

**In this edition...**

Markets have a tendency to favour certain sectors above others and within sectors favour certain stocks above others, regardless of fundamentals. But this is what investing is about – finding out what is being missed by the market, which despite certain theories is not perfect. Thus we present the case again for one stock that we regard as offering exceptional value, Cytopia, which this week released results of a Phase I trial of its cancer drug CYT997.

We also introduce a new stock wrap section to improve our coverage and communication to readers on less frequently discussed stocks

**The editors**

**Companies covered:** ACG, BIT, CYT, DIA, GIA, MVH, PBP

	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 (from 4 May '07)	-10.0%
<b>Cumulative Gain</b>	<b>194%</b>
<b>Av Annual Gain (6 yrs)</b>	<b>26.8%</b>

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Blake Industry & Market Analysis Pty Ltd  
ACN 085 334 292  
PO Box 193  
Richmond Vic 3121  
AFS Licence  
No. 258032

Enquiries for *Bioshares*  
Ph: (03) 9326 5382  
Fax: (03) 9671 3633  
Email: info@bioshares.com.au

**David Blake**  
Ph: (03) 9326 5382  
Email: blake@bioshares.com.au

**Mark Pachacz**  
Ph: (03) 9671 3222  
Email: pachacz@bioshares.com.au

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# Bioshares

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

Extract from *Bioshares* –

## **With Three Phase II Trials Planned, Cytopia Offers Exceptional Value**

As Cytopia (CYT: 51 cents) continues to drive its drug discovery and development engine room, its share price fails to respond to the progress being made. The company is capitalised at only \$38 million with \$14 million in cash at June 30, a ridiculously low market valuation that seems to contradict a general perception that company's work is well respected amongst peers and by institutional investors and investment managers active in the sector. However, we are confident that with three Phase II cancer trials to be launched in the next 12 months, it is difficult not to see a revaluation occurring with this stock over the coming year.

In a snapshot, Cytopia has one drug, CYT997, ready to move into Phase II clinical testing in cancer (multiple myeloma). It has a drug development partnership with **Novartis** in the area of auto-inflammatory diseases, which has a potential deal value of up to \$274 million. Only a handful of Australian companies, including Cytopia, have ever struck deals with large international pharmaceutical partners, and in our view the market has missed the point of how such a deal validates the capabilities of the company. Cytopia has two other patented preclinical assets in development: compounds that hit the JAK2 pathway, for the treatment of a range of cancers, cardiovascular disease and myeloproliferative disorders; and it has a program to find drugs that intercept and modulate the FMS kinase pathway.

### **Inflexion point approaching**

Cytopia is approaching a large value inflexion point. Within 18 months, it should by our estimates, have three drug candidates in clinical trials (CYT997, FMS candidate, JAK2 candidate) with Phase II results from at least one cancer indication.

What makes the Cytopia drug engine room so appealing is that a major focus on proteins involved in 'signal transduction pathways' (excluding CYT997). These are signaling pathways inside cells. The blocking of these lines of communications with very specific acting drugs represents a novel way to treat disease. The highly successful Gleevec drug from Novartis works on a kinase pathways and is about 95% effective in treating cancer (chronic myeloid leukemia). It perhaps explains the interest by Novartis in Cytopia, but Novartis also has a very important franchise in auto-immune disease.

### **Cytopia's Kinase Inhibitor Assets**

- JAK3 (rheumatoid arthritis, transplantation rejection, psoriasis, asthma) - Partnered with Novartis
- JAK2 (blood-based cancers, cardiovascular disease such as congestive heart failure, myeloproliferative diseases such as thrombocytopenia which is categorized by an increased level of blood platelets)
- FMS (oncology and bone degradation)

Cont'd over

## Cytopia's Lead Drug Candidate

· CYT997, a vascular disrupting agent and tubulin inhibitor, completed Phase I clinical study in 31 patients with solid tumours.

### Phase I CYT997 results

This week Cytopia reported Phase I results in 22 evaluable patients with a range of solid tumours. The aim of the trial was to establish the maximum tolerable dose of the drug. Patients started on very low doses (7 mg/m<sup>2</sup>) to the maximum dose (358 mg/m<sup>2</sup>). The patients enrolled in the trial had failed all other treatments.

A number of indicators in the trial suggests there is strong reason to continue development of this drug candidate, and in fact evidence that the drug is working in some patients.

CYT997 works by disrupting the tumour vasculature. In one patient with a mesothelioma tumour that had advanced to the abdomen, a MRI scan clearly showed that the blood vessel feeding the tumour were destroyed after only a few days of treatment with the drug. Using a biomarker (plasma von Williebrand factor) that measures blood vessel wall disruption, there was a clear increase on average in patients on the higher dosage groups. CYT997 works by breaking up blood vessels in solid cancers whilst leaving healthy blood vessels in tact.

Of the 22 patients, five had progressive disease with the remainder seeing their best response (not over the entire treatment time but the period between MRI scans) stabilise disease. Two patients recorded a reduction in tumour size. The pharmacokinetic data from this intravenous infusion study, which measures the length of time and the level of active drug maintained in the bloodstream, was very consistent with all patients.

## Upcoming Phase II CYT997 trials

Cytopia plans to begin a Phase II trial in patients with multiple myeloma at the **Alfred Hospital** in Melbourne. It plans to commence two other Phase II trials with CYT997 next year in solid tumours, possible melanoma and mesothelioma, although this remains undecided.

In laboratory studies using samples from patients with multiple myeloma, CYT997 was shown to stop the uncontrolled division of plasma cells that characterizes the disease, as well as overcoming the resistance mechanism often seen in patients being treated for multiple myeloma. Drug resistance is common in this disease and the possibility of stopping drug resistance with this drug (as well as potentially being an effective standalone therapy) may make it a useful drug to add to the current therapy regimes.

The multiple myeloma study will include an interim analysis after 11 patients have been treated, using an adaptive design process to help better guide the remainder of the trial. Cytopia has an open IND for CYT997. Other Phase II programs are likely to include trial sites overseas as well as in Australia.

Cytopia is also completing a Phase I trial with CYT997 dosed orally. This is an accelerated trial that allows patients to reach maximum dose more quickly. We estimate results should be available in the first half of next year.

## Comparative valuations

The table on this page shows a number of international oncology companies that are connected by their targeting of intracellular function. There is a spectrum of companies included. If biotech companies are successful in this area to develop first line oncol-

**Selected small molecule drug developers - oncology focus**

Company	Phase I	Phase II	Phase III	Market drugs	Comments	Enterprise Value (US\$M)
Onyx Pharmaceuticals				1 (Nexavar)	Co-marketed with Bayer, raf kinase inhibitor	\$2,840
Exelixis	8	6			One of best kinase drug discovery engines	\$761
Ariad Pharmaceuticals			1		Hits mTOR protein kinase	\$306
Rigel Pharmaceuticals	1	1			Oncology & JAK3 pathway for autoimmune	\$153
Kosan Biosciences		4	1		Hsp90 inhibitors	\$130
Infinity Pharmaceuticals	1				Collaborations with Astrazeneca, J&J and Amgen, Hsp90 inhibitors	\$71

**Selected Australian oncology companies**

Company	Phase I	Phase II	Phase III	Marketed drugs	Comments	Enterprise Value (\$M)
Chemgenex Pharmaceuticals		1	1		Expected to file for approval within 12 months	\$186
Progen Industries			1		Angiogenesis inhibitor	\$59
Cytopia		1			Collaboration with Novartis	\$24

Note: the above table indicates the number of drugs in trials, not the number of trials being conducted for different disease indications.

ogy treatments, and if they maintain some marketing rights, an enterprise value in the order of US\$3 billion can be achieved, as achieved by **Onyx Pharmaceuticals**. (**Imclone Systems** is another example, having developed the chimeric monoclonal antibody. It co-markets with BMS and has a enterprise value of US\$3.4 billion).

Companies that have developed powerful drug discovery engine rooms, such as **Exelixis**, can generate considerable value. The company has 14 different drugs in Phase I and Phase II and has an enterprise value of US\$761 million. A promising Phase III program can be worth around US\$300 million (**Ariad Pharmaceuticals**). Companies such as **Kosan Biosciences** and **Infinity Pharmaceuticals** developing drugs against the Hsp-90 (heat shock protein 90), which is acts a molecular ‘chaperone’, appear to reflect a lower value.

Of closer interest in this table for assessing Cytobia is **Rigel Pharmaceuticals**. It has one drug (a spleen tyrosine kinase inhibitor) in three Phase II trials for indications including rheumatoid arthritis and oncology (B-cell lymphoma). It has one preclinical program focused on the JAK3 pathway to treat transplant rejection and rheumatoid arthritis (the same pathway and indications as Cytobia), and it has a Phase I program to treat solid tumours (an aurora kinase inhibitor) which is partnered with **Merck Serono**. It also has a preclinical development program with **Pfizer**. Rigel has an enterprise value of US\$153 million.

### Considerably undervalued

With a technology value of only \$24 million, Cytobia is considerably undervalued. A technology value *in excess* of \$80 million for Cytobia would arguably be easily justified for the company, which translates to \$1.25 a share. The company has the challenge ahead to deliver on its milestones over the next 12 months, and delivering on these milestones will help its share price better reflect the value within the company.

### Milestones for the next year include:

- Start of Phase II multiple myeloma study
- Interim results from multiple myeloma study
- Final results from oral Phase I CYT997 study
- Start of two further Phase II studies with CYT997
- Possible collaboration for JAK2 program

Another surprising market value at present is that on **Progen Pharmaceuticals**, which has a technology value of only \$59 million. This may have to do with major milestones (results) for the Phase III liver cancer program being at least two years away. It also represents very good value for investors at its current price, although this stock is much more a binary play than Cytobia.

### Management and Board Changes

The founder of Cytobia, Dr Andrew Wilks, will be moving to a consulting and advisory role with the company in the new year. The company also announced changes to the board, with director John Hasker stepping down. The company would benefit from more international drug commercialisation experience at the board level.

### Summary

Cytobia has long been acknowledged as having a valuable drug discovery pipeline and this pipeline is now beginning to bear fruit for the company and its shareholders. It should be a pivotal period ahead for the company and at its current market value, it is an exceptionally attractive investment opportunity.

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

Bioshares

**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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**Bioshares**  
**PO Box 193 Richmond VIC 3121**  
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