NDF RESEARCH

Providing independent research coverage of
ASX-listed Life Science companies

Patrys (ASX: PAB)

Update note – Thursday 3 May 2018

Favourable data continues to accrue

This note updates our 19 December 2017 note headlined 'cell-penetrating monoclonal antibodies'. Patrys has been working since 2016 on a powerful new cancer treatment approach that combines the targeting strength of monoclonal antibodies with the cancer-killing ability of the PARP inhibitors. The company has made considerable progress since it first in-licensed from Yale University a cell-penetrating monoclonal antibody fragment called 3E10. The humanised and optimised version of 3E10, called PAT-DX1, has now shown *in vivo* on numerous occasions that it can penetrate to the nucleus of a cancer cell and interfere with DNA Damage Response mechanisms, in a similar fashion to the PARP inhibitors such as AstraZeneca's Lynparza that are set to become a blockbuster drug class. In this note we look at recent pre-clinical studies from the laboratory of Professor James Hansen at Yale showing that PAT-DX1, and another product called PAT-DX1-NP (PAT-DX1 conjugated to cancer-killing, drug-loaded nanoparticles) can localise to the site of tumours, bring about reductions in tumour size and extend survival *in vivo*. While neither product is expected to be in the clinic before 2019, the repeat evidence of the potential effectiveness of Patrys's lead products is exciting.

Rating	Risk	Current price	Target price
Buy	Speculative	$0.037	$0.13

Stock details

Daily Turnover: ~A$780,000
Market Cap: A$34.5m
Shares Issued: 931.6m
52-Week High: $0.066
52-Week Low: $0.004

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Please note: This report has been commissioned by Patrys and NDF Research has received payment for its preparation. Stuart Roberts holds shares in Patrys as at the date of this report. Please refer below for risks related to Patrys as well our General Advice Warning, disclaimer and full disclosures. Also, please be aware that the investment opinion in this report is current as at the date of publication but that the circumstances of the company may change over time, which may in turn affect our investment opinion.

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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.

NDF believes that ASX-listed companies have been largely overlooked in the global Life Sciences boom that began in late 2008, partly because of insufficient quality research. NDF's goal is to provide such research, and introduce investors around the world to potential future billion-dollar companies from 'Down Under'.

To learn more about the Life Sciences sector on the ASX and our firm, please visit ndfresearch.com.

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

In this report

Patrys – the favourable data continues to accrue

Who is Patrys? 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 humanised Deoxymab 3E10 antibody di-fragment suitable for human use called PAT-DX1[1], 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 nanoparticles that can carry cancer-killing drugs. 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. In 2017 Patrys garnered some favourable *in vitro* and *in vivo* data on the clinical effectiveness of both PAT-DX1 and PAT-DX1-NP in a variety of cancers. There has been more such good news in 2018:

PAT-DX1 CAN LOCALISE TO THE SITE OF A TUMOUR

PAT-DX1-NP in Triple-Negative Breast Cancer (TNBC), January 2018 – *In vivo* evidence of drug localisation at the site of the tumour. The laboratory of Professor James Hansen at Yale used a xenograft model of TNBC to show that PAT-DX1-NP was much better at localising to tumour sites than just the nanoparticles on their own. The localisation was not just to the primary tumours, but to lymph node metastases. This finding bodes well for Patrys should the company choose to pursue this indication for PAT-DX1 in the clinic, since lymph node metastases decrease survival in this setting[2]. Hansen and colleagues had already shown last year that this was possible when they found the same effect with PAT-DX1's precursor, the lupus autoantibody 3E10, conjugated to nanoparticles in a syngeneic mouse breast cancer model[3], while Patrys had announced in September 2017 that PAT-DX1-NP had performed similar localisation in an animal model of glioblastoma. The January 2018 announcement provided confirmatory evidence of the localisation effect of the humanised version of the 3E10, PAT-DX1. In all cases it is theorised that the increased presence of extracellular DNA in the tumour microenvironment is what allows the PAT-DX1 antibody di-fragment to bring the nanoparticles inside cells.

PAT-DX1 in glioblastoma, February 2018 – Notable availability of the drug above the blood-brain barrier, *in vivo*. The important part of Patrys's September 2017 announcement regarding PAT-DX1 in glioblastoma was that it suggested very strongly that PAT-DX1 could deliver above the blood-brain barrier, which is obviously important for a drug designed to treat a brain cancer. In February 2018 the Hansen lab at Yale showed that PAT-DX1 without the nanoparticle conjugations would work in an 'orthotopic' model of glioblastoma. In orthotopic models the human tumour is either implanted or injected into the equivalent organ from which the cancer originated[4] so it provides as reliable a model as possible for the real thing. In this setting the Hansen lab found significant tumour shrinkage with PAT-DX1.

[1] The engineering work behind PAT-DX1 has now been published – see Biochem Biophys Res Commun. 2018 Feb 12;496(3):858-864. Epub 2018 Jan 31. Patrys has now filed for composition-of-matter coverage of the various humanised variants of 3E10, which allows likely patient protection out to 2037 or 2038.
[2] Br J Cancer. 2016 Oct 25;115(9):1024-1031. Epub 2016 Sep 29.
[3] Oncotarget. 2016 Sep 13;7(37):59965-59975.
[4] The alternative is the easier-to-construct 'heterotopic' model.

PAT-DX1 in glioblastoma, March 2018 – Favourable survival outcomes *in vivo*. The February 2018 announcement related to PAT-DX1 in glioblastoma indicated that survival data from the treated versus untreated mice was pending. This data became available in March and showed the PAT-DX1 treated mice survived 20% longer than untreated control mice. This result not only had high statistical significance, with a p value of only 0.004, but was achieved where, so we learned with this result, the orthotopic model of glioblastoma was of the unmethylated MGMT variety – the one that does not generally respond to temozolomide therapy[5] and which occurs in around half of the patient population[6]. So, in a sophisticated model of the most difficult form of glioblastoma, Patrys showed a survival benefit using PAT-DFX1 as a single agent. One can only guess how this may evolve as Patrys moves to optimise dosing and formulation. Also in March 2018 Patrys reported that, in the same orthotopic model of glioblastoma, PAT-DX1 alone was superior to AstraZeneca's Lynparza alone, but that the two drugs together were not superior to Lynparza alone, presumably because the latter drug does not have bioavailability above the blood-brain barrier.

We note that this data, and the glioblastoma data from February 2018 were presented at the American Association for Cancer Research's annual conference in April 2018.

Where to from here? It seems that Patrys has positioned itself very well with the DX1 asset, and what was originally in-licensed as a discrete asset actually has the attributes of being an asset platform with multiple and varied applications. We expect that the rest of 2018 and much of 2019 will see a continued accrual of favourable data around both PAT-DX1 and PAT-DX1-NP. The various pre-clinical studies will likely guide the choice of initial clinical indications for both PAT-DX1 and PAT-DX1-NP in the second half of this year, after which the product can go into toxicology studies ahead of the commencement of clinical work from late 2019.

Background to Patrys

Patrys has a cell-penetrating antibody product. 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, which is a humanised and optimised version of 3E10, uses the same mechanism but works much more efficiently.

PATRYS' DEOXYMAB ANTIBODY IS CELL-PENETRATING

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

[5] MGMT, a gene located at chromosome 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.
[6] Fam Cancer. 2013 Sep;12(3):449-58.

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? 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.

PAT-DX1 GOES TO THE CLINIC NEXT YEAR

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.

If Patrys is so good, why was it recently available for only A$15.6m/US$11.9m? Patrys stock was depressed until late 2017 because of the company's failure to progress its old IgM platform. The progress than has been made with the new Deoxymab products has helped prompt a re-rating. We believe that Patrys can continue to re-rate as more pre-clinical evidence of the effectiveness of this PAT-DX1 is released and as PAT-DX1 moves towards the clinic.

Valuing Patrys

Our 13 cents per share price target remains unchanged. We previously valued Patrys at 7.3 cents per share base case and 18.3 cents optimistic case. With this note our valuation range changed to 6.3 cents base case and 14.7 cents optimistic case, for three reasons

1) The recent increase in the 10-year bond rate raises our WACC from 15.2% to 15.4% (Speculative)[7]
2) The company recently raised $2.4m at 1.7 cents per share in a 2 for 11 rights issues
3) We assume for valuation purposes a further $8m raise at 3.3 cents per share.

We are maintaining our 13 cent share price target, in spite of its sitting at the upper end of our valuation range, because we see continued momentum from the PAT-DX1 and PAT-DX1-NP programmes given the recent *in vivo* data these products have generated.

[7] 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 2.8%; 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'.

Our valuation approach for Patrys is as follows:

- Our WACC was 15.4%.
- 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.

We assume Patrys partners PAT-DX1 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[8];
- A licensing in FY21 or FY22, for US$25-50m upfront, US$100-200m in milestones and a 10-15% royalty rate[9];
- 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.
- Cash settlement of the A$360,000 owning the vendors of the Deoxymab programmes.

Table 1: NDF Research's valuation of Patrys

	Base	Optim.
Deoxymab (A$m)	57.6	158.9
Total programme value	57.6	158.9
Value of tax losses	17.7	17.7
Corporate overhead	-10.9	-10.9
Cash now (A$m)	2.8	2.8
Cash to be raised (A$m)	8.0	8.0
Option exercises less obligations (A$m)	0.2	0.2
Total value (A$m)	75.4	176.7
Total diluted shares (million)	1,204.0	1,204.0
Value per share	$0.063	$0.147
Valuation midpoint	$0.105	
Share price now (A$ per share)	$0.037	
Upside to midpoint	183.8%	

[8] Clin Pharmacol Ther. 2010 Mar;87(3):272-7. Epub 2010 Feb 3.
[9] 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'*.

Re-rating Patrys

We see the following developments helping to continue re-rating 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

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 of PAT-DX1 and PAT-DX1-NP may take longer than we expect to initiate.
- **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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Stuart Roberts holds Patrys shares as at the date of this report.

Recommendations

NDF Research issues a BUY recommendation in case of an expected total shareholder return (TSR, share price appreciation plus dividend yield) in excess of 25% within the next twelve months, an ACCUMULATE recommendation in case of an expected TSR between 5% and 25%, a HOLD recommendation in case of an expected TSR between -5% and +5% within the next twelve months and a SELL recommendation in case of an expected total return lower than -5% within the next twelve months.