NDF RESEARCH

Providing independent research coverage of
ASX-listed Life Science companies

Patrys (ASX: PAB)

Initiation of Coverage – Tuesday 19 December 2017

Cell-penetrating monoclonal antibodies

To understand this opportunity, you need to do two things at once. Think micro: recognising that Patrys has a world-first, cell-penetrating anti-DNA antibody. At the same time, think macro: recognising that its ground-breaking drug will play into a US$84bn antibody market. Taken together, these ingredients have the feel of blockbuster potential. The story started when Patrys in-licensed a ground-breaking antibody from Yale University in 2016. One way that cancer cells stay alive is by self-repairing their DNA when it breaks – and Yale's Deoxymab 3E10 prevents this. Importantly, Patrys has now upgraded this antibody for human use. And, on the basis of its pre-clinical work, it recently announced that its version (PAT-DX1) may have application for a broad range of cancers: glioblastoma, colon cancer, triple negative breast cancer; and possibly, melanoma and other cancers as well. This product will enter the clinic in 2019. Back in 2014, AstraZeneca gained FDA approval for Lynparza, the first of the revolutionary PARP inhibitor drugs for the treatment of cancer. For reasons explored further in this note, Patrys' product could be superior since it can prevent double-strand as well as single-strand cancer DNA repair. In addition, it can be synergistic with PARP inhibitors, and conjugated to other drugs of interest. This antibody is Patrys' current priority – but the company still retains (for possible future attention) the IP from its original work on creating a new class of monoclonal antibody drug. We value Patrys at 7.3 cents per share base case and 18.3 cents optimistic case. Our target price of 13 cents per share sits at the midpoint of our valuation range. We see Patrys being re-rated by the progress into the clinic of PAT-DX1 and continued commercial success for the PARP inhibitors.

Rating	Risk	Current price	Target price
Buy	Speculative	$0.020	$0.13

Stock details

Daily Turnover: ~A$78,000
Market Cap: A$15.6m
Shares Issued: 779.5m
52-Week High: $0.03
52-Week Low: $0.004

Analyst: Stuart Roberts
stuart@ndfresearch.com
+61 447 247 909

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NDF's Founder and Senior Analyst, Stuart Roberts, has been involved in Life Sciences since 2002 as a sell-side analyst as well as an executive of two ASX-listed immuno-oncology drug developers.

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Ferry at the end of a rainbow on Sydney Harbour, August 2014

In this report

Introducing Patrys, ASX: PAB

Patrys is working on potentially revolutionary new antibody-based cancer drugs. Patrys, which was originally built on a platform to engineer anti-cancer monoclonal antibodies of the IgM isotype, in 2016 strengthened its offering with the in-licensing from Yale University of Deoxymab 3E10, the world's first cell-penetrating anti-DNA antibody for the treatment of cancer. Having engineered a Deoxymab 3E10 variant suitable for human use called PAT-DX1, Patrys is now preparing that product for early-stage clinical work from late 2019. Following on behind PAT-DX1 is PAT-DX1-NP, in which PAT-DX1 is conjugated to cancer-killing nanoparticles. We argue that these products are potentially revolutionary because cell-penetrating antibodies have yet to be used to treat cancer (or indeed, any other disease), and because cancer drugs that work via DNA Damage Response pathways (also called DNA Damage Repair, still new to modern medicine) have the potential to markedly improve outcomes for cancer patients.

PATRYS' DEOXYMAB ANTIBODY IS CELL-PENETRATING

How is Patrys' antibody able to be cell-penetrating? Monoclonal antibodies, renowned for their exquisite targeting ability, are generally too large to make it through the cell membrane to attack intracellular targets of therapeutic interest. Deoxymab 3E10 is a notable exception. This antibody originated from work done on the autoimmune disease Systemic Lupus Erythematosus (SLE), which is characterised by antibodies that attack the patient's own DNA. Work by Yale's Dr James Hansen and colleagues have shown that Deoxymab 3E10 enters the cell via a transporter in the cell membrane and is then able to bind DNA in the cell nucleus. PAT-DX1 uses the same mechanism but works much more efficiently.

How does Patrys' cell-penetrating antibody kill cancer cells? One of the ways in which cancer cells stay alive is their ability to repair their DNA when it breaks. A revolutionary new class of cancer drug called the PARP inhibitors, the first of which, AstraZeneca's Lynparza, gained FDA approval in 2014, interferes with this DNA repair. The strong patient outcomes from these drugs has suggested the potential for one or more of the PARP inhibitors to ultimately become blockbusters. Patrys' Deoxymab-derived PAT-DX1 product is similar to the PARP inhibitors in that it can kill cancer cells by interfering with DNA repair. Indeed, it could be better than the PARP inhibitors because it can prevent double-strand as well as single-strand DNA repair. *In vitro* PAT-DX-1 has shown that it is complementary to the PARP inhibitors, which makes sense since the two have different mechanisms. Also, PAT-DX1 can be conjugated to other drugs of interest.

What is the path forward for Patrys' new lead product? Following the release of favourable pre-clinical data in September 2017, Patrys is currently preparing PAT-DX1 for a Phase 1 clinical study beginning in late 2019. The lead indication has still to be decided, although it could be glioblastoma or pancreatic cancer given the currently poor patient outcomes for these conditions. PAT-DX1-NP is at a roughly comparable state of development to PAT-DX1.

What happened to Patrys' original IgM antibody discovery platform? IgM antibodies have obvious clinical potential given their ability to bind multiple copies of a target on a cancer cell surface. They are, however, very large molecules, and therefore more difficult to make than conventional monoclonal antibodies of the IgG isotype. With its foundation platform, Patrys identified some interesting new IgM monoclonal antibodies, but difficulties

with separation columns to assist with the purification process hampered manufacturing efforts, hence the decision in 2016 to pause development of this platform in favour of Deoxymab, and seek licensing partners for the antibodies the company had developed. We look at the background to the IgM platform in Appendix 1a of this note.

If Patrys is so good, why is it only capitalised at A$15.6m/US$11.9m? We think Patrys' failure to progress its old IgM platform is the reason why Patrys stock remains depressed, in spite of the progress than has been made with the new Deoxymab products. We believe that Patrys can re-rate as more pre-clinical evidence of the effectiveness of this PAT-DX1 is released and as PAT-DX1 moves towards the clinic.

Ten reasons to look at Patrys

DEOXYMAB WORKS LIKE A PARP INHIBITOR

1) **Patrys has a cell-penetrating antibody that works like a PARP inhibitor.** Patrys' Deoxymab programme centres on a cell-penetrating monoclonal antibody that can bind to DNA in the cell nucleus. This remarkable capability suggests a future cancer drug that works via DNA Damage Response mechanisms. With that field now a reality thanks to the approval of the first PARP inhibitors, and those drugs widely expected to become blockbusters, we argue that Patrys has considerable upside with the products it is creating from Deoxymab.
2) **Deoxymab is a 'platform within a product'.** The benchtop evidence suggests that, not only can a variant of this antibody potentially be used as monotherapy, those variants can also be conjugated to drug nanoparticles, or simply used to increase the sensitivity of the tumour to chemotherapy and radiotherapy.
3) **Deoxymab may have advantages over PARP inhibitors**, if only because it can act on double-strand DNA breaks as well as single-strand DNA breaks. Patrys' pre-clinical data suggested that its Deoxymab products could prove complementary to the currently approved PARP inhibitors.
4) **Patrys now has a lead Deoxymab candidate moving towards the clinic**, with the company having recently engineered a single-chain variable di-fragment of the original Deoxymab antibody, and with that variant having worked well in various *in vitro* and *in vivo* settings. We expect that PAT-DX1, the first Deoxymab product, can be in the clinic by late 2019.
5) **Deoxymab has potential across a range of cancers**, with pre-clinical work announced in September 2017 showing that PAT-DX1 could work in glioblastoma, in colon cancer and Triple-Negative Breast Cancer. Patrys has also talked about its potential use in pancreatic, endometrial and ovarian cancer.
6) **There is potential for Deoxymab to be a new treatment option for hard-to-treat cancers**. While Patrys has yet to choose an initial indication for its Deoxymab products, glioblastoma looks particularly interesting given the role radiation therapy has in the current standard of care, and the demonstrated ability of Deoxymab to act as a radiosensitiser. Glioblastoma, an Orphan indication, is potentially a billion-dollar market opportunity, as is pancreatic cancer.

7) **There is still potential for Patrys to realise value from its foundation IgM antibody platform,** with the company retaining the IP and have licensed the Chinese rights to a gastric cancer IgM antibody.
8) **Patrys has a great management team**. CEO Dr James Campbell has diverse drug development experience from his years building Chemgenex Pharmaceuticals from start-up to regulatory stage drug developer. Backing James is a board with the relevant skills for an early stage developer that includes the ex-Genentech business development leader Suzy Jones, and a well-credentialed Scientific Advisory Board.
9) **Patrys is undervalued based on our numbers**. We value Patrys at 7.3 cents per share base case and 18.3 cents optimistic case. Our target price of 13 cents per share sits at the midpoint of our valuation range. We see Patrys being re-rated by the progress into the clinic of PAT-DX1 and continued commercial success for the PARP inhibitors.
10) **Patrys' collaborations with academic groups and other companies focused on DDR-based therapies could yield valuable know-how**. Consider, for a good example, the potential to create a bi-specific antibody that would leverage off Deoxymab's cell-penetrating ability to hit other intracellular targets of therapeutic interest. Such a product would effectively pioneer the field of cell-penetrating monoclonal antibodies. Patrys recently announced a collaboration with the Walter and Eliza Hall Institute over one such bi-specific.

PATRYS HAS A GREAT MANAGEMENT TEAM

DNA Damage Response – How Patrys is now playing in an important market space

Deoxymab is an antibody that can prevent cancer repairing its own DNA. Deoxymab, which has been Patrys' lead programme since March 2016, is a mouse monoclonal antibody called 3E10, and humanised variants and fragments thereof, that can penetrate the cell membrane and then target the DNA in the cell nucleus, thereby preventing cancer cell DNA repair. This capability makes the product potentially quite special in cancer therapy, for two reasons:

- One of the more exciting recent approaches to treating cancer has been drugs that can exploit DNA Damage Response (DDR) defects. The rise of the new class of drug called the PARP inhibitors has shown the therapeutic and commercial potential of such drugs, and Patrys with Deoxymab now has a new way of killing cancer via DDR mechanisms.
- Monoclonal antibodies provide a way to exquisitely target disease-specific antigens, but they are generally only good for extracellular targets because they are too large to get through the cell membrane. Deoxymab is one of the rare antibodies that are cell-penetrating, allowing it to go after DDR via intra-cellular targets.

Targeting DNA damage response represents an important new way to kill cancer cells. To understand the potential importance of the Deoxymab products in cancer, it's necessary first to understand how DDR has

emerged into the limelight in the last three years as part of a new cancer treatment paradigm. In healthy cells, DNA is being damaged and then repaired all the time. The mechanisms by which DNA is repaired are considered so important that the 2015 Nobel Prize for Chemistry was awarded to three scientists[1] who first elucidated some of the key molecular pathways involved. One important reason for understanding DNA repair is cancer - when DNA stops repairing itself properly, the result is the innumerable mutations that can start or maintain a tumour. Now, a fault in one DDR pathway isn't fatal to cancer cells, since there are other DDR pathways that can take over[2]. However, this DDR redundancy has, in recent years, caused the revival of an old idea called 'synthetic lethality', which holds that the knockout of two genes in a cell is lethal whereas the knockout of just one gene is, apparently, just fine[3]. In the updated version of this theory, the loss of a second DDR pathway is what kills the cancer cells. Synthetic lethality received significant validation in late 2014 with the FDA approval of a new drug for ovarian cancer from AstraZeneca called Lynparza[4]. That drug is the first of the so-called 'PARP inhibitor' class. PARP is short for Poly (ADP-ribose) Polymerase, a family of enzymes involved in DNA repair[5]. Lynparza is a small molecule that knocks down PARP1 and PARP2, two PARPs involved in a particular DDR pathway called the 'base excision' pathway that operates where a single strand of DNA has been broken[6]. When AstraZeneca's drug was given to late stage ovarian cancer patients where the patients had mutations in the well-known BRCA1 and BRCA2 cancer genes, the result was a high response rate in the treated patients, despite this being a fourth line treatment, because those BRCA mutations had already knocked out another DDR pathway called 'homologous recombination' that operates where a double strand of DNA has been broken[7]. With two DDR pathways down – one for single strand breaks, one for double – the ovarian cancer cells died as the theory of synthetic lethality suggested they would, on a surfeit of unrepaired DNA double-strand breaks. The clinical success of Lynparza, and two subsequently approved PARP inhibitors, has shown that DDR can be harnessed to treat cancer. The search is now on at both Big and Small Pharma for new drugs that work via DDR inhibition. We argue that Patrys is now well placed to attract partnering interest with its DDR-acting cell-penetrating antibody.

BIG PHARMA WANTS DRUGS THAT WORK VIA DNA DAMAGE RESPONSE MECHANISMS

The PARP inhibitors have started to show the clinical and commercial potential of DDR-based cancer therapies. There are now three PARP inhibitors that have gained FDA approval:

- AstraZeneca's Lynparza, approved in December 2014. As we noted above, Lynparza was initially indicated for BRCA-mutated advanced ovarian cancer as a fourth-line treatment.
- Rubraca[8], from the American drug developer Clovis Oncology[9], approved in December 2016 for BRCA-mutated advanced ovarian cancer, but this time as a third-line treatment.

[1] The Swede Tomas Lindahl (born 1938), the American Paul Modrich (born 1946) and the Turk Aziz Sancar (born 1946).
[2] Six primary pathways of DNA repair have been identified - mismatch repair, base excision repair, nucleotide excision repair, homologous recombination, nonhomologous endjoining, and translesion synthesis. See J Clin Oncol. 2006 Aug 10;24(23):3799-808. The Nobel laureates Modrich, Lindahl and Sancar respectively identified the first three.
[3] Nat Rev Genet. 2017 Oct;18(10):613-623. Epub 2017 Jun 26. The term 'synthetic lethality' was coined by the Russian-American geneticist Theodore Dobzhansky (1900-1975) in 1946.
[4] Generic name olaparib, see www.lynparza.com.
[5] The PARPs synthesise polymers of Adenosine Diphosphate Ribose, a kind of molecular glue.
[6] J Biol Chem. 2002 Jun 21;277(25):23028-36. Epub 2002 Apr 10.
[7] Oncogene. 2003 Sep 1;22(37):5784-91.
[8] Generic name rucaparib, see www.rubraca.com.
[9] Boulder, Co., Nasdaq: CLVS, www.clovisoncology.com.

- Zejula[10], from another American drug developer called Tesaro[11], approved in March 2017 in ovarian cancer as a maintenance therapy for platinum-based chemotherapy regardless of the BRCA status of the tumour.

There are six things to note about these drugs

- **They work well in difficult-to-treat cancers,** which is why Lynparza and Rubraca were both granted accelerated approval off the back of Phase 2 data where Objective Response Rate rather than hard survival data was the decisive factor[12]. Zejula had to complete Phase 3 but was shown to more than triple Progression-Free Survival in BRCA-mutated patients[13].
- **They are set to expand their usage**. Lynparza moved to second line in ovarian cancer regardless of BRCA status in August 2017[14]. AstraZeneca is now going for BRCA-mutated breast cancer[15] and for first line in ovarian cancer.
- **They reimburse at high prices**, in the order of US$9,800 to US$13,500 per month in the US market[16].
- **They are synergistic with conventional cancer treatments,** with considerable pre-clinical evidence showing that they work well with alkylating agents such as Temodar and topoisomerase inhibitors such as Camptosar[17], as well as radiotherapy[18].
- **They work well with immuno-oncology agents**[19]**.** There is evidence emerging that PARP inhibitors are synergistic with the PD-1 and PD-L1 inhibitors[20]. This is one reason by AstraZeneca partnered Lynparza with Merck & Co. in July 2017 in a multi-billion-dollar deal[21] which will see the two companies jointly develop Lynparza and where the companies will separately test the two drugs with AstraZeneca's Imfinzi, a PD-L1 inhibitor, and Merck's Keytruda, a PD-1 inhibitor[22]. Around the same time, Clovis Oncology announced a collaboration with Bristol-Myers Squibb over that company's PD-1 inhibitor, Opdivo. Merck earlier announced a collaboration with Tesaro around Zejula[23].
- **They leverage, albeit indirectly, off the heightened awareness of the BRCA cancer genes.** When the American actress Angelina Jolie drew significant public attention to BRCA1 in May 2013[24] there was a significant increase in testing for the celebrated BRCA1 and BRCA2 genes[25] which are known to indicate

THE PARP INHIBITORS ARE BELIEVED TO BE SYNERGISTIC WITH IMMUNO-ONCOLOGY AGENTS

[10] Generic name niraparib, see www.zejula.com.
[11] Waltham, Ma., Nasdaq: TSRO, www.tesarobio.com.
[12] 34% for Lynparza (Clin Cancer Res. 2015 Oct 1;21(19):4257-61. Epub 2015 Jul 17), 54% for Rubraca (Clin Cancer Res. 2017 Jul 27 [Epub ahead of print]).
[13] To 21.0 months, from a mere 5.5 months – see N Engl J Med. 2016 Dec 1;375(22):2154-2164. Epub 2016 Oct 7.
[14] See the AstraZeneca press release dated 17 August 2017 and headlined *'Lynparza receives additional and broad approval in the US for ovarian cancer'*.
[15] N Engl J Med. 2017 Aug 10;377(6):523-533. Epub 2017 Jun 4.
[16] See *Tesaro undercuts PARP rivals with $118K price tag on Zejula—or did it?* by Tracy Staton, FiercePharma, 20 April 2017.
[17] Pharmacol Res. 2005 Jul;52(1):25-33.
[18] Cancer Treat Rev. 2010 Nov;36(7):566-75. Epub 2010 Apr 20.
[19] See, for example, Clin Cancer Res. 2017 Jul 15;23(14):3711-3720. Epub 2017 Feb 6.
[20] Short for Programmed Death 1, PD-1, also known as C279, is an immune checkpoint known to turn down an immune response. PD-L1 is the ligand to PD-1. PD-1 turns down an immune response in part by promoting apoptosis in antigen-specific T cells while reducing apoptosis in regulatory T cells. PD-1 seems to regulate effector T cell activity within tissue and tumours. Merck's Keytruda and BMS' Opdivo are monoclonal antibodies to PD-1 which, by blocking this checkpoint, can help boost an anti-cancer immune response.
[21] The deal also included an AstraZeneca-developed MEK inhibitor called selumetinib. Merck paid US$1.6bn to AstraZeneca upfront as well as US$750m for certain license options and will pay up to US$6.15bn in regulatory and sales milestones.
[22] See the AstraZeneca press release dated 27 July 2017 and headlined *'AstraZeneca and Merck establish strategic oncology collaboration'*.
[23] See the Merck press release dated 30 May 2015 and headlined '*Tesaro and Merck to collaborate on a combination study of Niraparib and Keytruda (pembrolizumab)'*.
[24] Ms Jolie announced in a New York Times op-ed piece that she had a mutation in her BRCA1 gene and as a preventative measure had had a double mastectomy. The New York Times article was dated 14 May 2013 and was headlined '*My medical choice*'.
[25] BMJ. 2016 Dec 14;355:i6357.

a heightened breast cancer risk[26]. These genes, discovered in 1994 and 1995 respectively[27], code for tumour suppressor genes that are important in DDR pathways[28]. The PARP inhibitors now represent a chance to better help BRCA-mutated patients, where hitherto treatment options haven't been available. Around half of all patients with Triple-Negative Breast Cancer (TNBC), a version of the cancer which has poorer outcomes, have a BRCA1 mutation, as opposed to only 10-15% without such a mutation[29].

For all these reasons there is potential for PARP inhibitor drugs to reach blockbuster status. Lynparza in its third year on the market has reached US$259m in sales (the twelve months to September 2017) and there are some bullish expectations for the other drugs[30].

There are more PARP inhibitors coming. AbbVie may have experienced a couple of clinical failures with veliparib[31], however Pfizer is in Phase 3 with Talazoparib, a drug it acquired in the Medivation acquisition of 2016 and which was originally developed by BioMarin Pharmaceutical[32]. Telazoparib's initial indication is BRCA-mutated metastatic breast cancer. Coming behind Telazoparib is BGB-290 from a Chinese/American biotech company called BeiGene[33]. That drug candidate, now in Phase 1, has as one of its key competitive advantages a better brain penetration profile compared to the other PARP inhibitors.

The PARP inhibitors have been company-making. We argue that Deoxymab can have a not-dissimilar effect on the fortunes of Patrys as Rubraca did for Clovis Oncology and Zejula for Tesaro. Both companies have emerged as new specialty pharma companies because of PARP inhibitor candidates they picked up from Big Pharma:

THE PARP INHIBITORS HAVE BEEN COMPANY-MAKING

- Clovis Oncology, founded in 2009[34], acquired the programme that become Rubraca in June 2011 from Pfizer, when the drug was at Phase 1/2[35]. Clovis was private at the time. At its November 2011 IPO on Nasdaq, the company was valued at US$280m. It is now a US$3.2bn company[36].
- Tesaro, founded in 2010, had its first success with Varubi, a new drug for Chemotherapy-Induced Nausea and Vomiting (CINV) that gained FDA approval in September 2015[37], but Zejula, which Tesaro had picked up from Merck & Co. in June 2012, gained its FDA approval only eighteen months after Varubi in March 2017. Tesaro is now a US$4.2bn company[38].

[26] In the US the lifetime risk of breast cancer for women is estimated at 12% (source: National Cancer Institute, SEER Cancer Statistics Review, 1975-2009). For BRCA1 and BRCA2 the lifetime risk to age 70 has been estimated at 55-60% (see J Natl Cancer Inst. 2013 Jun 5;105(11):812-22. Epub 2013 Apr 29).
[27] In a celebrated and controversial race that was won by the biotech company Myriad Genetics (Salt Lake City, Ut., Nasdaq: MYGN, www.myriad.com) – for background see *Breakthrough: The race to find the breast cancer gene* by Kevin Davies and Michael White (New York: John Wiley & Sons, 1996). Myriad found BRCA1 on chromosome 17 at 17q21 and BRCA2 on chromosome 13 at 13q12. Myriad's patents were eventually invalidated by the US Supreme Court in a case called Association for Molecular Pathology v. Myriad Genetics that was decided in 2013.
[28] Oncogene. 2002 Dec 16;21(58):8981-93.
[29] J Clin Oncol. 2011 Nov 20;29(33):4373-80. Epub 2011 Oct 17.
[30] For some background here see *The top 10 drug launches of 2017* by Carly Helfand, FiercePharma, 30 January 2017.
[31] See the 19 April 2017 AbbVie press release headlined '*Abbvie announces topline results from two Phase 3 studies investigating veliparib in combination with chemotherapy for the treatment of patients with advanced or metastatic squamous Non-Small Cell Lung Cancer and early-stage Triple-Negative Breast Cancer.*'
[32] BioMarin (Novato, Ca., Nasdaq: BMRN, www.bmrn.com) out-licensed this drug to Medivation in August 2015 for US$410m upfront and US$160m in milestones.
[33] Waltham, Ma., Nasdaq: BGNE, www.beigene.com. This company's lead candidate, now in Phase 3, is BGB-3111, a BTK inhibitor for hematologic malignancies.
[34] By former executives of Pharmion, which had been sold to Celgene in November 2007 for US$2.9bn. Pharmion had developed Vidaza, for the treatment of Myelodysplastic Syndrome.
[35] Clovis agreed to pay Pfizer an upfront license fee settled with Clovis equity, as well as up to US$255m in development, regulatory and sales milestones.
[36] 18 December 2017 close on Nasdaq.
[37] It was originally developed by Schering-Plough.
[38] 18 December 2017 close on Nasdaq.

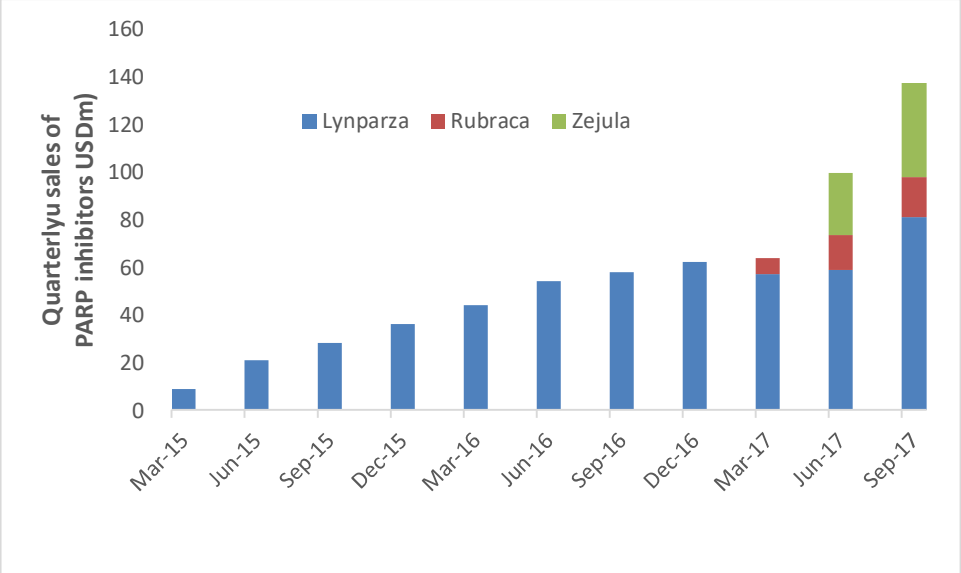

Figure 1: PARP inhibitor sales since 2015

Patrys' Deoxymab is a cell-penetrating monoclonal antibody that works like a PARP inhibitor. Deoxymab in its current form[39] was developed in the laboratory of Dr James Hansen, a radiation oncologist now at Yale University. We summarise the background to Deoxymab in Appendix Ib of this note. In October 2012 Hansen et. al. published a key paper in the journal *Science Translational Medicine* showing that a single chain variable fragment (scFv) of their mouse monoclonal antibody would not directly damage DNA but would[40]

- preferentially bind single-strand tails of DNA;
- inhibit DNA single-strand and double-strand break repair;
- sensitise cancer *in vitro* and *in vivo* to conventional cancer therapy, where that therapy works via DNA damage;
- kill BRCA2-deficient human cancer cells via synthetic lethality.

In other words, what Hansen et. al. had unexpectedly discovered was a product that had all the hallmarks of a PARP inhibitor without having to act on PARP enzymes. Indeed, it was potentially better than a PARP inhibitor because the approved drugs we described above only work on single-strand DNA breaks, with the double-strand breaks following during DNA replication. By contrast Deoxymab can work on both single and double strand breaks, suggesting that it can kill cancer cells faster.

PATRYS' DEOXYMAB MAY BE BETTER THAN A PARP INHIBITOR

Patrys' Deoxymab products may be better than the current PARP inhibitors. Currently Patrys is only pre-clinical with PAT-DX1, a humanised Deoxymab di-scFv product, and is in the process of working out which clinical

[39] ie as an anti-cancer antibody, not as a lupus autoantibody, where it was first studied.
[40] An antibody is made up of four polypeptides - two 'heavy chain' polypeptides that form the Y shape of the antibody, and two shorter 'light chains' that run parallel to the upper arms of the Y made by the heavy chains. Within this polypeptide structure there are two basic regions. The lower half of the antibody, which starts around midway down the arms of the Y, is called the 'constant region' and the upper half, in the tips of the Y, is called the 'variable region'. Single chain variable fragments (scFvs) are fusions protein of the variable regions of the heavy (VH) and light chains (VL) of the antibody. Obviously such scFvs are considerable smaller than the original antibody, making them easier to deliver.

indications to pursue from late 2019. However, we argue that the Deoxymab products will benefit from the success of the PARP inhibitors, as well as monoclonal antibodies, because

- The products may be better targeted than the PARP inhibitors due to their derivation from a monoclonal antibody;
- The products will allow multiple mechanisms to be harnessed alongside DDR inhibition, most notably through the conjugation of drug nanoparticles to the antibody variants;
- Products from the Deoxymab platform are likely to have better side effect profile than other classes of drugs;
- Deoxymab's ability to make it through the cell membrane opens opportunities for bi-specific antibodies that target intracellular targets;
- Deoxymab may be able to help to deliver therapies to other tissues where DNA is released, such as Acute Myocardial Infarction.

Deoxymab 3E10 scFv and di-scFv – Evidence that Patrys may be on to something big

Deoxymab 3E10 scFv provided Patrys with some important drug development clues. Patrys was never going to develop James Hansen's original scFv or di-scFv (that is, a fusion of two scFvs) from the original Deoxymab 3E10 antibody, because these scFv constructs are mouse antibody fragments discovered in a mouse model of lupus. Nonetheless, the evidence from the 2012 *Science Translational Medicine* paper (on scFv) and another 2015 paper from the journal *Cancer Research*[41] (on di-scFv) is compelling:

PATRYS' DEOXYMAB PRODUCTS SEEM TO WORK ACROSS MULTIPLE CANCERS

- **Deoxymab 3E10 scFv works in glioma, ovarian cancer and pancreatic cancer.** 3E10 scFv was able to sensitise a human glioma cell line called U87, and U87 xenografts, to doxorubicin, whose mechanism of action involves DNA damage[42] but which must be used sparingly because of cardiotoxicity[43]. The U87 xenografts were also sensitised to radiation. 3E10 scFv was able to kill PEO1 and Capan-1, respectively BRCA-mutated human ovarian and pancreatic cancer cell lines, as a monotherapy, as well as sensitise these cells to doxorubicin and radiation respectively[44].
- **Deoxymab 3E10 di-scFv works against both BRCA and PTEN mutations**. The 2015 paper was important because it showed that the di-scFv product could kill cancer cells associated not just with BRCA2 mutations but also with mutations in PTEN. Short for 'Phosphatase and Tensin homolog', PTEN is, like BRCA2, a tumour suppressor gene. PTEN is less well known than the BRCA genes because it was

[41] Cancer Res. 2015 Jun 1;75(11):2285-91. Epub 2015 Apr 1.
[42] Science. 1984 Oct 26;226(4673):466-8.
[43] Herz. 2011 Jun;36(4):296-305.
[44] Later, in the 2015 paper, Hansen et. al. showed that 3E10 di-scFv was able to reduce the growth of Capan-1 xenografts as a monotherapy, providing more evidence of synthetic lethality.

discovered later[45], but PTEN mutations are significant because they show up in a broad variety of cancers, including glioblastoma as well as endometrial, breast, thyroid and prostate cancers. PTEN, when it doesn't work properly, contributes to the cancer activity of the PI3K/AKT signalling pathway[46], and PTEN mutations also have consequences for DDR pathways[47]. Hansen et. al. demonstrated *in vitro*, with a human glioma cell called U251 that is PTEN-deficient, that their 3E10 di-scFv could be synthetically lethal to cancers with PTEN mutations. This finding was particularly important for a potential glioblastoma indication given that an estimated 60% of glioblastomas have a PTEN mutation[48].

PAT-DX1 – Patrys' new lead candidate

Patrys now has a compelling pre-clinical lead candidate, PAT-DX1. Patrys acquired the rights to the Deoxymab programme in March 2016. It then proceeded to develop, using *in silico* systems, an optimal version of the di-scFv, one that was as human as possible, had no lupus-related residues, and could show improved DNA binding and cell death in cancer cells already deficient in DDR capability (eg BRCA-mutated or PTEN-mutated cells). The result, by April 2017, was PAT-DX1. Patrys then proceeded to conduct *in vitro* studies to confirm if the new product worked as expected, which were favourable.

PAT-DX1 has worked well as a monotherapy in pre-clinical studies. In September 2017 Patrys announced that various experiments had confirmed the utility of PAT-DX1, with the product showing activity:

- *in vitro* in BRCA-mutated colon cancer;
- *in vitro* in explanted tumour cells from glioblastoma patients[49];
- *in vivo* in an animal model of Triple-Negative Breast Cancer.

PAT-DX1 has been shown *in vitro* to be synergistic with the PARP inhibitors. In December 2017 Patrys announced that it had tested PAT-DX1 and AstraZeneca's Lynparza PARP inhibitor drug in brain and colon cancer cell lines, and found synergistic activity from the combination, meaning that the level of tumour cell killing was higher than the additive effect of the two agents as monotherapies would suggest. This not only provided the first evidence for Patrys that its Deoxymab products would work with the PARP inhibitors, but also likely provides further method-of-use intellectual property protection for PAT-DX1.

PAT-DX1 IS SYNERGISTIC WITH THE PARP INHIBITORS

PAT-DX1 is now being prepared for the clinic. Patrys hasn't release data from either the monotherapy or combination experiments, but believes that they validate the published work related to Deoxymab 3E10 scFv and di-scFv. The company is now planning the requisite toxicology and other pre-clinical work ahead of an IND filing

[45] In 1997 – see Science. 1997 Mar 28;275(5308):1943-7. Also, it was discovered by an academic group rather than a biotech company in the case of the BRCA genes, the latter raising questions about the propriety of intellectual property over genes. PTEN is located on chromosome 10 at 10q23.
[46] PTEN regulates PI3K signalling by dephosphorylating PIP_3 – see Annu Rev Pathol. 2009;4:127-50. Ordinarily PI3K phosphorylates a molecule called PIP_2, which generates PIP_3. That molecule in turn induces an array of kinases including Akt to move to the cell membrane to be activated. Akt regulates many proteins involved in cell growth, proliferation, motility, adhesion, neovascularisation, and apoptosis. Akt's activity then feeds into mTOR, which serves as master regulator of cell growth responding to numerous environmental inputs including the availability of oxygen, ATP and so on. For an overview of PI3K/Akt/mTOR see Pharmacol Ther. 2014 May;142(2):164-75. Epub 2013 Dec 9
[47] See Cancer Lett. 2012 Jun 28;319(2):125-129. Epub 2012 Jan 18.
[48] Cancer Biol Ther. 2008 Sep;7(9):1321-5. Epub 2008 Sep 8.
[49] Hansen has previously looked at using Deoxymab in glioblastoma – see the Yale press release dated 8 August 2013 and headlined '*James Ernest Hansen, M.D. receives RSNA R&E Foundation research scholar grant*'.

for PAT-DX1 and the commencement of clinical work in late 2019. An important task in 2018 will be manufacturing of the product in a stable cell line under cGMP.

PAT-DX1 could work in numerous cancers. Patrys has cited prostate, pancreatic and endometrial cancers, as well as the three cancers mentioned in the September 2017 announcement, as potential future PAT-DX1 indications. Patrys has flagged that its first indication may be an Orphan one[50], and James Hansen has in the past studied glioblastoma. The latter cancer could be a billion-dollar opportunity despite the relatively small patient population, and allow Patrys to move towards late stage clinical studies reasonably swiftly.

There are multiple paths forward for PAT-DX1. There are four paths to follow for development of PAT-DX1.

- Single agent for treating cancers where there are already deficiencies in DDR;
- Combination with radiotherapy;
- Combination with chemotherapy;
- Combination of PAT-DX1 with nanoparticles (PAT-DX1-NP).

We expect Patrys will pursue all four approaches. After an initial Phase 1a studying PAT-DX1 as a monotherapy, we then expect a Phase 1b/2b in conjunction with standard-of-care chemotherapy or radiotherapy. Should glioblastoma be chosen as the first indication, it's reasonable to expect that a second Phase 2 could then lead to accelerated approval if the data was favourable.

PAT-DX1 – The market opportunity is immense

Take just three opportunities: The pancreatic cancer and glioblastoma indications that Patrys is evaluating for pursuit in the near term, and a potential medium-term opportunity in Triple-Negative Breast Cancer. The first two have in common a relatively low survival rate for current standards of care, meaning that clinical trials can be conducted more quickly. Both are also Orphan indications.

PANCREATIC CANCER AND GLIOBLASTOMA ARE LARGE MARKET OPPORTUNITIES

Pancreatic cancer. In the US ~54,000 people will have been diagnosed with pancreatic cancer in 2017 and ~43,000 will have died from it. As a comparison of these two numbers may have suggested, cancer of the pancreas is one in which patients have a particularly low life expectancy, in part because only 15-20% of patients have tumours amenable to surgery at the time of diagnosis[51] where median Overall Survival can be well over two years[52]. As recently as the late 1980s, when the only drug that worked in pancreatic cancer was 5-FU[53], a mere 4% of all pancreatic cancer patients could expect to be alive at the five-year mark. Then came Eli Lilly's Gemzar, generic name gemcitabine, whose first FDA approval, in May 1996, was in pancreatic cancer. Gemcitabine, a nucleoside

[50] See Patrys' 2016 AGM presentation, slide 16.
[51] Lancet. 2004 Mar 27;363(9414):1049-57.
[52] Surgery. 2016 Mar;159(3):893-900. For a recent example of extended survival in resectable pancreatic cancer, consider the case of gemcitabine plus capecitabine (ie Roche's, Xeloda, a prodrug of 5-FU). This combination increased survival over gemcitabine alone by 2.5 months, to 28 months (see Lancet. 2017 Mar 11;389(10073):1011-1024. Epub 2017 Jan 25).
[53] A drug introduced by Roche in the late 1950s that works by inhibiting take-up of DNA and RNA by cells, with rapid-growth cancer cells thereby being starved. 5-FU is generally administered with leucovorin, a metabolite of folic acid that increases the efficacy of the fluorouracil.

analogue[54], effectively doubled five-year survival to 9%[55]. There have been four more minor advances since Gemzar: A pancreatic cancer indication for Astellas' Tarceva[56] (November 2005[57]), the development in France of the 'Folfirinox' drug combination (May 2011), a pancreatic indication for Celgene's Abraxane[58] (September 2013), and a first FDA approval for Onivyde[59] (October 2015), a drug now marketed by the French specialty pharma company Ipsen[60]. We say 'minor advances' because the survival gain for patients from each of these developments has been low:

PANCREATIC CANCER LIFE EXPECTANCY IS STILL LOW

- Tarceva plus gemcitabine in Phase 3 only improved median Overall Survival from 5.9 months to 6.2 months[61].
- Folfirinox (5-FU, leucovorin, irinotecan and oxaliplatin) beat gemcitabine as a first-line treatment in pancreatic cancer by 4.3 months, with median Overall Survival of 11.1 months versus 6.8 months for gemcitabine. In addition, it improved Quality of Life for the patients, which was a surprise because the regimen had considerably more toxicity[62].
- Abraxane in Phase 3 increased median Overall Survival over gemcitabine by 1.8 months, from 6.7 months for gemcitabine alone to 8.5 months for the gemcitabine/Abraxane combination[63].
- Onivyde plus 5-FU, in Phase 3 for patients that had failed gemcitabine, registered 6.1 months in median Overall Survival versus 4.2 months for those treated with only 5-FU[64].

Gemcitabine has been generic in the US since 2010, however the Abraxane+gemcitabine combination can reimburse at >US$12,000/month in that market[65]. We believe pancreatic cancer is probably a US$4-5bn market opportunity based on 50,000 US patients and 80,000 in Europe[66] and US$35,000 p.a. pricing[67], meaning that an agent with strong survival data would almost certainly be a blockbuster. We list a number of companies working on pancreatic cancer in Appendix VIII of this note.

Glioblastoma. Glioblastoma is the most common form of brain cancer, affecting a particular neuronal support cell called the astrocyte. Historically, five-year survival for glioblastoma patients was only 2-4%[68], and today medium Overall Survival for patients on standard-of-care temozolomide plus radiotherapy is only 15 months[69]. We believe glioblastoma can be at least a ~US$500m opportunity for Patrys, based on roughly 10,000 patients p.a. in the US[70]

[54] The drug, by replacing cytidine during DNA replication, triggers cancer cell apoptosis.
[55] American Cancer Society, Cancer Facts and Figures 2017, Table 7.
[56] Generic name erlotinib, see www.tarceva.com. Erlotinib works by targeting the epidermal growth factor receptor (EGFR) tyrosine kinase.
[57] Tarceva was first FDA-approved in 2004, for Non-Small Cell Lung Cancer.
[58] Generic name nab-paclitaxel, see www.abraxane.com. Abraxane was first FDA-approved in 2005, for breast cancer. Celgene paid US$2.9bn in mid-2010 to buy Abraxis Bioscience, primarily because of Abraxane.
[59] Generic name irinotecan liposome injection, see www.onivyde.com.
[60] Boulogne-Billancourt, France, Euronext Paris: IPN, www.ipsen.com. Ipsen's current bestselling drug is Somatuline, a somatostatin analogue for the treatment of acromegaly. Ipsen bought Onivyde from the US drug developer Merrimack Pharmaceuticals (Cambridge, Ma., Nasdaq: MACK, www.merrimackpharma.com) for US$575m upfront and up to US$450m on approval of potential additional indications for the drug.
[61] See J Clin Oncol. 2007 May 20;25(15):1960-6. Epub 2007 Apr 23.
[62] See N Engl J Med. 2011 May 12;364(19):1817-25.
[63] See N Engl J Med. 2013 Oct 31;369(18):1691-703. Epub 2013 Oct 16..
[64] Lancet. 2016 Feb 6;387(10018):545-57. Epub 2015 Nov 29.
[65] Med Oncol. 2016 May;33(5):48. Epub 2016 Apr 11.
[66] Ann Oncol. 2014 Aug;25(8):1650-6. Epub 2014 Apr 23
[67] Should an agent show the kind of survival brought about by Folfirinox versus gemcitabine, priced at US$100,000 for a year's worth of treatment. That's reasonable in the light of the way cost-effectiveness tends to get calculated in the US. Cost effectiveness here is the cost of switching treatments from the current standard of care to the new therapy, as given in costs per Quality-Adjusted Life Year (QALY). Traditionally in the US an ICER under US$50,000 per QALY was considered 'cost effective' (Expert Rev Pharmacoecon Outcomes Res. 2008 Apr;8(2):165-78), however in more recent years the threshold seems to have lifted to US$100,000 or more to account for healthcare inflation (N Engl J Med. 2014 Aug 28;371(9):796-7).
[68] See J Neurooncol. 1998 Nov;40(2):151-60 and Can J Public Health. 2016 Jun 27;107(1):e37-42.
[69] N Engl J Med. 2005 Mar 10;352(10):987-96.
[70] Estimated using the American Cancer Society's annual Cancer Facts and Figures estimates.

and around 16,000 in Europe, and modest pricing of only US$20,000 p.a. – a price that reflects the relatively slender 2.5-month survival advantage afforded by temozolomide. That drug, an alkylating agent[71] originally marketed as Temodar, gained its first FDA approval for Schering-Plough in 1999. Its first indication, for refractory anaplastic astrocytoma, made it a US$400m drug but its second, and only other indication, was in newly diagnosed glioblastoma and was granted in both the EU and the US in 2005[72]. Glioblastoma was worth another US$600m in extra sales for Temodar as its potential developed in this indication over the next five years. The potential for PAT-DX1 can be a lot higher than Temodar if Patrys' drug can be shown to work in patients whose tumour is 'MGMT promoter unmethylated'[73], which constitutes 50-60% of the patient population[74]. Also, it's reasonable to expect better than US$20,000 pricing for the first new agent since Temodar, so long as the survival gain is notable. Consequently, we think glioblastoma is another billion-dollar opportunity for Patrys[75].

Triple-Negative Breast Cancer. Around 250,000 American women will have been diagnosed with breast cancer this year[76] and 40,000-50,000 of these will have had a more aggressive 'Triple-Negative' tumour. There are three receptors commonly found on breast cancer cells that typically fuel the cancer – one each for the sex hormones estrogen (ER) and progesterone (PR) and one for a growth factor receptor called HER2. Around three quarters of all breast cancer is ER+/PR+, while only around 15% is HER+. Some ER+/PR+ is HER2- and vice versa, but around 15-20% is Triple-Negative, that is, the cancer features none of the three receptors[77]. Triple-Negative Breast Cancer (TNBC) is often associated with the BRCA mutations we discussed above[78]. The reason TNBC has lower survival than the other subtypes[79] is because, while the hormone receptor positive patients can get tamoxifen and aromatase inhibitors, and the HER2+ patients can get Herceptin and its successor drugs, there is no targeted therapies suitable for Triple-Negative patients, leaving those patients to get older chemotherapies with lower survival outcomes. 50,000 patients receiving a US$100,000 p.a. drug[80] would make for a US$5bn market opportunity just in the US. TNBC is one reason why the PARP inhibitors are expected to become blockbusters – we noted above that Lynparza is expected to be indicated soon for BRCA-mutated breast cancer[81], and that Pfizer is going after this opportunity with Talazoparib.

TRIPLE-NEGATIVE BREAST CANCER MAY BE A FUTURE INDICATION FOR PATRYS TO PURSUE

The Deoxymab pipeline

PAT-DX1 can also be used to deliver therapeutic nanoparticles. In 2016 the Hansen lab at Yale showed *in vivo* that Deoxymab 3E10 di-scFv could be used to deliver cytotoxic drugs into cancer cells. The Yale scientists

[71] Alkylating agents binds to DNA and prevent proper DNA replication.
[72] See Clin Cancer Res. 2005 Oct 1;11(19 Pt 1):6767-71.
[73] MGMT, a gene located on chromosome 10 at 10q26, codes for a DNA repair enzyme. If the gene is methylated, it is silenced, meaning less DNA repair, making the glioblastoma cells susceptible to the effect of temozolomide - see J Cell Physiol. 2018 Jan;233(1):378-386. Epub 2017 May 16.
[74] Fam Cancer. 2013 Sep;12(3):449-58.
[75] For more on glioblastoma see the recent NDF Research report on Novogen headlined '*Picking up where Genentech left off*', which we published on 7 November 2017. Novogen, now Kazia Therapeutics, has a Genentech-developed glioblastoma drug as its lead candidate.
[76] Source: American Cancer Society, Cancer Facts and Figures 2017.
[77] Source: Analysis of Atlanta regional population incidence data in 2003/2004, where tumour subtype was known, from Lund et. al., Cancer Res 2009;69(24 Suppl):Abstract nr 3065.
[78] Breast Dis. 2010;32(1-2):25-33.
[79] One institution registered 62% five-year survival for TNBC versus 75% for non-TNBC – see Springerplus. 2014 Sep 23;3:553.
[80] See the discussion on drug cost-effectiveness above.
[81] AstraZeneca's FDA submission for this indication was accepted in October 2017.

conjugated Deoxymab 3E10 di-scFv to nanoparticles of Poly Lactic-co-Glycolic Acid (PLGA), a polymer often used in medical devices for drug delivery due to its biodegradability. They found that these conjugated nanoparticles were localising preferentially in cancer cells due to the increased presence of extracellular DNA in the tumour microenvironment[82]. The reason Hansen et al. used PLGA is that it made a good proxy for nanoparticles generally, and showed that nanoparticle conjugations with Deoxymab 3E10 di-scFv could be engineered. Patrys licensed this nanoparticle programme, called PAT-DX1-NP, from Yale in June 2017. We expect that the PLGA experiments will be repeated with PAT-DX1-NP, followed by experiments with nanoparticles loaded with chemotherapeutic agents, before Patrys selects the appropriate drug conjugate and indication to further develop the PAT-DX1-NP programme. Patrys announced in September 2017 that, in an animal model of glioblastoma, the nanoparticles from PAT-DX1-NP had localised at the tumour site, as expected. This ability to deliver above the blood-brain barrier bodes well for a future human glioblastoma study of either PAT-DX-1 or PAT-DX1-NP.

5C6 represents a second lupus autoantibody with anti-cancer properties. In addition to developing Deoxymab 3E10, the Hansen lab also discovered 5C6[83], another lupus antibody to which Patrys now has the rights. 5C6 was different to 3E10 in that Hansen *et. al.* were looking for a lupus auto-antibody that would directly damage DNA in BRCA2-deficient cells but not do so in cells with normal BRCA2 function. The utility of this antibody for Patrys is that it represents a candidate that works more aggressively in BRCA2 mutated cells, which, as we have seen, represents a seriously large market opportunity just with breast cancer.

A collaboration at the Walter and Eliza Hall Institute may further develop the therapeutic potential of cell-penetrating monoclonal antibodies. Monoclonal antibodies in 2016 were a US$84bn drug class. One of the more important developments in the monoclonal antibody field in the last ten years has been the rise of the 'bi-specifics' – antibodies that can bind to more than one target at once[84]. Patrys believes that it can use bi-specific antibody technology to engineer antibodies with the cell-penetrating capability of the Deoxymab products where those antibodies have a binding arm specific to an intracellular target other than DNA. The November 2017 announcement regarding a collaboration with the Walter and Eliza Hall Institute (WEHI) in Melbourne is therefore potentially important for the whole monoclonal antibody field.

A DEMOXYMAB BI-SPECIFIC COULD PIONEER CELL-PENETRATING MONOCLONALS

- **7D10 provides a test case**. The laboratory of Dr Ruth Kluck at WEHI have long focused on the Bcl-2 family of molecules that regulate apoptotic cell death[85]. Some members of this family are pro-apoptotic and some anti. One pro-apoptosis molecule the Kluck lab have studied extensively is Bak, and in 2014/15 the lab raised an interesting mouse antibody to Bak called 7D10[86] that, when it binds to its target, can activate the molecule[87]. What Kluck et. al. may have discovered is a way to make cancer cells undergo apoptosis. The Kluck lab and Patrys are now collaborating on using PAT-DX1 to evaluate its ability to

[82] Oncotarget. 2016 Sep 13;7(37):59965-59975.
[83] Sci Rep. 2014 Aug 5;4:5958.
[84] Generally, by having the each Fab arms of the antibody bind to a different target antigen. The first approved bi-specific was Amgen's Blincyto (blinatumomab), FDA approved in December 2014 for the treatment of Acute Lymphocytic Leukaemia. This drug is a 'BiTE', that is, a Bi-specific T cell Engager, meaning that it can bind both the CD3 receptor on T cells as well as the relevant cancer antigen (in this case CD19), allowing the T cells to be activated against the cancer.
[85] For a review of Bcl-2 see Curr Top Microbiol Immunol. 1995;200:107-21.
[86] See *Bak binding proteins*, WO/2015/176104, priority date 23 May 2014.
[87] By permeabilising mitochondria - see J Cell Sci. 2009 Aug 15;122(Pt 16):2801-8.

deliver 7D10 to Bak. The Kluck lab believes such a product may be effective in breast cancer, in part because Bak expression is known to sensitise breast cancer to paclitaxel therapy[88].

- **If the 7D10 collaboration works, the upside is significant**. It has been estimated that upwards of four-fifths of all potential drug targets are intracellular[89], but many of these targets are too flat to be targeted with small molecules, and large molecules with the appropriate binding capability can't get through the cell membrane to get to the target. Cell-penetrating antibody constructs can solve this problem, and arguably unlock multi-billion-dollar drug development opportunities as a result. One of the reason why the Belgian biotech company Ablynx[90] is currently capitalised at >US$1.8bn company[91] is that its nanobodies, derived from camel antibodies, can freely pass across membranes.

PERHAPS FOUR-FIFTHS OF ALL DRUG TARGETS ARE INTRA-CELLULAR

Valuing Patrys

We value Patrys at 7.3 cents per share base case and 18.3 cents optimistic case. Our target price of 13 cents per share sits at the midpoint of our valuation range. Our approach was as follows:

- Our WACC was 15.2% (Speculative)[92].
- We modelled a payoff only for PAT-DX1.
- We valued PAT-DX1 on a probability-weighted DCF approach.
- We model around 15 years of commercial exclusivity for PAT-DX1.

PAT-DX1 - We assume Patrys partners this asset after the first Phase 1. We assume

- US$5-10m more expenditure by Patrys and collaborators on the project prior to partnering;
- A 21% probability of the drug gaining approval, as per the historic success rates for molecules in Phase 1, small and large[93];
- A licensing in FY21 or FY22, for US$25-50m upfront, US$100-200m in milestones and a 10-15% royalty rate[94];
- First regulatory approval in FY24-FY25;
- Peak sales of US$0.7-1.2bn, with indications in glioblastoma and pancreatic cancer;
- 10% market share post-exclusivity for Patrys' licensee, with a 3-5% negative terminal growth rate;
- A 30% tax rate.
- A 4-6% royalty back to Yale/UCLA.

[88] PLoS One. 2015 Sep 25;10(9):e0138955.
[89] Nat Rev Drug Discov. 2006 Dec;5(12):993-6.
[90] Ghent, Belgium, Euronext Brussels: ABLX, www.ablynx.com.
[91] 18 December 2017 close on Euronext Brussels.
[92] For a relevant discount rate, we use WACCs of between ~11% and ~15% depending on the risk for Life Science companies. This is derived from a RFR of 2.5%; a MRP of 7.5%-11.5% (7.5% for 'medium risk' companies, 9.5% for 'high risk' companies and 11.5% for 'speculative' companies); and an ungeared beta of 1.1. 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'.
[93] Clin Pharmacol Ther. 2010 Mar;87(3):272-7. Epub 2010 Feb 3.
[94] That this is reasonable is suggested by the City of Hope / Sorrento deal of 2015, which had a total deal value of more than US$170m – see the Sorrento Therapeutics press release dated 28 September 2015 and headlined *'Sorrento Therapeutics and City of Hope announce exclusive license to develop first-in-class immunotherapies against intracellular targets'*.

- Cash settlement of the A$360,000 owning the vendors of the Deoxymab programmes.

Further capital. As at September 2017 Patrys held A$1.3m but had a modest A$190,000 per month burn. Our model includes a small capital raise at a discount to the current share price. Patrys believes that it can fund further development of the Deoxymab products through non-dilutive funding – reasonable given the high level of unmet medical need represented by glioblastoma and pancreatic cancer – and various risk-sharing arrangements including joint-development agreements.

Table 1: NDF Research's valuation of Patrys

	Base	Optim.
Deoxymab (A$m)	58.7	162.2
Total programme value	58.7	162.2
Value of tax losses	17.4	17.4
Corporate overhead	-11.1	-11.1
Cash now (A$m)	1.3	1.3
Cash to be raised (A$m)	2.0	2.0
Option exercises less obligations (A$m)	-0.1	-0.1
Total value (A$m)	68.2	171.7
Total diluted shares (million)	940.0	940.0
Value per share	$0.073	$0.183
Valuation midpoint	$0.128	
Share price now (A$ per share)	$0.020	
Upside to midpoint	540.0%	

Re-rating Patrys

We see the following developments helping to re-rate Patrys towards our target price:

- Initial production runs for PAT-DX1;
- Further animal data from PAT-DX1;
- Any deal-making in the PARP inhibitor space, and further sales success for the approved PARP inhibitors;
- Potential licensing of the IgM assets;
- Moves to take PAT-DX1 into the clinic, including an IND filing and filing for Orphan Drug Status.

SALES SUCCESS FOR THE APPROVED PARP INHIBITORS CAN HELP RE-RATE PATRYS

Patrys' leadership

We believe Patrys has a team that can create significant value from Deoxymab.

CEO **Dr James Campbell** was formerly Chief Operating Officer of ChemGenex Pharmaceuticals, a company that moved from start-up to regulatory-stage drug developer over the period 2002 to 2011 before it was acquired by Cephalon for A$230m. That deal took place after the completion of clinical development for Synribo[95], a Chronic Myeloid Leukaemia agent. Synribo gained accelerated approval from the FDA only one year after Chemgenex was sold. With his Chemgenex experience, we think Campbell has the smarts to go all the way with new drug candidates like those being developed from Deoxymab.

The Patrys board is one with the experience necessary to grow shareholder value. Chairman **John Read** brings technology evaluation expertise, having been a long-time executive of the Sydney-based venture capital firm CVC[96]. **Michael Stork**, a successful Canadian businessman, is well known as an angel investor and is Patrys' largest shareholder. And **Suzy Jones**, a former Genentech executive, brings considerable biotech experience from her time in research, product development (where she was part of the Rituxan and Avastin teams) and business development.

The Patrys Scientific Advisory Board, assembled in December 2016, has provided valuable input to Patrys on the way forward for the Deoxymab products. **Dr Pamela Klein** brings a product development perspective honed at Genentech and Intellikine[97] while **Dr Allen Ebens**, also a Genentech veteran, has spent research time at Exelixis[98], Juno Therapeutics[99] and NGM Biopharmaceuticals.

Appendix Ia – Background to Patrys

Patrys was originally built around a platform to discover and develop IgM antibodies. Patrys originated from work done by the late Professor Peter Vollmers[100], of the University of Würzburg in Germany, on natural human antibodies with anti-cancer properties. Vollmers believed that cancer patients naturally produce antibodies highly specific to their tumours which would be therapeutically useful if isolated[101]. Vollmers et al. developed a platform for discovery of such antibodies, where B cells would be obtained from human donors and the antibodies produced by the hybridomas screened to select those would attack cancer but ignore healthy tissue. A theoretical advantage of these antibodies is that they could be produced in a human cell line like PER.C6® with the proper glycosylation profile. The antibodies that worked best for Vollmers et al. were from the IgM class of immunoglobulin rather than

PATRYS ORIGINALLY WORKED ON IgM ANTIBODIES

[95] Generic name omacetaxine mepesuccinate, see www.synribo.com.
[96] See www.cvc.com.au.
[97] Acquired by Takeda in 2011 for US$190m. This company had developed small molecule inhibitors targeting isoforms of PI3K/mTOR.
[98] South San Francisco, Ca., Nasdaq: EXEL, www.exelixis.com. This company developed Cabometyx (cabozantinib), a receptor tyrosine kinase inhibitor FDA approved in 2012 for the treatment of metastatic medullary thyroid cancer and now used mainly in kidney cancer.
[99] Seattle, Wa., Nasdaq: JUNO, www.junotherapeutics.com. This company has been one of the pioneers of CAR-T immunotherapy for cancer.
[100] Peter Vollmers died in 2010.
[101] N Biotechnol. 2009 Jun;25(5):294-8. Epub 2009 Apr 11.

the IgG class where most of the currently marketed monoclonal antibody drugs had come from. Patrys went public on the ASX in 2007 to commercialise this platform.

Patrys developed some interesting anti-cancer IgM antibodies using the Vollmers platform. In September 2011, for example, Patrys reported a ten-year survival rate of 55% for 30 gastric cancer patients given the Vollmers lab's first IgM, called PAT-SC1, prior to surgery[102]. Ordinarily ten-year survival post-surgery for gastric cancer is ~30%. Other IgM antibodies that Patrys developed between 2007 and 2015 included PAT-SM6, an anti-GRP78 antibody for melanoma[103] and Multiple Myeloma, and PAT-LM1, for various solid tumours. In December 2013 PAT-SM6 completed a Phase 1a study in Multiple Myeloma showing stable disease in one-third of the patients[104].

Manufacturing of IgMs is challenging. Patrys stock underperformed the market after its IPO because, while the company could produce small quantities of its IgM antibodies, it encountered problems in manufacture at large scale and therefore missed expected development timelines. IgM antibodies may be the immune system's 'antibody of choice' as part of the innate immune system, and IgM antibodies have high avidity because of the large number of binding sites, but as antibody drugs they were potentially going to be difficult to make because of their size – typically an IgG antibody has a molecular weight of ~150 kDa whereas IgM antibodies are ~900 kDa. In November 2014 Patrys advised that it was having difficulty making enough PAT-SM6 to allow a Phase 1b/2a study of PAT-SM6 in Multiple Myeloma in conjunction with the Amgen drug Kyprolis. Patrys received a $1.2m insurance payout related to these production issues in the March 2015 quarter and there are, we understand, other insurance claims outstanding[105].

Patrys de-prioritised its IgM platform after 2016, but may still realise some value from it. James Campbell joined as CEO in April 2015 and proceeded, in conjunction with the Patrys board, to look for other drug development programmes to rebuild shareholder value. The result of this search was the Deoxymab programme, which Patrys acquired in March 2016, and which is now the core focus of Patrys. That said, there is still potential in IgM antibodies. In June 2015 Patrys announced that it had licensed the Chinese rights to the PAT-SC1 gastric cancer antibody to Hefei Co-source, a drug developer based in the Chinese city of Hefei. Patrys retains the relevant IP over the antibody candidates[106], PAT-SC1 and PAT-SM6 have Orphan Drug designations from the FDA, and it's reasonable to think that the engineering difficulties related to IgM antibody manufacture can be overcome by a group with enough capital and technical skill, given the current global knowledge base around antibody engineering[107].

PATRYS MAY STILL REALISE VALUE FROM IgM ANTIBODIES

[102] This follow-up was later published – see Oncol Rep. 2014 Mar;31(3):1059-66. Epub 2014 Jan 20.
[103] Melanoma Res. 2013 Aug;23(4):264-75
[104] Haematologica. 2015 Mar;100(3):377-84. Epub 2015 Jan 30. For a case study of a patient who received PAT-SM6 in combination with bortezomib and lenalidomide see Clin Cancer Res. 2016 Sep 1;22(17):4341-9. Epub 2016 Mar 30.
[105] In Patrys' 28 August 2017 Appendix 4E release the company indicated that it is '*committed to pursuing a number of insurance claims related to the failed manufacturing run of PAT-SM6 in 2014/15*'.
[106] There have been three recent US patent grants - 9,783,599 (October 2017), 9,273,125 (March 2016) and 9,265,817 (February 2016).
[107] For some perspective here see MAbs. 2012 Sep 1; 4(5): 555–561.

Appendix Ib – Background to Deoxymab

Deoxymab starts as a lupus research tool and evolves into a drug delivery vehicle, 1990-1999. Way back in 1990 the late Dr Richard Weisbart, a UCLA rheumatologist whose main research interest was autoimmune disease[108], was looking at one such disease called Systemic Lupus Erythematosus (SLE). In SLE the patient's body creates antibodies that attack healthy tissue in numerous organs, most notably the skin, joints, kidneys and brain. A notable characteristic of SLE is autoantibodies that attack DNA, the presence of which is diagnostic of the disease[109], and the level of which indicates disease severity[110]. In order to better study what made anti-DNA antibodies so pathogenic, Weisbart and colleagues isolated an antibody which they called 3E10 from the standard mouse model of SLE[111]. By 1996 the Weisbart lab had shown that 3E10 would penetrate cells by binding to extracellular DNA and translocate to the cell nucleus[112] and by 1998 work on recombinant Fab and single chain antibody fragments of 3E10 mutants had shown that the antibody's cell-penetrative capability could be markedly improved[113]. Around 1999 3E10 was tried out as an idiotypic vaccine[114] in a Phase 1 study in nine patients with SLE, most of whom developed antibodies to the idiotype[115]. Importantly, in this study 3E10 did not cause any adverse events over a two-year follow-up period. However, by the late 1990s Weisbart had started to think of 3E10 not as a vaccine, or even as a potential lupus treatment[116], but as a tool for intracellular drug delivery, since, unlike most lupus autoantibodies, it was not harmful to cells or tissues[117].

DEOXYMAB WAS ONCE THOUGHT OF AS A DRUG DELIVERY VEHICLE

Deoxymab is identified as an inhibitor of DNA Damage Response, 1999-2015. In the late 1990s and early 2000s James Hansen, a postdoctoral researcher in the lab of Weisbart's UCLA collaborator Robert Nishimura, worked on better identifying how 3E10 could make it into cells hauling a therapeutic drug cargo. By 2007 he had found that it was ENT2, a nucleoside salvage transporter[118], that did the trick[119]. Hansen, whose specialty is radiation oncology, took the 3E10 idea with him to Yale when he became Assistant Professor of Therapeutic Radiology there. At Yale Hansen initially considered using scFvs from 3E10 as a delivery system for radiopharmaceuticals[120]. However, what he unexpectedly discovered was that these scFvs would interfere with DNA Damage Response mechanisms, making them useful as a cancer therapies in their own right, with a mechanism involving synthetic

[108] Richard Weisbart died in late 2016.
[109] Autoimmunity. 2005 Feb;38(1):39-45.
[110] Scand J Immunol. 2001 Jul-Aug;54(1-2):211-9.
[111] J Immunol. 1990 Apr 1;144(7):2653-8.
[112] J Immunol. 1996 Sep 1;157(5):2082-8.
[113] J Autoimmun. 1998 Oct;11(5):539-46.
[114] ie where the aim is to prompt an antibody response to pathogenic antibodies.
[115] J Rheumatol. 1999 Dec;26(12):2602-8.
[116] Even though lupus remains a significant area of unmet medical need, since the only drug in this space in recent years has been GSK's Benlysta (belimumab), an antibody to B-cell activating factor (BAFF) FDA approved in 2011. That drug works by decreasing B-cell survival and, as a result, production of autoantibodies. Just over 100,000 people in the US have lupus (estimated from J Womens Health (Larchmt). 2004 Jul-Aug;13(6):713-8). GSK enjoyed US$465m in global sales for the drug in the 12 months to September 2017.
[117] For background see the article headlined '*My Antibody, Myself*' in UCLAInvents, Volume 4, 2009, page 14. UCLAInvents is a publication of the UCLA Office of Intellectual Property. For evidence of the utility of Deoxymab and its single chain variable fragment in drug delivery see Cancer Res. 2007 Feb 15;67(4):1769-74.
[118] This transporter had first been discovered in 1997 in the laboratory of Professor Steve Baldwin at the University of Leeds in the UK – see Biochem J. 1997 Dec 15;328 (Pt 3):739-43. Cells often 'salvage' nucleotides from DNA and RNA as the nucleic acids break down because they can't make them internally. ENT2 is one such pathway to pull nucleosides into or out of cells depending on what is needed within the cells.
[119] J Biol Chem. 2007 Jul 20;282(29):20790-3. Epub 2007 May 24.
[120] Specifically, he believed that a fusion protein of 3E10 scFv with Hsp70, a heat shock protein, would protect healthy cells against the effects of radiation. For background here see Brain Res. 2006 May 9;1088(1):187-96. Epub 2006 Apr 21 and Stroke. 2010 Mar;41(3):538-43. Epub 2010 Jan 14.

lethality[121]. Yale and UCLA filed for patent protection over this method of use for 3E10[122] and Hansen's work on it was published in 2012[123]. By 2015 the Hansen lab had a divalent scFv fusion protein from 3E10 with better cell penetrating ability[124] on which they published as well[125]. Around that time the Hansen lab also showed that their 3E10 variant would be preferentially taken up in cancer cells due to its ability to bind to the extracellular DNA that proliferates around tumours[126]. This led to work published in 2016 showing that conjugating drug nanoparticles to 3E10 would fulfil Weisbart's earlier idea of 3E10 as a drug delivery vehicle[127].

Deoxymab becomes Patrys' lead compound, 2016. James Hansen, his Yale colleague Dr Peter Glazer[128], and others, formed a company called Nucleus Therapeutics Pty Ltd around Deoxymab in 2015. Patrys acquired this company in March 2016[129].

Appendix II – A Patrys glossary

3E10 – See Deoxymab 3E10.

5C6 – A Patrys cell-penetrating antibody candidate.

Accelerated approval – Early approval of a drug based on the use of a surrogate endpoint.

Antibodies – Immune system proteins that can bind to an antigen and help to neutralise the potentially harmful effects of the cells carrying the antigen. Antibodies are commonly used in drug therapy for this reason.

Antigen – A molecule that stimulates the immune system to respond to a perceived threat. Antibodies work by binding to antigens.

Apoptosis – 'Programmed' cell death, that is, death that is naturally-occurring. Cancer cells tend to avoid apoptosis.

Autoantibody – An antibody against an antigen produced by the organism itself.

Base – A constituent of nucleic acids such as DNA that combines with sugar and phosphate in nucleotides. There are four bases – adenine (A), thymine (T), guanine (G) and cytosine (C).

Base excision – A DNA repair pathway in which specific enzymes recognize, cut out, and patch up bases in the DNA molecule. The PARP inhibitors interfere with the base excision pathway.

[121] Hansen and his colleagues believe this may explain why SLE patients have a lower risk for specific cancers – see the review article on their hypothesis, which they term 'the lupus butterfly theory' (Nat Rev Rheumatol. 2016 Jul;12(7):429-34. Epub 2016 Mar 24). For one meta-analysis that demonstrates this lower risk in breast, ovarian, and endometrial cancers see Br J Cancer. 2011 Apr 26;104(9):1478-81. Epub 2011 Apr 12.
[122] See WO2012/135831, priority date 1 April 2011. Another assignee on the patent application was the US Department of Veterans Affairs, by virtue of the fact that Weisbart's lab was located at the Sepulveda VA Hospital in the Los Angeles suburb of North Hills.
[123] Sci Transl Med. 2012 Oct 24;4(157):157ra142.
[124] WO/2016/033321, priority date 28 August 2014,
[125] Cancer Res. 2015 Jun 1;75(11):2285-91. Epub 2015 Apr 1.
[126] Sci Rep. 2015 Jul 9;5:12022.
[127] Oncotarget. 2016 Sep 13;7(37):59965-59975.
[128] Dr Peter Glazer is the Robert E. Hunter Professor of Therapeutic Radiology and Professor of Genetics at Yale University and Chairman of Yale's Department of Therapeutic Radiology.
[129] A$360,000 paid on settlement; A$180,000 to be paid upon the granting of certain patents associated with the technology; and A$180,000 to be paid on dosing the first patient in a Phase 1 trial. Patrys issued 50 million shares at 0.7 cents to settle the initial A$360,000.

BRCA1, BRCA2 – Tumour suppressor genes that contribute to pathways involved in DDR.

cGMP – Good Manufacturing Practice (GMP) is the set of standards that have been laid down by regulators such as the FDA for the production of clinical-grade pharmaceuticals. cGMP refers to 'current' Good Manufacturing Practice, since GMP standards tend to change over time.

DDR – Short for DNA Damage Response or DNA Damage Repair, mechanisms which cells use to re-join DNA when it has been broken.

Deoxymab 3E10 – Patrys' original cell-penetrating monoclonal antibody. Deoxymab 3E10 is a mouse antibody from which PAT-DX1 is derived.

di-scFv – See scFv.

DNA – Short for deoxyribonucleic acid, a complicated molecule in the nucleus of the cell that houses the body's operating instructions. It is made up of a long string of base pairs twisted around in a helical shape.

DNA repair – The enzymatic re-joining of DNA after it has been broken mistakes in transcription, ultraviolet radiation or chemicals. Deoxymab 3E10 interferes with DNA repair.

Doxorubicin – An off-patent anti-cancer drug that has been in use for some decades, mainly for treating breast and liver cancers. It was originally developed in the late 1960s as an antibiotic obtained from the bacterium *Streptomyces peuceticus*. It first gained FDA approval as a cancer drug in 1974.

Fab – See fragment.

Fragments – A portion of a full antibody obtained when the antibody is cleaved using the enzyme papain. The antibody's variable domains and the adjacent constant domains together form two Fab fragments, Fab standing for 'fragment antibody binding'. The remaining fragment is Fc, that is 'fragment crystallisable'.

Fusion protein – Two or more proteins expressed as a single protein construct.

Glioblastoma – Also called Glioblastoma Multiforme (GBM), a rare brain cancer that begins in the glial cells that surround and support neurons.

Glioma – A cancer of the glial cells that provide the 'structural backbone' of the brain through their support of the neurons. The highest grade of glioma is glioblastoma.

Homologous recombination – A DNA repair pathway in which there is an exchange of genetic information between related DNA molecules, allowing repair of double-stranded breaks.

Humanisation – The engineering of an animal antibody so that it is more like a human antibody.

IND – Short for Investigational New Drug application, an IND is a request filed with the FDA for authorisation to conduct human trials of a new drug or biological product in the United States.

In silico – A Latin term to refer to a biological experiment performed on computer or via computer simulation.

In vitro – Latin for 'in glass', referring to data obtained through testing in a test tube.

In vivo – Latin for 'in life', referring to data obtained through testing in live organisms including animal models and humans.

Line – The order in which drug therapy takes place. 'First line' is the first regimen used. When it fails, a patient moves to second line therapy, and so on.

Lupus – See Systemic Lupus Erythematosus.

Monoclonal antibodies – Antibodies cloned from a particular antibody-making cell where that antibody is highly specific for a particular antigen. Monoclonal antibodies are increasingly used as drugs.

Nanoparticles – Tiny particles with a diameter below 100 nanometres.

Nucleosides – Combination of sugar and one of four 'bases' that make up DNA. Deoxymab 3E10 uses a nucleoside transporter to get into the cell nucleus.

Nucleus – The 'control centre' of the cell, containing the DNA.

Objective Response Rate – The rate at which tumours shrink as a result of medical treatment, where the response is measured by the RECIST criteria. RECIST, short for the Response Evaluation Criteria in Solid Tumours, is a set of rules that define when a tumour has responded to treatment, is stable, or has progressed.

Orphan Drug – A drug that benefits less than 200,000 potential patients in the US. Orphan status provides tax benefits as well as market exclusivity in both Europe and the US.

Overall Survival (OS) – The percentage of subjects in a clinical trial who have survived for a defined period of time.

Pathway – The succession of biochemicals that interact with each other in order to signal a part of the body to perform a particular biological function. Often an aberrant signalling pathway is a cause of cancer.

PAT-DX1 – Patrys' cell-penetrating anti-DNA antibody product. PAT-DX1 is a humanised di-scFv derived from Deoxymab 3E10. PAT-DX1-NP is a nanoparticle conjugated version of this antibody.

PTEN – A tumour suppressor gene that contribute to pathways involved in DDR.

Progression-Free Survival (PFS) – The length of time a cancer patient undergoing treatment can see no worsening of his or her cancer.

Residue – Individual amino acids in a protein.

scFv – Short for 'single-chain variable fragment', a fusion protein of the variable regions of the heavy (VH) and light chains (VL) of antibodies. Di-scFvs are two scFvs linked together. PAT-DX1 is a humanised di-scFv derived from Deoxymab 3E10.

Systemic Lupus Erythematosus (SLE) – An autoimmune disorder characterised by multiple symptoms including rash and joint pain.

Synthetic Lethality – A genetic phenomenon in which the knockout of two genes kills a cell where the knockout of only one of these genes would have no effect.

Xenograft – An animal model of cancer in which a human tumour is grafted onto a mouse without a functioning immune system, so that the tumour will stay in place.

Appendix III – Patrys' intellectual property

Patrys' intellectual property around cell-penetrating cancer antibodies is covered by three disclosed patent families:

Cell-penetrating anti-DNA antibodies and uses thereof to inhibit DNA repair, WO/2012/135831, priority date 1 April 2011, invented by James Hansen, Peter Glazer, Richard Weisbart, Robert Nishimura and Grace Chan[130].

- This patent application covers the use of 3E10 in the treatment of cancer.

Multivalent fragments of antibody 3E10 and methods of use thereof, WO/2016/033321, priority date 28 August 2014, Invented by James Hansen, Richard Weisbart and Philip Noble[131].

- This patent application covers the di-scFv antibody fragments derived from 3E10.

Cell penetrating nucleolytic antibody based cancer therapy, US/20150376279, priority date 25 June 2015, invented by James Hansen, Richard Weisbart and Philip Noble.

- This patent application covers a lupus autoantibody called 5C6 that works against tumours by destroying cancer cell DNA.

Patrys has also licenced Yale IP relating to the linking of nanoparticles to 3E10, and filed on the humanised di-scFv derived from Deoxymab 3E10, but details of these patent families are not yet publicly available.

[130] The patent application was granted as US Patent 9,701,740 in July 2017.
[131] Philip Noble, then a postdoc in Hansen's Yale laboratory, is now a researcher with the Belgian pharma company UCB.

Appendix IV – Capital structure summary

		% of fully diluted	Note
Ordinary shares, ASX Code PAB (million)	779.5	96.6%	
Unlisted options (million)	27.1	3.4%	Average exercise price 0.8 cents, average expiry date 11-Nov-2021
Fully diluted shares	806.6		

Current market cap:	A$15.6 million (US$11.9million)
Current share price	$0.020
Twelve month range	$0.004 - $0.03
Average turnover per day (last three months)	8.2 million

Appendix V – Major shareholders

Patrys currently has two substantial shareholders:

- **Michael Stork** (12.3%).
- **Dr Dax Calder** (11.2%), a Perth periodontist.

Appendix VI – Papers relevant to Patrys

Weisbart et. al. (1990), *A conserved anti-DNA antibody idiotype associated with nephritis in murine and human systemic lupus erythematosus*. J Immunol. 1990 Apr 1;144(7):2653-8.

- This paper reported an idiotypic antibody[132] with which to study the 3E10 antibody. The idiotypic antibody seemed to be protective in lupus associated with nephritis, that is, kidney inflammation.

Zack et. al. (1996), *Mechanisms of cellular penetration and nuclear localization of an anti-double strand DNA autoantibody*. J Immunol. 1996 Sep 1;157(5):2082-8.

[132] In immunology an 'idiotype' is the unique variable region that sets a particular antibody apart from all others. Anti-idiotypic antibodies are used to identify antibodies with a particular idiotype of interest.

- This paper established that 3E10 was able to penetrate cells by binding to DNA.

Weisbart et. al. (1998), *An autoantibody is modified for use as a delivery system to target the cell nucleus: therapeutic implications*. J Autoimmun. 1998 Oct;11(5):539-46.

- This paper showed that single-chain antibody fragments of 3E10 could penetrate cells and make it to the cell nucleus, suggesting that they could be used to deliver therapeutic or other molecules to the nucleus.

Spertini et. al. (1999), *Idiotypic vaccination with a murine anti-dsDNA antibody: phase I study in patients with nonactive systemic lupus erythematosus with nephritis*. J Rheumatol 1999 26(12): 2602-8.

- Following on from Weisbart et. al. (1990) above, this paper reported that 3E10, used as an anti-idiotypic vaccine in lupus patients with nephritis, would generate the expected anti-idiotypic immune response.

Hansen et. al. (2007), *Intranuclear protein transduction through a nucleoside salvage pathway*. J Biol Chem. 2007 Jul 20;282(29):20790-3. Epub 2007 May 24 (full text available for free online).

- This paper showed that 3E10 scFv, the single-chain antibody fragment of 3E10, penetrates cells via a nucleoside salvage transporter called ENT2.

Hansen et. al. (2012), *Targeting cancer with a lupus autoantibody*. Sci Transl Med. 2012 Oct 24;4(157):157ra142 (full text available for free online).

- This paper demonstrated that 3E10, by preventing DNA repair, could sensitise tumour cells to therapies that would through DNA damage such as doxorubicin and radiation. 3E10 was found to work against BRCA2-deficient cancer – BRCA2 being a regulator of DNA repair – as a single agent as well as by sensitising the cells to doxorubicin.

Noble et. al. (2014), *A nucleolytic lupus autoantibody is toxic to BRCA2-deficient cancer cells*. Sci Rep. 2014 Aug 5;4:5958 (full text available for free online).

- This paper identifies 5C6 as another cell-penetrating antibody with potential in BRCA2-related cancers.

Noble et. al. (2015), *Optimizing a lupus autoantibody for targeted cancer therapy*. Cancer Res. 2015 Jun 1;75(11):2285-91. Epub 2015 Apr 1 (full text available for free online).

- This paper shows that divalent single chain variable fragments (di-scFv) of 3E10 can be engineered that improve the cellular penetration of the original antibody.

Weisbart et. al. (2015), *DNA-dependent targeting of cell nuclei by a lupus autoantibody*. Sci Rep. 2015 Jul 9;5:12022 (full text available for free online).

- This paper focused on how extracellular DNA improves uptake of 3E10 scFv into cells, suggesting that this improves preferential localisation into tumour cells since there is more extracellular DNA around tumours.

Noble et. al. (2016), *DNA-damaging autoantibodies and cancer: the lupus butterfly theory*. Nat Rev Rheumatol. 2016 Jul;12(7):429-34. Epub 2016 Mar 24.

- This review article discusses what was known in mid-2016 about anti-DNA antibodies from lupus and their potential role in cancer therapy.

Chen et. al. (2016), *A lupus anti-DNA autoantibody mediates autocatalytic, targeted delivery of nanoparticles to tumors*. Oncotarget. 2016 Sep 13;7(37):59965-59975 (full text available for free online).

- This paper showed that 3E10 conjugated to nanoparticles could be used to deliver doxorubicin to cells.

Appendix VII – Comparable companies

Aileron Therapeutics. This company is being built on 'stapled peptides' – peptides that are chemically stabilised so that they fold into a therapeutically useful 'alpha helical' shape and can be deliverable intracellularly. Aileron's lead candidate, ALRN-6924, targets the tumour suppressor protein p53. It has completed Phase 1 in both solid and liquid tumours.

Auris Medical. This company is working on therapies for inner ear disorders. The lead candidate is AM-111, for the treatment of acute sensorineural hearing loss. AM-111 is a cell-penetrating peptide designed to inhibit JNK, the kinase which regulates a range of biological processes implicated in neurodegenerative disorders. The product is now in Phase 3.

Cellectar Biosciences. This company's phospholipid drug conjugates (PDCs) deliver oncology drug payloads to cancer cells. The lead PDC, CLR-131, which delivers the radioisotope Iodine-131, is in Phase 2 in Multiple Myeloma as well as various leukemias and lymphomas.

Checkpoint Therapeutics. This company, which has a key focus on immuno-oncology, is in early stage clinical work with an anti-PD-L1 antibody and a small molecule EGFR inhibitor for lung cancer. A PARP inhibitor originally developed by Cephalon, and outlicensed to Checkpoint by Teva in January 2016, is pre-clinical.

Cyclacel Pharmaceuticals. This company's clinical programmes centre on inhibitors to Cyclin-Dependent Kinases, which are known to activate DNA damage checkpoint and repair pathways. CYC065, which inhibits CDK2 and CDK9, is in early clinical development in various advanced cancers. A sequential combination of sapacitabine, a nucleoside analogue, and seliciclib, a CDK inhibitor, is being studied in patients with BRCA-positive advanced solid tumours.

Emisphere Technologies. This company's Eligen technology centres on a library of absorption-enhancing compounds that harness natural passive transcellular transport processes for oral drug delivery. Eligen has been used for the delivery of various products including calcitonin, PTH, Vitamin B12, and oral GLP-1 analogues.

Endocyte. This company develops small molecules to various cancer targets of interest where the cell-killing ability of the product comes from its conjugation to a radioisotope. The company's lead compound is a small molecule conjugated to Lutetium-177 that targets Prostate-Specific Membrane Antigen. This product has completed Phase 2 in metastatic castrate-resistant prostate cancer.

Medicenna Therapeutics. This company engineers the cytokine interleukin-4 for a strong signal on receptor binding, and uses this 'superkine' to deliver therapeutic payloads into cells. The company's lead MDNA55 has bacterial *Pseudomonas* exotoxin A as the payload. That product is currently in Phase 2b in adults with recurrent glioblastoma.

OncoSec Medical. This cancer immunotherapy developer is in Phase 2 in metastatic melanoma with Immunopulse, a technology in which short-duration electrical pulses are applied to a tumour to allow the delivery of DNA-based IL-12, which in turn helps direct an anti-tumour immune response. Immunopulse is also in a second Phase 2 in combination with Keytruda.

Onxeo. This company's lead Belinostat product is a histone deactylase inhibitor now moving into Phase 2 in Peripheral T-Cell Lymphoma. AsiDNA, a DNA break repair inhibitor, is being prepared for Phase 1 studies in 2018. AsiDNA is a short double-stranded DNA molecule that triggers false DNA break signals, preventing actual DNA repair.

Sierra Oncology. This company has been built around various products involve in DNA Damage Response. The company's lead compound is SRA737, which inhibits Checkpoint Kinase 1 (Chk1), a mediator of DNA damage response. Chk1 is in two Phase 1 studies in advanced cancer, one as a monotherapy and one in conjunction with gemcitabine.

Sorrento Therapeutics. This immuno-oncology company has a range of antibody platforms including G-MAB for fully human antibodies (based on genetic sequencing of the variable regions of antibodies sourced from healthy donors) and iTab for intracellular targeting antibodies. The company is moving towards the clinic with a CAR-T and an Antibody-Drug Conjugate targeting CD38, both of which may be useful in Multiple Myeloma and liver cancer.

Table 2: Comparable companies to Patrys

Company	Location	Code	Market cap (USDm)	Web	Reason for inclusion
Sorrento Therapeutics	San Diego, Ca.	Nasdaq: SRNE	266	www.sorrentotherapeutics.com	Cell-penetrating antibodies
Endocyte	West Lafayette, In.	Nasdaq: ECYT	183	www.endocyte.com	Radioligand therapy
Sierra Oncology	Vancouver, BC	Nasdaq: SRRA	163	www.sierraoncology.com	Working on PARP inhibitor
Aileron Therapeutics	Cambridge, Ma.	Nasdaq: ALRN	144	www.aileronrx.com	Cell-penetrating peptides
Checkpoint Therapeutics	New York, NY	Nasdaq: CKPT	107	www.checkpointtx.com	Working on PARP inhibitor
Onxeo	Paris, France	Euronext Paris: ONXEO	65	www.onxeo.com	DNA Repair inhibitor
OncoSec Medical	San Diego, Ca.	OTCBB: ONCS	59	www.oncosec.com	Intracellular delivery of immunotherapies
Medicenna Therapeutics	Toronto, On.	TSX-V: MDNA	35	www.medicenna.com	Intrcellular delivery of toxins
Auris Medical	Zug, Switzerland	Nasdaq: EARS	21	www.aurismedical.com	Cell-penetrating peptides
Cyclacel Pharmaceuticals	Berkeley Heights, NJ	Nasdaq: CYCC	20	www.cyclacel.com	Cyclin Dependent Kinase inhibitors
Emisphere Technologies	Roseland, NJ	OTCBB: EMIS	20	www.emisphere.com	Intracellular delivery of large molecules
Cellectar Biosciences	Madison, Wi.	OTCQX: CLRB	18	www.cellectar.com	Phospholipid drug conjugates

Table 3: Companies involved in pancreatic cancer

Company	Location	Code	Market cap (USDm)	Web
FibroGen	San Francisco, Ca.	Nasdaq: FGEN	3,555	www.fibrogen.com
Halozyme Therapeutics	San Diego, Ca.	Nasdaq: HALO	2,793	www.halozyme.com
Five Prime Therapeutics	South San Francisco, Ca.	Nasdaq: FPRX	601	www.fiveprime.com
NantKwest	Culver City, Ca.	Nasdaq: NK	407	www.nantkwest.com
AB Science	Paris, France	Euronext Paris: AB	400	www.ab-science.com
Tyme Inc.	New York, NY	Nasdaq: TYME	378	www.tymeinc.com
Celyad	Mont-Saint-Guibert, Belgium	Euronext Brussels: C\	375	www.celyad.com
Erytech Pharma	Lyon, France	Euronext Paris: ERYP	341	www.erytech.com
NewLink Genetics	Ames, Ia	Nasdaq: NLNK	287	www.newlinkgenetics.com
ChemoCentryx	Mountain View, Ca.	Nasdaq: CCXI	284	www.chemocentryx.com
Merrimack Pharmaceuticals	Cambridge, Ma.	Nasdaq: MACK	136	www.merrimackpharma.com
Verastem	Cambridge, Ma.	Nasdaq: VSTM	117	www.verastem.com
RedHill Biopharma	Tel Aviv, Israel	Nasdaq: RDHL	103	www.redhillbio.com
PharmaCyte Biotech	Laguna Hills, Ca.	OTCQB: PMCB	58	www.pharmacyte.com
RedX Pharma	Macclesfield, UK	LSE: REDX	34	www.redxpharma.com
Genocea Biosciences	Cambridge, Ma.	Nasdaq: GNCA	32	www.genocea.com
Bio-Path	Houston, Tx.	OTCBB: BPTH	26	www.biopathholdings.com
Diffusion Pharmaceuticals	Charlottesville, Va	OTCBB: DFFN	19	www.diffusionpharma.com

Appendix VIII – Companies involved in pancreatic cancer

AB Science. This company's Masitinib product, a tyrosine kinase inhibitor, is in Phase 3 in various indications including pancreatic cancer. Phase 3 data from 2015 identified that the product seemed to provide a survival benefit in patients that expressed a biomarker called ACOX1[133].

Bio-Path. This company's technology facilitates liposomal delivery of antisense DNA. The company is in early stage clinical trials with prexigebersen (Liposomal Grb2) and BP1002 (Liposomal Bcl2) in Acute Myeloid Leukemia (AML) and Chronic Myeloid Leukemia (CML) respectively. A pre-clinical candidate is BP1003, which is liposomal Stat3 for pancreatic cancer.

Celyad. This company, a player in CAR-T therapy for cancer, has as its lead CAR-T construct one that expresses NKG2D, an activating receptor found on the surface of Natural Killer cells and which has ligands on a wide variety of tumour types, both solid and liquid. Pancreatic cancer is one of a number of indications of interest for CAR-T NKR2. The product is in Phase 1.

ChemoCentryx. This company, whose focus is drugs that act via chemokines, is in Phase 3 with Avacopan, a drug which targets a complement receptor and which is initially indicated for a rare inflammatory disorder of the blood vessels called anti-neutrophil cytoplasmic auto-antibody-associated vasculitis. A CCR inhibitor called CCX872,

[133] Ann Oncol. 2015 Jun;26(6):1194-200. Epub 2015 Apr 9.

designed to knock down myeloid derived suppressor cells in the tumour microenvironment, is in Phase 2 in pancreatic cancer.

Diffusion Pharmaceuticals. This company's lead product, a synthetic carotenoid called Trans Sodium Crocetinate (TSC), is designed to restore chemosensitivity to tumours by re-oxygenating the hypoxic micro-environment. Diffusion Pharmaceuticals is now preparing for Phase 3 in glioblastoma. The company intends for pancreatic cancer to be TSC's next indication.

Erytech Pharma. This company's technology allows therapeutic drugs to be encapsulated inside red blood cells, which allows them to remain inside the body longer. The company's lead product, Eryaspase, is encapsulated L-asparaginase, an enzyme that is sometimes used in the treatment of Acute Lymphoblastic Leukemia. Erytech has reached Phase 2/3 in this indication with its encapsulated formulation and has completed Phase 2b in pancreatic cancer.

FibroGen. This company's lead product, now in Phase 3, is Roxadustat for the treatment of anemia associated with Chronic Kidney Disease[134]. Pamrevlumab, an antibody to Connective Tissue Growth Factor, is in Phase 2 in various conditions including pancreatic cancer. The thinking is that by attacking the connective tissue of the tumour, unresectable tumours can become resectable.

Five Prime Therapeutics. This company has been built on a proprietary library of human extracellular proteins which the company screens looking for new targets. The company's lead Cabiralizumab monoclonal antibody targets the tumour-associated macrophages known to suppress an anti-cancer immune response. Cabiralizumab is being trialled in combination with Bristol-Myers Squibb's Opdivo PD-1 inhibitor in various cancers including pancreatic, where the thinking is that the two drugs will potentiate standard-of-care chemotherapy.

Genocea Biosciences. This company's Atlas platform identifies neoantigens suitable for personalised cancer vaccines by feeding these to a patient's own Antigen Presenting Cells. The actual vaccines are synthetic long peptides paired with an adjuvant. Genocea expects to take this approach to the clinic in 2018. Pre-clinically this platform has shown good data in prostate and pancreatic cancer.

Halozyme Therapeutics. This company's PEGPH20 product is a formulation of the hyaluronidase enzyme which, by degrading hyaluronan, a common factor in the tumour microenvironment, facilitates tumour access for cancer therapies. PEGPH20 is in Phase 3 in pancreatic cancer. Halozyme's hyaluronidase formulation has also been used to enhance delivery of large molecule drugs such as antibodies and IVIG.

Merrimack Pharmaceuticals. This company, whose core competency is the ability to model systems biology and thereby understand cancer-related signalling pathways, developed Ipsen's Onivyde drug for the treatment of pancreatic cancer. The company's two lead antibody therapeutics, both in Phase 2, are MM-121, targeting HER3, and MM-141, a bi-specific antibody targeting IGF1-R and HER3. MM-121 is indicated for lung and breast cancer, MM141 for pancreatic cancer

[134] The drug stimulates red blood cell production by inhibiting an enzyme called hypoxia-inducible factor-prolyl hydroxylase.

NantKwest. This company's platform centres on the use of Natural Killer cells for the treatment of cancer. The company intends to study a cancer vaccine based on activated NK cells in pancreatic cancer[135].

NewLink Genetics. This company is focused on inhibitors to an immune checkpoint called IDO. The company's Indoximod product is moving into a pivotal study in melanoma in conjunction with a PD-1 inhibitor. The same drug is at Phase 2 in pancreatic cancer with gemcitabine and Abraxane.

OncoMed Pharmaceuticals. This cancer drug developer's lead compounds are two monoclonal antibodies – Navicixizumab, a bi-specific antibody that targets DLL4 in the Notch cancer stem cell pathway as well as VEGF receptors, and Rosmantuzumab, which targets a pathway called RSPO-LGR. Navicixizumab is in Phase 1b in ovarian and colorectal cancers.

Pharmacyte Biotech. This company's cellulose-based live cell encapsulation technology allows cellular therapies to be implanted in patients protected from the patient's immune system. One application of this technology is live human cells that produce an enzyme designed to convert the cancer prodrug ifosfamide into its cancer-killing form. Such a product has potential in pancreatic cancer.

RedHill Biopharma. This company, which markets two prescription products for gastrointestinal disorders, has a pipeline of mostly gastrointestinal drugs including a combination antibiotic therapy for Crohn's disease in Phase 3. Mesupron, a protease inhibitor[136], has completed Phase 2 in pancreatic cancer.

RedX Pharma. This company's lead compound is RXC004, a 'porcupine inhibitor', porcupine being an enzyme in the WNT signalling pathway. The compound is intended to be studied as a single agent in pancreatic cancer and, in combination with a PD-1 inhibitor, in melanoma.

Tyme Inc. This company is in Phase 2 with a drug combination called SM-88, which comprises a tyrosine derivative plus phenytoin, methoxsalen, and sirolimus. The tyrosine derivative is designed to interfere with tumour cell metabolism. SM88 is now in Phase 2 in prostate cancer. A Phase 2 in pancreatic cancer is planned.

Verastem. This company's lead compound is Duvelisib, a PI3K inhibitor that has completed Phase 3 in refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma and for which Verastem is now preparing to file for FDA approval. Verastem's Defactinib candidate, an inhibitor of the Focal Adhesion Kinase (FAK) pathway, is in Phase 2 in ovarian cancer, in conjunction with Bavencio, Pfizer's PD-L1 inhibitor. Defactinib is being evaluated in pancreatic cancer in conjunction with Keytruda in two investigator-sponsored trials.

[135] See NCT03136406 at www.clinicaltrials.gov.
[136] Extracellular proteases play a key role in tumour cell invasion – see Clin Chim Acta. 2000 Feb 15;291(2):113-35

Risks related to Patrys

Risks specific to Patrys. We see five major risks for Patrys as a company and as a listed stock:

- **Clinical risk**. There is the risk that Patrys' compounds may fail to meet their primary or secondary endpoints in the clinical trials into which they are taken.
- **Funding risk**. More capital will likely be needed to continue clinical development of Patrys' compounds.
- **Drug class risk**. There is the risk that the PARP inhibitors may fail to enjoy the kind of sales potential we have discussed in this note, which would in turn impact the potential licensing interest in Patrys' Deoxymab-based products.
- **Timing risk.** There is the risk that the clinical studies we discuss in this note may take longer than we expect to complete.
- **Regulatory risk.** There is the risk that regulatory decisions may slow or stop the progress of Patrys' various products.

Risks related to pre-revenue Life Science companies in general.

- The stocks of biotechnology and medical device companies without revenue streams from product sales or ongoing service revenue should always be regarded as speculative in character.

- Since most biotechnology and medical device 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 device 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 abovementioned specific and general risks before buying any the stock of any biotechnology and medical device stock mentioned on this report, including Patrys.

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