

**In this edition...**

After 12 months of positive gains, the biotech bull run has come to an end, with Bioshares Index falling away slightly in the last quarter, by 3.7%. The biotech sector continues to play out, with only one new listing and existing companies such as Acrux having crossed the line and other companies such as CathRx and Chemgenex stumbling in the final stages of commercialization with further work to be done there.

We update readers on developments at Acrux and Bionomics, and at Mesoblast, for which changes to the US health care bill has delivered an unexpected benefit.

**The Editors**

**Companies Covered: ACR, BNO, MSB**

	Bioshares Portfolio
Year 1 (May '01 - May '02)	21.2%
Year 2 (May '02 - May '03)	-9.4%
Year 3 (May '03 - May '04)	70.0%
Year 4 (May '04 - May '05)	-16.3%
Year 5 (May '05 - May '06)	77.8%
Year 6 (May '06 - May '07)	17.3%
Year 7 (May '07 - May '08)	-36%
Year 8 (May '08 - May '09)	-7.3%
Year 9 (May '09 - Current)	61.7%
<b>Cumulative Gain</b>	<b>214%</b>
<b>Av Annual Gain (9 yrs)</b>	<b>19.9%</b>

*Bioshares* is published by Blake Industry & Market Analysis Pty Ltd.

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Individual Subscriptions (48 issues/year)  
**\$350** (Inc.GST)  
Edition Number 354 (9 April 2010)  
ISSN 1443-850X

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# Bioshares

9 April 2010  
Edition 354

*Delivering independent investment research to investors on Australian biotech, pharma and healthcare companies.*

*Extract –*

## **Bionomics – Competitor Drug Stumbles in Phase III Study**

Bionomics' (BNO: \$0.32) competitor **Antisoma/Novartis** has stumbled in a Phase III trial in non-small cell cancer with their vascular disrupting agent ASA404. This was the leading VDA in development, with Antisoma signing a major drug development deal with Novartis for the program in 2007 that has netted Antisoma at least US\$100 million to date.

UK-based Antisoma stated that continuation of the trial would be futile as there was almost no chance of showing a survival benefit as a first line treatment for NSCLC. There were no unexpected serious adverse events. The compound was originally developed by Professor Bruce Baguley and Bill Denny at the **University of Auckland**. It was a surprising result, given the strong Phase II data with a median survival of 14 months with ASA404 and chemotherapy versus 8.8 months with chemotherapy alone as a first line therapy. A Phase II trial in prostate cancer has been completed and a Phase I/II trial in women with breast cancer was expected to start this year. Novartis had anticipated filing the drug for approval in 2011.

The news caused a plunge in the Antisoma share price, which is now down 80% from its 12 month high. The company is capitalized at only GBP48 million, just above its cash reserves at the end of last year of GBP45 million.

Another VDA competitor, **Oxigene** also from the UK, went on the back foot in February this year with the company under financial pressures. The company will reduce its work force by 49% and the company has stopped its Phase II/III (anaplastic) thyroid cancer trial with its VDA Zybrestat, to focus on its Phase II trial in NSCLC. Results from this trial are expected to be presented at ASCO in June this year. Oxigene is capitalised at US\$75 million.

**YM Biosciences** completed its acquisition earlier this year of Melbourne-based **Cytopia** for \$14 million and its VDA is currently in Phase II trials for the treatment of glioblastoma.

By the measure of market capitalization, this makes Bionomics the leading global VDA development company. Bionomics is capitalised at \$102 million. Bionomics has two Phase II studies underway with its VDA, called BNC105. One is in renal cell carcinoma and the second in patients with mesothelioma.

The benefit for Bionomics from the setback with ASA404 is that it joins the leaders in the VDA space, and also potentially opens up some of the major cancer markets such as breast, prostate and lung cancer.

### **Bionomics' VDA – Points of Difference**

Bionomic's drug candidate has been developed as a significantly improved version of Zybrestat. Bionomics' CEO, Dr Deborah Rathjen, says there are a number of distinct

features of its drug candidate that provides advantages over ASA404. BNC105 is both a VDA and is directly cytotoxic, where ASA404 is not directly cytotoxic. The method of action for BNC105 is well understood (being a tubulin polymerization inhibitor, with successful existing cancer drugs such as taxanes, vinca alkaloids and epothilones also inhibiting tubulin). BNC105 has a much better tumour lock-in profile (around 24 hours) where published data on ASA404 shows that vascular shut down with ASA404 is leaky and incomplete. BNC105 has also shown single agent efficacy in animal models where ASA404 has not.

In comparison to Zybrestat, Bionomics has found that its drug candidate BNC105 shows a 100-fold selectivity for cancer cells (rather than for healthy tissues) and has a 10-fold greater therapeutic window over Zybrestat. The therapeutic window is the safe level of drug that can be dosed before serious side effects occur.

#### ***BNC105 – Renal cell cancer***

VDAs work by destroying cancer blood vessels. NSCLC has been a popular target for VDAs because they are highly vascularised. Renal cell carcinoma is another highly vascularised tumour and has been selected by Bionomics for this reason, and that there are no VDA competitors working in this space, and also that the market is very large (existing drugs for renal cell cancer generate between US\$500 million - US\$1 billion in sales each a year).

Bionomics has shown that BNC105 is effective in an animal model for renal cancer. In an abstract that from a poster that will be presented at AACR this month, Bionomics has also discovered that there should be a synergistic effect from combining BNC105 with an mTOR inhibitor (such as Afinitor which is the combination in the current Phase II trial). This is because the tumour recovery following VDA assault on the cancer blood vessels is believed to be assisted by activating the mTOR signaling pathway. Destroying the tumour blood vessel and then blocking one of the paths for the tumour to recover should deliver a more effective and longer lasting therapy.

Interim data from the renal cell cancer trial with BNC105 are expected by the end of 2010. The primary endpoint is progression-free survival which will not take long to measure given the nature of this disease. Progression free survival in previous trials has shown to be between three to five months, with existing treatments increasing this by six to 11 months.

Bionomics started recruiting in January in the US with 152 patients expected to be enrolled. Bionomics has recruited the **Hoosier Oncology Group** in the US to co-ordinate the trial. HOG operates in 50 sites in the US with 400 oncology physicians. The Bionomics trial will only require 10-12 sites. With continuous monitoring, under-performing sites will be dropped and there is a cash incentive for HOG to keep enrolment on track.

The primary endpoint will be progression-free survival at six months, as well as safety and tolerability. BNC105 will be compared against the most recently approved renal cancer drug, Afinitor, which reached the market in 2009. Bionomics has also

developed its own proprietary biomarker to test for polymerized versus non-polymerised tubulin, which will allow the company to monitor the vascular disrupting effect in patients. No other VDAs have been tested with the assistance of such an assay, and this should help set dosage levels for patients, so Bionomics can understand at which dose the tumours are being destroyed in each patient.

#### ***BNC105 – Mesothelioma***

Last month Bionomics opened its Phase II trial with BNC105 to patients who had failed chemotherapy for mesothelioma, for whom there are no other treatment options. In Australia, there are around 700 new cases of mesothelioma diagnosed each year.

In 20-30 years time, the incidence of mesothelioma is expected to spike in New York due to the terrorist attacks that destroyed the World Trade Centre buildings. The mechanism responsible for mesothelioma is still yet to be established, although it is thought the chronic inflammation caused by asbestos exposure leads to the eventual formation of cancer cells.

Mesothelioma causes cell growth on the pleura, the outside of the lung, which when advanced, continues to restrict the breathing capacity of patients. The cancer also grows on the inside of the lungs. The Phase II trial will enroll 24 patients initially. After an interim analysis, which will be revealed in the first half of 2011, the company will decide whether to continue with a further 36 patients in the trial. There will be no other drugs combined in this trial.

The trial will be conducted by the **Australian Lung Trials Group** and the **NHMRC Clinical Trials Centre**. It is not expected there will be any difficulty in recruiting patients. Progression-free survival will be a primary endpoint, with changes in lung capacity and quality of life secondary measures.

Mesothelioma is a difficult cancer to treat. There are limited treatment options and with some response seen in this cancer in the Phase I trial, it is worth investigating. The path to market for this indication if efficacy could be shown may be rapid given there are no treatment options for this patient population (who have failed first line chemotherapy) and life expectancy is around 12 months.

#### **Summary**

Over the next 12 months Bionomics is expected to have interim efficacy data from two Phase II cancer trials, one in renal cancer and the other in mesothelioma. These cancers were chosen because (1) of their highly vascularised nature, (2) that no other VDAs are being tested in these indications, (3) that efficacy has been shown in animal studies in both cancers, and (4) that early efficacy was shown in a small number of patients in the Phase I study (cancer progression was stopped in two patients with renal cancer and in one patient with mesothelioma) with no negative impact on cardiac function at higher doses unlike other VDAs. BNC105 is a cancer drug candidate that will be one to watch over the next 12 months.

*Bioshares* recommendation: **Speculative Buy Class A**

**How Bioshares Rates Stocks**

For the purpose of valuation, *Bioshares* divides biotech stocks into two categories. The first group are stocks with existing positive cash flows or close to producing positive cash flows. The second group are stocks without near term positive cash flows, history of losses, or at early stages of commercialisation. In this second group, which are essentially speculative propositions, *Bioshares* grades them according to relative risk within that group, to better reflect the very large spread of risk within those stocks.

**Group A**

Stocks with existing positive cash flows or close to producing positive cash flows.

**Buy** CMP is 20% < Fair Value  
**Accumulate** CMP is 10% < Fair Value  
**Hold** Value = CMP  
**Lighten** CMP is 10% > Fair Value  
**Sell** CMP is 20% > Fair Value  
 (CMP–Current Market Price)

**Group B**

Stocks without near term positive cash flows, history of losses, or at early stages commercialisation.

**Speculative Buy – Class A**

These stocks will have more than one technology, product or investment in development, with perhaps those same technologies offering multiple opportunities. These features, coupled to the presence of alliances, partnerships and scientific advisory boards, indicate the stock is relative less risky than other biotech stocks.

**Speculative Buy – Class B**

These stocks may have more than one product or opportunity, and may even be close to market. However, they are likely to be lacking in several key areas. For example, their cash position is weak, or management or board may need strengthening.

**Speculative Buy – Class C**

These stocks generally have one product in development and lack many external validation features.

**Speculative Hold – Class A or B or C**

**Sell**

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