EVOLUTION CAPITAL

ASX: NOX

Noxopharm Limited

Pioneering life-changing therapies

Equity Research

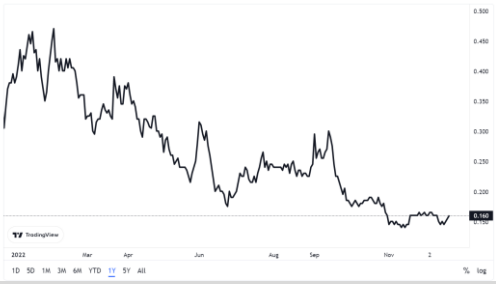
21 December 2022

BUY

Share Price	$0.16
Price Target	$0.51

52-Week Range	$0.135 - $0.495
NOX Shares Outstanding	292,237,950 m
Market Capitalisation	$45.29m
Cash (17 November 2022)	$14.9m
Enterprise Value	$31.9m
Substantial Shareholders	
Graham Kelly	3.77%
Eleanore Goodridge	3.58%
Laurence Freedman	2.22%
Top 20 Holders	11.9%

Board & Management:	
Frederic Bart	Non-Executive Chairman
Peter Marks	Non-Executive Director
Dr Gisela Mautner.	Managing Director/CEO
Boris Patkin	Non-Executive Director
David Franks	Company Secretary



Source: Tradingview

Overview: Noxopharm Limited (ASX: NOX) is an innovative Australian biotech company discovering and developing novel treatments for cancer and inflammation. It has three active drug development programs: its clinical drug candidate Veyonda®, plus two innovative technology platforms-Chroma™(oncology) and Sofra™ (inflammation and autoimmunity), provide the basis for active development of a growing pipeline of new proprietary drugs.

Investment Proposition

Noxopharm is focused on oncology, which is the largest therapeutic area, it is expected to represent 26 percent of pharmaceutical sales by 2022, with 107 new drug approvals in 2018 alone.

Veyonda is applicable in most solid tumours: IDX targets a unique feto-oncogene that is present in all forms of cancers tested to date meaning that IDX demonstrates anti-cancer activity against most forms of cancer.

Immuno-oncological Function of Veyonda has the potential to revolutionise cancer treatment, as immuno-oncology treatments have had difficulty in repopulating tumours with immuno-competent cells. Despite scientific efforts, a means of overcoming the S1P gradient preventing the re-entry of immune cells to tumours is yet to be discovered. NOX believes Veyonda may potentially be the first such drug to achieve this aim.

Late-stage prostate cancer is a major unmet medical need, with an estimated 350,000 men who die each year globally from this disease. The company's DARRT and LuPIN treatment regimens offer meaningful treatment options.

Veyonda's use extended into chemo-sensitisation. Veyonda is a potential treatment for sarcoma, a diverse form of cancer representing about 5% of all solid cancers with limited treatment options. **NOX was granted an Orphan Drug Designation (ODD),** which will help in expediting the drug approval process and provide prolonged market exclusivity for seven years upon approval.

Recommendation

We are initiating coverage of Noxopharm at $0.51 per basic share using a risk-adjusted NPV model focused strictly on the CEP-2 trial in Sarcoma as it is a 'rare cancer' market. Our valuation approach assumes a discount rate of 20%, including a probability of success of 10%. Furthermore, commencement of sales in 2026 and an initial market penetration of 1% before increasing to a peak market penetration rate of 9% and achieving peak sales of $ 1.98b by 2032. The marketing approval for rare cancers offer important commercial incentives with very little competition as well as highlighting the unmet medical need due to the aggressive nature of many sarcomas. It is usually accompanied by a poor response to chemotherapy, including the standard of care. We have estimated a gross margin of 70% and SG&A of 25% of sales revenue. Based on the above, we have placed a **BUY** recommendation on Noxopharm, reflecting an implied return of 218% from current levels. We also note, that in deriving this valuation, we have not considered the impact of dilution, which would increase depending on whether the company raises more capital as it progresses to more advanced clinical trials, whilst also noting that the impact of dilution would be offset by an increasing probability of success. We will adjust our assumptions as CEP-2 advances through clinical studies.

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Veyonda® is a newly derived concept in therapeutics, designed to recalibrate the body's immune system against cancer and septic shock. These two outstanding prime examples burden the healthcare system and therefore a therapeutic intervention is required.

1. Going back to its roots

Idronoxil (dehydroequol) is the active ingredient in Veyonda®, it is a synthetic small molecule which was first brought to attention in the year 1992 and was subsequently applauded for its unique properties of anti-cancer and anti-inflammatory functions. It is also favoured by a robust safety profile and greater tolerability in patients. Furthermore, its reputation over the years has grown as a potentially fundamental new anti-cancer drug prospect based on its multi-functional drug properties via a number of different anti-cancer mechanisms.

Cancer as a disease is very complex as it has a wide range of options in avoiding early detection, overriding bodily controls and affecting the overall longevity of a patient's life. Therefore, the more of these functions that can be blocked, the better the outcome will likely prevail for the patient. Initially, idronoxil was regarded as having the classic anti-cancer properties known as oncotoxic functions. The oncotoxic properties include:

- killing of the cancer cell via apoptosis (cell death)
- blocking the cancer cells from dividing or blocking the repair mechanisms that support the cells that are more prone to damage from chemotherapies and radiotherapy

Recent studies, however, have discovered two other properties of idronoxil such as:
i) It's ability to restore immune responses against cancer cells known as immuno-oncology functions); and
ii) it's ability to block excessive immune and inflammatory responses (anti-inflammatory functions) used by cancers to grow and spread, propelled by tissue damage caused by viral infections

Noxopharm has understood that the overall anti-cancer function of the drug is a result of all three functional properties - oncotoxic, anti-inflammatory and immuno-oncology, with increasing evidence pointing to the latter as being a major anti-cancer function.

Combined with increasing evidence of a hyper-immune/inflammatory response being the cause of septic shock, Veyonda® has also emerged as a potential treatment of debilitating symptoms and death from septic shock. Furthermore, Veyonda® is the final dosage form, it contains idronoxil in a proprietary fatty base which is delivered as a suppository. A suppository dosage form is a fundamental key to the drug's success, with absorption of idronoxil from the lower rectum taking place via the inferior hemorrhoidal vein, thereby avoiding the portal circulation and first-pass liver metabolism.

2. How it all works

Idronoxil (IDX) targets the enzyme known as external NAD oxidase disulphide-thiol exchanger Type 2 or (ENOX2). This enzyme sits on the outer surface of the cell and has two completely different functions, which is rare amongst enzymes:

The two functions include:

- **NAD oxidase function:** involved in the movement of atomic particles (electrons flowing in and protons flowing out) across the cell's outer membrane, demonstrating a battery-like transmembrane electron potential which generates the energy to power multiple functions in the cell membrane.
- **Disulphide-thiol exchange:** this exchange ensures the accurate folding of cellular proteins once they are made, and also allowing the cell to grow.

The double function is rare and what truly makes ENOX2 unique is its ability to switch on regular basis between two separate functions.

The switching or (oscillation time) occurs with atomic clock-like precision, serving as an integral internal time-keeping function also known as ultradian rhythm, which helps to regulate a wide range of metabolic functions within the cell.

Therefore, a blocking of the function of ENOX2 has three adverse effects for the cell such as:

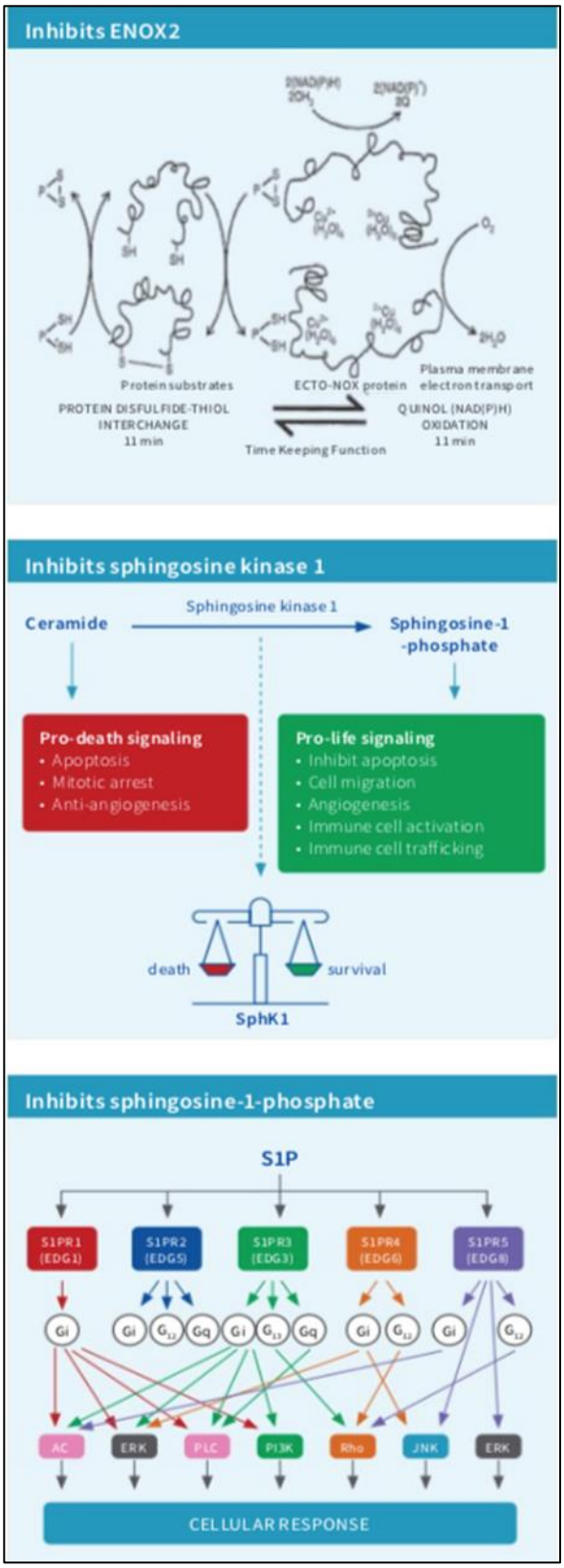
- the inability to run a myriad of functions which occur in the cell membrane and play an important role in the cell's ability to respond to bodily commands;
- the inability to grow, and
- multiple knock-on disruptions following the loss of internal timekeeping (ultradian rhythm), integral for fast-growing cells.

Idronoxil binds to a single protein target, however, the multiple functions of ENOX2 are so unique while the reliance of the cell on that protein is so broad, that the consequences of knocking out ENOX2 are equally unique and broad. Hence, idronoxil's ability to execute conflicting effects such as turning on an underperforming immune system in the case of cancer or turning off an over performing immune system in the case of septic shock makes it highly fascinating.

Human cells are reliant on two types of ENOX enzymes: ENOX1 and ENOX2 with majority of normal healthy adults expressing the ENOX 1 enzyme only. The normal cells that have a higher rate of turnover such as myeloid, gut mucosal cells and hematopoietic also mainly express ENOX1 and some ENOX2. On the other hand, cancer cells only express ENOX2 with all forms of cancers expressing only ENOX2 and not ENOX1. There is a differential in oscillation times between ENOX 1 and ENOX2 occurring at 24 and 22 minutes respectively. The shorter oscillation time of ENOX2 is associated with faster cell division and the need for higher rate of cell growth, coercing the preferential expression of ENOX2, noting that idronoxil only binds to and inhibits ENOX2.

The shutting down of ENOX2 function blocks the movement of atomic particles across the cell membrane, resulting in the accumulation of protons (H+) in the form of CoQ10H. High levels of COQ10H inhibit the enzyme, sphingosine kinase 1 (SphK1). SphK1 plays an important role in the sphingomyelin pathway in the plasma membrane, converting ceramide into sphingosine-1-phosphate (S1P). Ceramide and S1P are important secondary messengers, determining whether a cell lives or dies. S1P is responsible for determining the cell livability while ceramide governs the death component. Most cancers express high levels of SphK1 activity, resulting in very high levels of S1P.

S1P delivers its pro-survival effects by leaving the cell where it interacts with 5 S1P receptors which are located on the outer surface of the cell also known as S1PR1-5. Each S1P receptor is responsible in activating a range of pro-survival singling pathways, in a complex cross-promotional manner. Therefore, by inhibiting SphK1, levels of S1P drop preventing the activation of these critical survival pathways staving the cancer cells of its pro-survival advantages. Idronoxil's inhibitory effect is largely limited to cancer cells and leaving normal cells unscathed.



Source: Noxopharm

3. Veyonda® - anti-cancer effects

In summary, Veyonda® 's anti-cancer functions occur via the inhibition of ENOX2 which entails three mainstream biochemical outcomes involving:

- The decrease of protein thiol-disulfide exchange
- An increase in the ceramide levels and;
- A decrease in the S1P levels

Following from the above biochemical outcomes, occur the following functional outcomes which is categorised into two broad sections referred to as oncotoxic and immunological outcomes.

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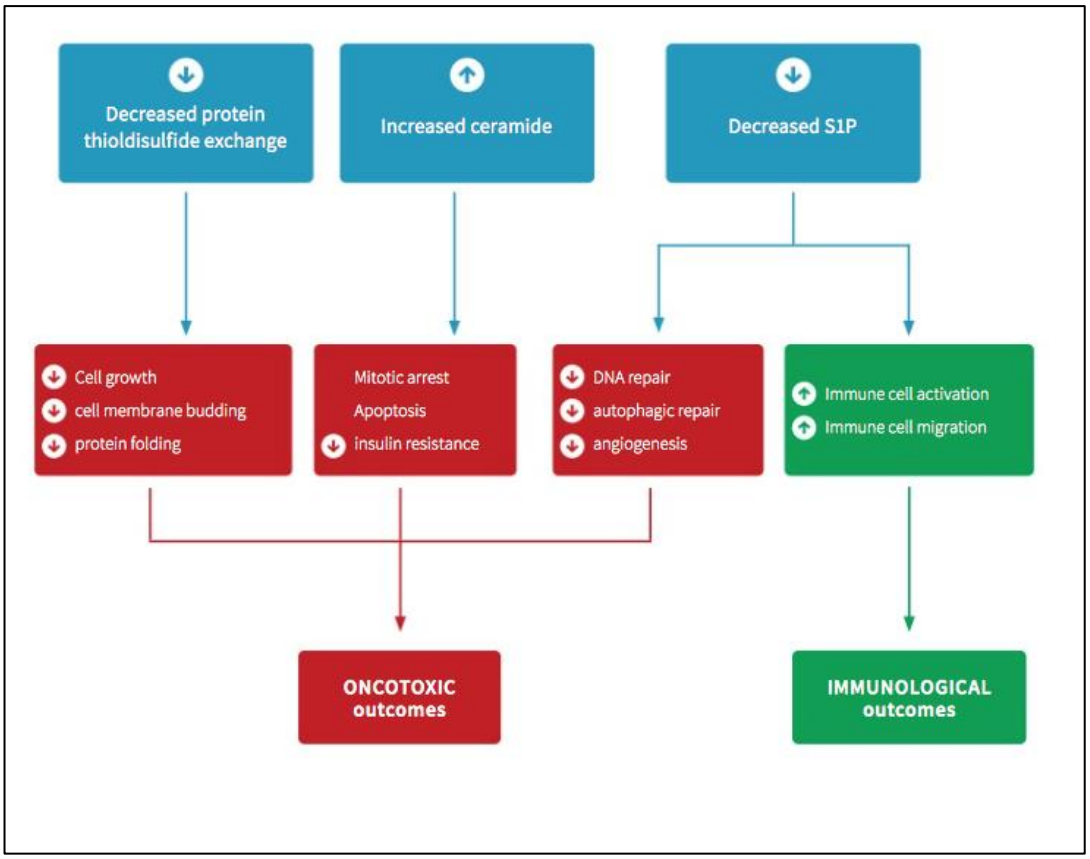

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i) Oncotoxic outcomes

The blocking of all three downstream biochemical pathways by IDX results in a variety of direct (oncotoxic) anti-cancer effects such as the blocking of cell growth and division, as well as direct killing of cancer cells. These physiological responses are reminiscent of standard chemotherapy effects, making Veyonda® a potential stand-alone chemotherapy option for a wider range of solid tumours. However, NOX sees a greater therapeutic outcome by using IDX as combination therapy as opposed to monotherapy (stand-alone) treatment.

ii) Immunological outcomes

The immunological effect of IDX comes from the inhibition of S1P levels. The correlation between S1P and the immune system stems via the S1PR1 and S1PR4 receptors, these receptors are predominantly expressed by lymphoid and hematopoietic cells. Furthermore, S1P plays a crucial role in the immune function within a tissue, by attracting immune cells into the tissue, and then warranting that their function remains balanced and controlled.

By inhibiting the action of S1P on S1PR1 and S1PR4 receptors, *IDX carries out three functional mechanisms such as:*

- directly stimulating the innate immune system, specifically the CD56+ natural killer (NK) cells.
- activating the CD4+ and CD8 T cells;
- increasing the trafficking of activated T cells leading to infiltration into tumours and activating the so-called COLD to HOT tumour conversion.

4. Veyonda® - anti-inflammatory effects

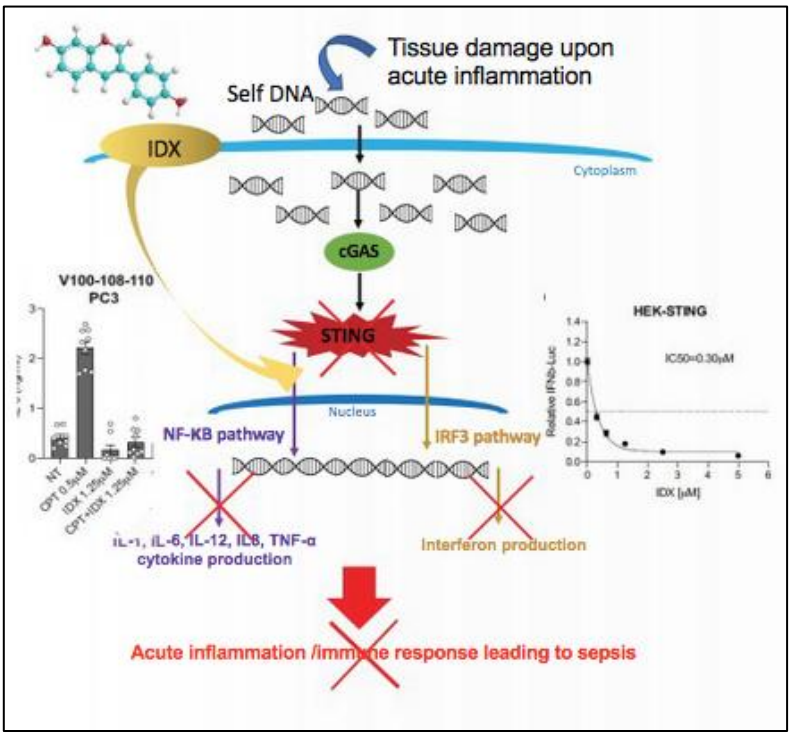
Inflammation also plays a crucial role in cancer as cancer is more susceptible to arise in tissues that are subjected to chronic inflammation, however, cancers also utilise inflammatory processes to aid their growth. These inflammatory processes involve factors such as angiogenesis (which is development of new blood vessels) to support aggressive tumour growth, through to manipulation of the local immune system to expand the tumour-promoting immune function at the behest of tumour-suppressing immune function. S1P plays a vital role in regulating all of these inflammatory processes. Hence, the S1P-inhibiting effect of Veyonda® bereaves the cancer cells of those S1P-driven inflammatory processes. Furthermore, the anti-inflammatory functions of Veyonda® are part of a continuum which consists of oncotoxic, immunological and anti-inflammatory functions all of which are interlinked via the original inhibition of ENOX2.

A further anti-inflammatory action of Veyonda® has also emerged which points to a potential role for the drug beyond cancer. That action is a potent inhibitory effect on the key pro-inflammatory singling pathway STING (Stimulator of Interferon Genes).

- Unregulated activation of STING is implicated in chronic inflammatory diseases and autoimmune diseases such as motor disease
- Excessive activation of STING is implicated in the cytokine release syndrome (CRS) which is associated with septic shock and COVID-19 related disability and death.

5. STING Inhibitor IDX to treat sepsis

IDX has recently been established as a potent STING inhibitor as mentioned above, through joint research conducted by NOX and the Centre for Innate Immunity and Infectious Disease at the Hudson Institute. IDX switches off STING's capacity to produce chemokines and cytokines upon the detection of DNA released after tissue damage, ceasing it from triggering an acute immunological response that would lead to sepsis shock.



Source: Noxopharm

6. Veyonda® - oncology program overview

The NOX clinical trial program includes a pipeline of indications designed to create and maximise the value proposition of Veyonda® while de-risking the portfolio. The primary focus is on the treatment of cancer with the use of Veyonda® to boost the effectiveness of four primary cancer therapies also known as the 4-pillars oncology program:

- External beam radiotherapy
- Radioligand therapy
- Chemotherapy
- Checkpoint inhibitor therapy

The 4-pillars oncology program will also be in tandem with other combination treatments. The oncology clinical development overview below highlights the status of the various studies of Veyonda® which includes the Chemotherapy Enhancement Program (CEP-1 and CEP-2), Radiotherapy Enhancement Program (DARRT) and the Combination with immune check point inhibitors (IONIC).

Veyonda® Oncology Clinical Development Overview

	Chemotherapy Enhancement Program (CEP)		Radiotherapy Enhancement Program (DARRT)			Combination with immune check point inhibitors (IONIC)
Study	**CEP-1**	**CEP-2**	**DARRT-1**	**DARRT-2**	**LuPIN**	**IONIC**
Status	Completed	Active	Completed	Active	Completed	Active
Patients	19	40	25	100	56	30
Target	Multiple tumour types	Sarcoma	End-stage prostate cancer	End-stage prostate, breast and lung cancer	End-stage prostate cancer	Multiple tumour types
Therapy	**Veyonda®** + chemotherapy	**Veyonda®** + chemotherapy	**Veyonda®** + low dose external beam radiotherapy	**Veyonda®** + low dose external beam radiotherapy	**Veyonda®** + internal radiotherapy ^{177}Lutetium-PSMA-617*	**Veyonda®** + immuno-oncology therapy (Opdivo®)**

* ^{177}Lutetium-PSMA-617 is owned by Novartis
** Opdivo (nivolumab) is owned by Bristol Myers Squibb

7. Veyonda® - Direct and Abscopal Response to Radiotherapy (DARRT)

The DARRT program aims to combine Veyonda® with low-dose radiotherapy (RT) in order to cause an immune/inflammatory response in a single tumour with that response then spreading systemically, leading to a widespread anti-cancer response known as an abscopal response. Furthermore, the objective is to achieve an anti-cancer response that ranges from prevention of tumour growth also known as stable disease (SD) through to tumour shrinkage or resolution defined as either partial or complete response (CR).

DARRT-1 (status Phase 1 study complete)

In this study, Veyonda® was combined with radiotherapy (RT) in patients with metastatic castration-resistant prostate cancer (mCRPC) that had progressed on all available treatments. Patients received palliative (low-dose) RT with Veyonda®. It is worth noting that the DARRT-1 patients had such advanced cancer that RT treatment was given for palliative care, with the intention of reducing pain and other symptoms in order to improve quality of life for a limited period.

The results of DARRT-1 were found to be rather encouraging as Veyonda®/low-dose RT treatment was safe and well tolerated and:

- Disease progression stopped (stable disease) or improved (partial response) in the majority of patients that were evaluable at the 12 and 24 week follow up respectively.
- A majority of patients achieved a clinically meaningful pain response at 12 and 24 weeks, with some patients achieving pain-free status at 24 weeks.
- The prostate specific antigen (PSA) levels dropped by 50% in a number of patients at 12 weeks. This effect was found to persist for most of those individuals at 24 weeks. PSA levels in cancer therapy is an indicator of disease activity.
- An abscopal effect was also noted in four patients. In these patients, both the irradiated tumour and tumours outside of the radiation field had shrunk.

8. DARRT-2 Phase 2 clinical trial

The DARRT-2 program is a Phase 1b/2a Multicentre Study of NOX66 and External Beam Radiotherapy in Patients with Metastatic Castration-Resistant Prostate Cancer and Other Solid Tumours. During Q3 2022, the DARRT-2 Safety Steering Committee reviewed the safety data from the second cohort of patients and found the dose to be safe and well tolerated. The trial has now advanced to enrolling a third cohort of patients with an increased dose level of 1600 mg of Veyonda®, and the treatment of some patients with this higher dose has already begun. Furthermore, a new DARRT-2 trial site in Hungary is now active and will soon begin enrolling patients.

The Cohort 3 Safety Steering Committee Meeting is expected in Q1 2023, with the current safety phase potentially finishing in Q1 2023 or early Q2 2023, after which the efficacy phase commences. NOX is actively exploring ways to reduce patient numbers and costs while bringing forward the efficacy data.

9. Veyonda® - LuPIN program

a. LuPIN: Lutetium-PSMA in Combination with NOX66 (Veyonda®)

The LuPIN program aims to enhance in men with mCRPC, the anti-cancer response to the radioligand, Lutetium-PSMA -617, resulting in longer patient survival. Traditionally the response to Lutetium-PSMA-617 is limited by rates of expression by cancer cells of prostate surface membrane antigen (PSMA) protein which is largely limited in many men. Thereby leading to delivery of potentially sub-lethal doses of radiation.

b. LuPIN Phase 1b/2a study status: (Complete)

An investigator-initiated Phase 1b/2a trial was led by Professor Louise Emmett at St Vincent's hospital in Sydney for the management of advanced prostate cancer that stopped responding to hormonal or chemotherapy. LuPIN involved 56 men with advanced mCRPC with 19 patients having less than 20 metastases, while 37 had greater than 20 metastases, whose disease had progressed following three lines of treatment (abiraterone/enzalutamide, docetaxel and cabazitaxel).

The study tested three dosages of Veyonda® ranging from 400mg, 800mg and 1200mg along with a constant Lu-PSMA dosage. The interim data on the first 32 patients was initially published in the peer-reviewed European Urology Oncology, at that stage the results were highly encouraging with a high PSA response rate and a mOS of 17.1 months versus a 4.5-month mOS for a comparable patient population receiving standard chemotherapy.

The study is now complete and data on the full 56 patient cohort was presented at the American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium, which was published in the Journal of Nuclear Medicine in 2021. The results presented were:

- High PSA response rate- 61% had a PSA reduction greater than 50%, with 53% of men suffering moderate to strong pain associated with cancer reporting a significant reduction in pain.
- Progressive free survival (PSF) of 7.5 months with five out of the 56 men not progressing ahead with the study. 46% of men were able to complete the full six cycles of treatment without cancer progression.
- Median overall survival (mOS) of 19.7 months versus a 4.5-month mOS for a comparable patient population receiving standard chemotherapy.
- A mOS of 19.7 months is noteworthy as the patients recruited had end-stage metastatic disease and their disease progressed despite a number of prior treatment pathways.

There are multiple studies on similar patient populations that were treated with Lu-PSMA-617 as a sole treatment; the LuPIN combination treatment incorporating Veyonda® compares favourably with these studies. The LuPIN mOS outcome of 19.7 months provides the best survival outcome when comparing to Lu-PSMA alone.

Study	Treatment	Patient number	Median overall survival (months)
LuPIN	Veyonda® + Lu-PSMA	56	19.7
WARMTH	Lu-PSMA	319	11.6
VISION	Lu-PSMA	551	15.3
Hofman et al	Lu-PSMA	50	13.3

10. Veyonda® -CEP program

11. CEP: Chemotherapy Enhancement Program

The aim of the CEP program is to demonstrate that in advanced solid tumours whereby poor sensitivity or refractory to chemotherapy occurs. The combination of Veyonda® plus standard chemotherapy could potentially be a more effective treatment compared to chemotherapy alone. The chemo-enhancing functions of Veyonda® allow the use of lower dosages of chemotherapy, providing considerable safety benefits, while still achieving similar or greater efficacy outcomes to that of standard chemotherapy alone.

a. CEP-1 (Phase 1)

A Phase-1 multi-centre study investigating Veyonda® alone, and in combination with carboplatin for patients with refractory solid tumours of the breast, head and neck, lung, prostate and ovaries. CEP-1 was a multi centre, open-label, non-randomised, 2-dose cohort study of NOX66 as a monotherapy (Phase 1a) and in combination with carboplatin (Phase 1b).

Patients with refractory solid tumours who had stopped responding to standard treatments were eligible to participate, 20 patients were screened and 19 enrolled into the study. The patients were divided into two groups: cohort 1 (n=8) received one suppository daily (400mg) and cohort 2 (n=11) received two suppositories daily (800mg) for 14 consecutive days followed by seven days of rest.

Patients who completed Phase 1a without experiencing significant toxicity moved to Phase 1b, where NOX66 was combined with carboplatin for up to 6x 28-day treatment cycles, with low-dose carboplatin (600 mg) for cycles 1B through 3B and standard dose carboplatin (900mg) for cycles 4B through 6B. The main outcomes assessed were safety (n=18) and efficacy signals (n=14).
The results concluded that NOX66 was well tolerated at 400 mg and 800 mg respectively, both as monotherapy and in combination with carboplatin in patients with refractory solid tumours.

The safety profile was consistent for oncology patients, with 77.8% experiencing at least one treatment emergent adverse event (AE). The most common AEs included blood and lymphatic system disorders (44.4%) followed by gastrointestinal disorders (16.7%); metabolism and nutrition disorders (16.7%).

b. CEP-2

CEP-2 is a Phase 1, open-label, dose-escalation and dose-expansion study of Veyonda® administered to cohorts of patients being treated with doxorubicin for the treatment of metastatic soft tissue sarcoma. Approximately 30 patients in the United States with a range of soft tissue sarcomas are being enrolled to be treated with Veyonda® /doxorubicin combination as first-line treatment. A number of major sites are also participating in CEP-2, such as the City of Hope Cancer, Mayoclinic, Rochester and Washington University to name a few.

In Q3 2022, NOX announced the CEP-2 Safety Steering Committee review of the safety data from the first cohort of patients in the trial.
The 800mg dose was found to be safe and well tolerated, allowing enrolment to continue with the next patient cohort to be treated with an increased Veyonda® dose of 1200mg.

In November 2022, the company further reported on the 1200mg dose which was found to be safe and well tolerated yet again. This safety milestone has allowed enrolment to continue with the next patient cohort set to be treated with an increased Veyonda® dose of 1800mg. This will be the last dose cohort for the safety phase of this study, and if tolerated satisfactorily, will pave the way for the efficacy phase to begin. The current safety phase will continue until approximately Q1 2023, after which the efficacy phase commences.

Soft tissue sarcomas are often fatal cancers, up to 50% of high-grade sarcoma patients develop metastases and die within 12 months. They are defined as a rare cancer, with fewer than 20,000
new cases diagnosed in the US in 2021. The CEP-2 program is based on pre-clinical and clinical findings of Veyonda®.

12. Ionic Trial-Checkpoint Inhibitors

a. IONIC: Immuno-Oncology with NOX66 (Veyonda®) in combination

IONIC-1 is a pilot Phase 1 trial exploring the safety and efficacy signals of Veyonda® combined with the Bristol Myers Squibb checkpoint inhibitor OPDIVO (nivolumab) for the treatment of a range of solid tumour types. This is the first time Veyonda® will be investigated with an Immuno-Oncology (IO) drug. The current status update of this investigator-initiated trial includes all sites activated with enrolment gaining momentum.

- 11 patients have been enrolled so far, more than one third of a planned total. Part 1 is nearing completion and the Safety Steering Committee meeting is scheduled for 1 December 2022.
- If no further dose escalations are required, the second part will begin immediately to explore efficacy.

13. Chroma™

NOX's science-driven strategy has led to the development of its Chroma™ technology platform. The team are highly skilled and have tremendous expertise in the development of drug candidates based on a scaffold structure known as functionalised benzopyrans; a structure that is found in a range of medications. Through methodically creating adaptations based on this scaffold structure, the company has generated a library of unique drug candidates that share novel bioactive properties to enhance anti-cancer activity while targeting specific receptors. The majority of these valuable early-stage assets in the Chroma platform predominantly signal anti-cancer activity, with several of the drug candidates having the potential to block inflammation as well.

a. Pancreatic Cancer

A number of molecules are being critically assessed in the Chroma platform. The most advanced is CRO-67, which has demonstrated a unique dual-cell activity against pancreatic cancer in preclinical research. Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer-related deaths in developed countries. The 5-year survival rate is 8% from diagnosis with minimal improvements in the past four decades medically. The chemotherapy treatments only extended life by 8-16 weeks.

In Q3 2022, the company announced encouraging new preclinical data from its long-term collaboration with University of New South Wales (UNSW). UNSW has recently developed a world-first model of pancreatic cancer for research purposes, using cancer tissue samples that have been surgically removed from pancreatic cancer patients. NOX's drug candidate CRO-67 was applied to the cancer samples in this model, after 12 days CRO-67 demonstrated to have dual-cell activity, killing both the tumour cells and the surrounding barrier cells.

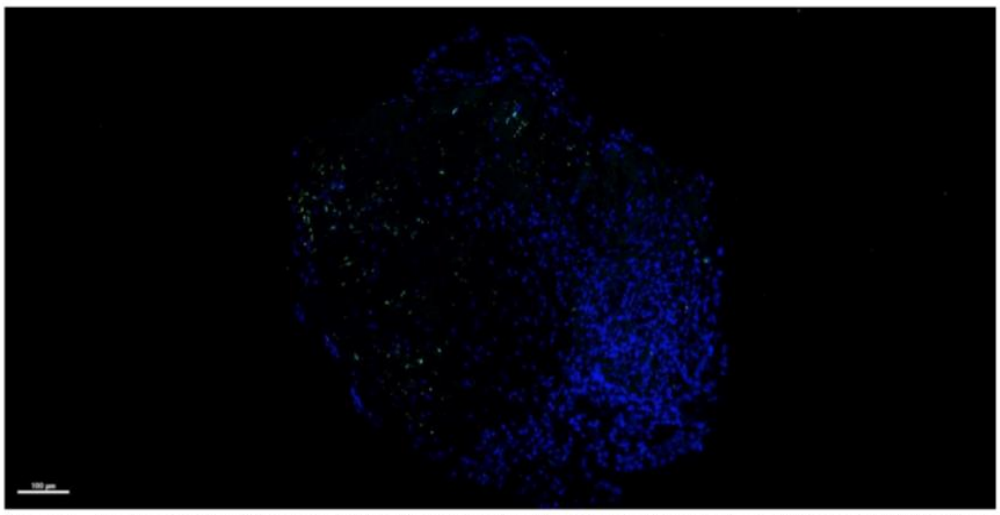


Image 1 – A representative tumour sample with no treatment. There are high numbers of living cells (blue) in the cancer tissue sample after 12 days without treatment.

Source: Noxopharm

This world-first study demonstrates CRO-67 as a novel dual-cell therapy, potentially destroying both the tumour and its surrounding barrier cells. These high promising results will now further drive studies to maximise the potential of this new approach to pancreatic cancer treatment.

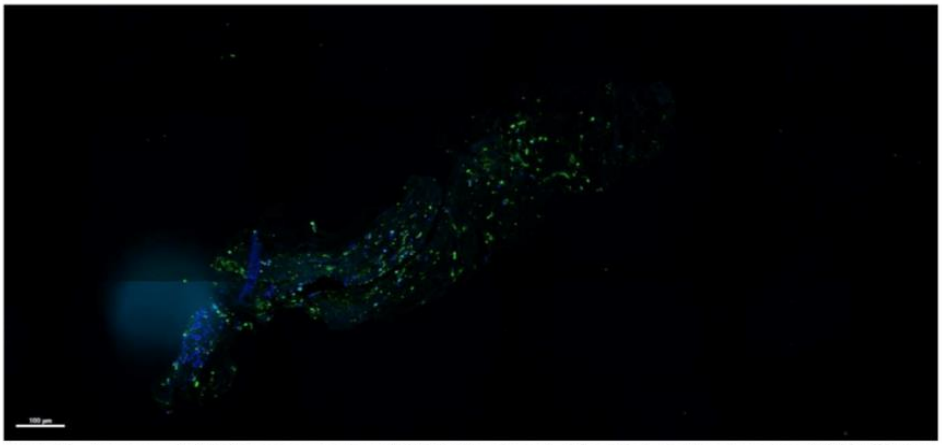
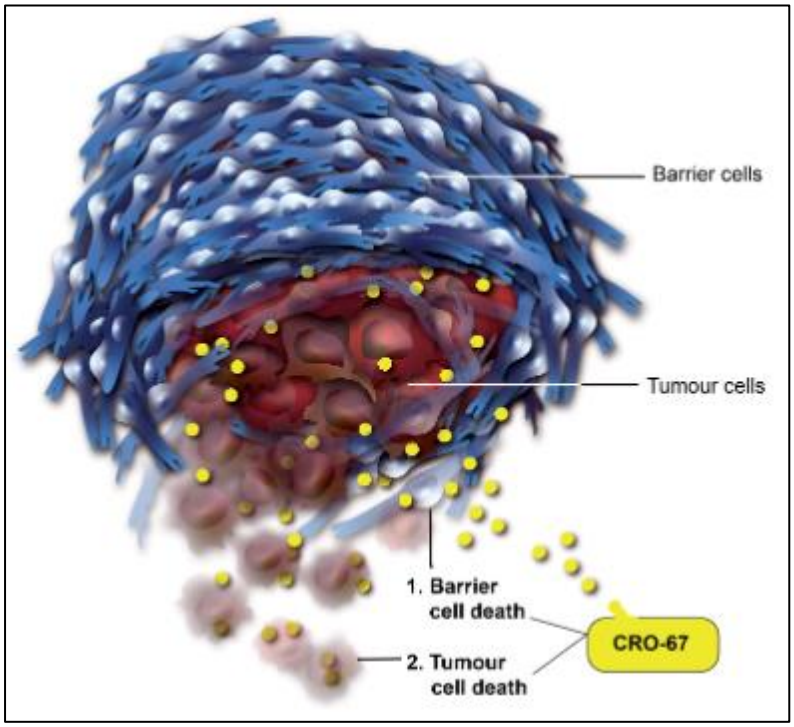


Image 2 – A representative tumour sample with CRO-67 treatment. After 12 days of treatment with CRO-67 there are predominantly dead cells (green) visible, and very few living cells (blue) remaining.

Source: Noxopharm



Source: Noxopharm

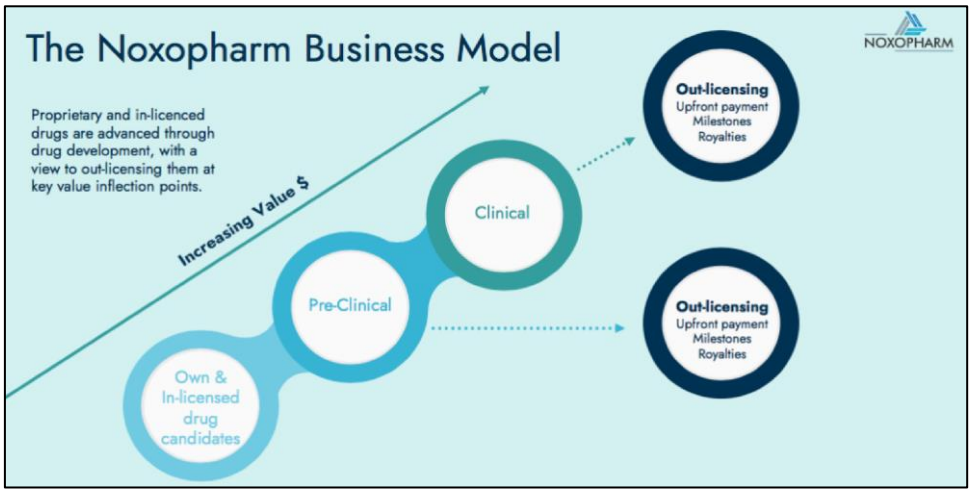
All four parameters demonstrated highly statistically significant results as follows:

- The number of tumour cells decreased
- The number of cancer associated fibroblasts (CAF) cells decreased
- Cell replication decreased
- Cell-death increase

14. Business model

NOX's business strategy entails a wide range of pre-clinical collaborations and clinical trial read-outs to realise the extensive opportunity it has in potentially meeting a range of urgent medical needs across diseases. The following strategies involve:

- the '4 Pillars Oncology' clinical development strategy for Veyonda® based on the concept of utilising the broad anti-cancer properties of IDX to allow Veyonda® to be used to enhance the effectiveness of other commonly- used anti-cancer treatments;
- the use of IDX's unique anti-inflammatory/immune sparing properties to position Veyonda® as a treatment of early-stage COVID-19 disease;
- to utilise the drug technology platform to develop a pipeline of drugs that block 'helper' signals from healthy support cells to target those tumours such as brain and pancreatic cancers that display highly aggressive growth; and
- to use the drug technology platform to develop a pipeline of drugs with unique anti-inflammatory actions to target a range of inflammatory diseases, through its subsidiary, Pharmorage, in partnership with Hudson Institute of Medical Research.



Source: Noxopharm

Licensing trends

Immuno-oncology (IO) made up 27% of transactions in the year 2021, while in 2020, IO was a focus of 49%of biopharmaceutical oncology drug licensing deals. A large number of these deals included multi-targeted approaches in combating cancer such as bispecific antibodies and antibody-drug conjugates (ADCs). In terms of development stage, there was a sharp increase in the number of deals associated with late-stage clinical assets in comparison to the previous years. Twenty-six deals involved Phase 2 assets, which accounted for approximately 20% of the total disclosed deal value. In 2021, the life sciences sector had an easier access to capital markets to finance their company-building efforts. Novartis was among the largest transactional dealmakers in 2021, owing to its IO ambitions.

The Swiss pharmaceutical company signed two significant deals with Chinese biotechnology firm, BeiGene. Bristol Myers Squibb (BMS), touted as an earlier leader in IO with Opdivo, was also very active in bio-partnering with three deals ranging in the billion-dollar range. BMS signed a potential $3.1 billion agreement with Eisai, a Japanese pharmaceutical to co-develop and co-commercialise the ADC MORAb-202 for advanced solid tumours. Furthermore, the appetite for technology platforms such as gene and cell therapies, ADCs and bispecific antibodies remains strong.

15. Market Overview

According to the findings from the IQVIA Institute's report titled 'Global Oncology Trends 2022: Outlook to 2026', the number of oncology trials reached a record high in 2021, up 56% from five years ago. As pharmaceutical companies focused on treating a range of cancer sub-types of particularly rare cancers. During the past five years, a total number of 104 oncology novel active substances (NAS) have been launched globally with the FDA approving 83 NASs compared to 58 in EU4+ UK, and 61 in China. In total 215 NASs have been launched since 2002 demonstrated by the chart below.

Furthermore, worldwide spending in oncology is expected to exceed $300 billion by 2026 as more patients seek early diagnosis and treatment options. In addition, larger pharmaceutical companies such as AstraZeneca, Novartis and Roche are working together in the Access to Oncology Medicines (ATOM). This is a collaboration to expand worldwide access to cancer medicine, particularly in developing countries by sharing their intellectual property (IP) along with providing access to off-patent medicines at affordable prices.

According to GlobalData, venture capitalists (VCs) are investing in oncology-focused startups across the globe during the last five years, with the UK leading the field with 44 deals compared to the rest of Europe. Many of these VCs target biological and small molecule NSAs in pre-clinical and discovery stages of development as opposed to the clinical phase; with a higher return on investment (ROI) compensating for the greater degree of risk.

The recent transactional (M&A activity) in the area of oncology involves pharmaceutical companies acquiring NASs which can either target novel cancer subtypes, be combined with approved products to extend the product lifecycle and their ROI or supersede approved products that are nearing their patent expiration. During the first three quarters of 2022, there have been more than a dozen number of high-profile pharmaceutical M&A agreements and strategic collaborations as depicted in the table below. The noteworthy names include Bristol Myers Squibb's $4.1 billion acquisition of the US biotechnology company, Turning Point Therapeutics to gain access to repotrectinib, a next generation, potential best-in-class tyrosine kinase inhibitor (TKI) targeting the ROS1 and NTRK oncogenic drivers of the non-small cell lung cancer (NSCLC) and other advanced solid tumours. GSK's $1.9 billion acquisition of Sierra Oncology with its lead candidate momelotinib, a treatment for myelofibrosis, a fatal cancer of the bone marrow impacting the normal production of blood cells.

In addition, numerous strategic collaborations have also been announced as biotechnology companies seek to expand their oncology franchises as depicted in table 1.1. These include Bristol Myers Squibb's $900 million collaboration with USA-based biotech BridgeBio Pharma to gain access to develop and commercialise BBP-398, a potentially best-in-class SHP2 inhibitor, in the field of oncology.

Furthermore, Moderna teamed up with USA-based Carisma Therapeutics, to discover, develop and commercialise in vivo engineered chimeric antigen receptor monocyte (CAR-M) therapeutics for the treatment of cancer. However, it is worth noting that not all collaborations are successful, given the risky nature of oncology therapies. In May 2022, Bayer terminated its collaboration with Atara Biotherapeutics and returned all the rights back to the company for its novel allogenic (off-the-shelf) EBV-T cell immunotherapies due to a concerning safety profile of the autologous mesothelin CAR T, ATA2271.

Table 1: Oncology M&A/dealmaking activity

Oncology start-up	Pharmaceutical company	Business description	Financial details
Turning Point Therapeutics	**Bristol Myers Squibb**	Acquisition to gain access to cancer therapeutic repotrectinib for NSCLC and other advanced solid tumours.	$4.1 billion in total equity value
Regeneron Pharmaceuticals	**Sanofi**	Sanofi is restructuring its immuno-oncology franchise collaboration with Regeneron, which now has worldwide exclusive rights to Libtayo (cemiplimab)	Sanofi is set to receive an upfront payment of $900 million, and 11% royalty on worldwide net sales of Libtayo. Sanofi is also entitled to a $100 million regulatory milestone payment upon the first approval by the FDA/EMA in combination with certain NSCLC patients
Kelun Pharmaceuticals	**Merck & Co**	Merck in-licenses development rights to an investigational cancer drug	Kelun Pharma will receive a non-refundable upfront payment of $47 million on signing the contract, as well as milestone payments of a maximum of $1.3 billion at different stages of the project
Cullinan Oncology	**Taiho Pharmaceutical (an Otsuka Pharmaceutical business)**	Taiko is set to buy part of Cullinan Oncology, picking up rights to co-develop and co-commercialise CLN-081 in the USA	Taiho will pay $275 million upfront and up to an additional $130 million tied to regulatory milestones
BioXcel Therapeutics	**Oaktree Capital Management and Qatar Investment Authority (QIA)**	Strategic investment to develop neuroscience and immuno-oncology drugs using artificial intelligence (AI)	Up to $260 million in gross funding
Sierra Oncology	**GSK**	Acquisition to gain access to cancer therapeutic momelotinib, treatment for myelofibrosis	$1.9 billion in total equity value

Table 1.1 Oncology strategic collaborations

Oncology start-up	Pharmaceutical company	Business description	Financial details
GO therapeutics	**Xyphos Biosciences (an Astellas Pharma subsidiary**	Collaboration to apply advances in glycoproteomics to develop antibody-based cancer therapeutics that specifically target cancer cells	Xyphos will pay GO therapeutics $20.5 million in upfront cash plus milestone and contingency payments of up to $763 million
Atara Biotherapeutics	**Bayer**	Bayer terminated the deal with Atara	Atara regains rights and licenses of its programs worldwide
DelSitech	**Anticancer Bioscience**	Collaborate to develop long-acting controlled release oncology treatments	Not disclosed
Proteros	**AstraZeneca**	Proteros signed an oncology expansion deal with AstraZeneca on the discovery and development of novel epigenetic drugs	Proteros will receive research funding and commercial milestone payments of up to $75 million plus tiered royalties on annual net sales
Vall d'Hebron Institute	**Ikena Oncology**	Generation and exploration of tumour and biomarker-specific data derived from specific patient populations	Not disclosed
BridgeBio Pharma	**Bristol Myers Squibb**	Collaborate to develop and commercialise BBP-398, a potentially best-in-class SHP2 inhibitor	BridgeBio will receive an upfront payment of $90 million, up to $815 million in development, regulatory and sales milestone and royalties
Innovent Biologics	**Eli Lilly**	Collaboration to strengthen the commercialisation of Cyrama (ramucirumab) and Retsevmo (selpercatinib) in China	Eli Lilly will make payments of $45 million on the commercialisation of Cyramza and Retsevmo in China following regulatory approval
Carisa Therapeutics	**Moderna**	Collaboration to discover, develop and commercialise in vivo engineered chimeric antigen receptor monocyte (CAR-M) therapeutics for the treatment of cancer	Carisma will receive $45 million upfront cash payment and $25 million convertible note plus, development, regulatory and commercial milestone payments

16. Valuation

The grant of the Orphan Drug Designation (ODD) status for the treatment of soft-tissue sarcoma is highly encouraging and as such, Evolution Capital recognises the value proposition of this particular indication. The ODD will aid NOX 's development of Veyonda® along with providing benefits to potential future purchasers or licensees of the molecule. The FDA grants Orphan designation to drugs that demonstrate a safe and effective treatment for diseases affecting less than 200,000 people in the USA per year. It also provides:

- seven years of market exclusivity;
- lower development costs; and
- waives new drug application fees which amounted to $2.9 million in 2021.

Sarcomas are cancers of the connective tissue, such as bone, muscle, nerves, fatty tissue and cartilage. Sarcomas fall into two broad categories, soft tissue sarcoma (STS) and bone sarcoma; along with the many varying histological subtypes. STS is a rare cancer, with an annual incidence of 2.4-3.6 new cases per 100,000 population-based studies. Wimber et al, reported that 15% percent of STS patients present with metastatic disease at initial diagnosis, and almost 50% of the rest will develop metastasis during follow-up. Furthermore, patients with metastasised STS generally have a poor prognosis, with a median survival of 12 months.

The current European Society for Medical Oncology (ESMO) clinical practice guideline recommends mainly systemic treatment for advanced and metastatic STS. Anthracyclines (doxorubicin) are advised as first-line of treatment with combination treatment strategies studied in various clinical settings. The combined treatment of doxorubicin and ifosfamide can lead to higher tumour response rates and a prolonged progression free survival (PFS), however, the side effects of this combination therapy outweigh the expected benefits of the treatment. Furthermore, Doxorubicin, in combination with the anti-PDGFRA biological olatumabm has been investigated but failed to demonstrate a survival benefit as compared to doxorubicin alone.

Surgery is the standard treatment for all patients with adult-type, localised STS, radiotherapy is also added in selected cases as it has shown to improve local control, but not overall survival (OS). The value of adjuvant or neoadjuvant chemotherapy remains a subject of considerable debate, as chemotherapy for treatment of metastatic STS (mSTS) is generally given with palliative intent, in order to block tumour progression, to reduce tumour size and control symptoms such as pain and or dysponea. The debatable nature of the benefits derived from the use of adjuvant and neoadjuvant chemotherapy brings to attention the relevance of affordability in treating these patients. There is very limited data on the resource use and medical costs of mSTS management. Available cost estimates focus either on a phase of treatment or on the cost-effectiveness of a particular therapy. As such, there isn't a comprehensive estimate of the economic burden caused by mSTS. The only estimation of the costs of mSTS was performed in 2006 by Judson et al, the mean medical cost was between €9141-€14753) for patients with a mean survival of 8.4 months from diagnosis of metastatic disease. As such, we are initiating coverage of Noxopharm at $0.51 per basic share using a risk-adjusted NPV model focused strictly on the CEP-2 trial in Sarcoma as it is a 'rare cancer' market. Our valuation approach assumes a discount rate of 20%, including a probability of success of 10%. Furthermore, the commencement of sales in 2026 and an initial market penetration of 1% before increasing to a peak market penetration rate of 9% and achieving peak sales of $1.98 bn by 2032. The marketing approval for rare cancers offer important commercial incentives with very little competition as well as highlighting the unmet medical need due to the aggressive nature of many sarcomas. It is usually accompanied by a poor response to chemotherapy, including the standard of care. We have estimated a gross margin of 70% and SG&A of 25% of sales revenue. Based on the above, we have placed a **BUY** recommendation on Noxopharm, reflecting an implied return of 218% from current levels. We also note, that in deriving this valuation, we have not considered the impact of dilution, which would increase depending on whether the company raises more capital as it progresses to more advanced clinical trials, whilst also noting that the impact of dilution would be offset by an increasing probability of success. We will adjust our assumptions as CEP-2 advances through clinical studies.

Product	Indication	Status	Probability of successful	Approval year	Peak sales (A$b)	Economics	rNPV (A$m)
CEP-2	Sarcoma	Phase 1	10%	2026	$1.98	100%	$292m

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