hardman&co

Pharmaceuticals & Biotechnology

Source: Eikon Thomson Reuters

Market data	
EPIC/TKR	**BNO**
Price (A$)	0.58
12m High (A$)	0.64
12m Low (A$)	0.34
Shares (m)	482.7
Mkt Cap (A$m)	280.0
EV (A$m)	275.2
Free Float*	89%
Market	ASX

**As defined by ASX Rule 1.1 Condition 7*

Description

Bionomics is an Australian biopharmaceutical company specialising in development of ion channel drugs for disorders of the central nervous system. In addition to a strong proprietary pipeline that includes ion channel allosteric modulators for anxiety, BNO offers contract drug development services.

Company information

CEO	Deborah Rathjen
CFO	Steven Lydeamore
Chairman	Errol De Souza
	+618 8354 6100
	www.bionomics.com.au

Key shareholders

Directors	0.7%
BVF Partners	10.2%
Ausbil Investment	8.1%
PPM	5.5%

Diary (calendar year)

Jun'18	Financial year-end
1H'18	BNC101 trial data
2H'18	PTSD trial data
1Q'19	Agitation trial data
1Q'19	Merck trial

Analysts

Martin Hall	020 7194 7632
	mh@hardmanandco.com
Dorothea Hill	020 7194 7626
	dmh@hardmanandco.com
Grégoire Pavé	020 7194 7628
	gp@hardmanandco.com

Bionomics

A big deal in oncology?

Bionomics (BNO) is an Australian biopharmaceutical company specialising in ion channel drug discovery for central nervous system (CNS) disorders such as anxiety and post-traumatic stress disorder (PTSD). BNO also offers contract and partnered drug discovery based on its proprietary technology platforms: MultiCore and ionX. The group sales model includes fees-for-service, licensing income and royalties from successful partnered products. Its strategic focus is on development of its lead candidate, BNC210, to completion of Phase II in PTSD. BNO is seeking to divest or out-license its off-strategy oncology programmes, which is the focus of this report.

- **Strategy:** BNO's recently refined strategy is to focus on development of its ion channel drug candidates, particularly allosteric modulators. It intends to partner its priority CNS candidate for late-stage development and commercialisation, and to monetise its clinical-stage, non-ion channel, oncology programmes.

- **Off-strategy assets:** Management has reiterated that it is in formal discussions for an oncology deal, a position originally announced at least eight months ago. The deal could take the form of a strategic partnership for clinical development of BNC101 from Phase Ia and/or of BNC105, currently in two Phase I trials.

- **New data:** New clinical information on BNC101 was presented at the AACR meeting in April 2018, which included data consistent with a pharmacodynamic effect of BNC101 in colorectal cancer patients. *In vitro* BNC105 data were also presented. BNO reiterated that this could assist partnering discussions.

- **Risks:** BNC101 is compelling as a first-in-class drug targeting the stem cell marker LGR5. However, there are significant risks in development of any drug, and there are no licensed cancer stem cell-targeting drugs. BNC105 has been through three trials in solid cancers but has failed primary end-points previously.

- **Investment summary:** BNO has a clear strategy to invest in developing its drug candidates to a stage that both interests big pharma and generates good potential returns for shareholders. Hardman & Co estimates the post-tax NPV of the two oncology assets to be around A$21m/$16m, and A$651m for the whole pipeline. The next inflection point is likely to be the BNC101 data in CY 1H'18.

Financial summary and valuation

Year-end June (A$m)	2015	2016	2017	2018E	2019E	2020E
Sales	6.79	7.14	5.53	5.90	6.20	6.50
R&D investment	-23.18	-24.77	-24.22	-24.00	-12.00	-12.00
Other income	1.35	2.59	14.62	14.81	34.41	34.60
EBITDA	-22.65	-24.95	-10.11	-10.35	21.25	21.55
Underlying EBIT	-24.37	-26.88	-11.86	-12.09	19.51	19.80
Reported EBIT	-24.35	-27.42	-12.36	-12.60	19.00	19.30
Underlying PBT	-24.28	-26.28	-12.62	-13.16	18.61	19.38
Statutory PBT	-24.27	-26.82	-13.13	-13.67	18.10	18.88
Underlying EPS (¢)	-4.06	-3.51	-1.30	-1.42	4.73	4.90
Statutory EPS (¢)	-3.27	-3.42	-0.14	-1.55	4.60	4.77
Net (debt)/cash	11.78	23.14	24.26	17.68	41.23	65.50
Capital increase	0.27	28.22	0.14	0.00	0.00	0.00

Source: Hardman & Co Life Sciences Research

Divestment of oncology assets

Strategy refocused on CNS in 2016

BNO's Board was remodelled in 2016, bringing in three new Non-Executive Directors and a new Chairman, in order to strengthen the company in 'areas (…) related to investment banking'[1]. This was followed by a major refocusing of group strategy, whereby BNO is now concentrating entirely on ion channel drug R&D. Its priority programme, BNC210, is in a Phase IIb trial for PTSD (described in our note 'Channelling expertise in CNS drugs'[2]) – BNO intends to partner it once Phase III is ready.

BNO is seeking to "monetise" (divestment or out-licensing) its off-strategy assets (non-ion channel programmes). These are the clinical-stage oncology drug candidates BNC101 and BNC105, which are currently in Phase I trials. The latest corporate announcements reiterate that management is in a formal process for partnering these programmes and has been since at least October 2017.

Non-ion channel drug candidates

Candidate	Action	Primary indication(s)	Trials ongoing
BNC101	Monoclonal antibody targeting LGR5 for cancer stem cells (CSCs)	Solid tumours, e.g. colorectal cancer	Phase Ia
BNC105	Small molecule vascular disrupting agent/anti-tubulin	Solid and blood cancers	Phase I

Source: Hardman & Co Life Sciences Research

Associated cost efficiencies included closure of its San Diego operations in 2017 (originally acquired for development of BNC101) and discontinued participation in the Cooperative Research Centre for Cancer Therapeutics, a partnership for translation of Australian cancer research to clinical development.

BNC101 – targeting CSCs

BNC101 is a first-in-class, allosteric inhibitor of LGR5. LGR5 is a marker of normal adult stem cells, but it is also over-expressed by colorectal tumour cells and associated with high relapse rates in colorectal cancer (CRC) patients. BNO's therapeutic hypothesis is that BNC101 inhibition of LGR5 will disrupt the signalling cascade that involves R-spondins (RSPOs) and Wnt, to reduce proliferation of CSCs and the potential for metastasis.

Phase Ia trial

The pre-clinical data for BNC101 is outlined in our recent initiation note[2]. The first Phase Ia trial of BNC101 is fully recruited (clinicaltrials.gov: NCT02726334) for investigation of dose and safety in 22 patients with 2nd line (for combination treatment with FOLFIRI) and 3rd line (for monotherapy) metastatic CRC (mCRC). Some data have been released: molecular data included evidence of target engagement in patient biopsies, and a recommended dose of 15mg/kg has been

[1] Company announcement: 'Bionomics Strengthens Board' (16th June 2016)
[2] http://www.hardmanandco.com/docs/default-source/company-docs/bionomics-ltd-documents/07.02.18-channelling-expertise-in-cns-drugs.pdf

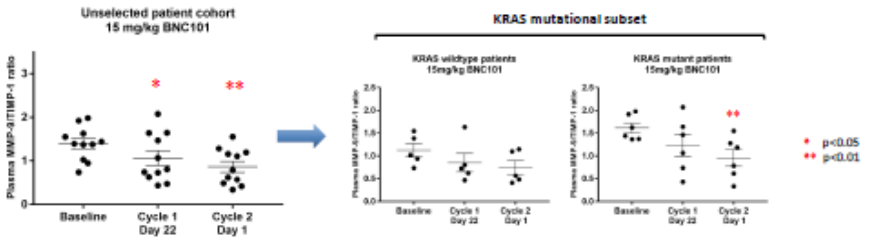
identified. Full data from the trial are expected by June 2018, which management suggests could aid a deal.

New data – April 2018

The most recent release of information on BNC101 was in a poster at the AACR conference on 17 April 2018. The new data presented here were on the potential pharmacodynamic effect of BNC101: the ratio of MMP-9 to TIMP-1 levels in blood plasma was reduced following treatment with BNC101. Matrix metalloproteases (MMPs) are involved in degradation of the extracellular matrix, a feature of invasion and metastasis in the tumour microenvironment, and are inhibited by Tissue inhibitors of metalloproteinases (TIMPs). A high ratio of MMP-9 to TIMP-1 is generally accepted to be indicative of increased MMP-9 proteolytic activity, and is used as a biomarker of poor prognosis in CRC[3]. Following treatment with BNC101, the reduction was apparent particularly in patients whose cancers had mutations in the gene coding for KRAS (who also had an elevated MMP-9/TIMP-1 ratio at baseline). This is relevant because it could inform the patient population to be studied in future enriched trials of BNC101.

Since LGR5 is highly expressed in normal intestinal crypt stem cells, gut health was assessed via the biomarker zonulin. Patients' plasma zonulin levels were normal, indicating that there was no gut toxicity associated with treatment.

MMP-9/TIMP-1 ratio: potential biomarker



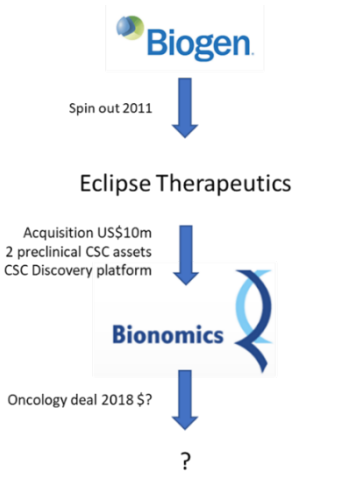
Source: Inglis DJ et al. Bionomics Ltd poster at AACR 2018

[3] *Do matrix metalloproteinases represent reliable circulating biomarkers in colorectal cancer?* D. Ligi & F. Mannello. BJC 2016 115

CSCs

BNO's CSC assets acquired in 2012

Origination of BNO's CSC assets



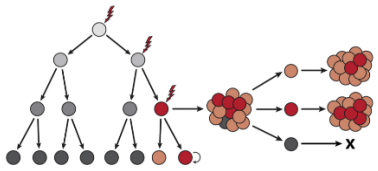
Source: Hardman & Co Life Sciences research

BNO gained its cancer stem cell (CSC) capabilities through the acquisition of Eclipse Therapeutics in 2012. Eclipse originated as a specialist CSC biotech when it was spun out from Biogen Inc. in 2011. Based in San Diego, it was acquired within a year by BNO for $10m. As part of the deal, BNO gained two pre-clinical assets, BNC101 (formerly ET101) and ET102 (target undisclosed), and the CSC Rx technology platform, a specialised discovery platform for identification of antibodies and small molecule drug candidates that specifically inhibit the function of CSCs. We understand that three senior Eclipse R&D scientists, including the two co-founders, joined BNO from 2011 to 2015.

BNO bought in its CSC technology at a time when CSCs were being intensely researched as a promising new approach to treating cancer, resulting in a run of industry deals. The (still) widely accepted view of tumour proliferation (the 'clonal evolution model') was disrupted in the 1990s by the identification of CSCs and the gain in popularity of a new 'hierarchical' model. This latter concept postulates that tumours are hierarchically organised, with CSCs at the start of the developmental process and the only subset of cells behind tumorigenesis. The existence of CSCs had been hypothesised for decades, but experiments by John Dick in the 1990s identified the existence of certain cells that could initiate Acute Myeloid Leukaemia (AML) in mice. This subpopulation of progenitor cells became widely known as CSCs and were then subject to intense focus as a new drug target.

CSCs as drug targets

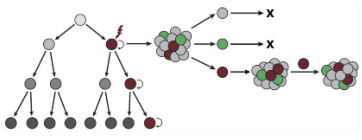
Clonal evolution model



Source: Adapted from Visvader and Lindeman[4]

Like other stem cells, CSCs are thought to be able to self-renew and to produce differentiated daughter cells. Unlike other stem cells, CSCs and their daughter cells would proliferate abnormally and, potentially, indefinitely. They are often identified within a population of cancer cells on a functional basis, such as on their ability to initiate tumours – for example, limiting dilution assays in mice are often used, whereby the cell subsets that can initiate a tumour at the lowest doses are identified. These are then characterised on particular surface markers.

CSC model



Source: Adapted from Visvader and Lindeman[5]

The origin of CSCs is subject to a great deal of research, as are the mechanisms that underpin their biology. However, CSC stemness is thought to be maintained by over-activated signalling pathways, including canonical Wnt signalling, which may re-programme differentiated cancer cells into CSCs. A blend of the clonal evolution and CSC models is now generally accepted, whereby tumours contain a subset of cells with stem-like properties. A therapeutic approach would, therefore, depend on a two-pronged approach, whereby the CSC population is targeted specifically, along with chemotherapy or a targeted approach for the tumour bulk.

CSC deals

The number of big deals for companies involved in CSC-directed drug research peaked around 2013. The biggest that we are aware of, valued at a total of $9.8bn, included a $5.5bn upfront payment by AbbVie to gain access to anti-CSC antibody candidates being developed by Stemcentrix. Rova-T was in Phase I/II clinical studies in Small Cell Lung Cancer (SCLC) when the partnership was announced in 2016. Even pre-clinical CSC assets have attracted high values, with GSK offering at least $1.4bn to OncoMed in 2007 for a partnership to develop Tarextumab in SCLC.

[4] *Cancer Stem Cells: Current Status and Evolving Complexities.*
[5] *Cancer Stem Cells: Current Status and Evolving Complexities.*

The risk-free upfront payment is not always disclosed in such deals, but in the strategic alliances outlined in the table below, it averaged about 5%-10% of the total deal value (depending on whether the AbbVie deal is included). On this simple basis, and assuming good data from the Phase Ia trial to be announced in the first half of calendar 2018, a strategic alliance involving BNC101 could have the potential to attract hundreds of millions of dollars in terms of the total deal size.

Transactions relating to selective CSC drug candidates

Year	Acquiror/ licensee	Licensor/ target	Deal type	Value ($m)	Upfront ($m)	Lead asset/ programme*	Development stage	Type
2018	–	Stemline Therapeutics	IPO	60	–	SL-401	Phase II (pivotal)	Biological
2016	Abbvie	Stemcentrix	Company acquisition	9,800	2,000	Rovalpituzumab tesirine	Phase I/II (pivotal)	ADC
2015	Tiziana	Cardiff Uni	Strategic alliances	>2.05	–	OH14	Pre-clinical	Small molecule
2014	Janssen (J&J)	Geron Corporation	Strategic alliances	935	35	Imetelstat	Phase I	Small molecule nucleic acid
2013	Celgene	OncoMed Pharma	Strategic alliances	3,300	155	Demcizumab	Phase Ib/II	Antibodies
2012	Dainippon	Boston Biomedical	Company acquisition	2,600	200	Napabucasin	Phase II	Small molecule
2012	–	Verastem	IPO	55	–	Defactinib	Pre-clinical	Small molecule
2011	Bionomics	Eclipse	Company acquisition	10	–	ET101 & CSC platform	Pre-clinical	Antibodies
2010	Bayer	OncoMed Pharma	Strategic alliances	>387.5	ND	Vantictumab	Pre-clinical	Antibodies
2008	Roche	Arius Research	Company acquisition	191	–	Pipeline & technology platform	Pre-clinical	Antibodies
2007	GSK	OncoMed Pharma	Strategic alliances	>1,400	ND	Tarextumab	Pre-clinical	Antibodies

**Not a comprehensive list; upfront may include equity*
ND = not disclosed; – = none
Source: Hardman & Co Life Sciences Research

Competition

Briefly, with respect to developmental drug candidates against CSCs for CRC, the target indication for BNC101, Dainippon has a Phase II combination trial running of Napabucasin (among multiple others of the same candidate). Enrolment of a Phase III trial of BB1608 in CRC was stopped in 2014, when it failed to meet efficacy end-points; however, Napabucasin has a different mechanism of action (MoA) from BNC101, being a small molecule quinone that inhibits the STAT3 signalling pathway.

Rosmantuzumab is being developed by the Celgene-OncoMed partnership, and is targeting a similar signalling pathway to BNC101 (RSPO – LGR receptor family signalling), also in CRC and gastric cancer. The ongoing trial is an enriched trial, being carried out in patients with the RSPO3 fusion genotype. In January 2018, OncoMed announced that it had not found 'convincing evidence of clinical benefit', although full Phase I data have not yet been announced.

Risks

Precedence

We are not aware of any CSC-directed therapies that have successfully reached the market. Many of the drug candidates listed in the above table have failed to reach primary efficacy end-points; on occasion, this has resulted in the termination of research programmes or the return of commercial licences. We list some examples below:

- **GSK-OncoMed partnership terminated**: Following the announcement that tarextumab had not met its end-points in a Phase II combination trial in SCLC,

GSK terminated the R&D collaboration and licence agreement in July 2017. The tarextumab programme appears to have been discontinued.

- **Bayer-OncoMed partnership:** In April 2017, Bayer terminated its option to license two anti-CSC candidates (vantictumab and ipafricept), programmes that now appear to be on hold. This was announced in parallel with the failure of demcizumab (partnered with Celgene) to meet progression-free survival (PFS) end-points in Phase II.
- **AbbVie:** A recent announcement (March 2018) included news that the Phase II trial of Rova-T, the programme acquired with Stemcentrix, had not met end-points in third-line SCLC patients. As a result, it was not able to apply for Breakthrough Technology Designation (BTD) from the FDA; however, Phase III/II trials in first- and second-line SCLC are ongoing. In addition, in April 2018, AbbVie terminated a Phase I trial of SC-007 (also acquired from Stemcentrix, target not disclosed) in CRC due to a lack of convincing positive data.

While clinical progress with CSC-targeted agents has often been disappointing, it does not necessarily set a precedent for the approach as a whole. BNC101 is first-in-class with respect to its MoA – it targets the LGR5 receptor – and, to our knowledge, competitors' candidates targeting other receptors in the LGR family are in ongoing trials (e.g. Dainippon, above). The development of the field as a whole, however, may make potential partners and the market more cautious than they would have been in 2011. The data reported so far from the Phase Ia trial of BNC101 in CRC have been positive with respect to dosing and safety, and have demonstrated at the molecular level BNC101 binding of LGR5.

Controversy

It is hard to miss the debate surrounding the nature of CSCs as a distinct subset of cancer cells and whether they are well-enough understood to be specifically targeted in the clinic. Simplified, this seems to be because of the following:

- **CSCs are hard to identify in the laboratory:** Their markers are often found on healthy adult stem cells, and the outcome of serial dilutions in mouse models may not reflect the development of cancers in patients (they may also identify tumour-initiating cells, rather than true stem cells).
- **CSCs are variable and not found in all cancer types:** This fuels the debate on the extent of the CSC model – some researchers are not convinced that CSCs are a discrete population of cancer cells (their phenotype may be reversible and evolving, and vary among patients with the same cancer).
- **The effects of CSC elimination in cancer are hard to measure:** CSCs are thought to be very rare within a population of cancer cells; therefore, combined with the above, it is difficult to access CSCs in the clinic and measure directly their reduction in trials.

Interestingly, some companies, which initially were founded as CSC companies, appear to have reduced the CSC messaging on their websites. This could suggest that their programmes, while originally based on the CSC concept, are showing positive data for different reasons – for example, 'CSC markers' may be expressed in broader populations of cancer cells, thus still representing valid targets.

CRC market summary

CRC is in the top five most common cancers in men and women, and causes an estimated 14.8 deaths per 100,000 people every year. Survival is dependent on the stage of the disease at diagnosis – around 30% of patients will be diagnosed when they have already developed metastatic disease, at which point there is only an 11-14% five-year survival rate (American Cancer Society), despite the range of available treatments. For example, chemotherapies such as the FOLFIRI regime are recommended by NICE in the UK as a second-line treatment in metastatic CRC following the FOLFOX regime. These are often combined with more targeted therapies.

Ongoing Phase III trials (of which there are 177 active or recruiting registered on clinicaltrials.gov) include the CPI Keytruda (Merck) in a certain patient subset that has not responded to chemotherapy – it is approved in this indication under accelerated approval only. BNO has suggested that there is a case for clinical investigation of BNC101 in combination with CPIs, since there is some initial evidence that CSCs suppress immunity in the tumour microenvironment (see *Appendix*).

Estimates for the size of the major markets for CRC treatments are at $11bn for 2025 (GlobalData website).

BNC105 - for solid and blood cancers

Clinical development

BNC105 is a small molecule candidate drug for solid and blood cancers, discovered using BNO's MultiCore platform. It has an FDA Fast Track designation in AML. Prior to the two currently ongoing trials, it has been tested on solid cancers in five clinical trials, as highlighted below:

- **Advanced solid tumours:** Phase I study, monotherapy, dose escalation.
- **Mesothelioma:** Phase II study, monotherapy.
- **Ovarian cancer:** Phase I study in combination with chemotherapy in ovarian cancer.
- **Renal cancer:** Phase II study, also in combination, but here with a targeted signal transduction inhibitor called Afinitor (everolimus, Novartis). In 2014, the trial did not meet its primary end-point of PFS.
- **Melanoma:** A combination trial with the CPI Keytruda (Merck) in advanced melanoma patients, unresponsive to targeted treatments, recently completed. It was funded by a A$2.25m grant from the Australian government's Victorian Cancer Agency – data are not yet available.

To our knowledge, BNC105 is no longer being investigated in the above indications, although a study to identify biomarkers, funded by Novartis, in biopsies from the renal cancer trial, is still under way. BNO hopes to identify biomarkers that may allow pre-treatment selection of patients most likely to benefit from BNC105 for future trials. The strategy is now on blood cancers, and there is a Phase I trial of BNC105 ongoing, which is in Chronic Lymphocytic Leukaemia (CLL), and is being carried out at the Norris Cotton Cancer Centre, Dartmouth College, US, as both a monotherapy and in combination.

New in vitro data

The new data presented at the AACR conference on 17 April 2018 were from *in vitro* experiments in cell lines from AML patients (not from a previous or ongoing clinical trial of BNC105). According to the poster, BNC105 induces apoptosis and cell death, targets leukaemic progenitor cell populations, and was more potent than competing developmental candidate drugs (e.g. OXi4503, Mateon Therapeutics). The authors conclude that these data warrant investigation in a clinical trial of AML patients with high unmet need.

Therapeutic hypothesis

BNC105 targets the colchicine-binding site on tubulin (a component of the cytoskeleton), causing chronic disruption of adhesion molecules, which are involved in interactions of cells with the extracellular matrix. It was discovered as a Vascular Disrupting Agent (VDA), a type of drug that aims to prevent tumour angiogenesis. More recently, BNC105 has been shown to restore the immune response within solid tumours – this is exciting because it is consistent with effective therapeutic use of BNC105 in combination with CPIs. It has been shown to also have direct cytotoxic activity on cancerous cells, suggesting that it may have potential in haematological cancers.

Valuation of oncology pipeline

NPV from royalties of BNC101 and BNC105

We assume that the company will monetise its oncology assets by out-licensing the IP to BNC101 and BNC105 (patents protected until 2035 and 2027, respectively). The partner would be responsible for all further R&D and trial costs, sales and marketing, and manufacturing. In this scenario, BNO would receive royalties on eventual sales by its licensees – so we have calculated an NPV for the two oncology assets (unchanged from our initiation report) based on risk-adjusted royalty rates. The advantage of this methodology is that, when assets move to the next clinical-stage in a single indication, it is easy to see the potential effect on the royalty stream and, therefore, the share price.

We have assessed the sales potential for the two assets by comparing them with actual ex-factory sales of appropriate comparator drugs when they were first launched. We arrive at a joint NPV for the oncology assets based on the following parameters:

- **Comparator for BNC101:** Given that BNC101 is first-in-class, we have taken as the best comparator a monoclonal antibody drug used for treatment of CRC. Lilly's total sales of Erbitux (cetuximab), which is indicated for treatment of wild-type KRAS, epidermal growth factor receptor-expressing, metastatic CRC (in combination with FOLFRI for 1st line treatment), peaked at $749m in 2008. Erbitux came off patent in 2016.

- **Comparator for BNC105:** Platinol is a relatively old chemotherapy drug used to treat multiple cancers, including CLL and melanoma, for which BNC105 is, or has been, tested in trials. Total sales by BMS peaked at $165m in 1995.

- **Royalty rate:** Given their phase of development, we have assumed both candidates will carry an average 8% royalty to BNO on net sales.

- **Risk adjustment:** We have adjusted the royalty estimates to account for the risk that they do not reach the market due to safety/efficacy or commercial/strategic reasons. We use long-standing industry data for these probabilities, which, at Phase I, carry a 5% probability of reaching the market.

- **Risk-adjusted NPV:** We apply a WACC of 10% to each year of potential risk-adjusted royalties, resulting in an NPV of A$27m/$20m for the oncology assets. Applying a conservative long-term tax rate of 20%, this equates to post-tax NPV of A$21m/$16m.

BNO royalty summary – oncology assets	
Pre-tax NPV (USD)	$20m
Pre-tax NPV (AUD)	**A$27m**
Tax rate	20%
Post-Tax NPV (USD)	$16m
Post-tax NPV (AUD)	**A$21m**

Spot rate used for currency
Source: Hardman & Co Life Sciences Research

It should be noted that there is a deferred consideration for the Eclipse acquisition on the company's balance sheet, which includes potential earn-outs to Eclipse security holders based on development or partnering milestones of up to $14.6m. In all likelihood, these would be transferred to the licensee or acquirer of BNC101.

Group valuation

Our valuation of the group is also unchanged, but may be reviewed following news of a CNS or oncology deal, or the 2018 full-year results. The NPV of the oncology assets outlined above is included in the group NPV of the royalty stream below.

Summary group valuation				
Year-end June (A$m)	--------- 2018E ---------		--------- 2019E ---------	
EV/sales	**10.0x**	**11.0x**	**10.0x**	**11.0x**
Service sales forecast	5.9	5.9	6.2	6.2
Implied EV	59.0	64.9	62.0	68.2
Net cash	17.7	17.7	41.2	41.2
NPV of royalty stream	651.0	651.0	651.0	651.0
Group market capitalisation	**727.7**	**733.6**	**754.2**	**760.4**
Shares in issue (m)	482.8	482.8	482.8	482.8
Valuation/share (A$)	1.51	1.52	1.56	1.58

Spot rates used for currency
Source: Hardman & Co Life Sciences Research

Investment conclusion

BNO has a clear strategy to invest in developing its drug candidates to a stage that both interests big pharma and generates good potential returns for shareholders. Of note is the number of times that companies developing novel CNS therapies have been acquired by major pharma in order to access the product(s) and/or technology (see initiation note[2]). Its lead candidate, BNC210, is addressing anxiety associated with CNS disorders – initially in PTSD, a disease for which there are limited available treatments.

Investment risks

The risk profile of BNO has altered over the past few years, with the announcement of the new strategy focused entirely on ion channel drug R&D. The company remains high-risk; however, it will become less capital-intensive if it monetises its clinical-

stage, non-ion channel oncology assets and partners its lead candidate, BNC210, for anxiety in CNS disorders, after Phase II (results from the RESTORE trial are due in the second half of 2018). This will de-risk the final stages of clinical development and commercialisation.

The decision to seek partners reduces, but does not eliminate, risk and cost to BNO. In the short term, there are three risks to BNO from this model: i) although discussions are under way for monetisation of the oncology assets, to our knowledge, a partner has not yet been secured, and deals can take some time to close; ii) for partnered candidates, real upside is dependent on receiving a royalty on net sales should they be successfully commercialised, and the agreed rate will be subject to extensive negotiation; iii) the clinical development and approval of out-licensed assets will not be completely within BNO's hands.

Potential news flow

Partnering deals can take years to agree and finalise. The company has been engaged in formal discussions for an oncology deal for at least eight months, according to corporate announcements – if finalisation of a deal is contingent on the outcome of trial results, and the BNC101 trial is due to report headline data within the next six weeks, then it is possible that there could be an oncology announcement in the near term. Headline data from the RESTORE trial in PTSD are expected in the third quarter of this calendar year. If the company can divest or out-license the oncology assets in the near term, it will be a more focused CNS company, with two clinical-stage programmes (BNC210 and its partnered programme with Merck). It could potentially then be subject to an acquisition by a pharmaceuticals company with an interest in CNS in the next year or so, or, if not, to a significant CNS partnering deal.

Financials and investment case

- **Forecasts:** Our forecasts have not changed since they were first published in our initiation note[2]. All forecasts are based on constant currency.

Summary financials						
Year-end June (A$m)	**2015**	**2016**	**2017**	**2018E**	**2019E**	**2020E**
AUD:EUR	1.437	1.524	1.446	1.446	1.446	1.446
AUD:USD	1.200	1.374	1.326	1.326	1.326	1.326
Profit & Loss:						
Sales	6.79	7.14	5.53	5.90	6.20	6.50
COGS	0.00	0.00	0.00	0.00	0.00	0.00
SG&A	-9.32	-11.85	-7.78	-8.80	-9.10	-9.30
R&D	-23.18	-24.77	-24.22	-24.00	-12.00	-12.00
EBITDA	-22.65	-24.95	-10.11	-10.35	21.25	21.55
Depreciation	-0.51	-0.62	-0.46	-0.46	-0.46	-0.46
Other income	1.35	2.59	14.62	14.81	34.41	34.60
Underlying EBIT	-24.37	-26.88	-11.86	-12.09	19.51	19.80
Net interest	0.08	-0.67	-0.77	-1.07	-0.90	-0.42
Pre-tax profit	-24.28	-26.28	-12.62	-13.16	18.61	19.38
Tax	0.33	0.73	-0.52	-0.52	0.74	0.77
Net income	-16.97	-16.05	-6.25	-6.85	22.76	23.57
Weighted av. shares (m)	417.6	457.3	481.4	481.5	481.5	481.5
Underlying Basic EPS (A¢)	**-4.06**	**-3.51**	**-1.30**	**-1.42**	**4.73**	**4.90**
U/l Fully-diluted EPS (A¢)	**-3.97**	**-3.43**	**-1.21**	**-1.33**	**4.41**	**4.56**
Balance sheet:						
Share capital	418.20	481.02	481.46	481.46	481.46	481.46
Reserves	-386.23	-436.86	-441.00	-448.47	-426.33	-403.37
Capitalised R&D	54.85	65.02	72.63	78.09	71.19	63.92
Liabilities	10.29	12.35	16.56	16.56	16.56	16.56
Debt	9.32	18.44	10.01	10.01	10.01	10.01
less: Cash	26.56	45.45	42.87	36.30	59.85	84.11
Invested capital	**90.02**	**102.59**	**109.23**	**113.79**	**105.48**	**96.90**
Net cash/debt	11.78	23.14	24.26	17.68	41.23	65.50
Cashflow:						
Underlying EBIT	-24.37	-26.88	-11.86	-12.09	19.51	19.80
Working capital	21.64	-2.49	-0.89	-6.57	23.55	24.26
Tax & interest	7.99	9.02	8.69	7.47	6.00	6.41
Operational cashflow	**12.73**	**-16.73**	**1.23**	**-6.33**	**23.80**	**24.51**
Capital expenditure	-0.85	-0.20	-0.25	-0.25	-0.25	-0.25
Free cashflow	**11.89**	**-16.85**	**0.98**	**-6.57**	**23.55**	**24.26**
Acquisitions	-0.39	0.00	0.00	0.00	0.00	0.00
Share issues	0.27	28.22	0.14	0.00	0.00	0.00
Change in net debt	**11.78**	**11.36**	**1.12**	**-6.57**	**23.55**	**24.26**
Hardman FCF/sh. (p)	2.85	-3.69	0.20	-1.37	4.89	5.04

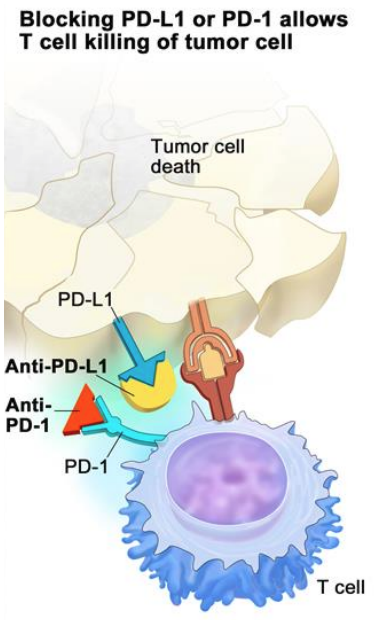
Source: Hardman & Co Life Sciences Research

Appendix: cancer treatment

Cancer describes disease caused by unregulated proliferation of abnormal cells. This can result in the growth of solid tumours and in development of blood cancers. Tumours are malignant if they invade, or if their cells spread (metastasise) to, new sites in the body. Simply put, this malfunction results from damage to a number of mechanisms that regulate cell division and that eliminate abnormal cells. We highlight further details below:

- **Mutation:** DNA mutations in the genes that code for proteins with a role in the cell cycle can result in cells that divide uncontrollably but that do not fully mature. Such mutations can be inherited, develop randomly, and/or be influenced by environmental factors such as smoking and UV light.
- **Immune surveillance:** The extent of the immune system's ability to identify and remove cancerous cells has been debated for decades. For example, natural killer cells may recognise abnormal cells, resulting in cytolysis, and antigen-presenting cells may present tumour-specific antigens, which leads to cytotoxic T cell responses against cancerous cells. However, a number of mechanisms, including down-regulation of tumour antigen expression by cancerous cells, may result in evasion of the immune system.
- **Tumour growth:** A solid tumour's requirement for oxygen and nutrients grows as the mass of cells grows. Angiogenesis (formation of new blood vessels from the existing vasculature) in the tumour microenvironment can be triggered by the tumour itself, allowing continued expansion of the tumour.
- **Microenvironment:** Tumours may also alter their microenvironment, so that it is immunosuppressive. This can result in immune tolerance – for example, through recruitment and activation of regulatory T cells.

Checkpoint inhibitor model



Source: Terese Winslow LLC 2015

Therapeutic approaches

A combination of approaches to killing cancer cells is used depending on cancer type. Localised surgery and radiation or chemotherapy are the core approaches, with the more recently developed approaches being more targeted as outlined in the table below.

Targeted approaches

Category	Description	Example
Hormone therapy	For hormone-sensitive or dependent cancers	Tamoxifen for breast cancer
Immuno-oncology	Harnessing the immune system to kill cancerous cells	
Passive	*Enhancing existing immune responses*	*Monoclonal antibodies, e.g. Yervoy for melanoma*
Active	*Directing the immune system to the cancer cells of interest*	*Therapeutic vaccines, e.g. Provenge for prostate cancer*
Precision medicine	Matching treatment to the cancer's genotype	
Stem cell transplants	An adjuvant therapy for high-dose chemotherapy	Treatment of some leukaemias

Source: Hardman & Co

Immuno-oncology

CPIs such as Yervoy (Bristol Myers Squibb) and Keytruda (Merck & Co) are immuno-oncology drugs that enhance killing of cancerous cells by the immune system. Cancer cells may survive immune surveillance by displaying proteins on their surface that cause a signalling cascade (*via* immune checkpoint molecules), which prevent the immune system (and T cells in particular) from recognising them as abnormal. CPIs are antibodies that bind to these antigens (or to the proteins on T cells that respond to them) to 'release' immune suppression.

Resistance to treatment

Most of these approaches were originally designed to reduce tumour size and prolong PFS. Unfortunately, responses are often temporary, and, until the mid-1990s, the widely accepted view was that relapse following a temporary period of remission was caused by incomplete killing of cancer cells, and/or the cancer developing resistance to chemotherapy. Analogous to rapidly dividing bacterial cells that evolve resistance to antibiotics, in the clonal evolution model, cancer cell lines may acquire mutations that allow them to survive chemotherapy – these are then able to go on to produce a population of resistant cancer cells under the selective pressure of the treatment.

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Hardman & Co Research Limited (trading as Hardman & Co)
35 New Broad Street
London
EC2M 1NH

+44 (0) 20 7194 7622
Follow us on Twitter @HardmanandCo

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Hardman team

Management team

+44 (0)20 7194 7622

John Holmes	jh@hardmanandco.com	+44 (0)20 7194 7629	Chairman
Keith Hiscock	kh@hardmanandco.com	+44 (0)20 7194 7630	CEO

Business development and investor engagement

+44 (0)20 7194 7622

Richard Angus	ra@hardmanandco.com	+44 (0)20 7194 7635	Business development
David Banks	db@hardmanandco.com	+44 (0)20 7194.7622	Corporate Advisory/Finance
Max Davey	md@hardmanandco.com	+44 (0)20 7194 7622	Investor engagement
Antony Gifford	ag@hardmanandco.com	+44 (0)20 7194 7622	Investor engagement
Ann Hall	ah@hardmanandco.com	+44 (0)20 7194 7622	Business development
Gavin Laidlaw	gl@hardmanandco.com	+44 (0)20 7194 7627	Investor engagement
Vilma Pabilionyte	vp@hardmanandco.com	+44 (0)20 7194 7637	Business development

Analysts

+44 (0)20 7194 7622

Agriculture		**Bonds / Financials**	
Doug Hawkins	dh@hardmanandco.com	Brian Moretta	bm@hardmanandco.com
Yingheng Chen	yc@hardmanandco.com	Mark Thomas	mt@hardmanandco.com
Building & Construction		**Consumer & Leisure**	
Tony Williams	tw@hardmanandco.com	Steve Clapham	sc@hardmanandco.com
Mike Foster	mf@hardmanandco.com	Mike Foster	mf@hardmanandco.com
		Jason Streets	js@hardmanandco.com
Life Sciences		**Media**	
Martin Hall	mh@hardmanandco.com	Derek Terrington	dt@hardmanandco.com
Dorothea Hill	dmh@hardmanandco.com		
Grégoire Pavé	gp@hardmanandco.com		
Mining		**Oil & Gas**	
Paul Mylchreest	pm@hardmanandco.com	Angus McPhail	am@hardmanandco.com
Property		**Services**	
Mike Foster	mf@hardmanandco.com	Mike Foster	mf@hardmanandco.com
Special Situations		**Tax Enhanced Services**	
Steve Clapham	sc@hardmanandco.com	Brian Moretta	bm@hardmanandco.com
Paul Singer	ps@hardmanandco.com		
Yingheng Chen	yc@hardmanandco.com		
Technology		**Utilities**	
Milan Radia	mr@hardmanandco.com	Nigel Hawkins	nh@hardmanndco.com

Hardman & Co

35 New Broad Street
London
EC2M 1NH

Tel: +44(0)20 7194 7622

www.hardmanandco.com