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ASX Limited
20 Bridge Street
SYDNEY NSW 2000

Veyonda® and Immuno-Oncology Effect Explained

ASX: NOX

Noxopharm Limited

ABN 50 608 966 123

Registered Office and Operational Office:
Suite 3, Level 4
828 Pacific Highway
Gordon NSW 2072
Australia

29 April 2019. Sydney: Noxopharm Limited (ASX:NOX) ('**Noxopharm'** or the '**Company'**) is pleased in response to shareholder enquiry to provide some context around its recent announcement of Veyonda® and its stimulatory effects on the immune system. That context is in relation to the direction currently being taken in the development of the next generation of anti-cancer drugs.

Background

After some 60 years of radiotherapy and 50 years of chemotherapy, mostly destructive treatments revolving around attempting to blast cancer cells out by damaging them, there is a new direction in cancer therapy.

That new direction is called immuno-oncology (i-o), and it is based on the simple rationale that if cancer represents a failure of the body's immune system to recognise the presence of abnormal cells and to eradicate them, then that is the problem that we should be addressing, not going in the opposite direction and hitting the body with drugs and radiation that in fact serve to damage the immune system.

The i-o approach first shot to fame with the introduction in 2011 of ipilimumab. I-o drugs function removing the block ('handbrake') preventing the body's immune system from attacking cancer cells. These drugs are known as *checkpoint inhibitors* (*CTL4*, *PD-1* or *PD-L1 inhibitors*). Currently marketed examples include ipilimumab (Yervoy; Bristol Myers Squibb), nivolumab (Opdivo; Bristol Myers Squibb) and pembrolizumab (Keytruda; Merck). A growing number of other checkpoint inhibitors are being developed, but drugs involving these three targets remain the principal only i-o drugs on the market. Projected sales for these three drugs in 2019 are US$16 billion-plus.

I-o drugs first came to market with high expectations and considerable fanfare; 8 years on, those expectations have been significantly dented. When they work, they do so dramatically, with extensive disease seemingly melting away, providing long survival benefits and even an apparent curative outcome in some patients. All of which goes to prove that the concept works. The problem is that it doesn't work in most cancer types and for most patients. While somewhere between 20-25% of patients with certain cancers such as melanoma or cancers of the lung, bladder and head and neck respond, the response rates across most other forms of cancer are poor. Across the board, only about 1 in 20 cancer patients will respond to the current crop of i-o drugs.

The i-o challenge

The global pharmaceutical industry currently is putting a major effort into finding a way to improve the low overall response rate to i-o drugs. All driven by the prospect of successful use of i-o drugs in most patients with cancer carrying an ultimate prize expected to exceed US$100 billion p.a.

The general consensus appears to be that the principle of checkpoint inhibitors is valid…..it is more a matter of the problem lying in the lack of immune cells within cancerous lesions. Without those

immune cells being present, any attempt at 'releasing the handbrake' appears unable to make any difference. Which has led to the concept of tumours being either 'hot' and 'cold', with the degree of 'hotness' relating to the presence or absence of local immune function within a lesion.

There now is increasing evidence that most lesions in most cancer patients are 'cold', reflecting exhaustion of the local, first-line immune cells, and that in order to work, i-o drugs need the presence and cooperation of an active, local, first-line defence system. Hence, considerable current industry efforts to develop drugs that will activate this local defence system. These drugs are referred to as STING agonists.*

*https://cen.acs.org/articles/96/i9/STING-fever-sweeping-through-cancer.html

Veyonda® and i-o function

Two key players in local defences are believed to be two types of lymphocytes known as Natural Killer cells (NK cells) and CD4+ cells. The NK cells have the ability to provide a first-line of defence by attacking and killing cancer cells in their own right, while the role of the CD4+ (also known as Helper T cells) is to recruit more second-line lymphocytes (known as CD8+ cells) to attack the cancer.

Veyonda® increases NK cells and CD4+ cell numbers in mice and has the same proliferative effect on human cells in the laboratory.

As far as we know, Veyonda® doesn't have any effect on the 'handbrake'. But by increasing the number of NK and CD4+ cells, the Company believes that Veyonda® could represent what is believed to be the current missing link in the i-o story – viz. the ability to convert 'cold' tumours into 'hot' tumours.

Apart from the opportunity of using Veyonda® in combination with one of the standard checkpoint inhibitors, Noxopharm also sees the i-o effect of Veyonda® as playing a role in the clinical benefits being seen from its use in combination with chemotherapy and radiotherapy. Both therapies are destructive of immune cells: the depressive effect of chemotherapies on the immune system is well known with an increased risk of serious infections; and while the effect of radiotherapy on immune function is somewhat more complex, the immune cells within any irradiated lesion inevitably would be damaged in parallel with the rest of the lesion.

In our current CEP and DARRT programs, we are using Veyonda® to allow dosages of chemotherapy and radiotherapy to be lowered to levels less likely to damage the immune system, with that sparing effect supplemented by the independent action of Veyonda® in boosting the number of immune cells and thereby hopefully promoting a stronger response to chemotherapy or radiotherapy.

Noxopharm sees Veyonda® as bringing a unique perspective to the global search for more efficient immuno-oncology therapy.

That global search is exemplified by Bristol-Myers Squibb decision in 2017 to pay US$1 billion for a STING technology that was only in the pre-clinical stage. Veyonda® is in the clinic, with a known safety profile and a growing body of evidence to support its i-o effects in the clinic.

That is the context in which Noxopharm views the i-o effects of Veyonda®.

About Noxopharm

Noxopharm is a clinical-stage Australian drug development company with offices in Sydney, Hong Kong and New York. The Company has a primary focus on the development of oncology drugs based on a flavonoid chemical structure, with Veyonda® the first pipeline product. Non-oncology indications are under development in subsidiary company, Nyrada Inc.

Investor & Corporate Enquiries:
Prue Kelly
M: 0459 022 445
E: info@noxopharm.com

Company Secretary:
David Franks
T: +61 2 9299 9690
E: David.Franks@automicgroup.com.au

Media Contact:

Cherilyn Cecchini, M.D.
LifeSci Public Relations

T: +1 646 876 5196
E: ccecchini@lifescipublicrelations.com

www.noxopharm.com

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