrogates acquired resistance to PARP inhibitors

One of the features of AsiDNA discovered more recently was its potential to abrogate resistance to PARP inhibitors. Onxeo presented the preclinical data at the 2019 American Association for Cancer Research Annual Meeting (AACR) in April 2019.

- In an *in vitro* study, breast cancer and small cell lung cancer (SCLC) cells were treated with talazoparib or olaparib standalone or in combinations with AsiDNA. Standalone treatment of the cancer cells with PARP inhibitors led to a rapid emergence of resistance, while the addition of AsiDNA significantly lowered the probability of cells developing resistance (Exhibit 11).
- Separately, the researchers were able to show that when treating already resistant breast cancer cells with a PARP inhibitor (talazoparib) plus AsiDNA, resistance was reversed in three out of five cell populations.

Exhibit 11: AsiDNA abrogates acquired resistance to PARP inhibitors



Source: Jdey et al, AsiDNA abrogates acquired resistance to PARP inhibitors. Poster presentation, AACR 2019

Indications

Multiple potential settings for AsiDNA

Cancers, such as ovarian, breast cancer, small cell lung and head and neck are known to have high degree of genomic instability and therefore can accumulate more DNA damage. These are also the primary target indications for AsiDNA to focus on in late-stage development.

Given that AsiDNA could be used independently of specific mutation, it opens various potential uses including in combination with existing other cancer therapies or as monotherapy. The currently ongoing DRIIV study is enrolling patients with solid tumours eligible to carboplatin with or without paclitaxel (TNBC, ovarian, lung, head and neck cancers). This could lead to a Phase II study in selected indications, which would position AsiDNA for use in combination with classic chemotherapy drugs, which are still standard of care in neoadjuvant treatment of TNBC and first/second-line treatment of advanced ovarian cancer. Another potential study will test AsiDNA's potential to abrogate tumour resistance to PARP inhibitors and will most likely focus on ovarian cancer patients. In addition to these, Onxeo envisions that AsiDNA could also be combined with radiotherapy in future trials.

Such plans imply a broad potential for AsiDNA. We included TNBC in our valuation when Onxeo acquired AsiDNA. With Onxeo repositioning the use of AsiDNA for systemic administration and to reflect a broader potential we now include two cancer in our valuation and broader use of AsiDNA. We believe that these two cancers are most likely to advance to late-stage development because PARP inhibitors are gaining traction in these indications among physicians, but other solid cancers with genomic instability, such as SCLC, could also be advanced eventually as well.

Breast cancer

According to the American Cancer Society, one in eight women in the US will develop breast cancer in her lifetime. Breast cancer is highly heterogeneous in its pathological characteristics; in some cases the cancer grows slowly with excellent prognosis, while in other cases it can be very aggressive. Breast tumours are grouped into different subtypes based on the expression of oestrogen receptors (ER) and progesterone receptors (PR), and HER2 oncogene. The most common driver mutations are in BRCA genes. Relevant breast cancer subtypes for Onxeo include:

- **TNBC**, where AsiDNA would be combined with carboplatin and paclitaxel before surgery (neoadjuvant).
- **Metastatic breast cancer, HER2-, BRCA-mutated (first or second line**), where AsiDNA would be combined with PARP inhibitors.

TNBC

By pathological definition, TNBC lacks an expression of ER, PR, and human epidermal growth factor receptor 2 (HER2). This type of cancer is typically more aggressive compared with other types of breast cancer and is unresponsive to hormonal and monoclonal antibody therapies (eg Herceptin). The standard initial treatment options are surgery, anthracycline and taxane-based chemotherapy regimens (eg doxorubicin, cyclophosphamide, docetaxel, paclitaxel) and carboplatin (Ferguson et al, 2014; Cardoso et al, 2019). A relatively new development in the area is the approval of the anti-PD-L1 antibody atezolizumab (Tecentriq, Roche) in March 2019. It was the first immunotherapy approved for use in combination with chemotherapy drug nab-paclitaxel (Abraxane) in locally advanced or metastatic TNBC that express PD-L1 protein and cannot be treated surgically. TNBC accounts for around 15% of total new cases each year, which would imply c 89k patients in the US and Western Europe combined (detailed calculations in Exhibit 16; US data from NCI SEER program; European data extrapolated for top 14 western European countries).

Metastatic breast cancer, HER2-, BRCA-mutated

In January 2018, Lynparza became the first PARP inhibitor approved for second-line BRCA-mutated, HER2 negative metastatic cancer, while Talzenna was approved in October 2018. While current indications include PARP inhibitor use as second-line treatment options, interest in using these new drugs earlier in the treatment cascade is growing. Around 6–10% of new breast cancer cases are initially Stage IV or metastatic, but it is estimated that the number of metastatic recurrences can be much higher at 20–30% of all existing breast cancer cases (Metastatic breast cancer network). It is known that about 17% of breast cancers overproduce the growth-promoting protein HER2, so around 83% of the patients are HER2 negative, and that BRCA mutation prevalence is about 5–10% in the overall breast cancer patient population (American Cancer Society). Using mid-rage values, the total addressable patient population in the US and Western Europe is c 9,200 (detailed calculations in Exhibit 16).

Ovarian cancer

Epithelial ovarian cancer is the most common type of ovarian cancer, making up around 90% of cases (cancer.org). Rare ovarian cancer types include teratomas, stromal tumours and sarcomas and are considered on a case by case basis. Ovarian cancer is the most lethal gynaecological disease due to the ineffectiveness of screening tests. Most patients who are diagnosed with ovarian

cancer have advanced disease (around 70–80%; Franzese, 2018; Narod, 2016), where the tumour has spread beyond the pelvic tissues, for example to the lymph nodes or peritoneum (stage III), or further to liver or spleen parenchyma (stage IV). AsiDNA has a broad potential in advanced ovarian cancer:

- **First-line treatment**. Typically, the first-line treatment in such patients includes surgery, followed by platinum-based chemotherapy (Franzese, 2018). The rationale to add AsiDNA in this setting would be the expected increase in response rate via the synergistic effect.
- **Maintenance treatment**. For most women, however, the cancer returns within three years of this initial treatment (cancer.gov). In this so-called maintenance setting, the three approved PARP inhibitors became standard of care (in patients who are still sensitive to platinum). Approximately 15% of epithelial ovarian cancer cases have the mutated BRCA gene, but PARP inhibitors were also shown to be effective in non-BRCA mutated ovarian cancers. Therefore, all three drugs are approved for patients despite BRCA status. The rapid adoption of these new drugs in ovarian cancer was underpinned by impressive progression-free survival (benefit of up to 15.5 months) in patients with the BRCA mutation. In patients with no BRCA mutations, the incremental approximate PFS advantage was smaller (median, 3–4 months; O'Cearbhaill, 2018). AsiDNA's ability to improve efficacy and abrogate resistance to PARP inhibitors forms the rationale to use it in this setting.

Cancer incidence data show that 50k new ovarian cancer cases were reported in 2018 (23k in the US and 27k in western Europe; US data from the American Cancer Society; European data extrapolated for the top 14 western European countries listed in Exhibit 16). Of that number, epithelial cancer accounts for 90%, which results in a total addressable population of 45k.

PARP inhibitors on the market and in development

AsiDNA is differentiated from other DNA damage repair therapeutics in development as it does not target a specific protein in the DNA damage response cascade, but acts as an agonist decoy for proteins responsible for damage repair. PARP inhibitors target a specific protein in the cascade and they are the only DNA damage repair drugs approved to date. Therefore, AsiDNA 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, only around 15% of all ovarian cancer patients have the specific BRCA mutation. We expect the new platON compound will be positioned for combinations with immunotherapies.

There are four PARP inhibitors approved so far: Lynparza (AstraZeneca), Rubraca (Clovis Oncology), Zejula (GSK/Tesaro) and Talzenna (Pfizer). BRCA-mutated advanced ovarian cancer (Lynparza, Rubraca and Zejula) and HER2 negative, BRCA-mutated, second-line metastatic breast cancer (Lynparza, Talzenna) are the only approved indications for PARP inhibitors so far. These cancers were seen as the low-hanging fruit for the development of PARP inhibitors due to the link between BRCA mutation and these tumours. The market for PARP inhibitors is expected to reach around US$1.6bn worldwide in 2019 and, according to consensus, the market for PARP inhibitors could reach US$5.6bn in 2024 (EvaluatePharma, Exhibits 12 and 13). This will be driven by growth in existing products, the introduction of new PARP inhibitors (2019 will be the first full year for Talzenna; pamiparib from BeiGene is in Phase III, fluzoparib from Jingsu Henrui is in Phase III and veliparib from AbbVie is in Phase III), the possible transitioning of second line products into first line, new indications (prostate cancer) and combinations with other drugs. Although further indications are being explored, ovarian and breast cancers are expected to remain the largest indications for PARP inhibitors into 2024.

Large pharma are very active in the space, in particular AstraZeneca and Merck KGaA, with several projects investigating ATM and ATR (HR pathways), DNA-PK (NHEJ pathway) and WEE1 pathways. The most advanced projects are in Phase II.

Exhibit 12: PARP inhibitor sales forecasts

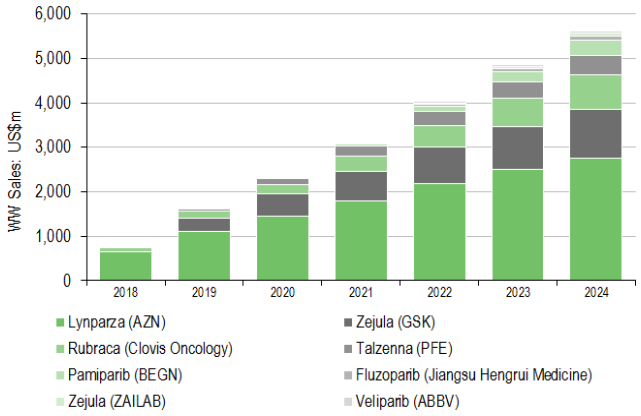
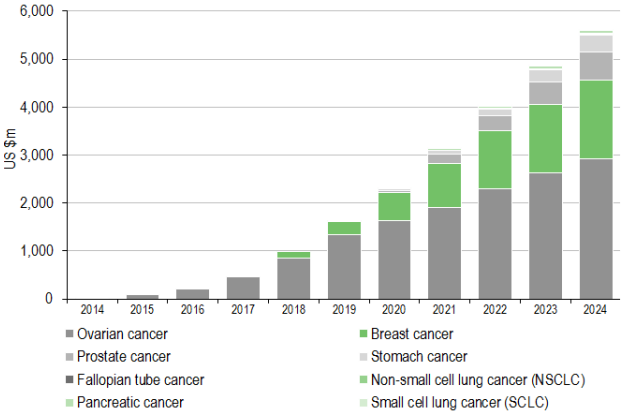


Exhibit 13: PARP inhibitor forecasts by indication



Source: Evaluate Pharma. Note: Forecasts for talazoparib by indication are not available.

Exhibit 14: Marketed and late development stage PARP inhibitors

Drug	Company	Cancer indications	Stage of development
Lynparza (olaparib)	Merck & Co, AstraZeneca	Breast	Marketed
		Fallopian tube	Marketed
		Ovarian	Marketed
		Prostate	Phase III
		Pancreatic	Phase III
Rubraca (rucarparib)	Pfizer, Clovis Oncology	Ovarian	Marketed
		Breast	Phase III
		Prostate	Phase III
Zejula (niraparib)	GSK/Tesaro	Fallopian tube	Marketed
		Ovarian	Marketed
		Breast	Phase III
Talazoparib	Pfizer, BioMarin	Breast	Marketed
		Prostate	Phase III
Pamiparib	BeiGene, Merck KGaA	Stomach	Phase III
		Ovarian	Phase III
Veliparib	AbbVie	Breast	Phase III
		Non-small cell lung	Phase III
		Ovarian	Phase III
Fluzoparib	Jiangsu Hengrui Medicine	Ovarian	Phase III

Source: Evaluate Pharma, ClinicalTrials.gov, Edison Investment Research. Note: Marketed drugs are approved for second and third line but in trials for first line.

Beleodaq was Onxeo's first commercialised drug

Belinostat (HDAC inhibitor for peripheral T-cell lymphoma (PTCL)) is marketed as Beleodaq in the US under a conditional FDA approval granted in July 2014 for relapsed or refractory peripheral T-cell lymphoma (r/r PTCL). This was based on the US Phase II BELIEF study in relapsed/refractory PTCL (n = 120). We expected that a Phase III controlled trial would address the conditional approval in the US, which could also be used for filing in Europe. However, since the out-licensing the drug is in the hands of the partner and no further progress has been announced. In addition, Spectrum Pharmaceuticals, which in-licensed and marketed Beleodaq, sold its portfolio of selected drugs including Beleodaq to Acrotech Biopharma earlier this year. Onxeo indicated that the transaction will not have any material effect on its near-term financials (Onxeo effectively sold the royalties from Beleodaq to SWK Holdings), but there is little visibility about the timelines for any potential further development of Beleodaq in the US and Europe if any.

Onxeo could also explore the potential to combine belinostat with future compounds from the platON platform. Onxeo has published proof-of-concept *in vitro* data supporting the rationale. The findings demonstrated that there was a clear synergistic effect on malignant cells compared with monotherapy of either of the drugs (AsiDNA or belinostat). Notably, the effect on healthy cells was minimal. Belinostat is a strong inducer of DNA breaks and therefore the combination with AsiDNA, a DNA break repair inhibitor, could potentially be synergistic. As Onxeo owns both technologies it could 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 asset AsiDNA progressing through clinical development. Clinical development would lead to an increase in R&D spending and would require additional investment if Onxeo continued the development beyond the ongoing Phase Ib plus chemotherapy. The company is pursuing a comprehensive development strategy aimed at accumulating an attractive data package for potential early out-licensing (after Phase Ib). However, we believe that the value inflection that the clinical trial readouts typically provide could be used to fund the Phase II studies, which would advance AsiDNA to late stage R&D and, presuming a successful clinical trial, would warrant much better licensing deal terms.

Onxeo announced in October 2017 that the court's decision in the litigation case regarding Loramyc was unfavourable and the company paid €12m in total 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 the delayed marketing of Loramyc. Onxeo sought all legal options to appeal the decision, but in the end paid the required amount. However, the company owns a 50% stake in SpeBio, which is a joint venture with SpePharm, therefore the net impact is not clear at present, but Onxeo aims to claim back the proportional payment from the joint venture. In addition, the international arbitration procedure, which was on hold pending decisions from the French courts, has resumed and Onxeo still seeks appeal in higher jurisdiction.

Valuation

Following Onxeo's decision to focus solely on AsiDNA, we have substantially revised our valuation. We calculate rNPV of €129m or €2.3/share (our last published valuation was €172m or €3.3/share). We have updated our model to include the second indication for AsiDNA, offset by a review of the Validive out-licensing deal, the removal of residual rNPV values of Beleodaq (the cash was received upfront after the royalty sale agreement) and the removal of the small residual rNPV of Sitavig/Loramyc, two legacy specialty products.

Ovarian breast cancers in our valuation

We added the TNBC indication to our model soon after the acquisition in DNA Therapeutics in March 2016. We have now expanded AsiDNA's use in advanced ovarian and breast cancers. The assumptions include:

- **Target patient populations:**

  - **TNBC**, where AsiDNA would be combined with carboplatin and paclitaxel before surgery (neoadjuvant). The total breast cancer incidence in the US and top 14 Western Europe is 590k. Around 15% or 89k are TNBC patients.
  - **Metastatic breast cancer, HER2-, BRCA-mutated** (first or second line), where AsiDNA would be combined with PARP inhibitors. Metastatic recurrence is estimated at 20–30% (we use 25%). Around 83% of patients are HER2 negative. BRCA mutation prevalence is estimated between 5–10% (we use 7.5%). Total addressable population equals to 9,200 patients (from the total incidence of 590k).
  - In **ovarian cancer**, AsiDNA's positioning potentially can be broad, from first-line treatment in combination with standard of care chemotherapy to maintenance treatment with PARP inhibitors. We therefore use total epithelial (90% of the total) ovarian cancer incidence of c 45k in the US and top 14 Western Europe.
  - Our calculated peak sales are US$1.9bn and US$4.1bn in ovarian cancer and breast cancer respectively reached in six years (assumed market penetration of 30%).
- **Timelines**. We assume the Phase II development in 2020-2023, followed by Phase III studies in 2023 and launch in 2026. We keep the probability of success at 15%.
- **Pricing**. We use a price of US$130k per patient in the US with a 30% discount in Europe. In our previous TNBC project we used a price tag of $70k, but PARP inhibitors achieved much higher price tags (Lynparza c $130k, Zejula c $140k), which in our view justifies the increase in our model.
- **Licensing deal terms**. We assume that AsiDNA will be out-licensed after the Phase II studies ie in 2022. This implies that Onxeo will need to raise more funds, as the current cash reach is to Q320 (see Financials). Onxeo employs a typical biotech model, where the company expects to reach value inflection points using its existing budget in order to raise funds for the next phase of the R&D. It is also a possibility that Onxeo will seek to out-license AsiDNA as soon as after the completion the current Phase Ib study later this year, which would allow it to focus on earlier-stage products in the platON platform. We used historical PARP inhibitor licensing deals as benchmarks for our valuation (Exhibit 17). In our model we include the total deal value of US$417m (average of the values of the three deals). This is split into an upfront payment of $40m (roughly 10% of the total value) with the rest split into R&D and commercial milestones (50:50). We use tiered royalty rates of 12–15%.
- **R&D costs**. Over 2020–2023 we assume €10m in R&D costs for the Phase II studies in both cancer indications. This could lead to a licensing deal, following which Onxeo would not incur any more R&D costs related to AsiDNA.
- **Intellectual property**. Composition of matter patents provide protection until at least 2031 with the possibility to extend up to five years. Issue and files method of use patents extend into late the 2030s even before an extension. Our model assumes market protection until 2036 before gradually tapering over the course of several years with no remaining terminal value.

Exhibit 15: Onxeo rNPV valuation

Product	Indication	Launch	Peak sales (US$m)	NPV (€m)	Probability (%)	rNPV (€m)	NPV/share (€/share)
AsiDNA	Ovarian cancer	2026	1,850	338.5	15%	59.0	1.1
AsiDNA	TNBC and metastatic, HER2-, BRCA-mutated	2026	4,060	675.6	15%	109.6	2.0
Validive milestones			67	45.4	25%	11.4	0.2
Net cash (last reported)				8.3	100%	8.3	0.1
Valuation				**729.3**		**129.2**	**2.3**

Source: Edison Investment Research

Exhibit 16: Assumptions for AsiDNA valuation

Product/indication	Comments
Ovarian cancer	■ **Target population**: c 45k epithelial ovarian cancer patients (90% of the total incidence). Assumed 30% market penetration at peak. ■ **Pricing**: US$130k per patient per year in the US, 30% discount in Europe. Peak sales in six years. ■ **R&D cost**: US$10m for Phase II trial, then out-licensed. ■ **Licensing deal terms** (split per both indications): out-licensed in 2022. Upfront of US$40m, US$417m in R&D and commercial milestones. Tiered 12–15% royalty rates used. ■ **IP rights**: composition of matter patent protection until 2031 in main markets with possibility for extension. Method of use patent protection to late 2030s.
TNBC and **Metastatic, HER2 negative, BRCA mutated**	■ **Target population**: the total incidence of 590k in the US and top 14 Western Europe – Around 15% or 90k are TNBC patients. – Metastatic recurrence 25%, HER2 negative 83%, BRCA mutation prevalence 7.5% equals to a total of 9.2k patients. – Assumed 30% market penetration at peak ■ **Pricing**: US$130k per patient per year in the US, 30% discount in Europe. Peak sales in six years. ■ **R&D cost**: US$10m for Phase II trial, then out-licensed. ■ **Licensing deal terms**: (split per both indications): out-licensed in 2022. Upfront of US$40m, US$417m in R&D and commercial milestones. Tiered 12–15% royalty rates used. ■ **IP rights**: composition of matter patent protection until 2031 in main markets with possibility of extension. Method of use patent protection to late 2030s.

Source: Edison Investment Research. Geographies: US and top 14 western European countries: Germany, France, United Kingdom, Italy, Spain, Netherlands, Belgium, Luxembourg, Denmark, Finland, Norway, Sweden, Austria and Switzerland.

Exhibit 17: Licensing deals involving PARP inhibitors

Date	Licensor	Licensee	Product	Stage	Rights	Upfront (US$m)	Total value (US$m)
24/08/2015	Medivation	BioMarin Pharmaceutical	talazoparib (Talzenna)	Phase III	Worldwide rights	410	570
06/04/2016	Johnson & Johnson	Tesaro	niraparib (Zejula)	Phase I	Prostate cancer only	35	500
31/05/2012	Tesaro	Merck & Co	niraparib (Zejula)	Phase I	Worldwide*	7	181

Source: Edison Investment Research, EvaluatePharma, company press releases. Note: *US$57m in R&D milestones for the first indication; up to US$29.5m in R&D milestones for each successive indication; up to US$87.5m in sales related milestones.

Other changes to our model

Onxeo out-licensed Phase III-ready **Validive** (mucoadhesive clonidine for oral mucositis) to Monopar Therapeutics in September 2017 for US$109m (US$1m received upfront). We previously included a bottom up model for this asset in our valuation with 50% probability of success based on the data reported by Onxeo. However, given that the asset is now in different hands and seeing no progress reported by Monopar, we have simplified the valuation and only use the discounted (at the same 12.5% rate) and risk-adjusted value of the agreed milestones, which is adjusted by a 25% probability of success to account for operational and technology risks.

In June 2018, Onxeo effectively sold the **Beleodaq** royalties to SWK Holdings Corporation in exchange for an immediate payment of US$7.5m. SWK Holdings Corporation is entitled to receive US$13.5m in future royalties from Spectrum. Using a bottom up model we calculated that there could be a residual value from Beleodaq after the repayment of royalties to SWK. However, with the introduction of the generic competitor istodax (Celgene's Romidepsin went off patent in 2018), which is also indicated for PTCL, we decided to remove the residual value of Beleodaq from our valuation. Furthermore, Spectrum Pharmaceutical, which had in-licensed Beleodaq from Onxeo and was marketing it in the US, sold some of its assets including Beleodaq to Acrotech Biopharma, which is a private company, and it did not indicate its intentions with regards to any additional R&D.

We have also removed the small residual values of two legacy products **Sitavig** and **Loramyc** (for labial herpes and oropharyngeal candidiasis), which included potential earn-outs, as Onxeo divested these assets to Vectans Pharma in July 2017. These earnouts were not disclosed and no updates have been provided.

Financials

Onxeo booked revenues of €6.1m in 2018. Recurring revenues of €2.3m came in from the sales of Beleodaq. On 7 June 2018, Onxeo announced that it had effectively sold the Beleodaq royalties to SWK Holdings Corporation in exchange for an immediate payment of $7.5m. SWK Holdings Corporation is entitled to receive $13.5m in future royalties from Spectrum. €3.8 million in non-recurring revenues were related to contractual payments from Vectans Pharma, which acquired Onxeo specialty drugs Sitavig and Loramyc in 2017.

Total operating expenses amounted €9.7m in 2018, which was a reduction from €28.7m in 2017. This significant fall was mainly due to lower R&D expenditure as a result of the conclusion of the Phase III ReLive study in September 2017 and subsequent cost cutting program. For 2019 and 2020 we forecast total operating expenditure of €15.0m and €15.3m respectively.

Onxeo reported a cash position of €6.3m at end-Q219. In June 2019, the company announced that it had renewed a 12-month equity financing line with Nice & Green. Remaining gross proceeds from this equity line would extend cash reach to around Q320. Over the course of the next 12 months Nice & Green will subscribe and exercise each month a number of share warrants corresponding to a monthly financing of €850k. The shares will be issued each month priced on the basis of the average volume-weighted share price over the three trading days preceding each issue, less a maximum discount of 5.0%. The total number of new shares to be created is limited to 12m (compared to 55.9m that existed before the issue).

Exhibit 18: Financial summary

€000s	2016	2017	2018	2019e	2020e
Year end December	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS					
Revenue	4,423	9,505	6,127	3,300	3,300
Cost of Sales	(655)	(634)	(215)	(215)	(215)
Gross Profit	3,768	8,871	5,912	3,085	3,085
EBITDA	(21,304)	(17,393)	(2,987)	(11,356)	(11,641)
Operating Profit (before amort. and except.)	(21,542)	(19,189)	(3,527)	(11,896)	(12,181)
Intangible Amortisation	(1,626)	0	0	0	0
Exceptionals	(43)	(47,188)	(12,117)	0	0
Operating Profit	(23,211)	(66,377)	(15,644)	(11,896)	(12,181)
Other	0	0	5,176	0	0
Net Interest	1,107	(491)	(691)	(3)	(3)
Profit Before Tax (norm)	(20,435)	(19,680)	(4,218)	(11,899)	(12,184)
Profit Before Tax (reported)	(22,104)	(66,868)	(11,159)	(11,899)	(12,184)
Tax	(566)	7,797	1,760	0	0
Profit After Tax (norm)	(21,001)	(11,883)	2,718	(11,899)	(12,184)
Profit After Tax (reported)	(22,670)	(59,071)	(9,399)	(11,899)	(12,184)
Average Number of Shares Outstanding (m)	47.0	50.4	50.5	53.2	55.9
EPS - normalised (€)	(0.45)	(0.24)	0.05	(0.22)	(0.22)
EPS - normalised fully diluted (€)	(0.45)	(0.24)	0.05	(0.22)	(0.22)
EPS - (reported) (€)	(0.48)	(1.17)	(0.19)	(0.22)	(0.22)
Dividend per share (€)	0.0	0.0	0.0	0.0	0.0
Gross Margin (%)	85.2	93.3	96.5	93.5	93.5
EBITDA Margin (%)	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
BALANCE SHEET					
Fixed Assets	88,232	48,111	42,874	42,874	42,874
Intangible Assets	87,213	47,535	38,573	38,573	38,573
Tangible Assets	713	344	296	296	296
Investments	306	232	4,005	4,005	4,005
Current Assets	36,868	29,962	20,376	18,789	11,123
Stocks	184	30	47	47	47
Debtors	1,548	552	1,479	1,479	1,479
Cash	29,243	14,277	11,253	9,666	2,000
Other	5,893	15,103	7,597	7,597	7,597
Current Liabilities	(12,417)	(18,841)	(8,393)	(8,393)	(8,393)
Creditors	(12,311)	(18,711)	(7,943)	(7,943)	(7,943)
Short term borrowings	(106)	(130)	(450)	(450)	(450)
Long Term Liabilities	(18,594)	(9,358)	(9,454)	(9,454)	(13,045)
Long term borrowings	0	0	0	0	(3,591)
Other long term liabilities	(18,594)	(9,358)	(9,454)	(9,454)	(9,454)
Net Assets	94,089	49,874	45,403	43,816	32,559
CASH FLOW					
Operating Cash Flow	(16,838)	(20,974)	(10,192)	(10,969)	(11,254)
Net Interest	(1,560)	317	6,149	382	(3)
Tax	538	(7,801)	(1,764)	0	0
Capex	(316)	(65)	(45)	0	0
Acquisitions/disposals	0	0	0	0	0
Financing	13,589	13,533	2,508	9,000	0
Dividends	0	0	0	0	0
Net Cash Flow	(4,587)	(14,990)	(3,344)	(1,587)	(11,257)
Opening net debt/(cash)	(33,724)	(29,137)	(14,147)	(10,803)	(9,216)
HP finance leases initiated	0	0	0	0	0
Other	0	0	0	0	0
Closing net debt/(cash)	(29,137)	(14,147)	(10,803)	(9,216)	2,041

Source: Onxeo accounts, Edison Investment Research

Contact details	Revenue by geography
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Management team

CEO: Judith Greciet

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.

CFO: Nicolas Fellmann

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

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 an MBA from ESCP Business School and a master's degree in public health & health economics.

Executive VP – US operations and corporate development: Philippe Maitre

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 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 immunoncology, 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	14.6
Dimensional Fund Advisors	2.2

Companies named in this report

Spectrum Pharmaceuticals (SPPI.US), Monopar Therapeutics, Vectans Pharma, AstraZeneca, Merck & Co, Tesaro, GSK

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