NOXOPHARM NEWSLETTER

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Noxopharm has just gone through a major growth spurt in terms of its science, intellectual property and clinical activity. So, an update is timely.

I will remind shareholders that the Company has been underway for just 2 years, a very short time in the context of drug development. In that time, we have achieved the 4 key milestones we originally set ourselves:

☑ To bring Veyonda®(NOX66) into the clinic. *(Now used in 43 patients to date; 1 study completed, 2 ongoing, 3 more planned to start in the next 6 months);*

☑ To confirm that the drug is well tolerated and can be used in combination with cytotoxic chemotherapy and radiotherapy without presenting any particular safety concerns. *(No toxicity identified)*;

☑ To obtain early evidence of a clinically meaningful anti-cancer effect in humans to warrant ongoing development;

☑ To have identified the preferred method of use and clinical indication to seek marketing approval. *(Confirmed as a radio-enhancer in prostate cancer).*

One unplanned milestone has been the development of 2 non-oncology drug programs and the acquisition of a third, which for initial funding purposes we housed in a subsidiary company, Nyrada Inc. Those 3 assets have emerged as highly valuable drug opportunities, effectively giving NOX shareholders a stake in a pipeline of 4 drug assets when you include Veyonda®, each of which has the potential to be transformative in its respective area of community health and any one of which is capable of turning NOX into a global company.

Our objectives for the next 12 months are:

- To have obtained IND (Investigational New Drug) status from the FDA, clearing the way for US patients to join the Veyonda® multi-national Phase 3 study
- To be well advanced in preparations for starting that Phase 3 registration study in late-stage prostate cancer patients
- To have raised the profile in both the oncology and share market communities of Veyonda® as a unique radio-enhancing/immuno-oncology drug, capable of inducing abscopal responses
- To have made major progress towards bringing NYX-330, NYX-205 and NYX-104 into first-in-human studies.

I hope you take the time in reading this newsletter to appreciate just how far we have come in 2 years, the opportunity that NOX now has, and the strategy we have put in place to capture that opportunity.

Graham Kelly CEO

NOX66 becomes Veyonda®

NOX recently announced that the trade mark, Veyonda®, has been approved in Australia as part of a world-wide application. NOX66 is due to embark next year on its final stages of clinical development. In view of this, it was considered timely to begin the branding of Veyonda®.

FROM THE CLINIC

Dr Marinella Messina, Clinical Operations Manager

DARRT clinical trial program update

The DARRT program is the leading edge of the Company's activities and an appropriate place to start this update. The Company believes that its DARRT program is the way in which Veyonda® will come to market.

DARRT is a new concept in cancer therapy. It stands for Direct and Abscopal Response to RadioTherapy and offers a potential curative outcome in late-stage cancer.

It means using Veyonda® to boost the effect of radiotherapy at the very least on the tumours being targeted by radiotherapy (**Direct Response**), and at very most on all tumours in the body (**Abscopal Response**).

A **Direct Response** potentially means making life more comfortable for end-stage cancer patients with better control over symptoms such as pain or pressure on the spine.

An **Abscopal Response** potentially means more comfort PLUS improved survival, right through to long-term remission.

Our expectation is that we will see a range of responses somewhere between those two extremes, depending on the individual and the type of cancer. Patient to patient variability is normal with any treatment, and it is likely that different types of cancer will be more likely than others to be open to an abscopal response.

The DARRT concept involves taking patients with late-stage cancer with metastatic disease (primary tumour plus multiple secondary tumours) who are eligible for palliative radiotherapy. The cancers are pre-loaded with Veyonda®, radiotherapy then applied to 1-2 tumours for 5 days, with Veyonda® treatment continuing over the course of radiotherapy plus an additional week.

The Direct Response should be an immediate effect, with shrinkage of the irradiated tumours being evident at 6 weeks and reaching full response by about 3 months.

The Abscopal Response, on the other hand, is likely to be a longer-term process that could take up to 12 months to reach full effect. This is why we plan to scan patients at 3, 6 and 12 months. We expect patients to steadily improve during this process.

We have started with late-stage prostate cancer (DARRT-1), which we believe is where Veyonda® will achieve its primary marketing approval.

With safety of the radiotherapy-Veyonda® combination now confirmed in DARRT-1, planning is underway to start 2 other DARRT programs, one in lung cancer and the other in sarcomas (generally), both programs being Phase 2 studies involving hospitals in Australia and Asia.

LuPIN clinical trial program explained

This program is testing the benefit of Veyonda® with a different form of radiotherapy known as intravenous brachytherapy (IB), sometimes also known as theranostics. IB is a new and emerging area of oncology that means being treated in the nuclear medicine department of a hospital rather than the radiotherapy department.

In the case of the LuPIN program, the radiation is being delivered in the form of an experimental drug known as ^{177}lutetium-PSMA-617. **PSMA** is a protein found mainly on the surface of prostate cancer cells; **617** is a peptide that binds to PSMA; **^{177}lutetium** is a radioactive isotope that is linked to 617. Together, when injected intravenously into men with metastatic prostate cancer, the radioactivity finds its way to all secondary tumours throughout the body in a way that traditional radiotherapy can never do.

^{177}lutetium-PSMA-617 (Lu-PSMA) is licensed to US biotech, Endocyte Inc (NASDAQ: ECYT), a company whose market cap has jumped from about US$50 million last March to US$1.3 billion today.

Lu-PSMA is injected on 6 occasions, 6 weeks apart. In general terms, about two-thirds of men fail to complete the full 36-week course of treatment, either because they fail to respond, or respond initially and then relapse.

The LuPIN-1 study is testing the ability of Veyonda® to boost the effectiveness of Lu-PSMA to allow more men to complete their 36-week course of treatment.

FROM THE LAB

By Dr John Wilkinson, NOX Chief Scientific Officer

Why we are running a pre-clinical program.

If Veyonda® is in the clinic, why is the Company bothering with pre-clinical studies? A question that some shareholders have asked us and to which I have 2 answers:

1. You don't need to know everything about a drug to get it into clinical studies, but you certainly need to by the time it is ready to come to market. Both government regulators and the doctors who will be prescribing the drug want to know as much as possible about how it works. This 'gap-filling' is standard procedure and is what the Pre-Clinical team are engaged in; and
2. as good as Veyonda® might be, successful companies don't rely just on the one product. We need to develop a pipeline of oncology drug candidates.

I'll leave a discussion about the second point for the next Newsletter, other than to say that we are not resting on our laurels with Veyonda®. If NOX is to realise its goal of becoming a global biopharma company, then it needs a portfolio of drugs, both oncology and non-oncology, based around some proprietary technology platforms, and that is what we are aiming at.

Going back to the first point above, we have a range of R&D programs underway, but I will focus in this edition on just 2 items.

Brain cancer. Our view is that radiotherapy, not chemotherapy, is the long-term answer for the successful treatment of brain cancer:

(i) Radiotherapy isn't affected by the blood-brain barrier which serves to exclude most drugs from entering the brain;

(ii) Radiotherapy can be used against secondary brain cancer originating from cancers outside of the brain and which respond poorly to the few chemotherapies that manage to cross into the brain.

We are working with the Lowy Cancer Research Centre at UNSW and the Sydney Children's Cancer Institute on using radiotherapy and Veyonda® to treat primary brain cancers including glioblastoma multiforme (GBM) in adults and diffuse intrinsic pontine glioma (DIPG) in children.

Those studies have already shown that idronoxil boosts the cancer-killing effect of radiotherapy on GBM and DIPG, and this now has progressed into animal studies. Success there is expected to clear the way to progress into the clinic, starting in adults, and then progressing into children once safety in adults is established.

We also believe that the brain has natural defence mechanisms against cancer and that Veyonda® may have the ability to activate these mechanisms, just as it does in the rest of the body with Natural Killer (NK) cells. Our aim is to bring the brain's natural defence cells into play, which is where we believe Veyonda® offers a unique treatment opportunity.

I look forward to bringing you news on this front in due course. To the best of our knowledge, we are on our own in pursuing this opportunity.

Idronoxil finally giving up its secrets

Veyonda® is the final packaged product and idronoxil is the active ingredient in that final product.

Idronoxil is a chemotherapy, but not what people generally understand to be a chemotherapy. Commonly used anti-cancer drugs essentially are poisons and strong enough to be used on their own. Idronoxil isn't a poison...it is a more gentle-acting drug that switches off different essential functions in the cancer cell. Its main purpose originally was seen as making other chemotherapies work better so that they could be used at lower, safer dosages without sacrificing any anti-cancer effect. And if that was the best that idronoxil offered, then it still would represent a significant advance in oncology.

Since then, work being undertaken by the Company's Pre-Clinical team has revealed two far more interesting and far more valuable sides to idronoxil.

One of those sides is its ability to make cancer cells, and only cancer cells, more likely to be killed by radiotherapy.

The second side is its ability to activate the so-called NK cells, whose job it is to identify and kill cells with the potential to become cancerous. In this sense, Veyonda® can be considered an immuno-oncology drug itself.

One of the truly recent ground-breaking developments in cancer is the recognition that a combination of radiotherapy and immune stimulation offers the prospect of curing cancer in a way that chemotherapy cannot.

Veyonda® has now entered that field with the distinction of being unique in offering both radio-enhancing AND immuno-oncology functions.

IND-enabling studies

IND stands for Investigational New Drug and is the test that any new drug candidate needs to pass before the US Food and Drug Authority (FDA) will grant permission for that drug to be tested in patients in the US. The IND process is regarded as the world's gold standard in terms of knowledge about an experimental drug and involves extensive pre-clinical testing.

Some countries (such as Australia) take the view that experimental drugs can come into the clinic for life-threatening diseases with a certain basic level of knowledge about the drug. This 'fail early-fail cheaply' approach means that you avoid spending a lot of money on an expensive pre-clinical program only to find that your drug fails at the first hurdle in a Phase 1 study.

NOX took advantage of this strategy by starting the clinical development of Veyonda® outside of the USA. Once we had confirmed that we had a drug that was working and was well tolerated, the plan then was to seek an IND in order to bring the USA into a worldwide program of late-stage clinical trials starting in 2019. And that would mean going back and filling in the gaps that are important to the FDA. It is important to point out that this gap-filling can go on concurrently with clinical trials.

We currently are in that gap-filling stage. This means more animal testing and a lot of detail about how the drug is manufactured and standardised. It also means conducting what is known as a Phase 0 study in humans, involving treating a small number of healthy volunteers with Veyonda® on a short-term basis to provide data on how the drug behaves in a healthy body. That study is scheduled to run over 2 months early in 2019.

Introducing our radiobiologist

Veyonda® is a radio-enhancer, which means our clinical program is built around radiotherapy of one sort or another.

Which is by way of introducing the most recent addition to the Pre-Clinical team – Dr Alesia Ivashkevich

Alesia's role is to help us get a better understanding of exactly how Veyonda® is interacting with radiotherapy, and in particular, how the two therapies are combining to create an *abscopal response*, the phenomenon where 1 or 2 tumours receive radiotherapy and respond, but where tumours in distant parts of the body that have not received any radiotherapy also end up responding.

This will be a multi-disciplinary effort involving radiation experts, immunologists and molecular biologists in different institutions across various countries, and Alesia will play a pivotal coordinating role in that effort.

The evidence points to a number of factors needing to happen in invoking an abscopal response. These include (i) destruction by radiation of a certain number of cancer cells (at least 1 tumour), (ii) a process known as epigenetics which involved the release of chemical signals from the destroyed cancer cells that switch on suicide genes in distant tumours, and (iii) activation of the body's immune system. If we are going to induce a long-lasting and complete abscopal response in most patients, then we need to understand the different contributions behind the phenomenon.

Alesia completed a MSc in Radiobiology at the University College of London and continued her training at the Helmholtz Centre in Munich where she was awarded her PhD. Alesia subsequently joined the Molecular Radiation Biology Laboratory at the Peter MacCallum Centre in Melbourne, where she worked on development of DNA binding radioprotectors as part of the Sirtex Research and Development program. Alesia has studied abscopal effects induced by synchrotron microbeam radiation therapy. Alesia's most recent appointment was as the Radiobiologist within the Radiation Oncology Department at Canberra Hospital.

FROM NYRADA

James Bonnar, Vice President, Research & Development

Nyrada was established in 2017 to hold the Company's non-oncology drug programs. From humble beginnings with 3 promising but very early stage drug programs, each program has emerged into a highly valuable drug candidate, each addressing areas of significant community need, and each the subject of considerable interest in the global pharmaceutical industry.

NYX-330. NYX-330 is a drug designed to be given orally to stop the blood protein, PCSK9, binding to the LDL cholesterol receptor in the liver. Blocking this binding at the same time as using standard of care statin cholesterol-lowering drugs brings blood cholesterol levels down a further 60% over statins alone, and that has been shown to translate into 2 very large studies (about 50,000 people) into significantly fewer heart attacks and strokes. NYX-330 is being positioned as an oral, more affordable alternative to the injectable, expensive PCSK9 inhibitors on the market.

NYX-205. NYX-205 is an anti-inflammatory drug candidate being developed for the treatment of a range of common chronic inflammatory conditions. We hope to be able to update shareholders on this exciting program in the very near future.

NYX-104. NYX-104 is a neuroprotectant. For the purist, it blocks glutamate-initiated excitotoxicity. For the non-purist, blocking this self-destruct reaction peculiar to the brain is expected to help protect the brain from the consequences of stroke, concussion and traumatic brain injury. The objective is to reduce the incidence of loss of brain function and to assist in the rehabilitation of patients.

Find out more at **www. nyrada.com**

FROM THE OFFICE

Prue Kelly, Investor Relations Manager

NOX prides itself on keeping its shareholders and the market in general informed about progress. The Company has a clear understanding of its ASX continuous disclosure obligations, but that needs to be balanced by a range of other factors including patient privacy laws, reporting obligations to regulators such as the TGA and hospital ethics committees, and the need for confidentiality surrounding new IP.

With those factors in mind, the following is a guidance of our anticipated news flow over the next 6 months.

Clinical:

- more interim data: 3- and 6-month safety and efficacy outcomes from DARRT-1
- further interim reporting on safety and efficacy outcomes in LuPIN-1
- progress on commencement of DARRT-2 (lung cancer) and DARRT-3 (sarcomas)

Pre-clinical:

- brain cancer studies
- NYX-330 status
- NYX-205 status
- NYX-104 status.

Several conference presentations are also planned and will be reported on at the time.

Meet the editor

Dr Olivier Laczka

I recently joined Noxopharm as the Director of Strategic Research Projects and among other tasks will be ensuring the regular release of the Noxopharm newsletter.

We will have more information to share with you on our website that we will be adding to as we progress. Please do drop by the website to find more about our story, our science, and our plans for the future.

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