

# Oncology Venture

Clinical outlook

## Multiple studies moving forward

Oncology Venture (OV) continues to make progress developing its oncology assets and the drug response predictor (DRP) companion diagnostic. The company has licensed six assets to date with prior clinical experience, with the hope of identifying patients with the DRP who will have an enhanced response. The most clinically advanced candidate is LiPlaCis (liposomal cisplatin). We are taking this opportunity to provide a comprehensive clinical outlook of the company.

Year end	Revenue (DKKm)	PBT* (DKKm)	EPS* (DKK)	DPS (DKK)	P/E (x)	Yield (%)
12/17	5.1	(31.0)	(1.27)	0.0	N/A	N/A
12/18	2.1	(22.5)	(0.44)	0.0	N/A	N/A
12/19e	3.6	(211.1)	(2.64)	0.0	N/A	N/A
12/20e	3.6	(96.0)	(1.25)	0.0	N/A	N/A

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

## FDA approval pathway clarified for LiPlaCis

OV recently received feedback from the FDA on the clinical pathway forward for LiPlaCis. The agency suggested OV perform a Phase III clinical study with approximately 200 randomised patients. This is a shift from the previous strategy of seeking approval with a single-arm study, but the same number of patients will be included in the trial. Therefore, we do not expect a significant impact on our financial projections from the new plan. LiPlaCis is being studied in Phase II for metastatic breast and prostate cancer.

## 2X-121 now being tested for ovarian cancer

The company announced in April 2019 that the first patient had been dosed in a new Phase II study examining the poly ADP ribose polymerase (PARP) inhibitor 2X-121 with the DRP in ovarian cancer. All PARP inhibitors approved to date have received approval for ovarian cancer. The drug is also in an ongoing Phase II study for metastatic breast cancer.

## Dovitinib DRP trained against new cancers

OV is analysing previously collected clinical data and patient samples for dovitinib from prior clinical trials performed by Novartis. The company recently announced the DRP can correctly identify dovitinib responders from previous liver cancer and breast cancer trials. This brings the total number of indications covered by the dovitinib DRP to five (including endometrial cancer, gastrointestinal stromal tumours and renal cancer, for which the company is seeking approval).

## Valuation: Increased to SEK1,301m

We have increased our valuation to SEK1,301m from SEK1,163.9m, but it is lower on a per-share basis (SEK18.47 from SEK23.13 per basic share) following the recent rights offering (20.2m units of one share and one warrant at SEK7.50 for SEK4.00 apiece). The increased cash from the offering (estimated at SEK34.9m net cash at Q119 after including offering proceeds, up from SEK24.6m net debt at 31 December 2018) is the primary cause of the increase, along with rolling forward our NPVs and offset by delaying APO010 because the programme has not advanced.

### Pharma & biotech

12 June 2019

**Price** **SEK3.65**
**Market cap** **SEK257m**

US\$/SEK 9.42/DKK6.61

Net cash (SEKm) at Q119 (includes subsequent offering) 34.9

Shares in issue 70.5m

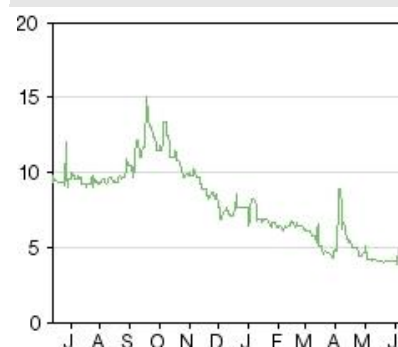
Free float 70.0%

Code OV

Primary exchange NASDAQ First North Stockholm

Secondary exchange N/A

### Share price performance



% 1m 3m 12m

Abs (12.5) (22.0) (54.1)

Rel (local) (13.3) (24.6) (55.8)

52-week high/low SEK12.71 SEK3.64

### Business description

Oncology Venture is a Denmark-based biopharmaceutical company focused on oncology. Its patent-protected mRNA-based drug response predictor platform enables the identification of patients with gene expression highly likely to respond to treatment. To date, the company has licensed six drug candidates with the intent to conduct focused Phase II clinical trials and then out-license the revamped drugs.

### Next events

Phase II LiPlaCis trial top-line data Upcoming

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## Investment summary

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### **Company description: Enhancing drugs with the DRP**

OV is a Danish pharmaceutical and diagnostic company developing the DRP, a diagnostic test that uses transcriptome data to identify patients likely to respond to a particular cancer treatment. The company has in-licensed six drug assets (with an option on a seventh) that have previously been tested in clinical trials. The goal is to revitalise these assets by pairing them with the DRP to identify patient subgroups where these drugs have enhanced activity. The company hopes to out-license these assets following completion of the ongoing Phase II clinical trials.

### **Valuation: Increased to SEK1,301m from SEK1,164m**

We have increased our valuation to SEK1,301m from SEK1,163.9m, but it is lower on a per-share basis (SEK18.47 from SEK23.13 per basic share). The increase is largely attributable to increased net cash (an estimated SEK34.9m Q119 net cash after including the offering's proceeds, from SEK24.6m net debt at 31 December 2018), advancing our NPVs and exchange rate effects, and offset by pushing back the timeline for commercialisation of APO010 (to launch in 2024 from 2023) due to lack of progress in the programme. We expect to update our valuation when data from the ongoing Phase II clinical studies become available.

### **Financials: SEK336m needed to complete studies**

The company recently had a rights offering of 20.2m units (of one share and one warrant exercisable at SEK7.50) at SEK4.00 a piece, raising a gross of SEK81m to finance its operations. We estimate that the company has SEK34.9m in net cash following the offering (the company reported DKK32.2m/SEK45.8m net debt at the end of Q119). We estimate that OV will have an operational loss of SEK203m in 2019, primarily attributable to increased clinical trial costs as the ongoing clinical studies advance. We expect the company to require DKK310m to finance its operations through Phase II studies for all of its assets, after which we expect it to meet its financing needs through out-licensing these assets for further development.

### **Sensitivities: Risks associated with proving the DRP thesis**

In addition to the unavoidable clinical development risks faced by OV, it also faces a series of risks specific to its strategy of using the DRP to enhance the value of previously discarded drugs. The company's strategy is to use the DRP to identify patient populations where the investigated drugs may have increased activity that can enhance the value of these assets, but there can be no guarantee that these patient groups can be identified. Moreover, most data available to date on these drug/DRP combinations have retrospectively assigned the parameters of the test, whereas for approval, data will need to show that the DRP can prospectively identify responders. Additionally, it must be demonstrated that the DRP can improve outcomes and is not simply identifying patients with improved prognoses, which cannot yet be demonstrated for the company's current assets. If the DRP works but a restrictive criteria for a positive test are defined, this may limit the number of patients available for treatment. Finally, OV faces significant partnering risk: the company may successfully complete any number of focused Phase II trials demonstrating that the use of drug-specific DRPs improves patient outcomes but not identify a partner to out-license to, which would have a negative effect on the company's financials.

## Leveraging the transcriptome to optimise drugs

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OV's key technology is the DRP, which uses transcriptome-level data to predict a patient's response to a particular cancer drug. OV's core strategy is to in-license discontinued oncology drugs that demonstrate activity in previously ignored patient sub-populations using its DRP biomarker technology. The goal is to conduct focused early clinical trials in those patients who have the highest likelihood of response and then either out-license or sell the Phase III-ready drugs with the respective DRP. The DRP biomarker platform assigns each patient a pre-treatment gene expression score that predicts the probability of either sensitivity or resistance to an anticancer agent. These values are derived from transcriptome analysis of cultured cell lines and normalised on a scale of 0 to 100, where a higher number is indicative of a greater likelihood of response. Patients are then elected to participate in a focused Phase Ib trial (eight patients to start) and, based on these initial results, OV may decide to either discontinue development or enrol more patients to complete a Phase IIa portion of the trial (approximately 20 patients).

The company in its current form was created by the merger of OV with the related company Medical Prognosis Institute (MPI) in August 2018, from which it previously spun off and with which it shared management. OV's pipeline consists of six oncology products (and an option to in-license a seventh) that target a variety of cancers with distinct mechanisms of action. OV is developing LiPlaCis, a liposomal formulation of cisplatin, for the treatment of breast cancer (BC) as well as other solid cancers in collaboration with Cadila Pharmaceuticals. OV's ownership of this programme is 39%. OV is also developing irifulven, a cytotoxic DNA binding agent, and APO010, a Fas receptor agonist. Moreover, OV incorporated two subsidiaries in 2016, Oncology Venture US (OVUS, formerly 2X Oncology, ~92% owned by OV) and OV-SPV2 (~55% owned by OV, 45% owned by Sass & Larsen Aps) with \$4.0m (SEK36.5m) in seed financing primarily from existing OV shareholders. OVUS has two development programmes, a novel liposomal formulation of a chemotherapy that encourages drug delivery across the blood-brain barrier (BBB) as well as a dual PARP and tankyrase (TNKS) inhibitor. OVUS is headquartered in Cambridge, MA, and Dr Buhl Jensen (CEO of OV) serves as chairman of the board. Furthermore, OV formed OV-SPV2 as a spin-out focused on the development of dovitinib, a tyrosine kinase inhibitor (TKI) that was in-licensed from Novartis. OV is fully devoted to the advancement of these subsidiary oncology programmes internally.

**Exhibit 1: OV pipeline**

Product (company, year acquired)	Indication	Mechanism	Stage	Ownership	Notes
LiPlaCis (LiPlasome Pharma, 2016)	mBC, prostate, head and neck, oesophageal, and skin cancers	Alkylating agent (liposomal formulation of cisplatin)	Phase II	39%	Received CE mark for LiPlaCis DRP in January 2017. OV is responsible for conducting Phase II trial in mBC. Collaboration agreement in place with Cadila Pharmaceuticals since 2016.
Irofulven (Lantern Pharma, 2015)	Metastatic prostate cancer	Cytotoxic DNA binding agent	Phase II	100%	Developed by University of California San Diego and previously investigated by MGI Pharma and Eisai (via acquisition of MGI). Received US patent in August 2017 for irofulven DRP. Lantern will receive licence fees, milestone payments and royalties, and OV will receive shares in Lantern. The financial terms of this agreement have not been disclosed.
APO010 (Onxeo, 2012)	MM	Fas receptor agonist	Phase II	100%	Developed and investigated by TopoTarget/Onxeo before in-licensing. OV was granted full rights to APO010, however, further details have not been disclosed.
2X-121 (Eisai, 2017)	mBC and ovarian cancer	PARP/ TNKS inhibitor	Phase II	92%	Owned via OVUS subsidiary. Initiated mBC Phase II trial Q118. Terms of the agreement have not been disclosed.
2X-111 (2-BBB, 2017)	BMBC, GBM	Anthracycline (GSH PEGylated liposomal doxorubicin)	Phase II ready	92%	Owned via OVUS subsidiary. Obtained US IND in June 2017. Terms of the agreement have not been disclosed.
Dovitinib (Novartis, 2017)	Renal cancer	TKI	NDA filing	55%	Owned through OV-SPV subsidiary. Previous Dovitinib activity in Novartis <a href="#">Phase III trial</a> demonstrated PFS of 3.7 months in third-line treatment of metastatic renal cell carcinoma patients versus Bayer's sorafenib activity (PFS 3.6 months). NDA being sought on the basis on non-inferiority. Terms of the agreement have not been disclosed.
Ixempra (R-Pharm, option to acquire)	mBC	Microtubule targeting agent	N/A	N/A	Originally developed by Bristol-Myers Squibb. Previous BMS data being processed to evaluation applicability of DRP to molecule. OV has exclusive option to European rights. Financial terms of agreement not disclosed.

Source: Oncology Venture. Notes: The company operates as a unified entity; Fas: first apoptosis signal; BMBC: brain metastasis from breast cancer; DHMA: Danish Medicines Agency; MM: multiple myeloma; GBM: glioblastoma; GSH: glutathione; PARP: poly ADP ribose polymerase; TNKS: tankyrase; TKI: tyrosine kinase inhibitor; PFS: progression-free survival.

## The scientific basis of the DRP

The DRP uses the transcriptome, which is the collection of the RNA sequences in a cell to identify patients most likely to respond to a particular anticancer therapy. The platform was developed in vitro using an established panel of 60 human tumour cell lines from the National Cancer Institute (NCI-60) to correlate the genetic expression profile of a tumour to either sensitivity or resistance to an anticancer drug. Gene expression profiles of the NCI-60 cancer cell lines are derived from a microarray (commercially available Affymetrix Gene Chips) to quantify the level of mRNA transcribed from a nucleic acid molecule that identifies biomarkers. A biological relevance filter is then applied such that only markers previously known to interact are used to reduce the number of false positives. This process generates a list of genes characterising the cell lines that are sensitive and resistant to the drug in question, which is subsequently used to identify a subpopulation of cancer patients most likely to respond to the drug in vivo.

These cell panels are further validated using patient tumour samples or diagnostic formalin-fixed paraffin-embedded biopsies (note these are highly variable sample sets). Gene expression in patients' cells is determined in the same manner as in the cell lines previously described. The sum of the expression levels of the patient's biomarkers is compared to the median of the sums derived from the training set population with the same tumour type to predict either sensitivity or resistance to the anticancer agent and provides an insight into how the drug will perform in the more variable clinical setting.

The efficacy of the DRP system has been supported in over 25 retrospective studies for a variety of cancers and therapies. One such study evaluated the development of a gene expression score that predicts response to fulvestrant in patients with locally advanced oestrogen receptor-positive (ER+)

breast cancer. The prediction score was based on baseline gene expression in the presence of fulvestrant where 103 genes showed increased expression in sensitive cell lines and 311 genes showed increased expression in non-responding cell lines.<sup>1</sup> The DRP was then used to predict patient sensitivity to fulvestrant based on the expression of each gene in the response profile of pre-treatment tumour biopsies obtained from AstraZeneca's [Phase II study](#) that investigated neoadjuvant endocrine therapy for women with ER+ breast cancer. These data are combined to produce a predictor score. The patients who clinically responded (ie partial response) to fulvestrant demonstrated a significantly higher sensitivity predictor score than the non-responders (ie stable disease and disease progression) ( $p=0.01$ ). Moreover, the addition of clinical covariates obtained from the study such as tumour stage and percentage of ER+ tumour cells demonstrated a significant difference ( $p=0.003$ ) between responders and non-responders. Within this trial the positive predictive value was 88% and the negative predictive value was 100%. The company has subsequently performed a similar study examining the ability of the DRP to predict the response to doxorubicin<sup>2</sup> and epirubicin<sup>3</sup> as a neoadjuvants, with similar results

In an external validation of the DRP system in collaboration with the MD Anderson Center, the test was evaluated in three distinct datasets including patients treated with epirubicin monotherapy for breast cancer, ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) chemotherapy for Hodgkin's lymphoma, and methotrexate for acute lymphoblastic leukaemia. MD Anderson independently selected datasets that satisfied specific conditions set by MPI (ie at least 100 distinct patients receiving the same treatment and availability of treatment outcomes) and sent the list of drugs used to treat the patients to MPI to develop a predictive model in vitro for each drug using the NCI-60 cell lines. MD Anderson then applied the model and compared the predictions with primary patient responses from existing records to evaluate the performance of the DRP. The prediction score in all three cases significantly predicted patient response ( $p=0.02$ ).<sup>4</sup> However, the study's sponsors concluded that although the sensitivity scores based on in vitro models predicted patient response better than chance, the results are not quite compelling enough to change clinical practice, and there may be an opportunity to develop the DRP for drug development purposes where existing clinical variables are not yet established, to predict the likelihood of patient response. Nonetheless, the DRP also has its limitations. In one retrospective trial, MPI developed DRPs based on in vitro assays to predict patient response (relapsed free survival) to irinotecan treatment for metastatic colorectal cancer. The irinotecan DRP identified 38 positively correlated genes.<sup>5</sup> The irinotecan DRP was unable to predict patient response to irinotecan ( $p=0.450$ ). The study found that the DRP most likely failed in this case because no significant effect was found with irinotecan treatment and that the population who did benefit from the drug may have been too small to detect using the available patient samples.

The DRP method is patented for more than 70 anticancer agents including vincristine, cisplatin, carboplatin, rituximab, etc.<sup>6</sup> Although the company continues to perform research on the DRP paired with commonly used cancer drugs, OV's business strategy is focused on mining

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- <sup>1</sup> Knudsen S, et al. (2014) Development and Validation of a Gene Expression Score That Predicts Response to Fulvestrant in Breast Cancer Patients. *PLoS ONE* 9, e87415.
  - <sup>2</sup> Buhl ASK, et al. (2019) Doxorubicin response prediction in neoadjuvant breast cancer therapy. *J Clin Oncol* 37, e12119.
  - <sup>3</sup> Buhl ASK, et al. (2018) Predicting efficacy of epirubicin by a multigene assay in advanced breast cancer within a Danish Breast Cancer Cooperative Group (DBCG) cohort: a retrospective-prospective blinded study. *Breast Cancer Res Treat* 172, 391–400.
  - <sup>4</sup> Wang, W., et al. (2013). Independent Validation of a Model Using Cell Line Chemosensitivity to Predict Response to Therapy. *JNCI: Journal of the National Cancer Institute* 105, 1284-1291.
  - <sup>5</sup> Buhl, I. K., et al. (2016) Cell Line Derived 5-FU and Irinotecan Drug-Sensitivity Profiles Evaluated in Adjuvant Colon Cancer Trial Data. *Plos One*, 11.
  - <sup>6</sup> US Patent No. 8,445,198

discontinued drugs for development to increase the probability of success of clinical trials by only treating the patient population most likely to respond. Before in-licensing an asset, OV first develops a DRP biomarker model in vitro with the drug and evaluates the model using clinical biopsies and blinded patient response data. If the evaluation is successful, the two parties enter into a licence agreement granting OV exclusive rights to further develop the asset. OV's plan is to include only the top 10–30% of patients who have the highest likelihood of response in focused Phase I/II clinical trials.

OV's clinical trial design is considerably cost saving. The company aims to screen approximately 100 potential patients for each new trial; it identifies those most likely to respond and waits to enrol them as soon as they relapse. Furthermore, the company thoroughly investigates interim data (on approximately the first eight patients) to determine whether to continue to develop the asset. These methods effectively save time, money and resources.

## LiPlaCis: Liposomal cisplatin chemotherapy

Platinum-based chemotherapy drugs (commonly called platins, ie, cisplatin, oxaliplatin and carboplatin) have been widely prescribed alone or in combination with other drugs for the treatment of solid tumours since the early 1970s.<sup>7,8</sup> Platins are DNA crosslinking agents that exert antitumor activity by interfering with transcription and/or DNA replication mechanisms. Platins also induce mitochondrial damage, hinder ATPase activity and disrupt cell transport mechanisms that subsequently trigger cytotoxic effects and apoptosis (or cell death).<sup>9</sup>

Nonetheless, platinum-based drug cytotoxicity is not limited to cancer cells and is consequently associated with severe dose-related cell damaging effects, immunosuppression, bone marrow suppression, ototoxicity, peripheral neurotoxicity and, most notably, renal toxicity. Platins inherently bind to extracellular and intracellular proteins, such as serum albumin, which inactivates enzymes and affects drug metabolism, efficacy and distribution throughout the body.<sup>10</sup> This leads to relatively short blood circulation times and inadequate pharmacokinetics.<sup>11</sup> Limitations such as these have motivated the development of liposomal platinum reformulations and targeted therapy to improve therapeutic efficacy and reduce toxicity.

A number of encapsulated platinum-based formulations have entered the clinic. However, commercialisation has not yet been achieved largely due to inferior response rates in comparison to free platins (Exhibit 2). The development of Aroplatin<sup>12</sup> and SPI-077<sup>13</sup> have similarly been discontinued essentially due to drug inactivity in early dose-escalation trials,<sup>14</sup> while the most clinically advanced liposome formulations are Lipoplatin and Nanoplatin. Regulon received

<sup>7</sup> Furtés, M., et al. (2003) Cisplatin Biochemical Mechanism of Action: From Cytotoxicity to Induction of Cell Death Through Interconnections Between Apoptotic and Necrotic Pathways. *Current Medicinal Chemistry*, 10(3), 257-266.

<sup>8</sup> Hang, Z., et al. (2016) Platinum-based anticancer drugs encapsulated liposome and polymeric micelle formulation in clinical trials. *Biochemical Compounds* 4, 1.

<sup>9</sup> Babu, A., Amreddy, N., & Ramesh, R. (2015) Nanoparticle-based cisplatin therapy for cancer. *Therapeutic Delivery*, 6(2), 115-119.

<sup>10</sup> Ivanov, A. I., et al. (1998) Cisplatin Binding Sites on Human Albumin. *Journal of Biological Chemistry* 273, 14721-14730.

<sup>11</sup> Wang, A., et al. (2013) Application of liposomal technologies for delivery of platinum analogs in oncology. *International Journal of Nanomedicine*, 3309.

<sup>12</sup> Dragovich, T., et al. (2006). A Phase 2 trial of the liposomal DACH platinum L-NDDP in patients with therapy-refractory advanced colorectal cancer. *Cancer Chemotherapy and Pharmacology* 58, 759-764.

<sup>13</sup> Harrington, K. J., et al. (2001) Phase I-II study of pegylated liposomal cisplatin (SPI-077 TM) in patients with inoperable head and neck cancer\*. *Annals of Oncology*, 12, 493-496.

<sup>14</sup> Bulbake, U., et al. (2017) Liposomal Formulations in Clinical Use: An Updated Review. *Pharmaceutics* 9, 12.

European Medicines Agency (EMA) orphan drug designation for Lipoplatin for the treatment of metastatic pancreatic cancer and is evaluating the drug in a Phase II/III study. Regulon completed a double-arm Phase III study directly comparing toxicity and efficacy of Nanoplatin versus free cisplatin in combination with paclitaxel (an antineoplastic chemotherapy) in 202 patients with inoperable stage IIIB and IV non-squamous cell non-small cell lung cancer (NSCLC).<sup>15</sup>

#### Exhibit 2: Liposomal formulations of platinum drugs

Product (company)	Encapsulated drug	Indication	Clinical status
Lipoplatin/Nanoplatin (Regulon)	Cisplatin	Metastatic pancreatic cancer/NSCLC	Phase III
LiPlaCis (Oncology Venture)	Cisplatin	mBC	Phase II
Aroplatin (Agenus)	L-NDDP (cisplatin)	Mesothelioma and metastatic colorectal cancer	Discontinued
SPI-077* (N/A)	Cisplatin	Advanced head and neck cancer, NSCLC	Discontinued
MBP-426** (MebioPharm)	Oxaliplatin	Gastric and gastroesophageal cancer	Discontinued
Lipoxal (Regulon)	Oxaliplatin	Advanced gastrointestinal cancer	Discontinued

Source: Company websites, Evaluate Pharma. Notes: \*SPI-077 is a PEGylated liposomal formulation of cisplatin originally developed by Sequus Pharmaceuticals and has been investigated by a number of academic institutions. \*\*MBP-426 is a transferrin (TF) PEGylated liposomal formulation of oxaliplatin. L-NDDP = liposomal formulation of a third-generation platinum complex analogue of cisplatin.

OV in-licensed LiPlaCis in 2016 from LiPlasome Pharma with the goal of developing a LiPlaCis DRP to identify patients with advanced solid tumours highly likely to respond to the drug. LiPlaCis is a liposomal formulation of cisplatin that is designed to be degraded by secretory phospholipase A2 (sPLA2), which is an enzyme expressed by cancerous cells. Increased expression of sPLA2s in tumours was found to be associated with the pathology of cancers of the colon, breast, stomach, oesophagus, ovaries and prostate.<sup>16</sup> The hope is that targeting sPLA2 can spare some of the toxicities (in particular, renal). In preclinical trials, the use of the sPLA2 enzyme effectively triggered targeted drug delivery.<sup>17</sup> However, LiPlasome Pharma discontinued the development of the asset due to severe renal toxicity and acute infusion reactions observed during an open-label dose escalating (10–120mg) Phase I clinical trial in 18 patients with advanced solid tumours.<sup>18</sup> Nephrotoxicity severity increased with dose and thus did not demonstrate any renal-sparing effect that the drug was intended to achieve. Additionally, there was no correlation ( $p=0.87$ ) between the baseline levels of sPLA2 and the initial half-life (or time required for the concentration of the drug to decrease by half) of the liposome, which therefore indicates that sPLA2 levels are not associated with the breakdown of LiPlaCis in vivo.

OV is nonetheless investigating LiPlaCis for the treatment of metastatic breast cancer (mBC) in a single-arm focused Phase II clinical trial treating only the top two-thirds of patients identified by the DRP. The Norwegian Research Council and Innovation Fund Denmark jointly granted OV and its co-development partner, Smerud, a contract research organisation (CRO), a total of SEK18m to further the development of the LiPlaCis programme. It is important to note that as Smerud is a CRO, it can access grant funds and will likely have a share of the project although this information has not been disclosed. In addition, OV has a collaboration agreement in place with Cadila Pharmaceuticals in which Cadila is sponsoring a later Phase III trial in mBC and four Phase II trials in prostate, head and neck, oesophageal and skin cancers. However, the degree to which Cadila is participating in development it is unclear at this point.

In February 2019, OV provided an update on its ongoing single-arm, open-label Phase II trial investigating LiPlaCis for the treatment of heavily pre-treated mBC patients. Patients are

<sup>15</sup> Stathopoulos, G. P., et al. (2011) Comparison of liposomal cisplatin versus cisplatin in non-squamous cell non-small-cell lung cancer. *Cancer Chemotherapy and Pharmacology* 68, 945-950.

<sup>16</sup> Brglez, V., et al (2014) Secreted phospholipases A2 in cancer: Diverse mechanisms of action. *Biochimie*, 107, 114-123.

<sup>17</sup> Jensen, S., et al (2004) Secretory phospholipase A2 as tumour specific trigger for targeted delivery of a novel class of liposomal prodrug anticancer etherlipids. *European Journal of Cancer Supplements* 2, 183.

<sup>18</sup> Jonge, M. J., et al. (2010) Early cessation of the clinical development of LiPlaCis, a liposomal cisplatin formulation. *European Journal of Cancer* 46, 3016-3021.

administered 40mg/m<sup>2</sup> LiPlaCis intravenously (IV) in three-week cycles on days one and eight with efficacy evaluation every six weeks. The response rate was 33% (or four out of 12 patients) in the top one-third of DRP-selected patients. These patients achieved partial response (PR) or better, which is defined as a 30% or greater reduction in tumour size measured in one dimension in a CT scan when treated with LiPlaCis. Moreover, the top third of patients also reached a median time to progression of 18 weeks versus seven weeks in the remaining enrolled patients (who had DRP scores between 33% and 67%, as those below 33% were excluded from the study).

Additionally, 40% of patients in the upper 20% of DRP-selected patients who have not previously received cisplatin also achieved PR or better. This marks the first time that OV has presented data using a 20% DRP threshold, highlighting that thresholding is under active investigation. The company may shift the DRP threshold up or down to optimise patient response to LiPlaCis. OV previously guided that top-line data from the ongoing study will be available in H119, so we expect a near-term data readout.

OV will be seeking approval for LiPlaCis via a pivotal study in 200 patients with mBC using the ongoing Phase II trial as a bridge. According to the company, it believes data from the Phase II study may support a 'breakthrough therapy designation' from the FDA, which would streamline the development and approval process by allowing some data to be gathered from post-marketing trials and would increase interaction with the agency.

In addition to its programme in mBC, LiPlaCis is also being evaluated for the treatment of metastatic castration-resistant prostate cancer (mCRPC) and it began including these patients in the ongoing Phase II study in March 2019. Platinum-based chemotherapy has previously been investigated for this patient population; however, its application has not endured clinical practice. In one study, 34 men with castrate-resistant prostate cancer with progression after monotherapy docetaxel were treated with a combination of docetaxel (60mg/m<sup>2</sup>) and carboplatin every three weeks. The overall response rate (ORR) to this combination therapy was relatively low at 14%.<sup>19</sup> Moreover, a comprehensive review article detailed response rates to a number of cisplatin regimens in metastatic prostate cancer. In three publications, the response rate of cisplatin monotherapy, defined as a greater than a 50% prostate-specific antigen decline, was 20%.<sup>20</sup> In total, 17 publications investigating cisplatin in combination with other chemotherapies reported response rates between 23% and 29% in mCRPC patients.<sup>20</sup>

Although response rates to platinum-based chemotherapy have previously been suboptimal, the use of OV's LiPlaCis DRP may reveal improved outcomes in patients assessed by the DRP as more likely to respond to the drug. According to the company, more than 80 patients with metastatic castration-resistant prostate cancer have consented to have their tumour tissue analysed by the LiPlaCis DRP.

## Breast cancer market and competitive environment

According to the National Cancer Institute, approximately 268,000 patients in the US will be diagnosed with BC in 2019, or 127.5 per 100,000 women on an age-adjusted basis, making it the most common cancer diagnosis in the country. The disease is less commonly diagnosed in the EU, at a rate of 80.3 per 100,000.<sup>21</sup> There will be an estimated 4,160 deaths in the US from the disease during 2019, which although large on an absolute scale, makes BC one of the most treatable

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<sup>19</sup> Hauke, R., & Teply, B. (2016) Chemotherapy options in castration-resistant prostate cancer. *Indian Journal of Urology* 32, 262.

<sup>20</sup> Hager, S., et al. (2016) Anti-tumour activity of platinum compounds in advanced prostate cancer—a systematic literature review. *Annals of Oncology* 27, 975-984.

<sup>21</sup> EUCAN



cancers. Due to screening efforts and other factors, the majority of BC is diagnosed during the early stages whereas only 7% and 5% are initially diagnosed at stage III or IV, respectively.

Chemotherapy can be given in the induction setting for advanced and metastatic tumours, although it is more common in the second line. In a retrospective study chemotherapy was used in 14% of patients in the first line and 31% in the second line (from a population of post-menopausal stage IV patents).<sup>22</sup> It is also significantly more common for patients that receive induction chemotherapy to receive follow-up systemic adjuvant chemotherapy. In addition to anthracyclines and taxanes, more aggressive chemotherapies such as cisplatin, gemcitabine and eribulin (to name a few) are used. Recent studies suggest that platins can potentially be used in the treatment of triple negative BC (TNBC)<sup>23</sup> where the gold standard treatment is combination chemotherapy,<sup>24</sup> which typically includes alkylator and anthracycline chemotherapy followed by consecutive taxane treatment.<sup>25</sup> Two TNBC subgroups (basal-like 1 and 2) express high levels of DNA-damage response genes and may be particularly susceptible to the LiPlaCis mechanism of action previously described.<sup>26</sup>

## mCRPC market and competitive environment

The National Cancer Institute estimates that 174,650 patients in the US will be diagnosed with prostate cancer in 2019, or 109.5 per 100,000 men on an age-adjusted basis, making it the second most common cancer among men in the US and fifth most common cancer among men worldwide.<sup>27</sup> There will be an estimated 31,620 deaths from the disease in the US during 2019. The stage of prostate cancer at diagnosis is a significant contributor to survival as patients with early local disease have a five-year relative survival rate of almost 100%, whereas patients with advanced metastasis have a relative five-year survival of 28%. Due to screening advances and more aggressive treatment, there has been an increase and decrease in incidence of localised disease and metastases, respectively.

Prostate cancer is initially treated with androgen deprivation therapy (or hormone therapy), but the disease inevitably progresses in nearly all cases and this is subsequently termed castration-resistant prostate cancer. Newer medicines such as Xtandi (enzalutamide, Pfizer) and Zytiga (abiraterone acetate, Johnson & Johnson, J&J) have significantly improved patient outcomes. The rate of progression-free survival at 12-month follow up in one Xtandi trial was 68%.<sup>28</sup> Xtandi and Zytiga brought in approximately \$3.0bn and \$3.5bn, respectively, in sales in 2018.<sup>29</sup>

## Irofulven: Cytotoxic DNA-binding agent

Irofulven is currently being studied by OV for potential activity in prostate cancer. The molecular pharmacology and precise mechanisms of action of irofulven are not well defined. However, preclinical models have demonstrated its ability to covalently bind to DNA and cellular proteins to

<sup>22</sup> Zanotti G, et al. (2017) Treatment patterns and real world clinical outcomes in ER+/HER2- post-menopausal metastatic breast cancer patients in the United States. *BMC Cancer* 17, 393.

<sup>23</sup> Eckstein, N. (2011) Platinum resistance in breast and ovarian cancer cell lines. *J Exp Clin Can* 30.

<sup>24</sup> American Cancer Society.

<sup>25</sup> Mayer, E. L., & Burstein, H. J. (2016) Chemotherapy for Triple-Negative Breast Cancer: Is More Better? *Journal of Clinical Oncology* 34, 3369-3371.

<sup>26</sup> Lehmann, B. D., et al. (2011) Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. *Journal of Clinical Investigation* 121, 2750-2767.

<sup>27</sup> Darves-Bornoz, A., Park, J., & Katz, A. (2014) Prostate Cancer Epidemiology. *Prostate Cancer*, 1-15.

<sup>28</sup> Beer, T. M., et al. (2014). Enzalutamide in Metastatic Prostate Cancer before Chemotherapy. *New England Journal of Medicine*, 371(5), 424-433.

<sup>29</sup> Evaluate Pharma

inhibit DNA synthesis and induce apoptosis independently of p53 and p21/WAF1 gene expression, which regulate cell cycle arrest.<sup>30</sup> The gold standard treatment for the castration-resistant population includes docetaxel, which is a taxane chemotherapy, in combination with prednisone, a corticosteroid.<sup>31</sup> However, studies suggest that approximately 50% of these patients are either resistant or develop resistance to docetaxel and do not respond to treatment.<sup>32</sup> p53 protein overexpression is one of several known mechanisms of resistance to docetaxel in prostate cancer as it blocks apoptosis. Therefore, this sub-population of metastatic castration and docetaxel resistant prostate cancer (mCDRPC) patients may be particularly susceptible to irifolven as it has been shown to inhibit DNA synthesis and induce apoptosis independently of p53 expression in preclinical development.<sup>30</sup> Irifolven's anticancer properties have been investigated in a number of clinical trials in solid cancers by its originator at the University of California San Diego, as well as by MGI Pharma, a US biotechnology company, which acquired the asset in 1993.

Early trials verified the efficacy of irifolven against advanced solid cancers, particularly in a population of patients with prostate cancer.<sup>33</sup> These findings guided MGI Pharma's investigation of the safety and efficacy of irifolven monotherapy in patients with metastatic hormone-refractory prostate cancer in a single-arm, open-label Phase II trial. In total, 42 patients were administered a median of three courses of irifolven. Overall, 15% and 14% of participants experienced grade 3 or 4 thrombocytopenia and neutropenia, respectively, which are common haematological toxicities caused by chemotherapy drugs used to treat hormone-refractory prostate cancer.<sup>34</sup> Four out of 32 evaluable patients experienced a partial response whereas 27 experienced stable disease. Median progression-free survival was 2.9 months. MGI was acquired by Eisai in 2007 for \$3.9bn and irifolven development was ceased in 2009 when Eisai returned it to its original developer. Lantern Pharma picked up the asset in 2015 and out-licensed it to OV soon after.

Together, Lantern Pharma and OV received a grant for \$800,000 from the Life Sciences International Collaborative Industry Program to support the development of an irifolven DRP to identify patients with metastatic castration- and docetaxel-resistant prostate cancer most likely to respond to treatment. OV developed an irifolven DRP based on 205 mRNAs and began the screening portion of the clinical trial at two Danish university hospitals with the intent to screen 300 mCDRPC patients in August 2016. In October 2018, the first prostate cancer patient was included in its Phase II irifolven trial. According to the company, interim data obtained from the first eight patients enrolled in the study (ie selected by the DRP algorithm to be sensitive to irifolven) will determine whether the company continues to develop this asset. If the selected patients experience a particular response, the entirety of the Phase II trial will include 13–27 patients with the highest likelihood to respond to irifolven. OV expects to see a 20% or higher response rate to irifolven in these patients, which is approximately on par with the standard of care. For example, current treatment options (ie hormonal therapy, chemotherapy, typically taxanes or CYP-17 inhibitors, the combination of chemotherapy and hormonal therapy, or immunotherapy) yield a tumour response

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<sup>30</sup> Alexandre, J. (2004). Phase I and Pharmacokinetic Study of Irifolven Administered Weekly or Biweekly in Advanced Solid Tumor Patients. *Clinical Cancer Research*, 10(10), 3377-3385.

<sup>31</sup> Hotte, S. J., & Saad, F. (2010). Current management of castrate-resistant prostate cancer. *Current Oncology*, 17(0).

<sup>32</sup> Magadoux, L., et al. (2014). Emerging targets to monitor and overcome docetaxel resistance in castration resistant prostate cancer (Review). *International Journal of Oncology*, 45(3), 919-928.

<sup>33</sup> Eckhardt, S. G., et al. (2000). Phase I and Pharmacokinetic Study of Irifolven, a Novel Mushroom-Derived Cytotoxin, Administered for Five Consecutive Days Every Four Weeks in Patients With Advanced Solid Malignancies. *Journal of Clinical Oncology*, 18(24), 4086-4097.

<sup>34</sup> Senzer, N., et al. (2005). Irifolven Demonstrates Clinical Activity Against Metastatic Hormone-Refractory Prostate Cancer in a Phase 2 Single-Agent Trial. *American Journal of Clinical Oncology*, 28(1), 36-42.

rate of 22.6% and correspond to median progression-free survival and overall survival of 7.6 months and 15.1 months, respectively.<sup>35</sup>

## APO010: Fas receptor agonist

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Death receptors are members of the tumour necrosis factor family and are desirable targets for anticancer therapy. One such receptor of interest is the first apoptosis signal receptor (Fas, also known as apoptosis antigen 1 or cluster differentiation 95 (CD95)). The Fas receptor is a transmembrane protein and is predominantly expressed in activated T-cells and natural killer cells.<sup>36</sup> The interaction between the natural Fas receptor and its ligand plays a critical role in the regulation of apoptosis and is associated in the pathogenesis of malignancies and immune system diseases.<sup>37</sup> In addition to triggering apoptosis, it has also been recognised that Fas induces cell proliferation in T-cells, liver cells and neurons.<sup>36</sup> The Fas agonistic molecule has remained a questionable target as it has demonstrated either too strong haematological toxicities, or negligible activity as most cancer cells are resistant to Fas-mediated apoptosis.<sup>38</sup>

APO010 is a synthetic hexameric formulation of natural Fas ligands that targets Fas receptors on cancer cells to potentially induce caspase-dependent apoptosis and antineoplastic activity.<sup>39</sup> The recombinant molecule was originally developed by Apoxis, a private biopharmaceutical company based in Switzerland, and was acquired by TopoTarget in 2007 (when Dr Buhl Jensen was the CEO of the company) from which OV in-licensed it in 2012. The terms of this agreement have not been disclosed.

TopoTarget (now Onxeo after the 2014 merger with BioAlliance Pharma) led a Phase I pharmacokinetic, dose-escalating trial of the IV administration of APO010 in 25 patients with non-resectable solid tumours once per week. The results of this trial have not been disclosed, however, according to OV, the study serves as the basis for conducting a focused Phase Ib/II APO010 trial using the DRP as a companion diagnostic. The Norwegian Research Council granted OV and Smerud approximately \$1.64m to cover the costs for the APO010 clinical proof-of-concept trial. Based on the gene expression profiles of 3,200 human tumours, OV developed a specific DRP to predict APO010 responsiveness. [The study](#) revealed multiple myeloma (MM) to be sensitive to APO010 in comparison to some solid tumours tested.<sup>40</sup> In May 2017, OV announced that the first patient was enrolled in the focused Phase Ib/II trial for the treatment of relapsed or refractory MM. OV is targeting enrolment of 15 patients most likely to respond to APO010 out of approximately 150 patient DRP screenings, but as of yet no responders have been identified. The company first aims to demonstrate effective APO010 monotherapy and follow up with combination trials with other agents such as PD-1 inhibitors.

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<sup>35</sup> Akaza, H., et al. (2018). Metastatic Castration-Resistant Prostate Cancer Previously Treated with DocetaxelBased Chemotherapy: Treatment Patterns from the PROXIMA Prospective Registry. *Journal of Global Oncology*, (4), 1-12.

<sup>36</sup> Peter, ME., et al. (2015). The role of CD95 and CD95 ligand in cancer. *Cell Death and Differentiation* 22, 549-559.

<sup>37</sup> Müller, M., et al. (1998). P53 Activates the CD95 (Apo-1/Fas) Gene in Response to DNA Damage by Anticancer Drugs. *The Journal of Experimental Medicine*, 188(11), 2033-2045.

<sup>38</sup> Eisele, G., et al. (2010). APO010, a synthetic hexameric CD95 ligand, induces human glioma cell death in vitro and in vivo. *Neuro-Oncology*, 13(2), 155-164.

<sup>39</sup> Villunger, A., et al. (1997). Constitutive Expression of Fas (Apo-1/CD95) Ligand on Multiple Myeloma Cells: A Potential Mechanism of Tumor-Induced Suppression of Immune Surveillance. *Blood*, 90(1), 12-20.

<sup>40</sup> Vangsted, A., et al. (2016) APO010 sensitivity in relapsed multiple myeloma patients. *Annals of Oncology*, 27, Suppl. 6.

## Market and competitive environment

An estimated 32,110 patients in the US will be diagnosed with MM in 2019, or 6.9 per 100,000 on an age-adjusted basis, and approximately 12,960 deaths from the disease are expected in the US during the same year.<sup>41</sup> The disease is less commonly diagnosed in the EU at a rate of 4.5 per 100,000.<sup>42</sup> According to the American Cancer Society, stage I, II and III MM are associated with median survival of 62, 44 and 29 months, respectively.

Front-line MM is commonly treated with autologous stem cell transplantation (ASCT). The combination of Velcade (bortezomib, J&J) with dexamethasone is a common treatment prior to ASCT.<sup>42</sup> J&J reported \$1,116m in worldwide sales (ex US and Japan for MM and non-Hodgkin lymphoma) in 2018. Takeda distributes Velcade to the US and Japan and reported sales of \$953m in 2018. For those who are ineligible for ASCT, MM is treated with the combination of bortezomib, melphalan and prednisone. According to one study, an estimated 61% and 38% of the patients with MM relapse and undergo second- and/or third-line treatment, respectively.<sup>43</sup> Relapsed or refractory MM is typically treated with Kyprolis (carfilzomib, Amgen) in combination with lenalidomide and dexamethasone. Amgen reported worldwide sales of \$835m (ex Japan and India) for 2017. Because APO010 presumably targets Fas receptors and preclinical studies have demonstrated the expression of functionally active FasL on B-cell malignancies (including MM),<sup>39</sup> APO010 may be useful in the MM patient population.

It is important to note that the drug development space for MM research is exceedingly competitive, although this is mitigated by the number of different therapies with which patients are treated. Furthermore, the disruptive force lies in the development of CAR-T cells for the treatment of MM. CAR-T products in development target B cell maturation antigens on the surface of MM cells. The results of an early Chinese clinical trial in 35 patients with MM were presented at the 2017 [American Society of Clinical Oncology](#) meeting. Of 19 evaluable patients, 14 had a stringent complete response and five had a partial response. In 2017, the FDA approved the first two CAR-T therapies, Kymriah (tisagenlecleucel, Novartis) for the treatment of relapsed acute lymphoblastic leukaemia (ALL), and Yescarta (axicabtagene ciloleucel, Kite) for the treatment of relapsed/refractory large B-cell lymphoma.

## 2X-121: Dual PARP/TNKS inhibitor

2X-121 is an orally bioavailable small molecule inhibitor of PARP-1/2 and TNKS-1/2 that was licensed from Eisai in July last year (previously named E7449). PARPs are a family of 17 enzymes that are involved in cellular metabolic regulation. PARP-1 is a critical anticancer target due to its role in DNA damage repair, maintenance of genomic stability and functions in transcriptional regulation. More specifically, PARP-1 and -2 nuclear enzymes are responsible for majority of PARP activity in the cell where they are recruited to and triggered by sites of DNA damage.<sup>44</sup> PARP enzymes repair single-strand DNA breaks; as a result, PARP inhibition causes double-strand breaks, which require BRCA1/2 for repair.<sup>45</sup> PARP inhibition is therefore particularly lethal to cancer cells containing BRCA1/2 mutations. TNKS enzymes also belong to the PARP family and are

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<sup>41</sup> NCI

<sup>42</sup> Moreau, P., et al. (2017) Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Annals of Oncology* 28, 1v52-1v61.

<sup>43</sup> Yong, K., et al. (2016). Multiple myeloma: patient outcomes in real-world practice. *British Journal of Haematology* 175, 252-264.

<sup>44</sup> Bai, P., & Cantó, C. (2012). The Role of PARP-1 and PARP-2 Enzymes in Metabolic Regulation and Disease. *Cell Metabolism*, 16(3), 290-295.

<sup>45</sup> Dziadkowiec, K.N. (2016) PARP inhibitors: review of mechanisms of action and BRCA1/2 mutation targeting. *PrzMenopauzalny* 15, 215-219.

involved in Wnt/ $\beta$ -catenin signalling<sup>46</sup>, which plays a central role in cancer biology. Wnt overexpression contributes to tumour progression<sup>47</sup> and, consequently, TNKS inhibition interferes with Wnt signalling.

In early clinical trials, 2X-121 demonstrated antitumor activity in BRCA-deficient in vivo models and increased the effectiveness of radiotherapy and chemotherapy.<sup>48</sup> 2X-121 was well tolerated in a Phase I trial in 41 patients with solid tumours and demonstrated a 7.1% partial response. OV's 2X-121 DRP was tested in a small 13-patient blinded retrospective trial using biopsy materials provided by Eisai. The DRP predicted that seven patients would respond to 2X-121 treatment and that six would not respond; the median times to progression in these groups were 296 and 155 days, respectively, albeit the data did not reach statistical significance (HR=0.29, p=0.14).

OV plans to develop 2X-121 for the treatment of ovarian and mBC. The mBC trial started in June 2018 and an ovarian study was initiated in April 2019. The laboratory in Europe is established with approximately 1,400 DRP-screened patients with breast cancer while the US lab is undergoing Clinical Laboratory Improvement Amendments validation.

## Market and competitive environment

Ovarian cancer shares many of the same characteristics as breast cancer, although it occurs less frequently, and is more deadly. According to the National Cancer Institute, an estimated 22,530 women in the US will be diagnosed with ovarian cancer in 2019 (11.4 per 100,000 women per year on an age-adjusted basis). Ovarian cancer is associated with a relative five-year survival rate of only 46.5% while breast cancer has a relative five-year survival rate of 89.7%.<sup>49</sup> Moreover, of these diagnoses, approximately 15%<sup>50</sup> of all ovarian and 5–10%<sup>51</sup> of all breast cancers have a BRCA germline mutation and are therefore responsive to treatment with PARP inhibitors.

There are several PARP inhibitors on the market and in development (Exhibit 3). Lynparza (olaparib, AstraZeneca/Merck) is approved for the treatment of BRCA1/2 mutated breast and ovarian cancers and is distributed by both AstraZeneca and Merck such that both companies can potentially take advantage of the potential interaction between the PARP inhibitor and their respective immune-oncology drugs, Imfinzi (durvalumab, AstraZeneca) and Keytruda (pembrolizumab, Merck). The companies reported annual sales of \$297m in 2017 (profit split 50/50).<sup>52</sup> Not only does 2X-121 inhibit PARP-1/2, but also it inhibits TNKS-1/2 and Wnt signalling, which differentiates the asset from the four PARPS on the market as well as those in development.

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<sup>46</sup> Kamal, A., Riet al. (2014) Tankyrase Inhibitors as Therapeutic Targets for Cancer. *Current Topics in Medicinal Chemistry* 14, 1967-1976.

<sup>47</sup> Polakis, P. (2012) Wnt Signaling in Cancer. *Cold Spring Harbor Perspectives in Biology* 4.

<sup>48</sup> Mcgonigle, S., et al. (2015) E7449: A dual inhibitor of PARP1/2 and tankyrase1/2 inhibits growth of DNA repair deficient tumors and antagonizes Wnt signaling. *Oncotarget* 6.

<sup>49</sup> NCI

<sup>50</sup> Neff, R. T., et al. (2017) BRCA mutation in ovarian cancer: Testing, implications and treatment considerations. *Therapeutic Advances in Medical Oncology* 9, 519-531.

<sup>51</sup> American Cancer Society

<sup>52</sup> Evaluate Pharma.

**Exhibit 3: Select PARP inhibitors on the market and in development**

Product	Status	Indication	Notes
Lynparza (Olaparib, AstraZeneca/Merck)	Market	Relapsed ovarian cancer, fallopian tube cancer, primary peritoneal cancer after response to platinum-based chemo. Advanced ovarian cancer with BRCA mutation and received three or more prior chemotherapy drugs. Metastatic HER2-breast cancer with BRCA mutation	Inhibitor of PARP1, PARP2 and PARP3
Rubraca (rucaparib, Clovis Oncology)	Market	Advanced ovarian cancer with BRCA mutation and have received 2 or more prior chemotherapy drugs	Inhibitor of PARP1, PARP2 and PARP3
Zejula (niraparib, Tesaro)	Market	Maintenance of recurrent epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer in complete or partial response to platinum-based chemotherapy	Inhibitor of PARP1 and PARP2
Talazoparib (Pfizer)	Market	Locally advanced/mBC with BRCA mutation	Phase III trial demonstrated median PFS of 8.6 months in talazoparib treatment arm vs 5.6 months chemotherapy in patients with locally advanced/mBC with inherited BRCA mutation
Veliparib (AbbVie)	Phase III	NSCLC and TNBC	Two failed Phase III trials
Pamiparib (BeiGene)	Phase II	Advanced solid tumours	Inhibitor of PARP1 and PARP2
2X-121 (2X Oncology)	Phase Ib/II	DRP identified mBC and relapsed ovarian cancer	Inhibitor of PARP1, PARP2, TNKS1 and TNKS2

Source: Company websites

## 2X-111: Penetrating the BBB with GSH

OV is also developing 2X-111, which is a glutathione (GSH) PEGylated liposomal formulation of doxorubicin (an anthracycline chemotherapy) for the treatment of brain metastases from BC (BMBC) and glioblastoma (GBM). Similar to 2X-111, Doxil (doxorubicin, J&J) is a generic liposomal formulation of doxorubicin (without GSH) that was first approved in 1995 as a refractory chemotherapy. J&J reported worldwide sales of \$204m in 2018.<sup>53</sup> 2X-111 was designed to enhance the delivery of doxorubicin to the brain and penetrate the BBB with 2-BBB Medicines G-technology, or GSH. The BBB is a natural barrier between the blood and the brain that maintains homeostasis in the brain's extracellular fluid by selectively allowing compounds to penetrate the brain; this limits the treatment of brain diseases.<sup>54</sup>

OV in-licensed the asset from 2-BBB Medicines, which demonstrated that the blood-to-brain ratio of doxorubicin was 4.8 times greater after administration with 2X-111 (previously 2B3-101) in comparison to the generic liposomal formulation ( $p=0.0016$ ) in a rat model measured by cerebral open-flow microperfusion.<sup>55</sup> A Phase I dose-escalation trial in 28 patients with brain metastases from solid tumours and recurrent malignant gliomas demonstrated 2X-111 tolerability.<sup>56</sup> Pharmacokinetic analysis revealed that drug exposure did not increase linearly or build up with dose escalation. In addition, the drug also demonstrated preliminary anti-tumour activity at doses greater than 40mg/m<sup>2</sup> whereas four brain metastasis patients, five patients with glioblastoma and three with grade III glioma demonstrated stable disease. The trial concluded that 2X-111 is safe and well tolerated up to 70mg/m<sup>2</sup> in both cancers and guided the Phase IIa expansion studies (Exhibit 4). It is important to note that the previous trials described did not make use of DRP technology.

<sup>53</sup> Evaluate Pharma.

<sup>54</sup> Maussang, D., et al. (2016) Glutathione conjugation dose-dependently increases brain-specific liposomal drug delivery in vitro and in vivo. *Drug Discovery Today: Technologies* 20, 59-69.

<sup>55</sup> Birngruber, T., et al. (2014) Enhanced Doxorubicin Delivery to the Brain Administered Through Glutathione PEGylated Liposomal Doxorubicin (2B3-101) as Compared with Generic Caelyx,®/Doxil®—A Cerebral Open Flow Microperfusion Pilot Study. *Journal of Pharmaceutical Sciences* 103, 1945-1948.

<sup>56</sup> Gaillard, P.J. (2014) Phase I dose escalating study of 2B3-101, glutathione PEGylated liposomal doxorubicin, in patients with solid tumours and brain metastases or recurrent malignant glioma. ACR annual meeting 2014; April 5-9, 2014; San Diego, CA.

#### Exhibit 4: Phase IIa 2X-111 established clinical history

Indication	No. of patients	Results
Brain metastases from breast cancer	17	PR: 12%; SD: 52%
GBM	20	PR: 5%; SD: 35%

Source: 2X Oncology. Notes: These trials did not use the 2X-111 DRP. PR: partial response; SD: stable disease.

OV obtained an IND for 2X-111 in June 2017. The company intends to select the top 40% and 10% of DRP scores for BMBC and GBM patients, respectively, that are most likely to respond to 2X-111 and enrol 20 patients in each trial. OV expects to report interim results in H119 and will determine whether it will consider discussing accelerated approvals with the FDA. For the GBM trial, if four or more patients demonstrate either partial response or stable disease after six months of 2X-111 treatment, the company will pursue accelerated approval. However, if only two to three patients respond, the company will enrol an additional 10 patients in the trial. For the BMBC trial, if 30% or more patients show partial response to 2X-111, the company will repeat the study and pursue accelerated approval with the FDA. However, if only four to five patients respond to treatment, the company will move to evaluate 2X-111 for the treatment of metastases other than in the brain.

## Market and competitive environment

Breast cancer is the second most common cause of brain metastases (after lung cancer) with rising incidence likely due to patients living longer with systemic therapies to control the disease.<sup>57</sup> Of the estimated 124.9 per 100,000 diagnoses made per year in the US (on an age-adjusted basis)<sup>58</sup> a median of 21% (range of 15–35%) of breast cancer metastases to the brain and risk of developing brain metastasis is highly dependent on primary tumour subtype (Exhibit 5). Despite local and systemic treatment of BMBC, such as whole-brain radiation therapy and stereotactic radiosurgery, only a few patients live longer than one year.<sup>57</sup> Also, cytotoxic therapies such as chemotherapy do not effectively cross the BBB.

#### Exhibit 5: Frequency of brain metastasis from breast cancer

	Frequency (%)
Median	21
Range	15 to 35
All subtypes	12 to 17
Luminal A	8 to 15
Luminal B	11
TNBC/basal	25 to 27
HER2+	11 to 20

Source: Adopted from Witzel, I., et al. (2016). Notes: TNBC: triple negative breast cancer; HER2+: human epidermal growth factor 2 positive.

GBM, commonly referred to as the ‘terminator’, is the most aggressive type of tumour of the central nervous system and affects fewer than 10 per 100,000 people in the US.<sup>59</sup> Despite treatment, (ie surgery to remove the tumour and adjuvant chemo- or radiation therapy) the disease is largely incurable and most patients with GBM have a median survival of about 14 to 15 months.<sup>60</sup> Although 2X-111 will not cure BMBC or GBM, the potential of GSH to facilitate the BBB crossing and deliver chemotherapy to the tumour site may effectively improve survival rates for these patient populations.

<sup>57</sup> Witzel, I., et al. (2016) Breast cancer brain metastases: Biology and new clinical perspectives. *Breast Cancer Research*, 18.

<sup>58</sup> NCI

<sup>59</sup> Holland, E. C. (2000) Glioblastoma multiforme: The terminator. *Proceedings of the National Academy of Sciences* 97, 6242-6244.

<sup>60</sup> Hanif, F., et al. (2017) Glioblastoma Multiforme: A Review of its Epidemiology and Pathogenesis through Clinical Presentation and Treatment. *Asian Pacific Journal of Cancer Prevention* 18, 3–9.

## Dovitinib: TKI from Novartis

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OV in-licensed dovitinib, an oral TKI that inhibits fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptors from Novartis in January this year. Although one of the most recent additions to OV's pipeline, dovitinib is the most clinically advanced. OV intends to initially seek approval of dovitinib for the treatment of locally advanced or metastatic renal cell carcinoma (RCC). The company has already completed an analysis of Novartis trial data demonstrating the DRP can identify dovitinib responders with RCC. Additionally, the company has performed similar retrospective analysis of Novartis trials of endometrial, breast and liver cancers and gastrointestinal stromal tumours (GIST), which may provide future directions for the drug.

Signalling through the FGF pathway regulates cell proliferation and differentiation, angiogenesis, which is the development of new blood vessels, as well as cell survival and wound healing.<sup>61</sup> Abnormal FGF signalling plays a critical role in clinical tumour progression effecting cellular proliferation, resistance to cell death and chemotherapies, as well as increased angiogenesis and metastases. Similarly, VEGF also modulates angiogenesis in cancer and is stimulated by cancer-causing genes, or oncogenes.<sup>62</sup> Tumour vasculature promoted by VEGF is structurally and functionally irregular although it provides the tumour with nutrients and oxygen for growth. Correspondingly, hyperactive PDGF-receptor signalling via overexpression is associated with the development of malignant disease as well as benign diseases characterised by increased cell proliferation.<sup>63</sup> Therefore, dovitinib may effectively inhibit the growth of highly vascularised cancers that are dependent on angiogenesis pathways such as RCC.

The safety of dovitinib was evaluated in a Phase I dose-escalating trial in heavily pre-treated (with VEGF and mTOR inhibitors) patients with advanced or metastatic RCC. The study showed the maximum tolerated dose (MTD) was 500mg/day on a five days on, two days off schedule in 28-day cycles and was generally well tolerated in this cohort.<sup>64</sup> Two of 15 patients demonstrated a partial response, a median progression-free survival of 8.1 months and overall survival of 13.3 months. This dovitinib MTD was later tested in a Phase III trial in contrast to Nexavar, an oral multi-kinase inhibitor that was approved in 2005 for the first-line treatment of advanced renal cell liver and thyroid cancer with an expected patent expiry in January 2020. Bayer reported worldwide sales of \$841m for 2018.

In the randomised open-label Phase III trial, patients with metastatic RCC who previously received one VEGF-targeted therapy and one previous mTOR inhibitor received either dovitinib (500mg orally, five days on, two days off schedule) or Nexavar (400mg orally 2x daily). 284 patients received dovitinib treatment and 280 patients received Nexavar. The median progression-free survival was 3.7 months in the dovitinib group compared to 3.6 months in the Nexavar group ( $p=0.063$ ).<sup>65</sup> Adverse events were also similar in both treatment arms including fatigue and hypertension. Novartis ceased dovitinib development because it did not show efficacy or safety benefit over Nexavar. OV plans to develop the drug and its DRP to identify patients with metastatic

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<sup>61</sup> Lieu, C., et al. (2011) Beyond VEGF: Inhibition of the Fibroblast Growth Factor Pathway and Antiangiogenesis. *Clinical Cancer Research*, 17, 6130-6139.

<sup>62</sup> Carmeliet, P. (2005) VEGF as a Key Mediator of Angiogenesis in Cancer. *Oncology* 69, 4-10.

<sup>63</sup> Heldin, C. (2013) Targeting the PDGF signaling pathway in tumor treatment. *Cell Communication and Signaling* 11, 97.

<sup>64</sup> Angevin, E., et al. (2013) Phase I Study of Dovitinib (TKI258), an Oral FGFR, VEGFR, and PDGFR Inhibitor, in Advanced or Metastatic Renal Cell Carcinoma. *Clinical Cancer Research* 19, 1257-1268.

<sup>65</sup> Motzer, R. J., et al. (2014) Dovitinib versus sorafenib for third-line targeted treatment of patients with metastatic renal cell carcinoma: an open-label, randomised phase 3 trial. *The Lancet Oncology* 15, 286-296.



renal cancer and liver cancer most likely to respond to treatment and plans to develop the asset to commercialisation via its Denmark-based subsidiary.

OV's current strategy is to seek initial approval submit an NDA to the US FDA for marketing approval of dovitinib on the basis of existing non-inferiority data versus Nexavar using existing Novartis data. The company hopes that marketing approval for dovitinib in mRCC on the basis of non-inferiority will pave the way for sNDAs for dovitinib in combination with a PD-1/PD-L1 and its unique DRP biomarker. Treatment of mRCC with PD-1/PD-L1 inhibitors is emerging as a new axis of treating the disease (in addition to TKIs), and approval of a combination would improve inclusion in this protocol.

As part of the licensing agreement, OV also received an ample amount of biopsy and gene expression data from previous studies by Novartis. OV received positive feedback from FDA biostatisticians to move forward with building the pre-NDA documents based on these data. However, if the original dovitinib NDA is not approved, the company may move forward with the dovitinib + PD-1/PD-L1 combination programme via a new NDA pathway and may require more time and more patients to fulfil NDA requirements. If the NDA is approved, the sNDA for consecutive trials may require smaller clinical trials.

OV intends to use its new combination PD1/PD-L1 and dovitinib DRP biomarker to identify mRCC patients highly likely to respond to this treatment regimen. However, to run these trials successfully, OV will need to partner with a PD-1/PD-L1 manufacturer. We assume OV and its future PD-1/PD-L1 partner(s) will be required to run at least a Phase Ib/II trial followed by a Phase III trial, most likely in patients with mRCC receiving second-line therapy.

## Market and competitive environment

The National Cancer Institute estimates that 73,820 patients in the US will be diagnosed with RCC in 2019, or 16.1 per 100,000 adults on an age-adjusted basis. There will be an estimated 14,770 deaths in the US from the disease during the same year. Moreover, the disease is associated with a relative five-year survival rate of 74.1%. Treatment for localised RCC includes either partial or radical removal of the kidney followed by adjuvant therapy, such as Sutent (sunitinib, Pfizer). Pfizer reported \$1.0bn in sales of the drug for FY18. Management of advanced or metastatic RCC involves as many lines of targeted therapies that a patient may benefit from (Exhibit 6).<sup>66</sup> However, most patients develop resistance to TKIs via a number of mechanisms (ie genetic alterations, activation of other signalling pathways, or the increase in expression of a specific molecule in response to inhibition).<sup>67</sup>

**Exhibit 6: RCC competitive landscape**

Product	Mechanism	Indication	Notes
Nexavar (sorafenib, Bayer)	TKI of VEGF-1, -2 and -3, FLT3, KIT, and PDFGR- $\beta$ as well as intracellular kinases	Advanced RCC	Median PFS: 5.6 months
Sutent (sunitinib, Pfizer)	TKI of VEGF-1 and -2, FLT3, KIT, and PDFGR- $\alpha$ and - $\beta$	Advanced RCC	Median PFS: 11.8 months (treatment-naïve patients)
Votrient (pazopanib, Novartis)	TKI of VEGF-1, -2, and -3, FGFR-1 and -3, KIT, and PDFGR- $\alpha$ and - $\beta$	Advanced RCC	Median PFS: 9.2 months
Inlyta (axitinib, Pfizer)	TKI of VEGF-1, -2, and -3	Advanced RCC after failure of systemic therapy	Median PFS: 6.7 months
Afinitor (everolimus, Novartis)	mTOR inhibitor	Advanced RCC following failure of one or more therapies (ie Nexavar, Sutent).	Median PFS: 4.9 months

Source: Company websites. Notes: TKI: tyrosine kinase inhibitor; PFS: progression free survival; VEGF: vascular endothelial growth factor; FLT3: Fms-like tyrosine kinase-3; FGF: fibroblast growth factor; KIT: stem cell factor receptor; mTOR: mammalian target of rapamycin.

<sup>66</sup> Ko, J. J., et al. (2014) First-, second-, third-line therapy for mRCC: Benchmarks for trial design from the IMDC. *Brit J Can*, 110(8), 1917-1922.

<sup>67</sup> Bielecka, Z., et al. (2014) Mechanisms of Acquired Resistance to Tyrosine Kinase Inhibitors in Clear - Cell Renal Cell Carcinoma (ccRCC). *Current Signal Transduction Therapy*, 8(3), 219-228.

TKI and PD-1/PD-L1 combination therapy is being investigated by several notable pharmaceutical companies, for example, the combination of Lenvima (lenvatinib, Eisai) and Keytruda (pembrolizumab, Merck) for metastatic clear cell RCC. Lenvima, a TKI, in combination with everolimus (a chemotherapy) is approved for the treatment of second-line advanced RCC. Top-line data from the open-label [Phase Ib/II trial](#) were presented at the 2018 American Society of Clinical Oncology. The [Phase III trial](#) of Lenvima + Keytruda and Lenvima + everolimus (chemotherapy) versus Sutent (sunitinib, Pfizer) for the first-line treatment of advanced RCC is ongoing. Similarly, top-line data from the [Phase III trial](#) (Javelin Renal 101) of Bavencio (avelumab, Pfizer), a PD-L1, + Inlyta (axitinib, Pfizer), a TKI, versus Sutent as first-line treatment of advanced RCC were presented at the 2018 European Society for Medical Oncology Congress (Exhibit 7).<sup>68</sup> Overall survival data were not presented as the dataset was not yet complete.

**Exhibit 7: Javelin Renal 101 top-line data**

	Bavencio (10mg/kg IV every two weeks) + Inlyta (5mg orally twice daily) (n=442)	Sutent (50mg orally, once per day, four weeks on and two weeks off) (n=444)
Median PFS (months)	13.8	8.4
ORR (%)	51	26

Source: Motzer et al.<sup>68</sup>

## Ixempra: Potential future directions

On 4 April 2019, OV announced it had obtained an option to in-license the European rights to Ixempra (ixabepilone) from R-Pharm, which previously acquired it from Bristol-Myers Squibb in 2015. Ixempra is a chemotherapy that received FDA approval in 2007 (and 18 other markets worldwide) for the treatment of metastatic or locally advanced BC with tumours that are resistant/refractory to anthracyclines, taxanes and capecitabine. However, Ixempra is not approved by the EMA. Bristol-Myers Squibb withdrew its marketing authorisation application in 2009 following negative feedback on safety, specifically the number of patients developing severe neuropathy, from the EMA Committee for Medicinal Products for Human Use.

Based on previous treatment results and tumour gene data published by Bristol-Myers Squibb, OV has evaluated the potential ability of its DRP to identify the patients most likely to benefit from Ixempra therapy. According to the agreement, OV will evaluate Ixempra with its DRP in new European clinical trials in patients with mBC and, if these results are positive, OV will have the option to exclusively in-license European commercial rights. The financial terms of this agreement have not yet been disclosed. According to the company, the inclusion of this programme will not increase its cost base as the clinical development will be financed through a joint venture offering to interested investors. Note that we do not include the Ixempra programme in our valuation of OV at this time, although we may add it later if the joint venture advances and the drug enters the clinic.

## Sensitivities

The many of the risks OV faces are typical of clinical drug development companies, but it also has unique risks associated with its business strategy. All OV's drug programmes were previously abandoned at one point during clinical development due to poor pharmacokinetics, considerable toxicity profiles and/or minimal activity. Therefore, the success of these programmes is contingent on the ability of the DRP to mitigate these risks. There is independent evidence of the utility of the DRP, but it was insufficient to change clinical practice in the context of optimising existing care

<sup>68</sup> Motzer RJ, et al. (2018) AVELIN Renal 101: a randomized, Phase III study of avelumab + axitinib vs sunitinib as first-line treatment of advanced renal cell carcinoma (aRCC). In: Proceedings from the 2018 ESMO Congress; October 19-23, 2018; Munich, Germany.

(from the MD Anderson validation study). There can be no absolute assurances that the DRP can consistently identify responders for any drug being examined. Moreover, to demonstrate clinical utility, the test must be able to improve outcomes by informing drug choices, and this has not been demonstrated in a prospective fashion. However, the financial risks associated with these clinical programmes are limited by the targeted clinical trial design, usually starting with small pilot studies. The selection of a strict DRP threshold for inclusion significantly limits market potential of each asset. Finally, OV faces significant partnering risk: the company may successfully complete any number of focused Phase II trials demonstrating that the use of drug-specific DRPs improves patient outcomes but not identify a partner to either out-license or exit to, which would negatively affect the company's financials.

## Valuation

We have increased our valuation to SEK1,301m from SEK1,163.9m, but it is lower on a per-share basis (SEK18.47 from SEK23.13 per basic share). The increase in valuation is driven primarily by new net cash (estimated SEK34.9m net cash at Q119 after including offering proceeds, from SEK24.6m net debt at 31 December 2018) following the recent rights issue. This offering substantially increased the number of shares (70.5m from 50.3m) and the number of dilutive securities (23.5m dilutive warrants from 3.3m). Additionally, we have rolled forward our NPVs to the most recent period, and exchange rate effects have increased our valuation. These are offset by a delay in the APO010 programme: we have delayed the launch of the product to 2024 (from 2023) following the lack of progress obtained in the programme in the past 12 months. Otherwise our estimates remain unchanged. We may update our valuation if data become available for any of the ongoing clinical studies.

**Exhibit 8: Valuation of Oncology Venture**

Development programme	Indication	Clinical stage	Prob. of success	Launch year	Launch pricing	Peak sales (\$m)	rNPV (mSEK)	% owned by OV	OV rNPV (mSEK)
LiPlaCis	Metastatic breast cancer and metastatic prostate cancer	Phase II	25%	2023	\$91,000	259.8	740.4	39%	288.8
Irofulven	Metastatic prostate cancer	Phase Ib/II	20%	2023	\$129,000	52.6	65.9	100%	65.9
APO010	Multiple myeloma	Phase Ib/II	20%	2024	\$146,000	78.8	108.9	100%	108.9
2X-121	Metastatic breast cancer and ovarian cancer	Phase II	25%	2023	\$132,000	116.4	191.7	92%	176.3
2X-111	Glioblastoma and brain metastases from breast cancer	Phase Ib/II	25%	2024	\$169,000	212.6	322.0	92%	296.2
Dovitinib	Renal cancer	Phase Ib/II	35%-50%	2024-2025	\$145,000	176.9	601.4	55%	330.8
Total									1,266.9
Net cash (Q119 + offering) (SEKm)									34.9
Total firm value (SEKm)									1,301.8
Total shares (m)									70.5
Value per basic share (SEK)									18.47
Warrants and options (m)									23.5
Fully diluted shares in issue (m)									94.0
Fully diluted value per share (SEKm)									15.49

Source: Oncology Venture reports, Edison Investment Research

## Financials

The company recently performed a rights offering in which 20.2m units (of one share and one warrant exercisable at SEK7.50) were offered at SEK4.00 each, generating approximately SEK81m in gross proceeds. The company ended Q119 with DKK32.2m (SEK45.8m) in net debt which, when combined with the offering, leaves SEK34.9m in net cash. We expect OV's capital requirements to increase significantly in 2019 (SEK209m operational loss for 2019) with the advancement of its multiple clinical studies. We expect the company to require an additional DKK310m to advance all

its clinical programmes to the partnering stage (through Phase II trials), which we record as illustrative debt. However, these financial needs may be mitigated in part by selectively advancing certain assets and we expect at least some of the required financing to be met through these partnering activities. We may update our forecasts in the future to reflect any of these developments.

**Exhibit 9: Financial summary**

	DKK'000s	2017	2018	2019e	2020e
Year end 31 December		IFRS	IFRS	IFRS	IFRS
<b>PROFIT &amp; LOSS</b>					
Revenue		5,145	2,147	3,646	3,646
Cost of Sales		0	0	0	0
Gross Profit		5,145	2,147	3,646	3,646
EBITDA		(23,794)	(32,258)	(210,596)	(96,862)
Operating Profit (before amort. and except.)		(23,848)	(32,471)	(209,072)	(95,818)
Intangible Amortisation		0	0	0	0
Exceptionals/Other		0	0	0	0
Operating Profit		(23,848)	(32,471)	(209,072)	(95,818)
Net Interest		(7,132)	(192)	(2,015)	(212)
Other		0	10,146	0	0
Profit Before Tax (norm)		(30,980)	(22,517)	(211,087)	(96,030)
Profit Before Tax (IFRS)		(30,980)	(22,517)	(211,087)	(96,030)
Tax		590	6,973	21,041	1,989
Deferred tax		0	0	0	0
Profit After Tax (norm)		(30,390)	(15,544)	(190,046)	(94,041)
Profit After Tax (IFRS)		(30,390)	(15,544)	(190,046)	(94,041)
Average Number of Shares Outstanding (m)		24.3	33.8	71.9	75.5
EPS - normalised (ore)		(1.27)	(0.44)	(2.64)	(1.25)
EPS - IFRS (DKK)		(1.27)	(0.44)	(2.64)	(1.25)
Dividend per share (ore)		0.0	0.0	0.0	0.0
<b>BALANCE SHEET</b>					
Fixed Assets		4,883	237,096	238,610	237,566
Intangible Assets		135	236,733	235,885	235,885
Tangible Assets		4,424	363	2,725	1,681
Other		324	0	0	0
Current Assets		8,102	14,401	99,622	82,326
Stocks		1,048	0	0	0
Debtors		3,048	5,262	12,756	10,274
Cash		3,326	1,547	58,954	42,152
Other		680	7,592	27,912	29,901
Current Liabilities		(10,540)	(35,407)	(79,337)	(13,432)
Creditors		(10,540)	(16,515)	(79,337)	(13,432)
Short term borrowings		0	(18,892)	0	0
Long Term Liabilities		0	(34,234)	(224,378)	(374,378)
Long term borrowings		0	0	(187,435)	(337,435)
Other long term liabilities		0	(34,234)	(36,943)	(36,943)
Net Assets		2,445	181,856	34,517	(67,917)
<b>CASH FLOW</b>					
Operating Cash Flow		(10,702)	(31,392)	(153,027)	(166,802)
Net Interest		(170)	(2,391)	(8,784)	0
Tax		2,527	6,159	0	0
Capex		0	0	0	0
Acquisitions/disposals		(784)	9,855	1,550	0
Financing		7,478	198	49,060	0
Dividends		0	0	0	0
Other		(308)	(3,299)	0	(102)
Net Cash Flow		(1,959)	(20,870)	(111,201)	(166,904)
Opening net debt/(cash)		(5,488)	(3,326)	17,345	128,481
HP finance leases initiated		0	0	0	0
Exchange rate movements		(203)	(199)	(65)	0
Other		0	398	130	102
Closing net debt/(cash)		(3,326)	17,345	128,481	295,283

Source: Oncology Venture reports, Edison Investment Research

<b>Contact details</b>		<b>Revenue by geography</b>	
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<b>Management team</b>			
<b>CEO and co-founder: Peter Buhl Jensen</b>		<b>CSO and co-founder: Steen Knudsen</b>	
Dr Buhl Jensen is one of the co-founders of OV and has served as the CEO since its inception in 2012. He is also a member of the board at Medical Prognosis Institute where he has been the CEO since 2012. Since 2010, he has been acting CEO of LiPlasome Pharma from which OV has in-licensed the drug LiPlaCis. Formerly, Dr Buhl Jensen co-founded TopoTarget (now Onexo) where he was CEO from 2001 to 2010 and worked on the development of the oncology drug belinostat (Beleodaq, Spectrum Pharmaceuticals H117 net sales of \$6.3m).		Dr Knudsen is the CSO and co-founder of OV. Dr Knudsen is also one of the founders of Medical Prognosis Institute where he has been the CSO since 2004. He is the inventor of the DRP technology, which OV licensed from Medical Prognosis Institute. Dr Knudsen has a PhD in microbiology.	
<b>COO and founder: Ulla Hald Buhl</b>		<b>Chairman: Duncan Moore</b>	
Ms Buhl is one of the co-founders of OV and has served as the COO since its inception in 2012. In addition, she has served as the COO of Medical Prognosis Institute since 2012. Since 2010, Ms Buhl has served as CCO of LiPlasome Pharma from which OV has in-licensed the drug LiPlaCis. Formerly, she led investor relations at TopoTarget from 2006 to 2010 and head of regulatory development from 2001 to 2006.		Dr Moore has served as the chairman of the board of OV since 2015. He is also a partner in the company East West Capital Partners (since 2007), serves as chairman of the board of Lamellar Biomedical (2013), deputy chairman at Braidlock (since 2015), and non-executive director at Forward Pharma (since 2016). Formerly, Dr Moore served as the global head of healthcare research at Morgan Stanley. Dr Moore has a PhD in biochemistry.	
<b>Principal shareholders</b>			<b>(%)</b>
UBS Switzerland			16.64
Sass & Larson APS			16.57
Buhl Krone Holding APS			8.35
BNY Mellon SA/NV			5.13
<b>Companies named in this report</b>			
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