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Companies covered: CGS, VHL

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Year 1 (May '01 - May '02)	21.2%
Year 2 (May '02 - May '03)	-9.4%
Year 3 (May '03 - May '04)	70.6%
Year 4 (May '04 - May '05)	-16.3%
Year 5 (May '05 - May '06)	77.8%
Year 6 (May '06 - May '07)	17.4%
Year 7 (May '07 - May '08)	-36%
Year 8 (May '08 - May '09)	-7.4%
Year 9 (May '09 - May '10)	50.2%
Year 10 (May '10 - May'11)	45.4%
Year 11 (May '11 - May '12)	-18.0%
Year 12 (May '12 - May '13)	3.1%
Year 13 (May '13 - May '14)	26.6%
Year 14 (May '14 - current)	7.7%
Cumulative Gain	**385%**
Av. Annual gain (14 yrs)	**16.6%**

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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) 9329 3350
Email: info@bioshares.com.au

David Blake - Editor
Ph: (03) 9326 5382
Email: blake@bioshares.com.au
Mark Pachacz - Research Principal
Ph: 0403 850 425
Email: pachacz@bioshares.com.au

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Bioshares

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Extract from Bioshares –

Viralytics and the Next Wave of Cancer Immunotherapies

Cancer therapy, led by melanoma treatment, has been shaken up by the emergence of two groups of immunotherapies, being in the main monoclonal antibodies that target CTLA-4 and 'checkpoint targets' PD-1 and PD-L1.

CTLA-4 is shortened from cytotoxic T-lymphocycte antigen 4, PD-1 stands for programmed death 1 and PD-L1 stands for programmed death ligand 1.

The relevance of these new therapeutics for Viralytics' (VLA: $0.29) novel oncolytic virotherapy, CAVATAK, is the potential for even better treatment outcomes to take place when CAVATAK is combined with one of these promising new approaches. Already there are many combination trials underway of these new therapeutics, to see not only if additive benefits are possible, but if multiplicative benefits are achievable.

Performance to Date of these New Drugs

This new generation of cancer treatments dates from the approval of Yervoy (ipulimumab) (Bristol-Myers Squibb), a CTLA-4 inhibitor, in 2011.Yervoy was approved for the treatment of unresectable or metastatic melanoma however has a label which includes a Black Box warning for the risk of fatal immune-mediated adverse reactions, with warnings applying for immune-related enterocolitis, hepatitis, dermatitis, neuropathy and endocrinopathy.

Cont'd over

Selected CTLA-4, PD1, PD-L1 Monoclonal Antibody Drugs in Development

Company	Drug	Target	Status
Bristol Myers Squibb	Yervoy (ipilumumab)	CTLA-4	**USA approved 2011** for melanoma; in multiple combination trials
Bristol Myers Squibb	Opdivo (nivolumab)	PD-1	**Japan approved July 2014** for unresectable melanoma; in multiple combination trials; EU MAA validated; PDUFA March 30, 2015
Merck	Keytruda (pembrolizumab) (MK3475)	PD-1	**US approved Sept 5** for secondary treatment after yervoy failure
Pfizer	Tremelimumab	CTLA-4	Various combination Phase I and II trials; Phase III lung cancer
Roche	MPDL3280A (RG7446)	PD-L1	Combination trials: Phase I - lung cancer, melanoma; Phase II - renal cancer, melanoma. Has a **Breakthrough Therapy** designation for bladder cancer
Curetech	Pidilizumab (CT-011)	PD-1	Various combination Phase II trials
AstraZeneca	MEDI14736	PD-L1	Phase II

Sources
Adapted and abridged from Immuno-Oncology Combinations: A Review of Clinical Experience and Future Prospects
Antonia SJ, et al; Clin Canc Res 23-10-2014
Company announcements

Yervoy has been a breakthrough medicine for treating metastatic melanoma, generating 10 months median overall survival alone, compared to 10 months in combination with gp100 and 6 months for gp100 alone.

Opdivo, a PD-1 inhibitor, was approved earlier this year in Japan, with a US PDUFA date scheduled for March 2015. Bristol-Myers Squibb, the sponsor of Opdivo, recently released interim results from its CheckMate 037, 370 patient, Phase III trial, which is evaluating Opdivo against an investigator's choice of chemotherapy (ICC) in patients previously treated with Yervoy. Drugs used in the ICC arm were dacarbazine or carboplatin. Co-primary endpoints are overall response rate and overall survival.

The objective response rate in the Opdivo arm (in the first 120 of the 268 patients) was 32% versus 11% in the ICC arm (in the first 47 of the 102 patients) in patients with at least six months of follow up, with 95% of responses in the Opdivo arm still ongoing.

A Phase I study with Opdivo, published in the *New England Journal of Medicine* in June 2012, reported response rates of 18% for non-small cell lung cancer, 28% for melanoma patients and 27% for renal cell cancer. The surprise from this and a related study was the observation of the response rates in cancers other than melanoma, which had been characterized to date as a strongly immunological cancer. The implications for the PD-1 (and similar) classes of drugs is that they may have wide application.

A combination study of Opdivo and Yervoy, with 53 patients treated concurrently in patients with advanced melanoma, demonstrated a one year survival rate of 82%, and roughly 70% surviving to more than 30 months. Data for the trial led by Dr Jedd Wolchok was first published in the *New England Journal of Medicine* (July 2013), with this more recent survival date communicated to the authors of Immuno-Oncology Combinations: A Review of Clinical Experience and Future Prospects (Antonia SJ, et al; *Clin Canc Res* 23-10-2014).

Merck's PD-1 drug Keytruda demonstrated a 69% one year survival rate in advanced melanoma patients and an estimated 18 months survival rate of 62%. Curetech's PD-1 drug candidate pidilizumab demonstrated an 84% survival rate at 18 months in 72 patients with large B-cell lymphoma following autologous stem cell transplantation.

Implications for Viralytics' CAVATAK Therapy

The investigation of Viralytics' oncolytic virotherapy Cavatak in combination with a PD-1 inhibitor could result in an efficacious as well as more tolerable regime for treating various cancers.

Already, the data from Viralytics' single arm Phase II study in melanoma patients has shown a one year survival rate of 73% (from 33 out of 45 subjects) and an overall response rate of 28% (from 16 out of 57 patients). Most importantly, no grade 3 or 4 drug related adverse events have been reported. In contrast, the percentage of grade 3 or grade 4 drug related adverse events reported in the Wolchok study mentioned above (with Opdivo and Yervoy) was 72%.

How the CTLA-4 and PD-4 Inhibitors Work: Taking the Foot off the Brake

Tumours grow and spread because they develop various means to evade surveillance and response by the body's immune system. Tumours can express, or shed, a protein called PD-L1 which can cause T-cells to halt their surveillance for cancer cells.

When the PD-L1 (the ligand, or circulating protein) binds to PD1 receptors on T-cells, which are a key component of the body's active immune response, the immune response is suppressed. By stopping PD-L1 from binding by blocking the PD1 binding site, or 'soaking up' the circulating PD-L1, then T-cells can remain active.

Yervoy (ipulimumab) acts in a similar way with its blocking of CTLA-4 binding to cell receptors CD80/86.

PD-1 and CTLA-4 are negative regulators of the immune system, which means they act as brakes on the immune system. So by releasing the brakes, the immune system can get back to the job of attacking cancer cells and tumours.

Toxicity is a considerable issue for immune-modulating therapies, as is even more clearly shown by Yervoy's Black Box label.

Viralytics is exploring additional studies in melanoma patients where CAVATAK is administered in combination with checkpoint inhibitors such as Opdivo, or Yervoy, or even with another class of small molecule drugs that have a similar immune-modulatory function (the BRAF/MEK inhibitors).

Recent Combination Drug Animal Studies

Animal studies conducted by Viralytics showed that CAVATAK, administered intra-lesionally and combined with an anti-PD1 drug, resulted in 75% (of animal subjects) being tumour free after 45 days, in contrast to 0% with CAVATAK alone and 0% of anti-PD1 alone being tumour free at 45 days.

While animal data should always be treated with circumspection, it is interesting to note that the combination of CAVATAK and an anti-CTLA-4 antibody achieved an estimated 45% survival out to ~78 days. However, a 100% survival effect persisted much longer in the combination group than any other treatment group in the study (to ~51 days); 100% survival persisted to ~43 days for CAVATAK alone and ~37 days for anti-CTLA-4 alone.

These data would appear to be supportive of clinical studies in human subjects in which CAVATAK is combined with anti-PD1 or anti CTLA-4 therapies.

Cont'd over

Selected Recent Clinical R&D Deals for Immunotherapy Programs

Date	Company	Partner	Subject	Terms
October 23, 2014	Curetech	Medivation	World wide rights to pidilizumab - a PD1 inhibitor	US$5 M upfront; US$85 M in MSPs; tiered royalties from 4%-11%; includes manufacturing and supply agreement

Selected Recent Pre-clinical R&D Deals for Immunotherapy Programs

Date	Company	Partner	Subject	Terms
October 20, 2014	NewLink Genetics	Genentech (Roche)	NLG919, an IDO pathway inhibitor	US$150 M upfront; > US$1 B in MSPs; escalating double digit royalties; retains co-promotion rights
March 17, 2014	Five Prime	Bristol Myers Squibb	Discovery and development of therapies for two undisclosed immune checkpoint pathyway inhibitors	US$20 M upfront; research funding US$9.5 M; US$21 M for 5% of stock; up to US$300 M in MSPs; tiered mid single digit to low double digit royalties
March 13 ,2014	Anaptys	Tesaro	Development of mabs targeting TIM-3, LAG-3 and PD-1 (all checkpoint receptors)	US$17 M upfront: US$18 M for development milestones; US$90 M for certain US and ex US reg submissions; tiered single digit royalties
Feb 12, 2014	Aurigene (India)	Pierre Fabry (France)	World-wide rights to AUNP-12	Undisclosed upfront payments and milestone payments

Outlook

Viralytics' goal is to produce a package of data for CAVATAK which can build the case for a strong partnering outcome. Hence, the availability of interim results from its intravenous study (STORM) in 2015, along with survival data from the CALM study in Q1 2015 should set Viralytics up for a period of share price re-calibration in the first half 2015.

An even stronger partnering outcome might be achieved once clinical data emerges from some of the possible combination therapy trials which may take place.

Viralytics retained cash of $23.8 million at September 30, 2014. Viralytics is capitalised at $54 million.

Bioshares recommendation: **Speculative Buy Class B**

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. For both groups, the rating "Take Profits" means that investors may re-weight their holding by selling between 25%-75% of a stock.

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

Corporate Subscribers: Cogstate, Bionomics, Impedimed, QRxPharma, LBT Innovations, Tissue Therapies, Viralytics, Phylogica, pSivida, Benitec BioPharma, Admedus, Calzada, Invion, Imugene, Analytica, Circadian Technologies, Reproductive Health Science