PITT STREET RESEARCH

Noxopharm Ltd

A potential blockbuster in Veyonda®

Share Price: A$0.18

ASX:NOX

Sector: Healthcare

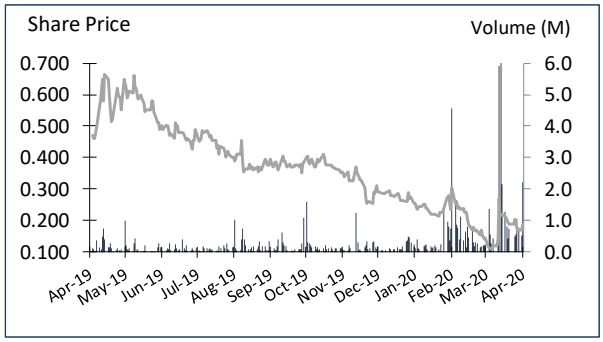
23 April 2020

Noxopharm (ASX: NOX) is a clinical stage, drug discovery and development company headquartered in Sydney, Australia. NOX currently has a focus on oncology with a pipeline of drugs. The first pipeline asset is an anti-cancer drug trademarked as Veyonda®, a proprietary suppository dosage form of idronoxil (IDX). IDX is a unique-acting drug that helps restore the ability of the body's immune system to fight cancer. Veyonda® is designed for the largest market sector in oncology – patients with Stage 4 cancer who have no remaining treatment options other than palliative care, often involving low-dose radiotherapy for symptomatic (pain) relief. Veyonda® is intended to shift palliative treatment into a meaningful therapeutic effect, and in doing so has the potential to become one of the most widely used drugs in oncology.

Market Cap. (A$ m)	27.4
# shares outstanding (m)	152.3
# share fully diluted	183.1
Market Cap Ful. Dil. (A$ m)	33.0
Free Float	100%
12-month high/low	0.665 / 0.11
Avg. 12M daily volume ('1000)	309
Website	noxopharm.com

Source: Company, Pitt Street Research

Share price (A$) and avg. daily volume (k, r.h.s.)



Source: Thomson Reuters, Pitt Street Research

Valuation metrics	
Fair valuation (A$)	0.42-0.89
WACC	13.5%
Assumed terminal growth rate	-3% to-5%

Source: Pitt Street Research

Investment case

The investment case for Veyonda® lies in its breakthrough and first-in-class action on the immune system, helping tip the balance against the cancer in favour of the body, an action that NOX believes will lead it to become a standard of care drug in many forms of cancer.

The immune system is designed to detect and eliminate foreign and abnormal or defective cells. Cancer cells are *abnormal,* and yet they gain a foothold and then spread throughout the body because of their ability to avoid the body's immune system. Restoring the balance in favour of the immune system is widely seen as the obvious future of cancer therapy. That is known as **immuno-oncology therapy.**

Activating the immune system is not the challenge – a number of technologies readily do that including radiotherapy and CAR-T therapy. The challenge lies in those activated immune cells being able to access the tumour cells and one of the key ways that cancer avoids the immune system is by blocking immune cells gaining entry to the tumour. This problem is identified as the main barrier to the universal success of immuno-oncology therapy.

Veyonda® may be the first drug known to overcome this problem, potentially turning so-called 'COLD' (immune-deficient) tumours into 'HOT' (immune-competent) tumours.

That potential puts Veyonda® in the front-line of cancer therapies and one of the most exciting drug prospects to emerge in recent years.

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Analyst: Stuart Roberts

Tel: +61 (0)447 247 909

Stuart.roberts@pittstreetresearch.com

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1. Introducing Noxopharm Ltd (ASX: NOX)

Noxopharm is an Australian, listed (ASX: NOX), primarily oncology-focused, clinical-stage drug development company with offices in Sydney and New York. NOX listed on the ASX in August 2016.

Veyonda®

The Company's lead drug candidate **Veyonda®** (previously known as NOX66) is a re-formulation of the experimental anti-cancer molecule, **idronoxil (IDX)**, designed to protect IDX from metabolic breakdown in the body.

IDX is a first-in-class inhibitor of sphingosine-1-phosphate (S1P), yielding novel dual anti-cancer functions of direct actions (working directly on cancer cells from preventing them dividing through to killing them) and indirect actions (restoring immune function to tumours).

Veyonda® is being positioned as a final line therapy for patients with end-stage cancer, with end-stage prostate cancer the initial clinical indication.

Veyonda® can help restore immune function to tumours

Veyonda® - A Novel Immuno-Oncology Drug Candidate

NOX believes that Veyonda® offers something that the global pharma industry is actively seeking – a drug that restores immune function to tumours. While medicine has a range of treatment options to trigger the ability of the immune system to attack and kill cancer cells, the challenge is to get those activated immune cells where they are needed – inside tumours. The great majority of human cancers are referred to as being 'COLD', meaning that not only are they devoid of immune cells, but they also employ a mechanism that actively excludes immune cells from the tumour mass. Overcoming that mechanism in an efficient and well tolerated manner has proven too great a challenge to date.

S1P is a key player in this immune cell exclusion mechanism. By inhibiting S1P, Veyonda® is designed to overcome the exclusion of immune cells, converting tumours from 'COLD' to 'HOT' across most forms of cancer and in a well-tolerated way.

Veyonda® - The Opportunity

The rationale behind the use of Veyonda® is a straightforward two-step process:

Step 1: trigger the production of active immune cells

Step 2: ensure that those immune cells then can enter tumours anywhere in the body.

NOX is achieving Step 1 by the use of low-dose radiotherapy, a known activator of immune cells[1] . Step 2 is achieved through the concurrent use of Veyonda®.

NOX is testing combinations of Veyonda® with two forms of radiotherapy. The first is with the traditional form of radiotherapy known as external beam radiotherapy (EBRT); this is referred to as the **DARRT treatment regimen**. The second is an experimental form of internal radiotherapy, where the radiation is delivered intravenously through drugs known as radiopharmaceuticals. This is referred to as the **LuPIN treatment regimen**.

NOX is concentrating in the first instance with both forms of radiotherapy on late-stage prostate cancer. This is in part (i) because of the significant unmet need and ready availability of patients with late-stage prostate cancer to undergo clinical trials, and (ii) because palliative radiotherapy (an immune trigger) is commonly used in men with Stage 4 prostate cancer.

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NOX believes that in the case of prostate cancer, Veyonda® will become a standard form of treatment with both forms of radiotherapy eventually, with the particular combination being a matter of the cancer type and the individual patient's disease situation.

The Company does not see the DARRT and LuPIN treatment regimens as mutually exclusive. There is no reason why a patient could not receive one regimen first and the other second.

The drug development strategy is as follows.

- The Company's primary goal is to achieve marketing approval for Veyonda® in combination with EBRT (**DARRT regimen**) in men with late-stage, metastatic, castration-resistant prostate cancer (mCRPC);
- A secondary goal is to confirm that Veyonda® boosts the anti-cancer effectiveness of the Novartis radiopharmaceutical, ^{177}lutetium-PSMA-617 (**LuPIN regimen**), in men with late-stage mCRPC;
- A further secondary goal is to test whether Veyonda® can boost the anti-cancer effectiveness of immunotherapy drugs known as checkpoint inhibitors (IONIC regimen).

The commercial strategy is to seek a strategic alliance for any of the three strategies above on the basis of Phase 1b or 2a/b data.

Pipeline

Noxopharm intends to build a pipeline behind Veyonda®

Veyonda® is the Company's first clinical asset, with a pipeline of a number of early-stage drug candidates under development, based on the same chemical technology platform that produced Veyonda®.

The long-term strategic objective of the Company is to evolve into a biopharmaceutical company with a robust pipeline of oncology drugs across multiple clinical indications, all based on the same chemistry platform.

A glutamate-inhibitor to treat glioblastoma multiforme is the second key asset to join the pipeline.

We understand that a number of other assets are under development and will be announced as and when they pass key proof-of-principle tests.

Vision

The Company's vision is to focus on drug discovery and mid-stage drug development, developing assets to a point of value realization and seeking to partner with larger companies to bring its assets like Veyonda® through to market.

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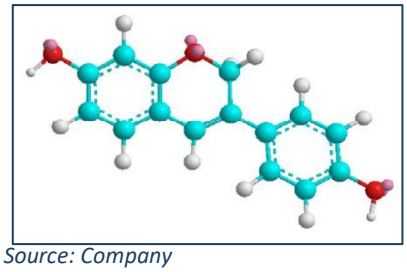
2. Veyonda® - a new form of idronoxil

Veyonda® is a re-formulation of a compound known as idronoxil (IDX) (Figure 1).

Idronoxil is a diphenolic (isoflavonoid) molecule also known as:

- 3-(4-hydroxyphenyl)-2*H*-chromen-7-ol
- Phenoxodiol
- Dehydroequol
- Haginin E

Figure 1: Chemical structure of idronoxil



Source: Company

IDX was discovered in 1992 as a result of research conducted at the University of Sydney Medical School by Dr Graham Kelly. IDX subsequently came to international attention because of its mechanism of action with its ability to kill most forms of cancer cells in the laboratory, with no apparent ill effects on healthy cells.

IDX became the subject of considerable research involving US, European and Australian universities and hospitals, with some 50 studies subsequently being published in the international scientific literature. Those studies revealed an interesting and novel mechanism of action (MoA) that appears to remain unique to this day.

Veyonda® has a long development history

IDX initially was developed by Australian biotech company, Novogen Ltd (ASX:NRT; Nasdaq:NVGN). IDX underwent a series of clinical studies between 2000-2009, being tested in both oral and intravenous dosage forms under the name phenoxodiol. The clinical strategy was based on the chemo-sensitising function of IDX, using the S1P-inhibitory action of IDX to restore sensitivity to platinums and taxanes in ovarian cancer.

Between 2000 and 2009 IDX was the subject of over 15 clinical studies (Phase 1-Phase 3), principally focusing on its use to restore sensitivity of ovarian cancer cells to chemotherapy in women with end-stage chemo-resistant disease.

An oral dosage form of IDX known as phenoxodiol eventually failed a multi-national Phase 3 study (OVATURE) in 2009.[2]

NOX speculated that the failure of OVATURE was the result of extensive metabolism of IDX and subsequent loss of bio-activity. As the result of further research, NOX re-formulated IDX as a proprietary suppository dosage form (Veyonda®) intended to protect the molecule from extensive metabolism and degradation.

NOX is leveraging off the estimated >$100M spent by Novogen on IDX over some 10 years of R&D, which enabled it to have Veyonda® in a well-advanced clinical program within 3 years of listing.

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3. Veyonda® is a novel dual-acting drug candidate

3.1. Summary of Mechanism of Action

The active ingredient in Veyonda®, idronoxil, demonstrates anti-cancer activity against most forms of cancer

The active ingredient in Veyonda®, IDX, has two broad mechanisms of action.

The first action is a **direct anti-cancer effect** (blocking cancer cell growth, and sensitising cancer cells to chemotherapy drugs and radiotherapy).

The second action is an **indirect immuno-oncology effect** (restoration of immune function to tumours). Together, these two effects offer a novel and potentially important new approach to the treatment of cancer.

The mechanism of action of IDX is best viewed as a 3-step process, all of which occur in the cell's plasma (external) membrane.

Step 1: IDX binds to and inhibits an enzyme on the external surface of the cancer cell known as **ENOX2**

↓

Step 2: Loss of ENOX2 function causes downstream blockage of the enzyme, sphingosine kinase

↓

Step 3: Loss of sphingosine kinase function prevents production of sphingosine-1-phosphate (S1P), a key pro-survival factor over-expressed in most cancers

↓

S1P drives three primary functions in cancer:

↓ ↓ ↓

cancer cell growth | resistance to therapies | suppression of immunity

By blocking S1P, IDX exerts 3 main anti-cancer functions:

↓ ↓ ↓

Blocks cancer cell growth	Sensitises chemo- and radio-therapy	Restores tumour immune function

3.1.1. Mechanism STEP 1: ENOX2

IDX targets an enzyme known as ENOX2 that cancer cells are highly dependent on for their survival

The primary molecular target of IDX is the enzyme **Ecto-NOX disulphide-thiol exchanger type-2 (**or **ENOX2)**[3, 4]. IDX binds to and inhibits the function of this enzyme.

ENOX2 belongs to the Ecto-NADH oxidase (ENOX) family of enzymes that sit on the outside of the plasma membrane of all animal cells.

ENOX enzymes perform two important functions (Figure 2):

1. The first function is the movement of electrons and protons across the cell surface to the exterior where they form water. This movement of these highly charged atomic particles releases energy that supports the various functions of the cell membrane.
2. The second function is protein disulphide-thiol interchange - a key function in the correct folding of newly produced proteins.

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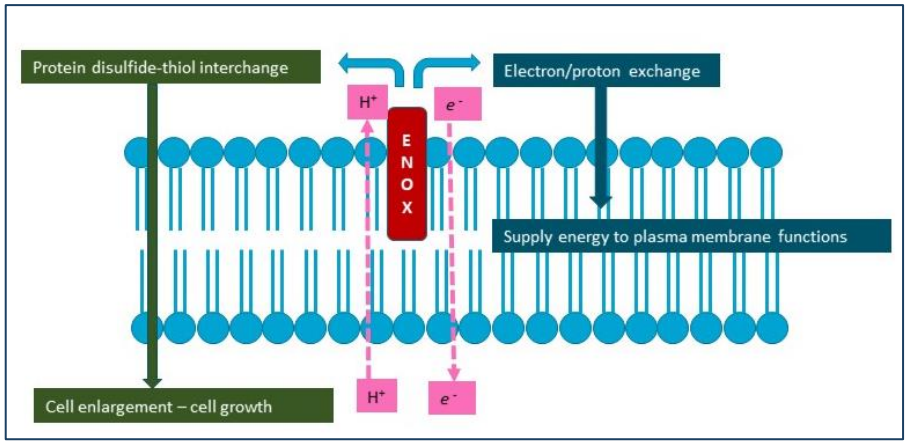
ENOX oscillates between these two functions in a precise manner, suggesting a third critically important time-keeping function in the cell.

Figure 2: Dual functions of ENOX enzymes



Source: Company

Veyonda® acts on an oncogene called ENOX2

Mammals express 2 main forms of ENOX enzymes called ENOX1 and ENOX2. Both perform the same two functions, just at different levels of activity. ENOX1 oscillates between its electron transfer and protein folding function with an interval of 24 minutes; with ENOX2, the interval is 22 minutes.

This shorter oscillation interval makes ENOX2 a higher-performing enzyme compared to ENOX1. Cells with high rates of growth require more energy and therefore more frequent movement of protons and electrons across the plasma membrane. This pressure for higher energy levels exerts pressure on the cell genome that results in activation of the ENOX2 gene and greater expression of ENOX2. ENOX1, with a lower rate of energy production, on its own, appears unable to sustain a high cell growth rate.

- Healthy adult cells with normal rates of growth (the vast majority of the body's cells) are reliant almost solely on ENOX1[5]
- Normal adult cells with high rates of turnover (eg. cells lining the gut, bone marrow cells etc) express a mixture of ENOX1 and ENOX2, generally with a predominance of ENOX1
- Cancer cells express both ENOX1 and ENOX2, but predominantly ENOX2
- There is some evidence in animals that foetal cells (with high growth rates) also are highly reliant on ENOX2, prompting description of ENOX2 as a feto-oncogene.[6]

IDX only binds to ENOX2.

- ENOX2 differs from ENOX1 through a small sequence difference on the protein's quinone-binding motif. IDX binds to this distinguishing feature on ENOX2 (Figure 3). There is no binding of IDX to this motif on ENOX1.[7]

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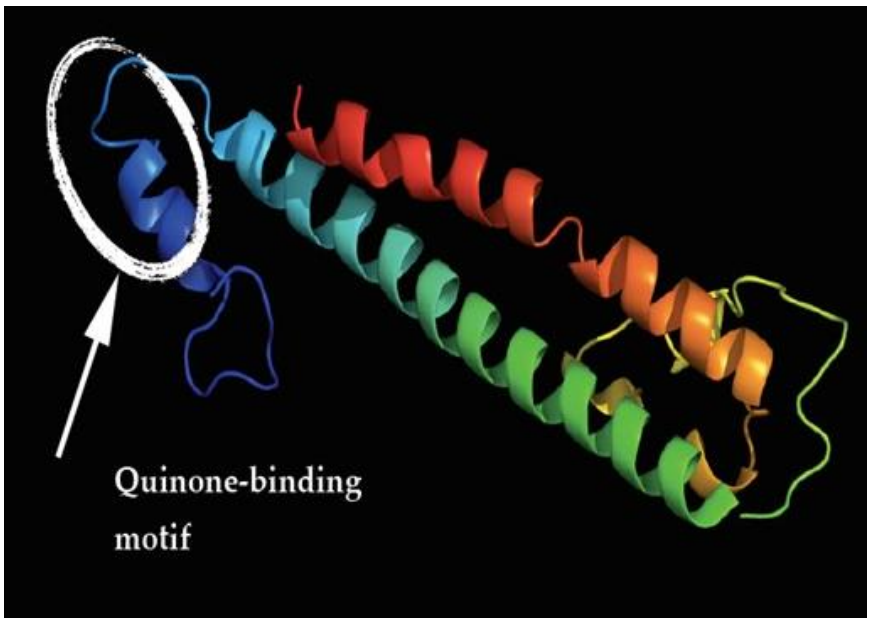
Figure 3: Binding site for IDX on ENOX2



Source: Company

- The general reliance of cancer cells on ENOX2 accounts for why IDX is active in the laboratory against all forms of cancer tested to date
- The lesser reliance on ENOX2 of high turnover healthy tissues such as gut mucosa and bone marrow accounts for the low levels of side-effects (dry mouth, stomatitis, fatigue and mild anaemia) reported in patients treated with IDX

Shutting down ENOX2 at the least disrupts cancer cell function and at most kills them

The consequences of the loss of ENOX2 function are as follows (Figure 4):

- loss of protein disulphide-thiol interchange activity, and
- inhibition of the cells' electron (e-) and proton (H+) pumping activities across the plasma membrane

Protein disulphide-thiol interchange activity is essential to cell enlargement, and loss of that function blocks the ability of the cell to divide.[8]

Loss of electrons/protons across the plasma membrane deprives the plasma membrane of its primary source of energy, but also leads to a build-up of protons in the plasma membrane, with that build-up specifically inhibiting the function of enzymes in the so-called sphingomyelin pathway, a dynamic process within the plasma membrane that ultimately determines the fate of the cell – either living or dying. The build-up of protons shifts the cell towards death, with the outcome either being complete and the cell dying (apoptosis) or incomplete, resulting in a cancer cell that remains alive but is unable to grow and to divide, unable to maintain its resistance to chemotherapy and radiotherapy, and unable to suppress the immune system.[9]

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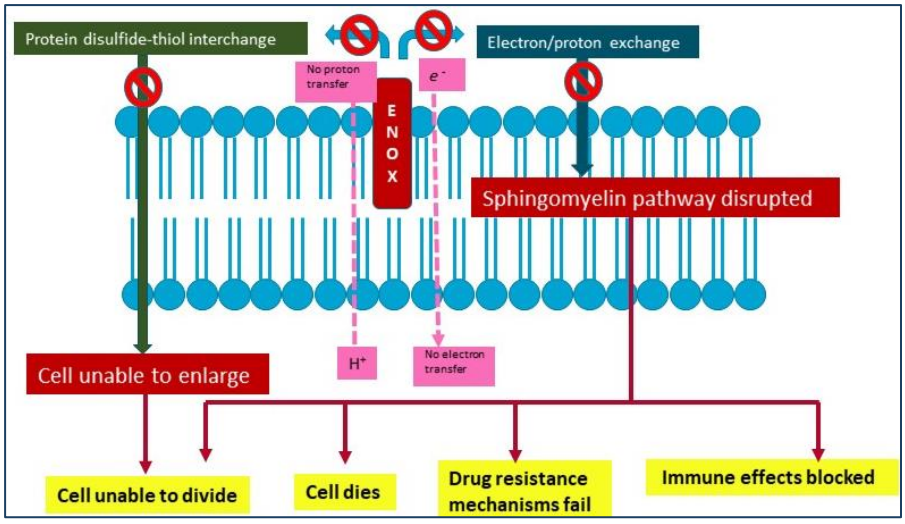
Figure 4: Binding site for IDX on ENOX2



Source: Company

The anti-cancer effects of IDX stem from its inhibition of sphingosine-1-phosphate

3.1.2. Mechanism STEP 2: Inhibition of sphingosine kinase

The plasma (or external cell) membrane is a bilayer of fatty structures known as sphingolipids. This bilayer provides an architectural support for all the enzymes and receptors that link the cell to the rest of the body. About 20% of these sphingolipids are a sub-group known as sphingomyelins and they do a lot more than serve a passive structural role – they are in a constant state of reversible flux as follows:

sphingomyelin ⇆ **ceramide** ⇆ sphingosine ⇆ **sphingosine-1-phosphate**

The purpose of this flux is to respond to signals coming both from within the cell and externally that are meant to determine whether the cell should live or die. The two key players in this process are **ceramide** and **sphingosine-1-phosphate** (**S1P**).

Both of these compounds are so-called secondary messengers, forming two of the most important determinants of a cell's fate. **Ceramide is pro-death**, triggering cell death via apoptosis; **S1P is pro-survival**, activating a broad range of signaling pathways responsible for cell survival and growth.

Each step in the sphingomyelin pathway is controlled by 2 enzymes – one enzyme progressing the left-to-right reconfiguration, and the second enzyme reversing that process.

The enzyme responsible for converting sphingosine to S1P is **sphingosine kinase**. Having sphingosine kinase fully functional is critical to life because it ensures that the sphingomyelin pathway in the cell keeps moving to the right, thereby keeping ceramide levels low and SIP levels high = cell survival. If sphingosine kinase activity is blocked, the pathway moves to the left and ceramide starts accumulating = cell death.[10]

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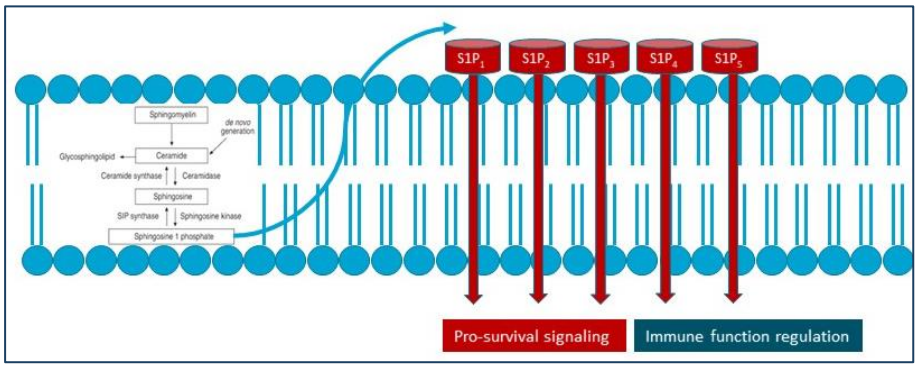
Note. Sphingosine kinase is the one enzyme in the sphingomyelin pathway specifically inhibited by the high levels of protons that accumulate in the membrane following the inhibition of ENOX2 by IDX. IDX has no direct inhibitory effect on sphingosine kinase. Its inhibitory effect is via ENOX2, which is why IDX does not inhibit sphingosine kinase in normal cells. In patients receiving Veyonda®, IDX is only shutting down sphingosine kinase activity in cancer cells and a small proportion of high turnover cells such as bone marrow and gut lining cells.

3.1.3. Mechanism STEP 3: Inhibition of sphingosine-1-phosphate

Once S1P is produced within the cell membrane in the sphingomyelin cycle, it leaves the cell and interacts with 5 different receptors on the outside of the cell known as $S1P^1$, $S1P^2$, $S1P^3$, $S1P^4$, $S1P^5$ (Figure 5).

Figure 5: Sphingosine-1-phosphate. Critical roles in cell survival and immunomodulation



Source: Company

Each of these five receptors triggers important cellular pro-survival signaling cascades including PI3K, AKT, mTOR, PLC, NF-kB, PLC and cJUN, with considerable cross-talk between all five receptors.

Veyonda® is an S1P inhibitor

S1P levels higher in cancer cells. Most cancers have considerably increased levels of sphingosine kinase activity, in turn leading to abnormally high levels of S1P.

These high S1P levels in turn over-activate the various pro-survival signaling pathways, an effect thought to be a prime driver of cancer cell survival and growth.

Among the broad range of cellular functions vital to cell survival that S1P drives, two functions stand out in terms of how IDX works –

(i) sensitisation to chemotherapy and radiotherapy

(ii) restoration of immune competence of tumours.

The anti-cancer effects of IDX stem from its inhibition of sphingosine-1-phosphate

IDX blocks the production of S1P, while at the same time increasing ceramide levels.[11, 12]

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3.2. Consequences of S1P inhibition

3.2.1. Chemo-sensitisation/radio-sensitisation

By inhibiting S1P, IDX makes cancer cells more sensitive to chemotherapy and radiotherapy

Hyperactivity of S1P in cancer cells drives excessive cell growth, mitotic activity, cell migration and infiltration, DNA repair and the development of multi-drug resistance mechanisms.

By blocking these functions, IDX sensitises a wide range of cancer cells to standard cytotoxic drugs, including highly chemo-resistant cells. The degree of chemo-sensitisation to drugs including taxanes, platinums, doxorubicin and gemcitabine is in the order of several thousand-fold.[13] The degree of sensitisation to radiation is less sensitive, in the order of 2-3-fold. Specifically -

- IDX inhibits cyclin-dependant kinases, causing mitotic arrest and rendering cancer cells more susceptible to DNA damage[14, 15]
- IDX inhibits the main enzymes of DNA repair (topoisomerase 2 and PARP 1 and 2,) in turn increasing the likelihood of cell death.[16]

Veyonda® has the potential to offer multiple advantages over currently available treatments:

- It has the ability to enhance the anticancer effects of standard chemotherapies and radiotherapies.
- In instances wherein humans are not responsive to standard therapies (radio- or chemotherapy) alone it can restore the anti-cancer effects of these therapies.
- The drug potentially allows to lower the dosage of cytotoxic drugs to a level that is less likely to be associated with unwanted side effects. This presents an opportunity for a significant number of patients with late-stage cancer who stop using chemotherapy due to associated side effects.
- It can kill a broad range of cancer cells, with limited adverse effects on healthy cells. The poisoning effects of the drug for the most part are limited to cancer cells.

3.2.2. Restoration of immune competence

S1P performs many vital functions, but one important function is to help stop the immune system from over-reaching and morphing into chronic inflammation/autoimmune disease. Immune cells play an important role in tissue repair activities but need to leave the tissue once that repair process is finished. Their staying on risks the repair process evolving into chronic inflammation/autoimmune disease. S1P serves to dampen down the immune response, expelling immune cells from the tissue and preventing their re-entry. Cancers highjack this natural function by up-regulating S1P activity to the extent that the tumour flourishes in an environment devoid of any immune cells, with activated immune cells, capable of attacking the cancer cells, unable to enter the tumour.

Hyperactivity of S1P in cancer cells drives excessive cell growth, mitotic activity, cell migration and infiltration, DNA repair and the development of multi-drug resistance mechanisms.

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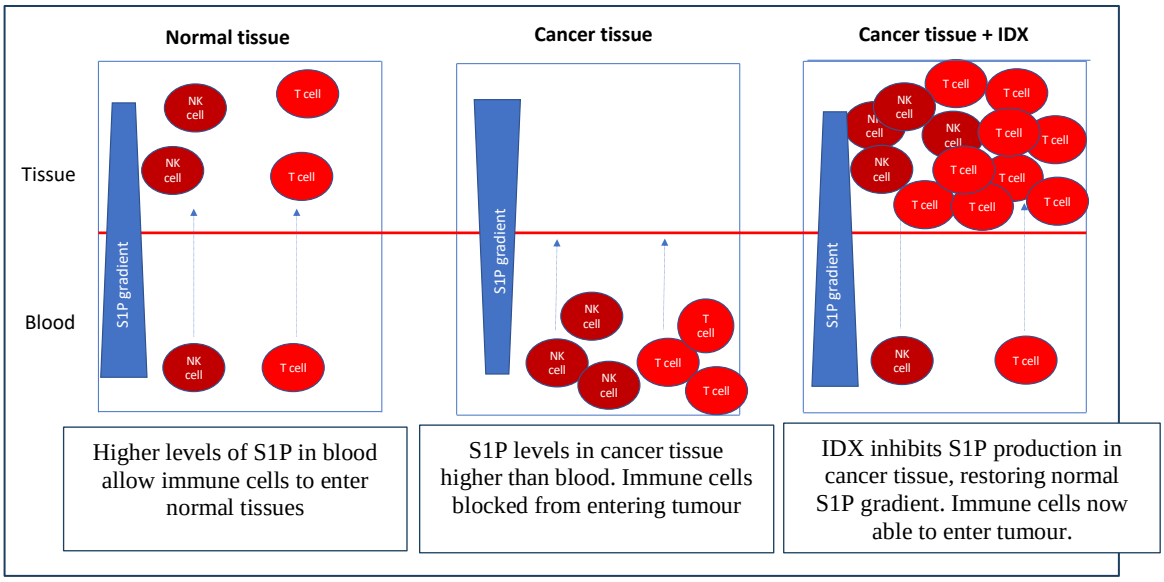
Promoting immune cell trafficking. S1P levels normally are lower in body tissues and higher in blood, creating a so-called S1P gradient. This gradient permits inflammatory and immune cells to enter tissues. In most tumours, this gradient is reversed, blocking immune cells from entering tumours.[17, 18]

By inhibiting S1P levels, the normal tissue-blood S1P gradient is restored, immune cell trafficking is increased, 19 allowing immune cells to enter the tumour (Figure 6).

Figure 6: IDX reverses the S1P gradient



Source: Company

4. Veyonda® - a re-formulation of IDX

Phase 2 metabolism of IDX ultimately proved to be a barrier to its working in the clinic

Noxopharm was founded on the belief that the failure of OVATURE was caused by unrecognised problems with the pharmacological behaviour of the drug.

IDX is a diphenolic molecule, and therefore is highly water-insoluble, making it susceptible to Phase 2 metabolism (conjugation to glucuronide and sulfate Phase 2 metabolites), an enzymatic process that takes place in gut mucosa and liver and is designed to render the molecules water-soluble and thereby transportable in blood and excretable via urine (Figure 7).

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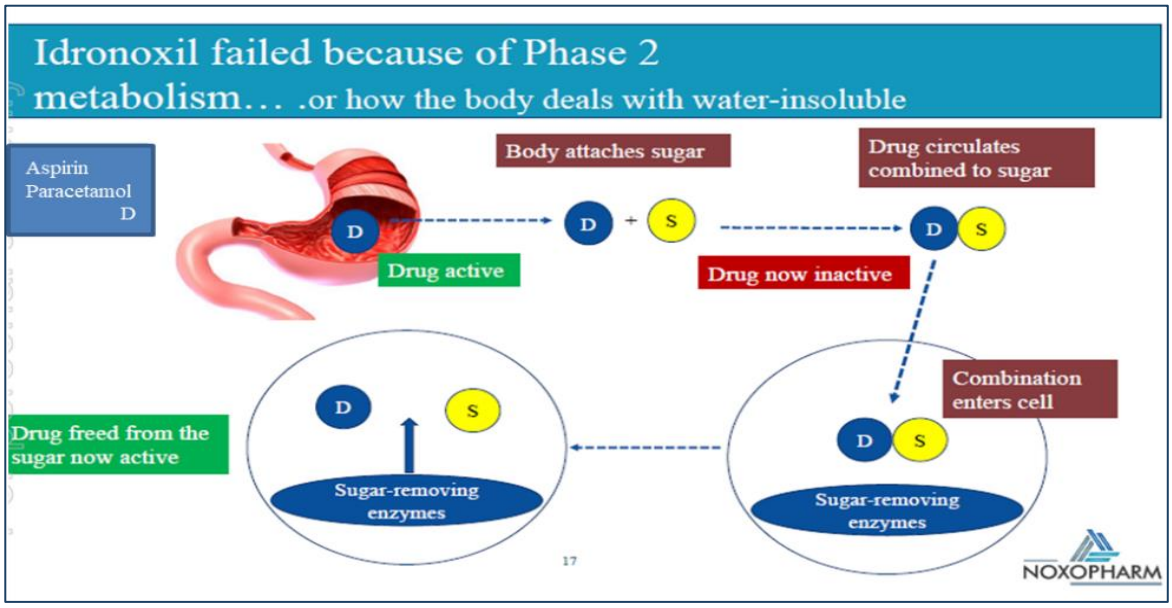
Figure 7: Phase 2 metabolism



Source: Company

Diphenolic molecules in humans are virtually completely metabolised in this way and IDX shares this fate with other diphenolic-based drugs including aspirin, paracetamol, codeine, steroidal hormones (estradiol, cortisone) etc.

Phase 2 diphenolic metabolites are biologically inactive, the attached sugar or sulfate group preventing binding to their molecular target. Reactivation requires exposure to deconjugating enzymes (glucuronidases, sulfatases) in order to liberate the free, active drug. Most healthy tissues display this deconjugating activity, accounting for the therapeutic activity of diphenolic drugs such as aspirin.

Noxopharm has learned the lessons of the OVATURE study

Noxopharm reasoned that the failure of the OVATURE study was due to the target cells for IDX being cancer cells, not healthy cells, a major point of distinction to other diphenolic drugs such as aspirin. It was reasoned that cancers may be shutting down their deconjugating activity along with the change in many metabolic functions that form multi-drug resistance mechanisms.

Noxopharm addressed this problem through a proprietary diphenolic drug delivery technology known as LIPROSE with the purpose of protecting IDX from Phase 2 metabolism. The LIPROSE technology is designed to put IDX into a lipid form that is delivered by suppository (Veyonda®). The distal part of the rectum passively absorbs these proprietary lipid forms via the distal haemorrhoidal vein directly into the inferior vena cava, thereby avoiding first-pass liver metabolism (Figure 8).

The lipid form of IDX readily circulates in the bloodstream with an extended half-life (>10 hours) as the lipid form is unable to be excreted in the urine. Excretion occurs via the bile (entero-hepatic circulation), with 12-hourly dosing delivering continuous steady-state blood levels.

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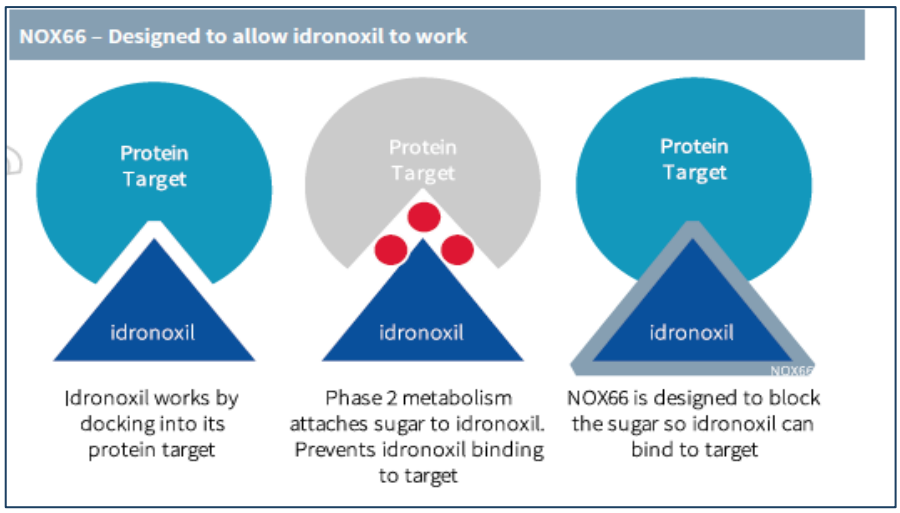
Figure 8: NOX66 design to overcome phase 2 metabolism



Source: Company

5. Drug pipeline

NOX is using the same diphenolic chemistry and LIPROSE drug delivery technology platforms to develop a pipeline of oncology and non-oncology assets. The rationale behind the pipeline is the development of small molecule therapies for therapeutic indications of high unmet need.

A number of assets are under development, the most prominent being a **glutamate receptor inhibitor.** The objective of this program is a drug to treat glioblastoma multiforme (GBM). This program is based on the recent discovery that the aggressive growth of GBM tumours is driven largely by synaptic connections with neuronal cells, with the main neurotransmitter, glutamate, serving as a key growth stimulant.[20] The Company has identified a family of compounds that are novel, first-in-class inhibitors of glutamate activation of metabotropic glutamate receptors, designed to spare the NMDA glutamate receptors that are so critical to general brain neurotransmission and function.

6. Ten reasons to look at Noxopharm

1. **Veyonda® should apply to most forms of cancer**. IDX targets a unique feto-oncogene that is present on all forms of cancer tested to date, meaning that IDX shows anti-cancer activity against most forms of cancer, both solid and non-solid. This gives Veyonda® the potential to become a standard of care drug in oncology broadly.
2. **Immuno-oncological function** of Veyonda® has **the potential to revolutionise cancer treatment.** Veyonda® has the potential to overcome the major limitation of current immuno-oncology treatments - the difficulty in repopulating tumours with immuno-competent cells. Despite considerable efforts over recent years, a means of overcoming the S1P gradient preventing the re-entry of immune cells to tumours has yet to be found. NOX believes that Veyonda® is the first such drug to achieve

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this aim, giving it the potential to become an early market leader in the booming immuno-oncology field.

3. **Veyonda® provides a viable treatment option for patients on palliative care**. Typically, patients with Stage 4 cancer who have exhausted all available treatment pathways are put on to palliative care for temporary treatment of symptoms (pain etc), with no realistic expectation of any change in the progression of the disease. Initial trial results suggest that Veyonda® is effective in restricting disease progression in late-stage prostate cancer patients. This opens up a significant and unique market opportunity for Veyonda® to aid the management of patients on palliative care, the largest market sector in oncology.
4. **Late-stage prostate cancer is a large and major unmet need.** An estimated 350,000 men die each year globally from prostate cancer. The Company's DARRT and LuPIN treatment regimens offer meaningful treatment options in this large and growing cancer sector.
5. **DARRT treatment regimen has the potential to be applicable to a wide range of cancer.** NOX is aiming to bring its DARRT treatment regimen to market for the treatment of late-stage prostate cancer, but equally believes that the regimen will be applicable to a wide range of cancer types including lung, breast and ovarian.
6. **Opportunity for LuPIN treatment to be relevant to Novartis or other radiopharmaceutical companies**. The LuPIN program is combining Veyonda® with the Novartis-owned experimental radiopharmaceutical, ^{177}lutetium-PSMA-617. Novartis paid US$6bn in 2018 to acquire this technology. If the LuPIN-1 study continues to deliver encouraging evidence of a survival advantage in combining with Veyonda®, then this is something that could be of commercial interest to Novartis or other companies that have similar radiopharmaceuticals in their portfolio.
7. **Veyonda® use being extended into chemo-sensitisation**. Veyonda® is a potential treatment for sarcoma, a diverse form of cancer representing about 5% of all solid cancers which currently has very few treatment options. NOX plans on testing a combination of Veyonda® and doxorubicin in soft tissue sarcomas. Noxopharm has recently received IND approval from the US FDA to conduct a Phase 1 study. Sarcoma is a rare cancer that offers the opportunity to receive Orphan Drug designation, which will help in fast-tracking the drug approval process and give prolonged market exclusivity.

Veyonda® has high potential to capture significant market share upon commercialisation

8. **Noxopharm is leveraging its Veyonda®-based expertise to discover other anti-cancer agents, with the aim to diversify into a biopharmaceutical company**. With the Veyonda® program successfully transferred to the clinical drug development stages, the Company is using its knowledge base around diphenolic drug chemistry and its LIPROSE diphenolic drug delivery platform to build a robust pipeline of anti-cancer drug candidates. The company aims to fully own this pipeline and transform into a full-fledged biopharmaceutical organisation. The plan will help Noxopharm solely reap the benefits of successful drug launches throughout the exclusivity period of the drugs and beyond.
9. **Company caters to the oncology therapy area, which accounts for the major share of medicine spending**. In 2018, oncology accounted for the highest share of total spending on medicines in major developed and emerging (eg China, India and Brazil) markets. Indicated by encouraging clinical trial results, Veyonda® has a high potential to gain traction in such a huge market.

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10. **NOX restructures/recapitalises with entry into pre-commercial phase.** The Company recently has undergone a restructuring and recapitalisation designed to prepare it for an anticipated considerable growth spurt over 2020/2021. Restructuring has involved expanding the Board with 2 NEDs with extensive experience in public companies. Recapitalisation has involved retiring a convertible note facility.

7. Metastatic cancer represents a major opportunity for Noxopharm

Cancer is the second leading cause of death globally

According to the World Health Organization (WHO), cancer is the second most common cause of death from disease after cardiovascular disease, being responsible for an estimated 9.6 million deaths in 2018. The most common cancer deaths being from:

- Lung (1.76 million)
- Colorectal (862,000)
- Stomach (783,000)
- Liver (782,000)
- Breast (627,000)

Source. https://www.who.int/news-room/fact-sheets/detail/cancer

Despite considerable advances over the last 20 years in cancer treatment, chemotherapy with cytotoxic drugs and radiotherapy remain the standard of care for the majority of patients with most forms of solid cancer. However, both forms of therapy remain challenged by the ever-present problems of cancer cells readily developing resistance to chemotherapies and radiotherapies, coupled with the problem of toxic side-effects limiting the use of more effective dosages.

Metastatic cancer rarely is cured with treatment focused on extending life. Patients with end-stage metastatic cancer represent the largest sector of the cancer market

Metastatic cancer rarely is cured, and regardless of ongoing improvements in 1st, 2nd, 3rd and 4th lines of therapy, the majority of patients with metastatic cancer inevitably reach the point of palliative care and eventually succumb to their cancer. Treatment at this end-stage of the disease typically involves alleviation of symptoms designed to make the patient's remaining time as comfortable as possible.

Cancer patients undergoing palliative care is the largest sector of the oncology market, with no real expectation of being able to do anything for the patient beyond providing temporary symptomatic relief.

Most experimental anti-cancer drugs, even those intended to be used earlier in the disease process, are required to be tested initially in patients where all standard treatments have failed – that is the nature of drug development.

In the case of Veyonda®, this end-stage cancer patient is exactly where Veyonda® is designed to be. The Company is confident that Veyonda® eventually could prove to be effective in combination with radiotherapy in earlier lines of treatment, but the initial target is the large cohort of patients who have failed all forms of therapy and are now in the end-stage of their disease.

Offering patients with end-stage cancer something more than palliative care is a major unmet need. NOX anticipates Veyonda® filling this void, being not just a last-line salvage therapy providing improved palliative care, but a treatment offering meaningful anti-cancer activity.

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Veyonda® is not competing with current therapies as no other drug has achieved an indication involving combination with radiotherapy.

The potential value of this strategy is highlighted by the size of the overall global oncology therapeutic medicine market, which is expected to surpass US$200bn by 2022 as per IQVIA 2018 estimates. In 2018, sales of the top 10 anti-cancer products were valued at US$63.74bn. A majority of leading anti-cancer drugs are sold by Genentech/Roche, including Rituxan, Avastin and Herceptin (Table 1)[21, 22].

Table 1: Top cancer product revenues (2018)[23]

Top Cancer Drugs (Pharma)	Indications	2018 Revenue (US$, bn)
Revlimid (Celgene)	Multiple cancers	9.68
Opdivo (Bristol-Myers Squibb/Ono Pharmaceutical)	Multiple cancers	7.57
Keytruda (Merck)	Multiple cancers	7.17
Herceptin (Roche/Genentech)	Breast cancer; Gastric cancer	6.95
Avastin (Roche)	Multiple cancers	6.82
Rituxan/MabThera (Genentech/Roche, Biogen)	Multiple cancers	6.75
Imbruvica (AbbVie/Johnson & Johnson)	Multiple cancers	6.21
Neulasta/Peglasta (Amgen/Kyowa Hakko Kirin)	Neutropenia; Radiation injuries	4.68
Ibrance (Pfizer)	Breast cancer	4.12
Xtandi (Astellas Pharma/Pfizer)	Prostate cancer	3.62
Total		**US$63.74bn**

Source: Proclinical.com

8. Late-stage metastatic prostate cancer the selected path to market

mCRPC is the primary disease target for marketing approval for Veyonda®

NOX has identified metastatic castrate-resistant prostate cancer (mCRPC) as the primary route for Veyonda® to come to market.

Only about 1 in 10 men who are diagnosed with prostate cancer go on to be at risk of dying from the cancer. In most men, the disease either is diagnosed early enough and treated such as by prostatectomy, or the cancer is so slow-growing and poorly invasive that they manage to successfully live with the disease.

The 1 in 10 men who go on to develop mCRPC account for over 350,000 prostate-cancer-related deaths worldwide[24] every year.[25] These deaths occur predominantly in men where the cancer has spread beyond the prostate gland at the time of diagnosis, making surgical intervention impractical, or where a prostatectomy has been performed but where the cancer has already escaped the prostate gland.

Treatment for men with aggressive prostate cancer involves a number of steps which can be modified according to the individual patient (Figure 9).

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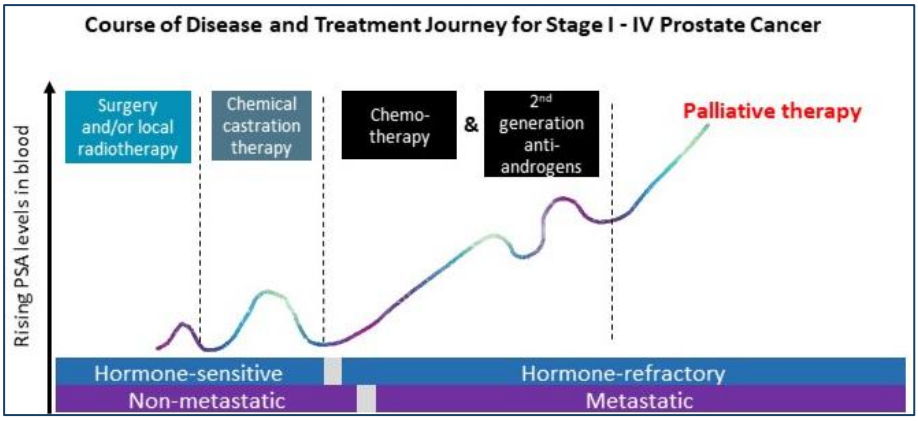
Figure 9: Prostate cancer treatment options



Source: Company

There are various lines of mCRPC treatment, but the disease remains incurable

- The first therapeutic step typically involves surgery and/or radiotherapy to the pelvic region, focusing on the prostate gland and immediate surrounding tissues (but sparing the bowel and bladder).
- The next step is typically chemical castration therapy designed to reduce testosterone production in the body to negligible amounts, thereby removing the main driver of growth of the cancer cells. On failure of second-line therapy, the disease is referred to as **castration-resistant disease**. Typically, the disease at this stage is metastatic **and is referred to as metastatic** castration-resistant prostate cancer (mCRPC)
- The first-line therapy for mCRPC usually involves cytotoxic chemotherapy with the taxane, docetaxel
- As next line therapy the 2nd generation anti-androgens (abiraterone, enzalutamide), introduced several years ago, can be administered
- Third line therapy typically involves another cytotoxic chemotherapy with the taxane, cabazitaxel.

Despite significant advances in the treatment of mCRPC, it remains incurable, with each of these lines of therapy generally offering a temporary anti-cancer effect lasting some months to a few years at most. Virtually every man with mCRPC eventually exhausts all standard forms of therapy and reaches the final stage of palliative care with the objective of making the patient as comfortable as possible at the end of their life. Prostate cancer spreads throughout the body predominantly in the skeleton; soft tissue spread (liver, lungs and brain) also occurs but is less common. Pain is a particular feature with mCRPC because of the bone secondaries. High dose analgesia with opioids, and radiotherapy to selected large lesions to try and reduce pain, constitute the main form of palliative therapy.

It is men at this stage of their disease that Veyonda® is targeting in the first instance and which the Company has selected as its path to market.

The aim is to use Veyonda® in conjunction with radiotherapy with the goal of shifting a palliative response (seeking to make the patient as comfortable as possible) into a therapeutic response producing a meaningful anti-cancer outcome with

- greater pain relief (and thereby less opioid use)
- slower tumour growth or delayed tumour growth.

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- potentially increasing the length of survival

The Company is running two parallel programs utilising different methods of delivering the radiotherapy.

The first program (known as DARRT) uses radiotherapy delivered by the standard form known as external beam radiotherapy (EBRT). This is the standard form of radiotherapy delivered during palliative care of mCRPC patients and involves the delivery of radiation to between 1 and 2 selected tumours.

The second program (known as LuPIN) uses radiotherapy delivered intravenously via a type of radioactive drug known as a radiopharmaceutical, with the objective of delivering a low dose of radiation to prostate cancer cells throughout the body versus the highly localised and selective number of cancer cells able to be irradiated with EBRT.

8.1. Veyonda®, mCRPC and DARRT

The path to market for Veyonda® - DARRT and mCRPC

Noxopharm is positioning Veyonda® and its DARRT treatment regimen as an adjunct to low-dose radiotherapy for late-stage mCRPC.

DARRT stands for *Direct and Abscopal Response to Radiotherapy*. It is based on the radio-sensitising effect of Veyonda® and its potential to increase the ability of radiotherapy to trigger an immune response in 1-2 irradiated tumours. Additionally, the immuno-oncology effects of Veyonda® are then intended to facilitate the entry of the activated immune cells into the remaining tumours in the body that have not received radiotherapy. An enhanced anti-cancer response in the irradiated tumours is the **direct effect** and any anti-cancer effect in the non-irradiated tumours is known as an **abscopal response**.

The radiotherapy in DARRT-1 is external beam radiotherapy (EBRT). A low dose (palliative dose) of radiation is delivered to between 1 and 2 separate tumours over 5 days (total dose = 20-25 Gy), with the aim of triggering inflammation and an immune response in those tumours.

Veyonda® is administered for 14 days in conjunction with the radiotherapy.

A high proportion of patients with late stage mCRPC receive palliative radiotherapy for pain relief. In DARRT, NOX simply is adding Veyonda® to this palliative treatment with the aim of converting it into a more therapeutic treatment.

DARRT-1 clinical data

The DARRT-1 Study is a Phase 1b study conducted in 25 men with Stage 4 mCRPC that had progressed on all forms of standard therapy.

Patients were eligible for low-dose (palliative) radiotherapy for relief of symptoms such as pain, with little or no expectation of it changing the course of the disease.

The data showed that adding Veyonda® to low-dose (20Gy) palliative radiotherapy applied to one or two lesions changed the course of disease to a considerable degree in at least 67% of men, with a halt to disease progression and high levels of pain relief lasting at least for the 6-months of observation.

At the end of study at 6-months, of the 25 enrolled patients:

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• 9 had withdrawn, died or been lost to follow-up
• 16 completed the study of whom 15 were measurable radiographically.

Across all 3 Veyonda® dosages (400, 800, 1200 mg):
• 1/15 patients had a partial response, 9/15 had stable disease and 5/15 had progressive disease, giving an overall tumour response rate of 67%
• 5/16 patients (31%) had a PSA Response (>50% fall from baseline), with PSA reductions ranging from 61-98%
• 10/16 patients (62%) had a Pain Response (>30% fall from baseline), with falls ranging from 43-100% (pain-free).

The trial's primary end-point of safety was met with no significant or dose-limiting toxicities.
The secondary end-point of efficacy clearly was achieved based on rates of PSA Response, Pain Response and Tumour Response (RECISTv1.1) in a high proportion of men.

8.2. Veyonda, mCRPC and LuPIN

The LuPIN (**L**u-**P**SMA and **I**dro**N**oxil) program is investigating the safety and efficacy of Veyonda® when used in combination with ^{177}Lu-PSMA-617 (Lu-PSMA) to treat patients with late-stage mCRPC.

^{177}Lu-PSMA-617 is a radiopharmaceutical comprising a peptide (PSMA-617) that targets prostate cancer cells, with an attached radionuclide (^{177}lutetium). When injected intravenously, the peptide seeks out prostate cancer cells, attaching to them and delivering the radioactive isotope to inflict damage on the cancer cells.

Lu-PSMA is still experimental but is reported to deliver an anti-cancer effect showing PSA and pain reduction and potentially longer survival.[26]

The technology is licensed to U.S. company Endocyte Inc that was acquired in 2018 for US$2.1bn by Novartis.

Veyonda® may be able to increase the response rate to Lu-PSMA therapy

The LuPIN-1 study is an investigator-initiated study being conducted at St Vincent's Hospital Sydney with the purpose of evaluating if Veyonda® can increase the response rate to Lu-PSMA therapy in a well-tolerated way.

Lu-PSMA treatment involves up to six intravenous injections of Lu-PSMA 6-weeks apart.

In the LuPIN-1 study, Veyonda® is dosed for 10 days beginning on day 1 of each cycle.

LuPIN-1 clinical data (as of February 2020)

All patients had received and failed two prior lines of therapy (docetaxel and abiraterone or enzalutamide) and most patients (29/32) had failed a third line of therapy (cabazitaxel) prior to entering the trial.
The advanced nature of the disease in the LuPIN patients was highlighted by the following:
• The extensive treatment history of most LuPIN patients means that their disease is more advanced and more resistant to therapy than in other studies where patients have had fewer lines of drug therapy

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- The majority of patients (65%) had a significant tumour burden with over 20 secondary tumours mainly in the bones and lymph nodes
- All patients had progressive end-stage prostate cancer.

Key efficacy findings

- Median Overall Survival was 17.1 months, indicating a significantly longer survival duration than clinically expected
- 47% of patients (15/32) were well enough to receive all 6 cycles of therapy, indicating a durable response, enabling them to continue to receive treatment until the end of the study
- 87% of patients (28/32) had a fall in PSA (an important marker for anti-cancer activity) and 62.5% (20/32) had a strong PSA response of over 50%
- Half of the patients with severe pain at study start (12/24) had a significant reduction of their pain due to the secondary tumours, supporting the above efficacy results.

Efficacy summary

The combination treatment had a beneficial impact in more than half of the patients.

Key safety findings

Veyonda® combined with ^{177}Lu-PSMA-617 continues to have a good safety profile, with approximately half the patients experiencing only mild adverse events, such as dry mouth (17/32), fatigue (15/32) and anaemia (14/32). Minimal higher-grade side effects were reported and all were manageable.

8.3. DARRT vs LuPIN

Developing alternative treatments for the same patient population is a highly unusual but an extraordinarily valuable strategy and opportunity.

DAART remains the key value-creation step for Noxopharm

Noxopharm currently sees its DARRT program as the preferred path to market because the DARRT program has the potential to achieve considerably higher sales with its potential to be used across a broad range of cancer types, while the LuPIN program is specific just for mCRPC.

Nevertheless, we see the two treatments as being complementary, not mutually exclusive. At the very least, this dual program strategy means that Noxopharm is putting itself in the position of having two alternative treatments for end-stage mCRPC come to market, with the side-effect profile, individual patient needs and treatment costs determining which program is the best option for the patient. In fact, it is highly likely, that a patient with mCRPC will be treated with both options at different time points.

At most, it puts Noxopharm in the enviable position of owning a drug that could mean for a major pharma company the difference between market success or market struggle for its own drug.

9. Veyonda® – beyond prostate cancer

While the Company is confident that the rationale behind the DARRT treatment program will be applicable to a wide range of different cancer types, it has flagged no immediate plans to pursue indications other than mCRPC, although we would expect them do so once the mCRPC DARRT

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program has more matured. Other treatment programs currently being explored are as follows.

9.1. Opportunities in immuno-oncology (IONIC program)

Arguably, this is the largest opportunity open to the Company – the opportunity to combine Veyonda® with immune-checkpoint inhibitors to increase the reach of these drugs across more patients and more forms of cancer.

Immune checkpoints are proteins produced to help balance immune responses in tissues. They regulate the ability of immune cells such as activated T cells to recognise foreign cells such as cancer cells and attack them. Checkpoints include receptors such as lymphocyte-activation gene (LAG-3), programmed cell death protein 1 (PD-1), programmed cell death ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4).

Many forms of cancer employ checkpoint proteins as a means of preventing the immune system from attacking them. Immune checkpoint inhibitors are drugs that remove these inhibitors, thereby allowing immune cells to attack cancer cells. The immune checkpoint drug market (predominantly PD-1 and PD-L1 inhibitors) was valued at US$10.5bn in 2017 and is anticipated to reach US$56bn by 2025.

Currently available immune-checkpoint inhibitors are known to be effective in only certain individuals. Across the full cancer spectrum, their benefit currently is restricted to select types of cancers such as lung cancer, melanoma, bladder cancer, head and neck cancer, and Hodgkin's lymphoma with an estimated 12% of cancer patients considered eligible and likely to respond to checkpoint inhibitors.[27]

Noxopharm believes Veyonda® can make 'cold' tumours 'hot'

In order to be effective, checkpoint inhibitors require activated immune cells to be present in the tumour to take advantage of having the barrier removed. The reason that checkpoint immunotherapy fails in some patients is thought to be the result of tumours lacking a population of immune cells. These are the so-called 'cold' tumours.

The enormous potential of Veyonda® lies in its ability to restore immune function to tumours, converting 'cold' (± immune cells) tumours to 'warm' (++++ immune cells) tumours. Noxopharm anticipates that combining Veyonda® with a checkpoint inhibitor such as Keytruda or Opdivo will lead to a larger number of patients with different forms of cancer responding with meaningful anti-cancer outcomes.

If successful, this would open up a lucrative market to NOX through developing Veyonda® as an immuno-oncological drug that could enhance the response rate and cancer coverage of currently available standard immune checkpoint inhibitors such as PD-1 or PD-L1.

IONIC-1 is a proposed Phase 1b study under consideration as an investigator-initiated study combining Veyonda® and a checkpoint inhibitor in patients that have failed to respond to a checkpoint inhibitor alone.

9.2. Sarcoma

The Company recently received grant of Investigational New Drug (IND) status by the U.S. FDA for Veyonda® in combination with doxorubicin in patients with soft tissue sarcomas. This application was based on pre-clinical data using a range of sarcoma cells showing IDX both killing the cancer cells on its own as well as enhancing the killing effect of doxorubicin. Sarcoma is a cancer of the body's connective tissues and is divided for ease of description into soft tissue sarcomas (muscle, blood vessels, fat, tendons, etc.) and hard tissue

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sarcomas (bone, cartilage). Sarcomas are rare cancers embracing over 80 different types, collectively accounting for about 1% of all adult tumours.[28]

CEP-2 is a proposed pilot safety and efficacy Phase 1b study involving Veyonda® plus doxorubicin in doxorubicin naïve patients with various soft tissue sarcomas.

The CEP (chemotherapy enhancement program) is built around pre-clinical experiments showing that IDX is a potent enhancer of the cytotoxic effects of most standard chemotherapies.[13]

CEP-1 study generated encouraging results that highlighted Veyonda's success in enhancing the efficacy of chemotherapy :

This concept was tested in a Phase 1 study known as CEP-1. That study entailed a combination of Veyonda® and carboplatin in patients with end-stage disease involving solid cancers and who had been heavily pre-treated. The objective was to see if Veyonda® was safe to administer in combination with carboplatin and to see if there are signals to suggest that it could be used to boost the effectiveness of carboplatin to the extent of using lower-than-normal dosages of carboplatin in a way that delivered meaningful anti-cancer responses in a well -tolerated way.

The study included 19 patients with metastatic solid tumours (breast, prostate, lung, and ovarian) who had stopped responding to chemotherapy, including carboplatin.

Overall, the study demonstrated positive safety results and efficacy signals for the combination of Veyonda® and carboplatin. The drug was able to halt cancer progression at 6 cycles of treatment in almost 50% of the patients who had stable disease at 3 cycles (Table 2). In addition, it was well tolerated as a monotherapy, with just one case of anaemia attributed to it. The drug did not exacerbate carboplatin cytotoxicity at a concentration of 400 mg and 800 mg.

Table 2: NOX66 – CEP-1 study (efficacy data)

Dose cohort	Assessment time point*	Count n	Partial response	Stable disease	Progressive disease
Cohort 1 NOX66 400mg, n (%)	Cycle 3	5	0 (0.0)	4 (80.0)	1 (20.0)
	Cycle 6	2	0 (0.0)	1 (50.0)	1 (50.0)
Cohort 2 NOX66 800mg, n (%)	Cycle 3	9	0 (0.0)	7 (77.8)	2 (22.2)
	Cycle 6	6	1 (16.7)	4 (66.7)	1 (16.7)

RECIST 1.1 Data for evaluable patients after 3 and 6 cycles

Source: Company

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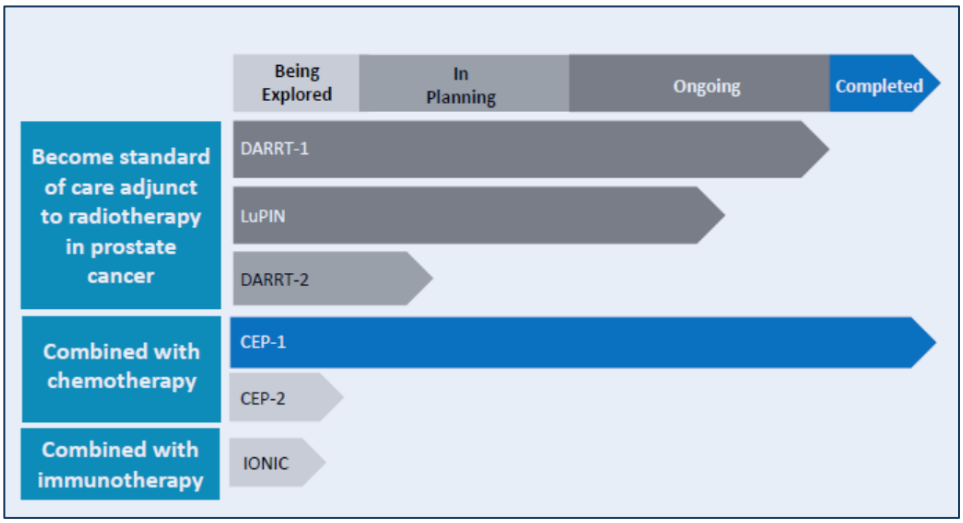
10. Clinical Trial Program



Source: Company

11. Valuing Noxopharm

We valued Noxopharm on a probability-weighted DCF basis. We value Noxopharm at $0.42 base case and $0.89 optimistic case using a probability-weighted DCF approach. We valued only Veyonda®.

General assumptions.

- **Discount rate.** We used a WACC of ~13.5%, appropriate in our view for a 'Speculative' risk rating[1];
- **Probability of success.** We assumed a probability of success of 21%, which reflects the risk of a drug in Phase 2;
- **Time horizon**. We used a 14-year time horizon in our DCFs followed by a terminal value;
- **Currency**. We assume the AUD/USD exchange converges on 0.7 over a three-year period from now.
- **Capital.** Purely for valuation purposes, we assume a further $20m is raised at $0.15 cents per share.
- **Commercial life of future products.** We assume that Veyonda® enjoys 15 years of commercial exclusivity, after which sales erode due to generic competition[2].

[1] For a relevant discount rate, we use varying WACCs depending on the risk for Life Science companies. We start with an RFR of the Australian ten year bond rate and an ungeared beta of 1.1 but use a variable MRP of 7.5%-11.5% (7.5% for 'medium risk' companies, 9.5% for 'high risk' companies and 11.5% for 'speculative' companies). We regard Life Science companies with existing businesses, or who have enough capital to reach the market with their products, as 'Medium' risk. Companies that have small revenue streams from marketed products but that are still potentially in need of capital are 'High' risk. Everything else is 'Speculative'.

[2] While patent protection for a drug is notionally 20 years, patent term extension in the US only covers that part of clinical programme after the filing of an IND. This reduces the exclusivity window by a few years. For large companies marketing blockbuster drugs, the window is around 15-16 years. Consider the Roche/Genentech cancer drug Herceptin. It gained FDA approval in September 1998 and enjoyed peak sales in 2014, for a 16-year window. Going further back in time, Amgen gained FDA approval for Epogen in June 1989. Its peak sales year was 2004, another 16-year window.

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Table 3: Our valuation of Noxopharm

	Base	Optim.
Veyonda (A$m)	92.1	243.5
Total programme value	92.1	243.5
Value of tax losses	12.1	12.1
Corporate overhead	-9.3	-9.3
Cash now (A$m)	4.7	4.7
Cash to be raised (A$m)	20.0	20.0
Option exercises (A$m)	12.1	12.1
Total value (A$m)	131.7	283.0
Total diluted shares (million)	316.4	316.4
Value per share	$0.416	$0.894
Valuation midpoint	$0.655	
Share price now (A$ per share)	$0.180	
Upside to midpoint	263.9%	

Valuing Veyonda®. To value Veyonda®, we assumed payoffs from future licensing transactions and estimated a base case and an optimistic case for the following elements:

- Level of expenditure required prior to a licensing deal;
- Timing of a prospective licensing deal;
- Level of upfronts in the deal (in US$);
- Level of milestones in the deal (in US$) – we assume that the probability of receiving those milestones declined evenly over time. We weighted the dollar value of milestones towards completion of Phase 2 and 3 as well as including some sales milestones.

We also, estimated a base case and an optimistic case for the following elements:

- Date of product launch in the US;
- Date of product launch for the Rest of the World (RoW);
- Level of royalties, as a percentage of net sales;
- The level of sales (in US$) to be achieved in the US at year five post launch;
- The level of sales (in US$) to be achieved in the RoW at year five post launch;
- The growth rate of sales in both the US and the RoW between years 6 and 14;
- The percentage of the US and RoW markets still held by the product when it goes generic;
- The terminal growth rate of the product franchise.

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The parameters for each license were as follows[3]:

	Veyonda project	
	Base case	**Optimistic case**
NOX investment required (AUDm)	7	4
License date	2023	2022
License upfront (USDm)	50	100
License milestones (USDm)	200	400
Royalty rate	10.0%	15.0%
Earliest approval	2026	2025
Peak sales (USDm)	1,100	1,500

12. Re-rating Noxopharm

We see a number of factors contributing to a re-rating of Noxopharm towards our valuation range.

- Continuation of positive results from the ongoing LuPIN study
- Commencement of the IONIC study with a possible collaboration with a major pharma company with an approved or experimental checkpoint inhibitor
- Grant of Orphan Drug status and a Fast Track approval for the sarcoma study
- Approval to start DARRT-2

[3] Note: The peak sales numbers are reasonable in the light of the worldwide sales of Merck & Co.'s Keytruda immune-oncology drug – these wrre US$11.1bn in calendar 2019.

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13. Noxopharm is led by highly experienced professionals

The company's management comprises leaders with high expertise and knowledge base across various business domains

Dr Graham Kelly PhD is the current CEO and Executive Chairman. Dr Kelly founded Noxopharm as a private biotechnology company to commercialise NOX66, which was developed by him in a private capacity in early 2012. He served as CEO and Executive Director of Noxopharm till April 2019, post which he moved to an Executive Chairman role, primarily to establish the company's footprint in the US. Graham has vast experience in founding and leading biotech companies. He founded Novogen (now Kazia Therapeutics) in 1994, Marshall Edwards (now MEI Pharma) in 2001 and Noxopharm in 2016. He spearheaded Novogen from a market capitalisation of A$12m in 1994 to A$900m in 2003. Graham graduated with degrees in Science (1968) and Veterinary Science (1969) from the University of Sydney.

Dr Gisela Mautner is the Chief Medical Officer of Noxopharm. She brings a wealth of experience to her role, having held medical leadership roles in the pharma and biotech industry in the USA, Europe and Australia. As a medical doctor, she is dedicated to making the lives of patients better, and as an industry advocate, she is excited by new developments in treatments that provide new hope to many people.

In her early career she was a research scientist at the National Institutes of Health (NIH) in Bethesda, MD, USA and at the Kyoto Prefectural University in Kyoto, Japan. She transitioned to the pharma industry to focus on taking new drugs out of the lab and making them widely available to patients. She has had many successes launching new products for Merck (MSD), Bayer and Amgen. She is proud of her leadership role in one of the most successful drug launches in Australia.

For the last decade her passion has been new therapies in oncology. Her interests encompass small molecules, biologics, gene-modified viruses and radiopharmaceuticals for many different cancer types and from early to late stage disease. She fuels her passion with the knowledge that her efforts improve the life of patients on a daily basis. Balancing patient care and commercial interests has been part of her responsibilities as the medical lead throughout most of her career as well as directing the medical strategies and operations, budget management, compliance and staff performance in Medical Affairs Departments of multinational companies.

Dr Mautner has built and nurtured a broad network of medical doctors, especially oncologists in Australia and in the USA. In addition, she is extensively connected to pharmaceutical professionals in Australia as well as in the USA through her work as the President of the Australian Association for medical and scientific Professionals in the Pharmaceutical industry (APPA).

Alex Hunter is an experienced company executive with a diverse financial, business and operational background. Prior to joining Noxopharm he worked for 15 years in executive roles encompassing corporate finance, capital raising, M&A and growth company operations and strategy in Australian and US operating environments.

He was previously Chief Financial Officer of an ASX listed energy company that successfully transformed a US based business to grow annual revenue from $0 to over $200m, complete asset acquisitions of over $250m and raise over $300m in equity and debt. Former roles include General Manager Business Development at ASX listed growth company Drillsearch Energy and Associate

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Director at Australian & UK based corporate finance advisory firm RFC Ambrian.

Prior to his career in corporate finance Alex worked for 10 years in project management of engineering and construction projects and corporate change management roles.

Alex holds an MBA from University of Southern California Marshall School of Business, a Bachelor of Engineering, and postgraduate qualifications in corporate finance and business law.

John Wilkinson is the Chief Scientific Officer (CSO) of Noxopharm since February 2018. John has ~30 years' experience in pharmaceutical and research settings across multiple regions, such as Australia and the UK. Prior to joining Noxopharm, he worked as CSO at Biotron Limited (an Australian biotechnology company) where he was responsible for overseeing Biotron's antiviral and HIV-1 clinical programmes. He completed his graduation (BSc Honours) from the University of Portsmouth, England, and PhD in HIV-1 Immuno-virology from the University of New South Wales, Sydney. His expertise in translating novel laboratory findings into human clinical trials makes him a perfect fit for the CSO role at Noxopharm, where he is responsible for driving scientific, research and technological operations, and help the company set research and scientific priorities.

Shawn Van Boheemen has been the Chief Financial Officer (CFO) of Noxopharm, since March 2019. He has a total experience of ~30 years, across a number of finance leadership roles in manufacturing and professional services companies. He has held various company secretarial positions, the role of compliance head, and various IT, administration and human resources positions in multiple companies, including Covance, Unomedical, MD Sass and New York Life Insurance. He has in-depth working knowledge related to compliance, regulatory affairs and financial reporting for the Australian Stock Exchange, the Australian Securities and Investments Commission (ASIC) and the US SEC. With him at the helm of financial affairs at Noxopharm, the company has achieved the perfect balance of expenses, revenue and funding.

The company has a stable Board, comprising the following members:

Graham Kelly, Executive Chairman of Noxopharm.

Noxopharm's board has members with entrepreneurial experience and expertise in raising capital and scaling up businesses

Peter Marks, who serves as Non-executive Deputy Chairman, comes with over 30 years' experience in corporate advisory and investment banking roles. He has expertise in raising capital for pre-IPO and listed companies, cross-border M&A transactions, corporate underwriting and venture capital transactions for companies primarily in the life sciences, biotechnology and medical technology space. He has been the Director and Chairman of several public companies. He has been serving as a Director at Prana Biotechnology (listed on ASX and NASDAQ) since 2005, Chairman at Armadale Capital (listed on London Stock Exchange) since 2009 and Non-executive Director at Emefcy Group (listed on ASX) since 2015. Peter holds a Bachelor of Economics, a Bachelor of Law and a Graduate Diploma in Commercial Law from Monash University, Australia. He also holds an MBA from the University of Edinburgh, Scotland.

Ian Dixon serves Noxopharm's board in the capacity of Non-executive Director. He brings an extensive entrepreneurial background in founding, building and running public companies. He specialises in recognising the commercial value of early-stage drug development and tackling related

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challenges. In his previous role, he co-founded Genscreen (a biotechnology incubator with focus on cancer therapeutics) and Cynata (a company focused on stem cell manufacturing at a commercial scale), which is now known as Cynata Therapeutics. He holds a PhD in Biomedical Engineering from Monash University, Australia, and an MBA from Swinburne University, Australia.

Boris Patkin brings comprehensive market knowledge, thorough research and years of experience in investment markets & Business Consulting. His experience lends itself to Financial & Investment advising but also as a business consultant to further enhance business opportunities in Medical technology and in sourcing other opportunities to enhance investments. Boris has worked extensively with Israeli companies to explore various opportunities in the medical and disruptive technology space. He has developed an in-depth understanding of industry trends and gained valuable insight into domestic and international markets. Boris has specialised in reconstruction of companies, investments and international trade. He has completed a Bachelor of Science (Industrial Chemistry) and is currently a member of MeSAFAA and an AR with Morgans Financial.

David Franks is the company secretary of Noxopharm. He is a chartered accountant, fellow of the Financial Services Institute of Australasia and registered tax agent. He has ~20 years' experience as a director and company secretary for a number of publicly listed companies, including Armidale Investment Corporation, Elk Petroleum, JCurve Solutions, Pulse Health and White Energy Technology.

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Appendix I – Glossary

Abscopal Response – This effect is a hypothesis in the treatment of metastatic cancer, whereby tumours with no direct access to treatment shrinks concurrently with shrinkage of tumours within the scope of the localised treatment.

Active Pharmaceutical Ingredient (API) – A chemical in the drug that produces therapeutic effect.

Adjunct Drug – An adjunct drug is a medicine that is taken along with the main treatment. It is not an essential part of the treatment, however, may help in managing the side effects and prolonging the action or increasing the efficacy of the main treatment.

Chemotherapy – A type of cancer treatment that uses one or more anti-cancer drugs as part of a standardised chemotherapy regimen. It may be given with a curative intent, to prolong life or to reduce symptoms, such as pain.

Chromosome – A threadlike structure composed of nucleic acids and protein, present in the nucleus of most living cells, and which carries genetic information in the form of genes.

Clinical trial – A test of am drug of medical device in people. The outcome of clinical trials forms the basis of drug approval by regulatory authorities.

Cytotoxicity – The quality of being toxic to cells, with the potential of permanent damage.

External Beam Radiotherapy (EBRT) – A form of radiotherapy, where the patient sits or lies on a couch and an external source of ionizing radiation is pointed at a particular part of the body.

Intellectual Property – A category of asset that includes intangible creations of the human intellect.

Internal Radiotherapy – A form of radiotherapy where the radiation is delivered from sources that are either injected or inserted into the body.

Gene – A unit of hereditary information that occupies a fixed position on a chromosome.

Isoflavonoid – A class of flavonoid phenolic compounds, many of which are biologically active.

Metabolism – A term that is used to describe all chemical reactions involved in maintaining the living state of the cells and the organisms.

Pharmacokinetics – The branch of pharmacology that is concerned with the determination of movement of drugs within the body.

Radiotherapy – A type of cancer treatment that uses precisely targeted X-ray beams to kill cancer cells.

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Appendix II – IP Position

Noxopharm has a family of the following four patents:

***Improvements in cancer treatment*, WO/2017/173474, priority date 6 April 2016, invented by Graham Kelly:** This patent application covers a composition containing Idronoxil – an analogue of the anti-cancerous isoflavonoid genistein – in a theobroma oil base. The composition is usually used in the form of a suppository and helps improve the bioavailability of Idronoxil in cancerous tissues.

***Targeted drug delivery*, WO/2017/173497, priority date 6 April 2016, invented by Graham Kelly:** This invention relates to isoflavonoids, to formulations for rectal, urethral or vaginal delivery of therapeutic compounds, to pharmacokinetics, and to delivery of compounds to the central nervous system, especially the brain parenchyma.

***Isoflavonoid composition with improved pharmacokinetics*, WO/2017/173498, priority date 6 April 2016, invented by Graham Kelly and Porter Kate:** This application pertains to a method of maintaining the concentration of Idronoxil in a patient's blood over an extended period of time. The method involves repetitive administration of a suppository containing Idronoxil in an oleaginous base every 4–8 hours. The high concentration helps sensitise cancer cells to chemo/radiotherapy.

***Radiotherapy improvements*, WO/2017/173496, priority date 6 April 2016, invented by Graham Kelly:** This application covers the use of Idronoxil in combination with radiotherapy. This combination is more likely to result in desirable abscopal responses (i.e., shrinkage of non-irradiated/non-treated tumours) in patients with multiple tumours.

***Chemotherapy improvements*, WO/2017/181242, priority date 22 April 2016, invented by Graham Kelly:** This application pertains to the use of Idronoxil in combination with established chemotherapeutic agents – platins and taxanes. The combination is more effective than platin therapy, taxane therapy or a combination of the two. It allows the use of these toxic chemotherapeutic agents in lesser quantities and can be administered to the patient more frequently.

Immuno-oncology therapy, provisional patent filed in 2019.

Appendix III – Major Shareholders

Following are the two major shareholders in Noxopharm:

- Milligene Pty Ltd (The GE + PR Kelly Family Trust), Bende Holdings Pty Ltd, Phytose Corporation Pty Ltd (Boundaryone Super Fund), Graham Kelly and Prue Kelly (20.67%)
- Goodridge Nominees Pty Ltd (The Goodridge Family A/C) (6.98%)

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Appendix IV – Companies to Watch

Company	Location	Code	Market cap (US$m)	Web
Nanobiotix	Paris, France	ENXTPA:NANO	168.4	www.nanobiotix.com
Spago Nanomedical	Skåne County, Sweden	NGM:SPAG	10.4	www.spagonanomedical.se
DelMar Pharmaceuticals	Vancouver, Canada	NASDAQ: DMPI	6.6	www.delmarpharma.com
Noxxon Pharma	Berlin, Germany	EPA: ALNOX	16.9	www.noxxon.com
Noxopharm	**New South Wales, Australia**	**ASX:NOX**	**20.8**	**www.noxopharm.com**

Source: Company, Pitt Street Research

The market has a limited number of players focused on STING mechanism and adjunct drug therapy for cancer treatment

Nanobiotix. This France-based clinical-stage nano-medicine company is developing hafnium-oxide-based products that will enhance the effects of radiotherapy without an increase in its dose. According to the company, its products can be administered intravenously, inside the tumour or in the tumour bed through surgery. In April 2019, the company received regulatory approval for its product Hensify (NBTXR3) for commercialisation in European markets. The product is intended for use in the treatment of locally advanced soft tissue sarcoma.

Spago Nanomedical. This Sweden-based biotechnology company is developing nanomaterials for cancer diagnostics and treatment. Currently, it is working on the 'Tumorad' project, wherein nanoparticles are loaded with radionuclides (radioactive isotopes) to selectively deliver radioactive substances to tumour cells, thereby enabling irradiation of multiple tumours and metastases for better treatment of cancer patients.

DelMar Pharmaceuticals. This Canada-based biopharmaceutical company is focused on developing and commercialising new cancer therapies for cancer-related scenarios specific to patients becoming intolerable to modern targeted/biologic treatments. Just like Veyonda, the company's lead drug candidate 'VAL-083' has the ability to cross the blood–brain barrier, which is essential to act against CNS tumours.

Noxxon Pharma. This Germany-based clinical-stage biopharmaceutical company is focused on improving cancer treatment by targeting the tumour microenvironment – by breaking the tumour protection barrier and blocking tumour repair. Its primary goal is to enhance the effectiveness of cancer treatments, including immune-oncology approaches (such as immune-checkpoint inhibitors) and the current standard of care (chemo or radiotherapy).

In addition, AbbVie acquired **Mavupharma** – a discovery-phase pharma company focused on STING-pathway (which plays an important role in the generation of an immune response directed at tumours) – in July 2019. Mavupharma's lead clinical drug candidate 'MAVU-104' poses direct competition to Noxopharm's Veyonda®.

Further, Genzyme, Merck and Bristol-Myers Squibb have drug candidates that produce abscopal responses when they are used in combination with external beam radiotherapy (EBRT).

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Appendix V – Risks for Noxopharm

Risks specific to Noxopharm. We see four major risks associated with Noxopharm as a company and as a listed stock.

- **Clinical risk**. There is a risk that **Veyonda® m**ay fail to meet the primary or secondary endpoints in the clinicalstudies.
- **Financial risk**. There is a risk that Noxopharm may not be able to obtain sufficient funds in the US markets.
- **Timing risk**. Veyonda® clinical studies in mCRPC or other indications could take longer than expected.
- **Regulatory risk**. Regulatory decisions may slow down or stop the market authorisation process for Veyonda®.

Similar to other pharma companies, Noxopharm faces uncertainties related to drug authorisation

- **Risks related to pre-revenue life sciences companies in general.** The stocks of biotechnology and medical devices companies without revenue streams from products or services should always be regarded as speculative in character. As most biotechnology and medical devices companies listed on the Australian Securities Exchange fit this description, the term 'speculative' can reasonably be applied to the entire sector. The fact that the intellectual property base of most biotechnology and medical devices lies in science not generally regarded as accessible to the layman adds further to the riskiness with which the sector ought to be regarded.

Caveat emptor. Investors are advised to be cognisant of the above-mentioned specific and general risks before buying any biotechnology or medical device stocks mentioned in this report, including Noxopharm.

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