20 July 2020 **Sydney, Australia**

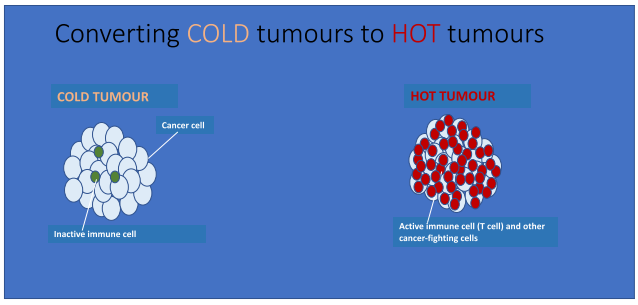
Independent Data Confirms Idronoxil Achieves Major Industry Goal of Converting 'COLD' Tumours to 'HOT' Tumours

Key points:

- **Pre-clinical data indicates that idronoxil (active ingredient in Veyonda®) achieves major goal in converting immunologically 'COLD' tumours to 'HOT'**
- **'COLD' to 'HOT' conversion restores cancer-fighting immune cells to tumours, seen as a prerequisite in expanding the annual US$20 billion immuno-oncology drug market**
- **Two independent laboratories separately confirm the effect in different cancer types**
- **Noxopharm to commence discussions with global oncology firms**
- **Patent lodged on potentially highly valuable intellectual property**

Sydney, 20 July 2020: Important pre-clinical data from two independent research groups confirms that idronoxil (IDX), the active ingredient in Veyonda, achieves a major goal in restoring cancer-fighting immune function within 'COLD' micro-tumours by converting them to 'HOT'. This action has long been regarded as a fundamental goal to enable immuno-oncology drugs known as immune checkpoint inhibitors (ICIs) to work in more patients and in more cancer types. ICIs have been hailed as the future of cancer therapy, but are poorly effective in 'COLD' tumours. With 'COLD' tumours believed to be the majority of human tumours,[1] a treatment combining ICIs with a drug that makes a tumour 'HOT' has very significant commercial potential and is a major priority of global oncology firms.

Other pre-clinical and clinical data held by Noxopharm, together with the new research data, leads the Company to believe it is close to claiming the first drug capable of converting 'COLD' tumours to 'HOT' tumours across multiple cancer types in a well-tolerated way.



Dr Graham Kelly, Noxopharm CEO, said, "This is exciting news because it suggests that Veyonda could hold the answer to arguably the biggest challenge currently facing the oncology world, that of restoring the

cancer-fighting ability of the body's immune system in order to achieve higher response rates to immuno-oncology drugs."

Immune checkpoint inhibitors (ICIs)

ICIs came to market in 2011 to enormous acclaim and hope because of remarkable responses in some melanoma and lung cancer patients. Since then, it has become clear that the benefit of these drugs is restricted largely to a small group of cancers (e.g. melanoma, lung cancer, kidney cancer, bladder cancer, Hodgkin's lymphoma).[2] Despite this limitation, sales of ICIs reached US$22 billion in 2019 and analysts expect that to reach US$40 billion in 2025.[3] The challenge with ICIs is to lift the modest response rates in those cancers where they do work, as well as allowing them to work in the majority of cancers where they presently deliver little or no benefit – e.g. breast, prostate, ovarian and colo-rectal. Noxopharm believes that achieving that goal would create a market arguably in excess of US$200 billion per annum. **Noxopharm is working to position Veyonda as a key component of that market.**

Kelly continued, "In order to respond to ICIs, individual tumours need to contain cancer-fighting immune cells, something that the majority of human tumours lack. The pre-clinical data we are reporting today supports the use of Veyonda to convert COLD tumours to HOT across multiple cancer types and in a well-tolerated manner."

Dr Olivier Laczka, Noxopharm Director of Drug Discovery and Research, explained, "One of the key ways that tumours become COLD is by increasing levels of the molecule sphingosine-1-phosphate (S1P).[4] That sets up a chemical barrier that expels immune cells and then keeps them excluded. IDX is an S1P inhibitor, so it was a logical question to ask whether removing this S1P barrier with IDX would turn COLD tumours into HOT tumours. I am excited to report that the data released today confirms this. Studies by two highly respected research centres have confirmed that IDX does two things – it primes immune cells to attack cancer cells, and then goes that crucial extra step and enables those cells to repopulate tumours, effectively converting so-called COLD tumours into HOT tumours, and leading to their destruction. Our understanding is that this is a unique double action, marking Veyonda as an exciting first-in-class immuno-oncology drug candidate."

Patent

Final patent specifications including today's data were lodged on 16th July 2020 under the international Patent Cooperative Treaty as PCT/AU2020/050730 entitled *Immuno-oncology therapy.* This patent application has a priority date of 17 July 2019.

Discussions with Oncology Leaders

Noxopharm now is in a position to discuss with industry partners the opportunity to use Veyonda to enable ICI drugs to work in patients whose cancers fail to respond to the ICI drug alone. In the case of lung cancer, for example, only about one-third of patients respond meaningfully to ICI drugs, creating a major opportunity in that one cancer alone.[5]

New Independent Data

Idronoxil (IDX) has been tested at two research centres: (i) The Institute of Biochemistry, Faculty of Medicine of the Goethe-University, Frankfurt and (ii) the Department of Clinical Oncology and the Centre

for Cancer Research at Hong Kong University. Both centres were selected for their expertise in the immuno-oncology field.

The *in vitro* studies were conducted using human immune cells (lymphocytes), particularly those immune cells (T-cells) predominantly responsible for attacking cancer cells and known as $CD4^+$ cells, $CD8^+$ cells and double $CD4^+CD8^+$ cells. The cancer targets were clusters of human cancer cells known as spheroids, regarded in cancer research as representative of small (micro-) tumours.

Goethe-University, Frankfurt study

Additional to confirming the capacity to IDX modulate the S1P pathway in cancer cells, this study showed that IDX activates immune cells ($CD4^+$ cells, $CD8^+$ cells) which then start clustering and proliferating (Figure 1A). Those immune cells then infiltrate into lung cancer cell spheroids, with the size of the spheroids then reducing as the cancer cells are killed (Figure 1B).

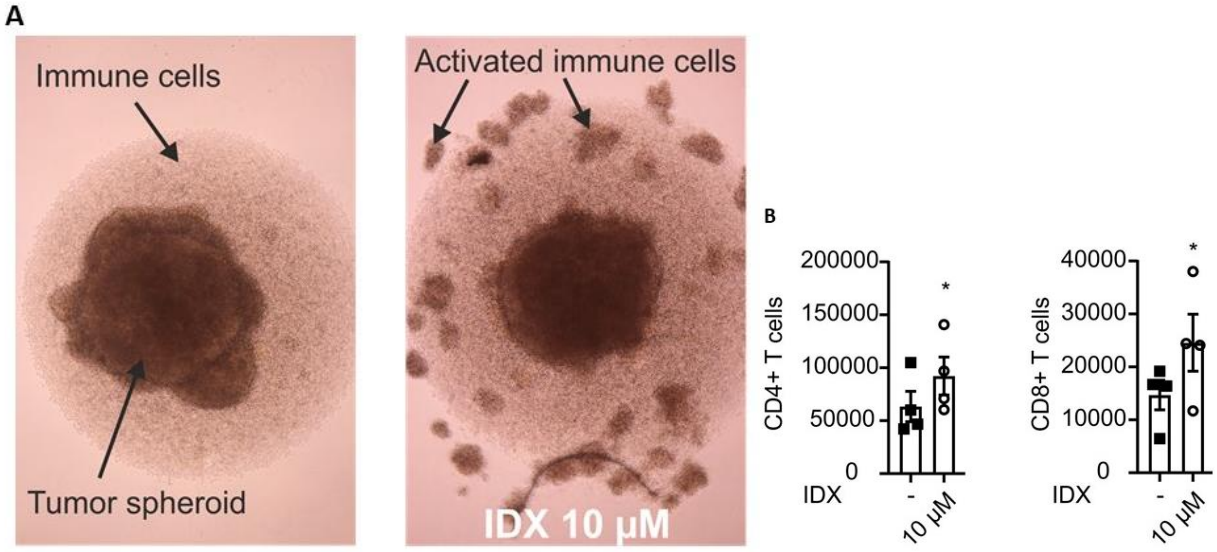


Figure 1: A549 lung cancer cell spheroids morphology (A) and number of immune cell infiltrates (B) 6 days after treatment with idronoxil alone. * $p \leq 0.05$ when compared to control (DMSO).

Hong Kong University (HKU) study. This study examined the effects of IDX on tumour-lymphocyte interactions in nasopharyngeal carcinoma (NPC) cells, a major cancer in Southern China and South-East Asia.

Interestingly, combining IDX with the chemotherapy drug, cisplatin, enhanced the expansion and trafficking of immune cells compared to cisplatin alone, pointing to the immune-priming effect of IDX possibly also playing a role in clinical responses to combinations of Veyonda and chemotherapy.

Their results show that a low dose of IDX activated T-cells ($CD4^+$, $CD8^+$ and double-positive ($CD4^+CD8^+$) cells) (Table 1), causing them to proliferate and to infiltrate the cancer cell spheroids (Table 2). This increased infiltration positively correlated with increased killing of the NPC cancer cells.

	Cisplatin alone	Cisplatin + IDX 1 µM
CD4+	5	37*
CD8+	52	61*
Double positive (CD4+ CD8+)	39	78*

Table 1: Average proportion (%) of $CD4^+$, $CD8^+$ and double positive $CD4^+CD8^+$ T-cells is increased upon addition of IDX (1 µM) to cisplatin (1.2 µM), relative to control (DMSO) * p ≤0.05 when compared to control (DMSO).

	Cisplatin alone	Cisplatin + IDX 2 µM
After 24h	89	109*
After 72h	53	165*

Table 2: Average number of infiltrated immune cells in NPC spheroids upon treatment with IDX (2 µM) and cisplatin (1.4 µM). * p ≤0.05 when compared to control (DMSO).

A manuscript summarizing the data has been submitted for publication and an abstract relative to this work was presented at the ASCO conference at the end of May 2020 (ASX release 14 May 2020).

References

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4. Reimann C-M et al (2015) Sphingosine-1-phosphate (S1P) in cancer immunity and development. Transl Cancer Res 4:460-468
5. Regzedmaa O et al (2019) Immune checkpoint inhibitors for small cell lung cancer: opportunities and challenges. Onco Targets Ther 12:4605-4620

Glossary

COLD tumour.	A tumour that lacks cancer-fighting immune cells
HOT tumour	A tumour that contains a high level of cancer-fighting immune cells
IDX	Idronoxil. The active ingredient in Veyonda
ICI	A drug that inhibits immune checkpoints serving to block the ability of an immune cell to kill a cancer cell
S1P	Sphingosine-1-phosphate. A key pro-survival cell messenger. Immune cells follow a high-to-low gradient of S1P. Higher levels of S1P in a tumour compared to blood, expels immune cells from the tumour
T-cells	A type of white blood cells involved in immune responses
CD4+ cells	Also known as T-helper cells. Play a key role in immune responses including assisting cytotoxic T cell function and suppressing tumour cells
CD8+ cells	Cytotoxic T-cells
CD4+CD8+ cells	T-cells expressing both $CD4^+$ and $CD8^+$ markers with possible dual function
NPC cells	Nasopharyngeal carcinoma cancer cells

About Noxopharm
Noxopharm is a clinical-stage Australian drug development company with offices in Sydney and New York. The Company has a primary focus on the development of Veyonda® and is the major shareholder in the non-oncology drug development company, Nyrada Inc. (ASX:NYR).

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Graham Kelly, CEO and Executive Chairman of Noxopharm, has approved the release of this document to the market on behalf of the Board of Directors.

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