EDISON

Viralytics

AACR update

Cavatak/Yervoy combo enters the spotlight

Pharma & biotech

Viralytics' presentations at AACR highlighted an impressive 36% response rate when melanoma patients refractory to the best available PD1/L1 checkpoint inhibitor therapy were treated with its Cavatak virotherapy plus Yervoy. It has expanded the Phase Ib MITCI trial to recruit an extra 44 patients who have failed prior PD1/L1 therapy, which could put it on track to a pivotal study or even provide a potential pathway to accelerated approval. The CAPRA study of Cavatak plus Keytruda in melanoma was expand to enrol up to 50 patients following a 60% response rate in the first 15 assessable patients. We increase success probability for Cavatak from 35% to 40% and lift our valuation to A$408m or A$1.70/share from A$385m.

Year end	Revenue (A$m)	PBT* (A$m)	EPS* (c)	DPS* (c)	P/E (x)	Yield (%)
06/15	2.5	(5.5)	(3.0)	0.0	N/A	N/A
06/16	4.7	(8.0)	(3.8)	0.0	N/A	N/A
06/17e	4.3	(11.7)	(4.9)	0.0	N/A	N/A
06/18e	4.8	(11.4)	(4.7)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding amortisation of acquired intangibles, exceptional items and share-based payments.

Compelling benefit from Cavatak/Yervoy combo

The tumour response rate in the first 22 melanoma patients receiving Cavatak plus Yervoy in the MITCI trial is substantially higher than the response rates for either Cavatak or Yervoy on their own reported from previous studies (28% and 11% respectively). Importantly, there was a 36% response rate among a subgroup of 11 patients who had failed prior treatment with the best available immune checkpoint inhibitor (ICI) therapies. The combination was well tolerated with only 8% of patients reporting serious treatment-related adverse events.

Expanded MITCI study could prove pivotal

The high response rate in MITCI prompted Viralytics to expand the trial to recruit a further 44 patients with advanced melanoma who have failed ICI therapy. If the strong response rates and low adverse events rates are maintained in the additional patients, the Cavatak/Yervoy combination could progress to a pivotal study in patients who have failed prior ICI therapy. Depending on the results and whether any alternative treatments are approved in the interim, the expanded MITCI study could potentially be the basis for an accelerated approval application.

CAPRA expanded and Keynote 200 on track

The CAPRA study of Cavatak plus Keytruda has been expanded to enrol up to 50 patients following a 60% response rate in the first 15 patients, while the iv Keynote 200 trial has commenced enrolling expansion cohorts in lung and bladder cancer.

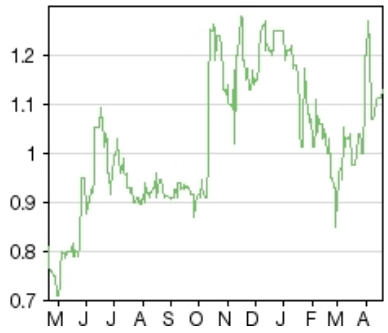
Valuation: Increased to A$408m or A$1.70/share

We lift our valuation to A$408m or A$1.70/share (undiluted) from A$385m or A$1.60/share due to increased 40% (vs 35%) probability of success for Cavatak in melanoma.

19 April 2017

Price	**A$1.13**
Market cap	**A$272m**
	US$0.76/A$
Net cash (A$m) at 31 March 2017	38.8
Shares in issue	240.3m
Free float	85%
Code	VLA
Primary exchange	ASX
Secondary exchange	OTCQX

Share price performance



%	1m	3m	12m
Abs	15.9	4.6	63.8
Rel (local)	15.3	2.2	45.2

52-week high/low	A$1.3 A$0.7

Business description

Viralytics is a biopharmaceutical company developing Cavatak oncolytic virotherapy to target late-stage melanoma and other solid tumour types. It is trialling Cavatak as a monotherapy and in combination with checkpoint inhibitors. The virus can be delivered intravenously or by intralesional injection.

Next events

Keynote 200 Keytruda combo update	H2 CY17
MITCI Yervoy combo trial update	H2 CY17
CAPRA Keytruda combo trial update	H2 CY17

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Investment summary

Company description: Improving cancer immunotherapy

Viralytics is developing the oncolytic virus Cavatak for use in immunotherapy treatments for a range of cancers. Cavatak is a proprietary formulation of a common cold virus, Coxsackievirus A21 (CVA21), in clinical development for late-stage melanoma, lung and bladder cancer, with potential applications in a range of other cancers. When injected into melanoma lesions, Cavatak achieved a 28% response rate as a single agent, and preliminary response rates of 60% and 64% when combined with ICI drugs Keytruda and Yervoy, respectively. Adverse events rates have been low in all Cavatak trials so far, even when combined with therapies usually associated with high adverse event rates. Initial results from the Keynote 200 Phase I/II study (in collaboration with Merck) produced encouraging signs that Cavatak will also be effective when administered intravenously (iv); iv Cavatak is being trialled in combination with Merck's Keytruda in lung and bladder cancer.

Valuation: rNPV of A$408m, or A$1.70 per share (undiluted)

We value Viralytics at A$408m, or A$1.70 per share (undiluted), using a risk-adjusted net present value method to discount future cash flows through to 2033 in metastatic melanoma, bladder cancer, non-small cell lung cancer and prostate cancer. We apply a 40% (previously 35%) probability of success to intralesional injection of Cavatak in melanoma to reflect positive clinical data and the clear market opportunity for Cavatak plus Yervoy in patients who have failed PD1/L1 ICI therapy, and 15% probability in other indications. Our approach assumes a partnering deal or out-licensing of Cavatak in FY18, with costs of subsequent clinical development borne by the partner/licensee. Of note, while our model does include upfront payments and clinical/regulatory milestones from a potential licensing deal, these have been risk-adjusted.

Sensitivities: Keynote 200 and combo trial outcomes are key

Viralytics is subject to typical biotech company development risks, including the unpredictable outcome of trials, regulatory decisions, success of competitors, financing and commercial risks. In particular, it has a very high single-product risk, with the entirety of its value residing in Cavatak. The investment case hinges on the outcome of clinical trials and, assuming data are positive, the company's ability to secure a partnership (or further capital) to advance Cavatak into late-stage trials. Ideally, a partner would have an established oncology franchise with the resources and experience to evaluate Cavatak in multiple cancer indications. The rapidly evolving treatment landscape for melanoma means that the greatest commercial opportunity for Cavatak is likely to be in combination with checkpoint inhibitors or other targeted agents. Initial results from STORM/Keynote 200 suggest that Cavatak replicates in melanoma, lung and bladder cancer tumours following IV administration, but the situation in prostate cancer is unclear. Results from the Keynote 200 lung and bladder cancer expansion cohorts will be important pointers to utility beyond melanoma, although we also see the potential for the efficacy of iv Cavatak in other cancer types to be boosted by judicious use of ultrasound or CT-guided intralesional injections.

Financials: Sufficient cash to initiate a pivotal trial

Viralytics reported cash of A$39m at 31 March 2017. The company has the resources to complete ongoing Cavatak combination clinical trials (MITCI, CAPRA and STORM/Keynote 200), plus additional Cavatak combination trials being planned. If a partner is not secured for Cavatak, Viralytics has sufficient resources to initiate a pivotal trial of Cavatak plus Yervoy in melanoma patients who are refractory to ICI therapy, but may need additional funds to complete the trial. Given the positive signs of efficacy to date, prospects for attracting a big pharma partner appear promising.

Building evidence of efficacy for a Cavatak deal

Viralytics is actively pursuing a clinical trial programme to confirm the potential of Cavatak as an anticancer therapy, with an emphasis on combination immunotherapy and demonstrating that Cavatak is efficacious when administered intravenously. Exhibit 1 summarises the ongoing Cavatak clinical trials.

Exhibit 1: Cavatak clinical trial programme

Route of admin	Indication	Stage	Development notes
Intratumoral	Melanoma	Phase Ib	MITCI Phase Ib study in combination with Yervoy (N=26, interim results ORR 50% (11/22), ORR 36% (4/11) in patients who had failed prior ICI therapy; ORR 64% (7/11) in ICI naive patients). Expansion cohort of 44 patients who had failed prior therapy with PD1/L1 ICI commenced recruitment Q117 (total n=70).
Intratumoral	Melanoma	Phase Ib	CAPRA Phase Ib study in combination with Keytruda (interim results ORR 60% (9/15)). In April 2017 the trial was expanded to enrol up to 50 patients vs the original target of 30 patients. None of the subjects has undergone prior PD1/L1 ICI therapy.
Intravenous	Melanoma, bladder, lung, prostate	Phase I	Phase I STORM part A trial (N=18; ORR in high dose cohort 10% (1/10, 1 PR in a patient with prostate cancer). Analysis of tumour biopsies suggests that Cavatak replicates in melanoma, lung and bladder tumours after iv administration.
Intravenous	Bladder, lung	Phase IIa	Phase I/II Keynote 200 (STORM Part B) trial of iv Cavatak plus Keytruda. Two stages: enrolment in the three safety cohorts is complete (n=10), which confirmed the combination is well tolerated with only one grade 3 adverse event. Recruitment underway in the expansion cohorts that will recruit ~40 bladder and ~40 lung cancer patients.
Intratumoral	Melanoma	Phase IIa	Phase II CALM study in malignant melanoma (n=57, ORR 28%, durable response in 21% of patients). Monotherapy. Study complete.
Intratumoral	Melanoma	Phase IIa	Phase II CALM immune-profiling extension study in malignant melanoma (n=13). Collected tumour biopsies and other immune response measures. ORR 30%. Study complete.
Not specified	Solid tumours	Phase Ib	Additional Phase Ib studies in combination with checkpoint inhibitors in other solid tumours in planning stage.
Intravesicular	Non muscle-invasive bladder cancer	Phase I	Phase I CANON study – enrolment complete (n=16). Intravesicular administration of Cavatak as a single agent and with mitomycin C, followed by transurethral resection of tumour tissue on day 8. CR in one of first three treated at highest dose. Cavatak increases immune cell infiltrates and PD-L1 expression vs untreated controls.
Intratumoral	Head and neck	Phase I	On hold Phase I head and neck cancer complete.

Source: Edison Investment Research. Note ORR = overall response rate

Checkpoint inhibitors strengthen immune responses

Immune checkpoint inhibitor (ICI) drugs have markedly improved the treatment prospects for a number of cancers by “taking the brakes off” the immune response. Responses to the approved ICI are frequently long-lasting, but response rates to single-agent ICI therapy are relatively low, typically in the range of 10-35%.

The most widely used class of ICI therapies targets the action of PD1 (programmed death 1 receptor), which is an inhibitory receptor present in activated T-cells. Binding of the PD1 receptor to its signalling protein or ligand (programmed death ligand 1 or PD-L1) downregulates activated T-cells. Two types of drugs block the interaction between the PD1 receptor and its ligand: i) anti-PD1 monoclonal antibodies (mAb) that bind to the receptor; or ii) anti-PD-L1 mAb that bind to the ligand. Both classes of drug work by blocking the interaction between the receptor and its ligand so they are seen to be largely equivalent – we refer to them together as PD1/L1 therapies. The marketed PD1/L1 drugs are shown in Exhibit 2.

The first ICI drug approved was Yervoy, an anti-CTLA-4 (cytotoxic T-lymphocyte-associated protein 4), but it is less widely used because it is associated with both lower response rates and more severe side effects. CTLA-4 acts earlier in the immune response cycle when antigen presenting cells (APC) interact with T-cells to initiate an immune response. CTLA-4 is a negative regulator of T-cell activation, and anti-CTLA-4 antibodies prevent this inhibition. The high response rates seen when Cavatak is used in combination with Yervoy suggest that the two drugs may be working synergistically to trigger a stronger initial immune response.

Exhibit 2: Marketed immune checkpoint inhibitor drugs

Drug name and manufacturer	Class
Opdivo (nivolumab) BMS	anti-PD1
Keytruda (pembrolizumab) Merck	anti-PD1
Tecentriq (atezolizumab) Roche	anti-PD-L1
Bavencio (avelumab) Merck KGaA and Pfizer	anti-PD-L1
Yervoy (ipilimumab) BMS	anti-CTLA-4

Source: Edison Investment Research

Cavatak/Yervoy combo targets an attractive niche in crowded immuno-oncology space

From clinical trial results seen so far it seems highly likely that combination with Cavatak will substantially improve response rates to ICI immunotherapies by "priming" or initiating an immune response that can then be strengthened by combination with ICI therapy, which loosens the host "immunological handbrake". What is less clear is how these response rates will compare to other combination therapies that are currently under development. The cancer immunotherapy space is developing rapidly; for example, Merck's Keytruda is being trialled in over 360 clinical studies as a monotherapy or in combination in at least 22 different cancers.

In this environment trialling Cavatak in combination with the CTLA-4 inhibitor Yervoy in patients who have failed prior with PD1/L1 ICI therapy in the MITCI study looks like a smart move. Anti-PD1/L1 drugs are increasingly being used as first-line therapies in advanced melanoma, so it is likely that the majority of patients requiring second- or third-line treatment will have failed one of these therapies, ensuring that there is a large addressable market. Yervoy is not widely used as a first-line therapy due to poor tolerability, but the 36% response rate seen so far for Cavatak plus Yervoy in patients who have failed PD1/L1 therapy would be expected to see the combination widely used in these patients who have few treatment options, and even more so if the low adverse event rate seen in the small number of patients treated so far is maintained when a larger number of patients has been studied.

Cavatak is also being trialled in combination with the PD1 ICI Keytruda as first- to third-line therapy in melanoma, lung and bladder cancers in the CAPRA and Keynote 200 studies, with the goal of improving response rates to initial therapy with this leading ICI drug. The initial results from the CAPRA study are very encouraging, with a 60% response rate in the first 15 patients assessed, compared to ~33% for Keytruda monotherapy[1] in advanced melanoma. However, PD1/L1 inhibitors are being tested in combination with a wide range of immunotherapies including those targeting IDO, LAG-3 and CTLA-4, and other oncolytic viruses, as well as in combination with chemotherapy treatments that kill cancer cells and release cell debris that can stimulate an immune response. In this crowded environment, high response rates will probably be required to ensure commercial success in first-line combination therapy.

Cavatak could potentially come to be used in combination with Keytruda to improve responses in first-line therapy and used in combination with Yervoy in patients who experience disease progression after ICI therapy.

In addition to ongoing studies in melanoma, lung and bladder cancer, preclinical or early clinical studies indicate that Cavatak could potentially be effective in a range of other cancers including prostate, breast, pancreatic and head and neck cancers, as well as multiple myeloma and chronic lymphoid leukaemia.

The ongoing STORM/Keynote 200 study is testing whether Cavatak is effective in combination with Keytruda in lung and bladder cancers when the virus is delivered intravenously. While high response rates in this study would be the ideal outcome, it seems to us that efficacy following iv

[1] Robert et al, N Eng J Med 2015, 372:2521-2532.

administration could potentially be boosted by combining it with one or more intralesional injections delivered under ultrasound or CT guidance. Interventional radiologists are already accustomed to taking biopsies of tumours using these methods, so intralesional injections should be quite feasible.

We defer deal timing, but prospects look good

The encouraging Cavatak data, which include high response rates and low adverse event rates, are likely to attract attention from potential partners. We model a licence deal but, given that Viralytics is a single-product company, we expect that potential partners would also consider an outright acquisition of the company.

Given the attractive market opportunity for Cavatak in combination with the CTLA-4 inhibitor Yervoy, we would expect BMS, which markets Yervoy, and AstraZeneca, which has its CTLA-4 inhibitor tremelimumab in Phase III trials in combination with its anti-PD-L1 antibody durvalumab, to be closely following the progress of the Cavatak trials. Similarly, Merck, which is already collaborating with Viralytics in trials combining Cavatak with pembrolizumab, would be an obvious potential partner.

We had previously modelled a licence deal in FY17 but, given that the expanded trials will generate additional data of interest to potential partners, we now model a licence deal in FY18 (assumed deal terms are unchanged, as outlined in the valuation section).

Updates on key programmes presented at AACR

Viralytics' Cavatak clinical trials featured in three presentations at the American Association for Cancer Research (AACR) Annual Meeting held in Washington DC (US) on 1-5 April 2017, including two prestigious podium presentations.

MITCI update confirms high response rate to Cavatak/Yervoy

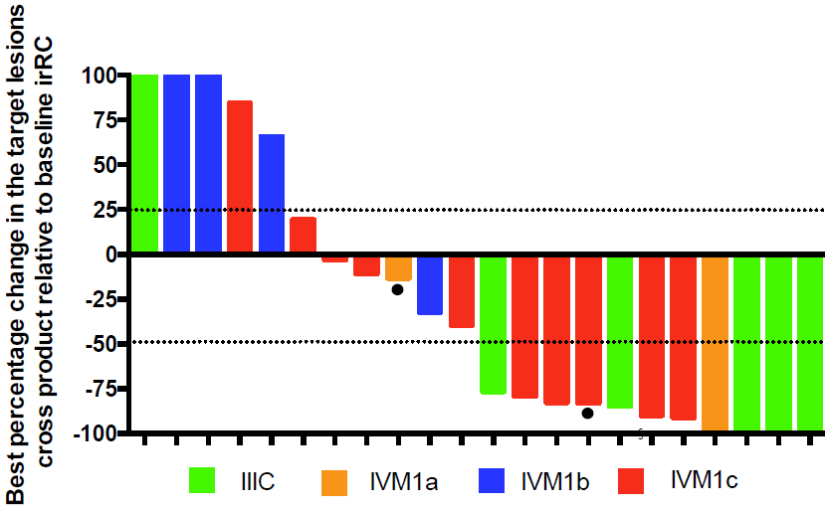
A podium presentation by Curti et al at AACR showed that the encouraging 50% preliminary response rate previously reported the MITCI trial has been maintained as the trial progressed to included response assessments on 22 patients. MITCI is a Phase Ib trial of intratumoral Cavatak in combination with the anti-CTLA-4 ICI Yervoy in patients with advanced melanoma. A total of 25 out of the target of 26 subjects had been recruited at the data cut-off date for the conference presentation, but only 22 patients had reached the first tumour response assessment at day 106.

In the trial at least one melanoma lesion was injected with Cavatak four times over a three-week period before treatment with Yervoy commenced, and Cavatak continued to be injected every three weeks for up to a year. Four doses of Yervoy were administered at 3mg/kg iv every three weeks starting at day 22.

A majority of the 25 patients who have been treated had previously undergone systemic immunotherapy. To date, no Cavatak-related grade 3 or higher adverse events have been reported, but there have been two (8%) Yervoy-related grade 3 adverse events (one fatigue, one anaemia). This is lower than the 23% grade 3 or higher treatment-related adverse event rate reported for Yervoy on its own in advanced melanoma.

Exhibit 3 shows that 11 (50%) of the 22 patients who reached the first tumour evaluation assessment experienced confirmed objective responses, including four (18%) complete responses. Six additional patients showed stable disease at day 106, bringing the disease control rate (tumour shrinkage or stable disease) to 77% (17/22).

Exhibit 3: Changes in melanoma tumour burden by disease stage

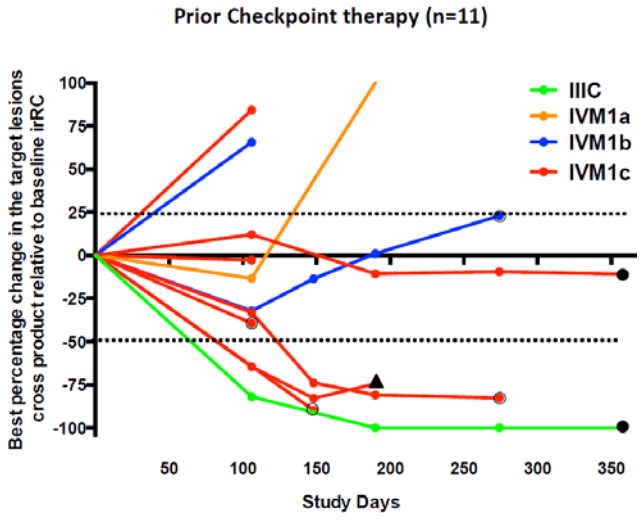


Source: Curti et al presentation AACR April 2017. Note: • = positive level of anti-CVA21 serum antibodies at baseline.

Exhibit 4 shows the change in tumour burden over time for patients with a history of prior ICI therapy. Importantly, Exhibits 4 and 5 show there have been four (36%) responses among 11 patients who had failed previous treatment with ICI drugs. This is an impressive response rate in patients who have failed to respond to the best available therapies. The disease control rate was 82% (9/11).

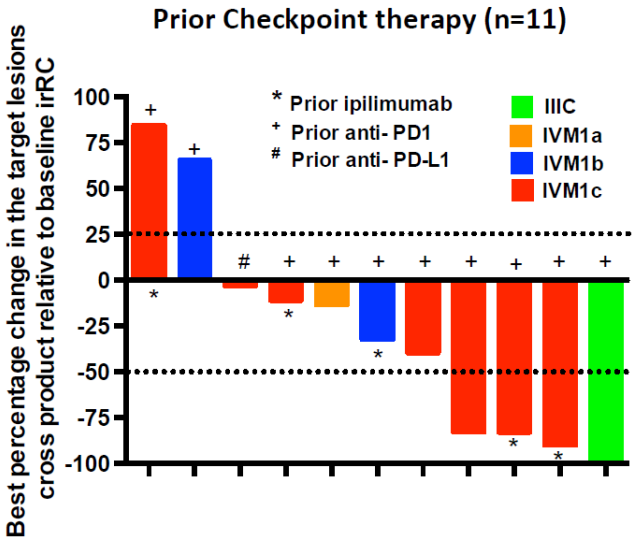
A notable feature shown in Exhibit 4 is that in most cases the tumours continued to shrink long after treatment with Yervoy stopped (on day 85).

Exhibit 4: Changes in melanoma tumour burden by disease stage for patients who failed prior ICI therapy



Source: Curti et al presentation AACR April 2017

Exhibit 5: Best overall response for patients who failed prior ICI therapy



Source: Curti et al presentation AACR April 2017. Note: Response rates as per immune-related response criteria (irRC).

The efficacy data are very encouraging for a highly pre-treated patient group with advanced melanoma. The MITCI response rate is comparable to the 56% (10/18) response rate reported by Puzanov et al at ASCO 2015 for Yervoy combined with Amgen's approved oncolytic virotherapy, Imlygic (T-Vec). We note that the Puzanov study was in patients who had not undergone any systemic therapy and included patients with less severe Stage IIIB disease.

Most importantly, the 36% response rate among patients who had failed treatment with one or more PD-1 ICI drugs compares to a response rate of only 13% (13/97) when patients who had failed treatment with the PD-1 drug Keytruda were treated with Yervoy on its own.

The 36% response rate and 82% disease control rate among the 11 patients who had failed prior treatment with the best available ICI therapies has prompted Viralytics to expand the MITCI trial to recruit a further 44 patients with advanced melanoma who have failed anti-PD1/L1 ICI therapy.

Potential for an accelerated approval application if circumstances are right

Viralytics has pointed out that the expanded MITCI trial could put it on the path to undertake a pivotal study of Cavatak plus Yervoy in melanoma patients who have failed treatment with PD1/L1 therapies. However, we believe that under certain circumstances the MITCI data could also be used to support an application for accelerated approval in the US. This would depend on continued high response rates in the additional 44 patients (preferably together with continued low adverse events rates) and there continuing to be a significant unmet need for an effective treatment for this patient group (in this regard Amgen's Imlygic/Yervoy combo trial (NCT01740297) will be an important one to watch).

We note that the FDA approved Bavencio (avelumab) for metastatic Merkel cell carcinoma in March 2017 based on a 33% response rate in an 88-patient, single-arm trial. This data set is not much larger than the one Viralytics will have at the completion of the enlarged MITCI study.

At this stage, it is difficult to tell how realistic a prospect an application for accelerated approval would be; in our forecast we continue to assume that a Phase III study will be required before Cavatak receives market approval.

CAPRA combining intralesional Cavatak with pembrolizumab

Viralytics is testing the combination of intralesional Cavatak with Keytruda (pembrolizumab) in advanced melanoma (Stage IIIB/C and IV) in the Phase Ib CAPRA study. The Cavatak dose regimen used in this trial is similar to that in the CALM trial.

Phase Ib data from the first 15 assessable patients presented at AACR showed a disease control rate of 87% (13/15). The objective response rate was 60% (9/15) and stable disease was observed in 27% (4/15). These response rates are higher than the published rates for either agent used alone: Cavatak 28% and Keytruda c 33% in patients with late-stage melanoma.

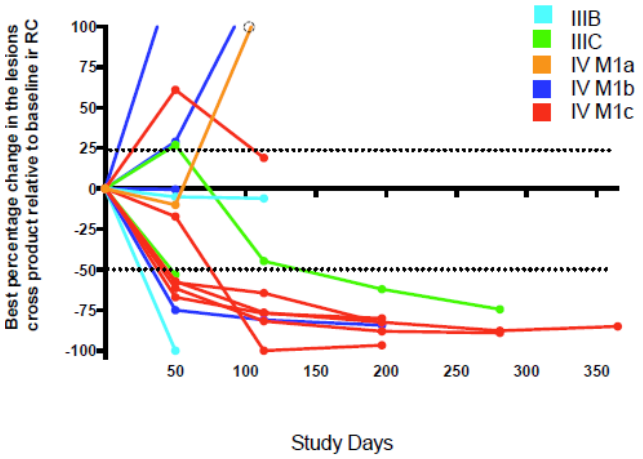
In patients with the most advanced Stage IV M1c disease the response rate was 83% (5/6).

No grade 3 or higher treatment-related adverse events have been reported, which compares to a 10% adverse event rate for Keytruda monotherapy in advanced melanoma.

Interestingly, a disease control rate of 100% (7/7 lesions) was observed in individual non-injected visceral and non-visceral lesions, with an objective response rate of 86% (6/7).

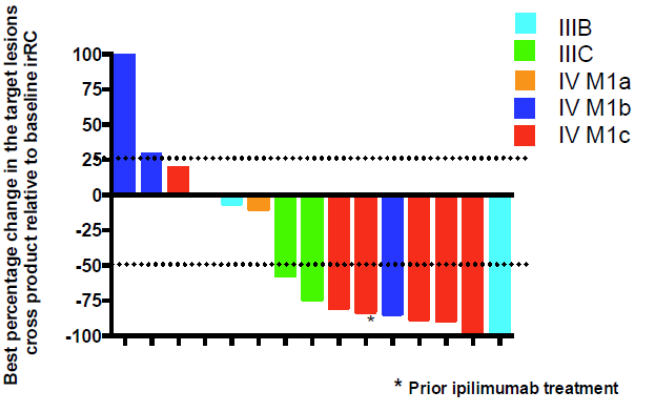
Encouraged by the positive results to date, Viralytics has expanded the trial to enrol up to 50 patients (vs 30 originally), including patients who are refractory to anti-PD1 therapy.

Exhibit 6: Changes in melanoma tumour burden by disease stage



Source: Silk et al poster AACR April 2017

Exhibit 7: Best overall response by irRC criteria

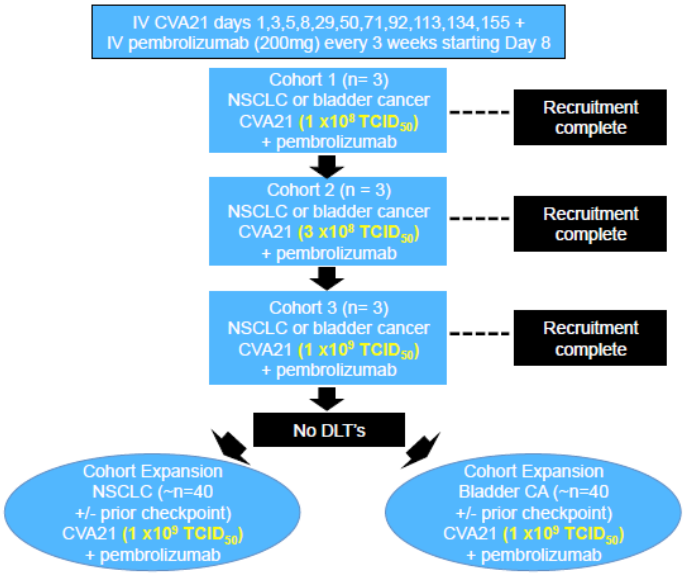


Source: Silk et al poster AACR April 2017. Note: irRC = immune-related response criteria.

Keynote 200 (Storm Part B) enters expansion phase

At AACR, Viralytics presented updated data from the first 10 patients treated in Part B of the STORM study (Keynote 200), which is being conducted in collaboration with Merck. The study is testing iv Cavatak in combination with the anti-PD-1 ICI antibody Keytruda (pembrolizumab).

Exhibit 8: Progress of Keynote 200 Part B – iv Cavatak with pembrolizumab



Source: Pandha et al AACR presentation April 2017

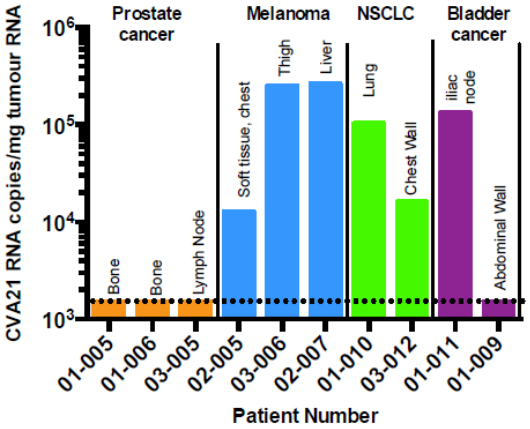
Keynote 200 started by confirming that the three doses of iv Cavatak that were tested as a monotherapy in Part A of the trial are safe to use in combination with pembrolizumab. Ten patients have been enrolled in three dose cohorts, which confirmed that Cavatak is well tolerated at doses up to $1x10^9$ $TCID_{50}$ when administered iv in combination with pembrolizumab; only one unconfirmed grade 3 treatment-related adverse event and no dose-limiting toxicities have been observed. Recruitment is currently underway in the expansion cohort, which will treat ~80 patients (~40 NSCLC and ~40 with metastatic bladder cancer) at a dose of $1x10^9$ $TCID_{50}$.

No responses were observed in the two lower-dose cohorts, and none of the patients in the third (high-dose) cohort has undergone the first tumour response assessment at day 92.

Testing of serum from patients in the Keynote 200 trial confirmed that none of the patients developed neutralising antibodies against the Cavatak virus during the first three days of treatment, and only one patient had developed neutralising antibodies by day 5 when the third dose of Cavatak is administered. This confirmed that there is a window allowing for repeated iv dosing without interference from neutralising antibodies.

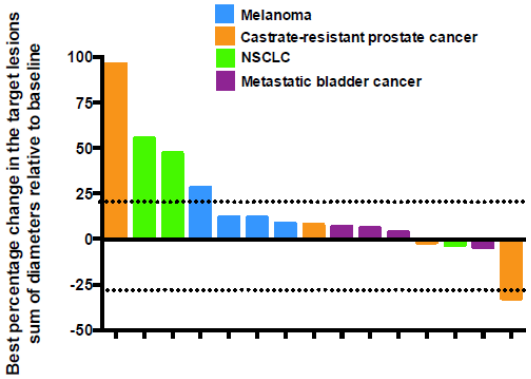
Viralytics had previously presented data from patients administered iv Cavatak in Part A of the Phase I STORM study showing that viral RNA was detected in tumour biopsies of all three melanoma patients, both NSCLC and one of the two bladder patients, but in none of the three prostate cancer patients tested (Exhibit 9). As Exhibit 10 shows, of the 15 subjects, one prostate cancer patient experienced a partial tumour response, 10 subjects had stable disease and four experienced disease progression.

Exhibit 9: CVA21 RNA expression in tumour tissue at day 8



Source: Pandha et al AACR presentation April 2017. Note: Dotted line represents limit of detection (1,500 copies/mg) .

Exhibit 10: CVA21 monotherapy – best overall response



Source: Pandha et al AACR presentation April 2017

Imlygic sales modest – we expect Cavatak to do better

The FDA approved Amgen's Imlygic (talimogene laherparepvec, commonly known as T-Vec) oncolytic virotherapy in October 2015. Imlygic is approved for the local treatment of unresectable cutaneous, subcutaneous and nodal lesions in patients with melanoma. Imlygic has not been shown to have an effect on visceral metastases, so it is not considered suitable for the treatment of patients with life-threatening forms of melanoma, ie those with lung, liver or other visceral metastases (Stage IV M1b or M1c melanoma).

Amgen has not disclosed Imlygic sales in its quarterly results presentations, instead lumping them in the "other" category together with MN Pharma, Bergamo, and Corlanor. Total sales for "other" products in 2016 were US$60m in the US and US$250m worldwide (vs US$204m worldwide in 2015). Evaluate Pharma reported consensus analyst forecasts of US$45m and US$250m for worldwide Imlygic sales in 2016 and 2022, respectively.

We forecast worldwide peak sales of Cavatak in melanoma to be US$1.0bn in 2026, substantially higher than the current 2022 consensus forecasts for Imlygic. We expect this outperformance to be driven by Cavatak's efficacy against visceral metastases when used as a single agent (response rate in non-injected target lung and liver lesions was 38% [6/16] in the CALM Phase II trial of intralesional injection of Cavatak in melanoma patients), and by the high response rates seen when Cavatak is used in combination with ICI therapies.

We also assume potential peak sales of a further US$1.5bn in other solid tumour types such as lung, bladder and prostate cancers for treatment delivered intravenously or via ultrasound or CT-guided intralesional injections.

Imlygic combinations with Yervoy and Keytruda being studied

Amgen is studying Imlygic in combination with both Yervoy and Keytruda in advanced melanoma patients. While Amgen is not specifically targeting enrolment of patients who have failed anti-PD1/L1 therapy in its Phase I/II trial of Imlygic plus Yervoy, those patients will be eligible to participate in the Phase II component of the trial. The outcome this trial may influence the market opportunity for Cavatak plus Yervoy in PD1/L1 refractory patients.

Amgen reported a 50% overall response rate (ORR) from the Phase I component of the Phase I/II trial of Yervoy plus Imlygic in first- or second-line therapy in ICI naive patients (NCT01740297). The ORR in visceral tumours was also 50%. That Phase I trial only enrolled patients with previously untreated melanoma (ie first line), a group of patients who typically experience higher response rates. The trial has been expanded to include a 173-patient Phase II cohort as first- or second-line therapy (prior ICI therapy allowed, can be third-line therapy if BRAF mutant) randomised to either Yervoy or Yervoy plus Imlygic. Recruitment ended in March 2016, and interim data on the first 82 patients assessed were reported at ESMO in October 2016. The confirmed ORR was 36% for combo vs 18% for Yervoy alone. When unconfirmed responses were included, ORR was 50% for combo and 28% for Yervoy.

A 660-patient Phase III trial of Imlygic plus Keytruda as first-line therapy (prior BRAF inhibitor therapy allowed for BRAF V600-mutated tumours) in unresected melanoma (Keynote-034) has an expected completion date of December 2018 (NCT02263508). The trial is recruiting patients with Stage IIIB to IV M1c melanoma for whom surgery is not recommended. In the Phase Ib component of the trial the ORR was 57% (48% confirmed ORR). Response rate in visceral tumours was 28%.

Valuation

We lift our valuation of Viralytics to A$408m or A$1.70/share (undiluted) from A$385m or A$1.60/share due to the increased likelihood of success for Cavatak and rolling forward the DCF model, partly offset by deferring assumed out-licence deal timing from FY17 to FY18 and resultant increases in forecast trial costs to be funded by Viralytics before partnering. We have increased our forecast probability of success for Cavatak in melanoma from 35% to 40% due to the continued positive data from combination trials and the potential for accelerated approval in combination with Yervoy for patients who have failed prior ICI therapy (conditional on trial outcomes and potential competition from Imlygic in this indication). Our valuation uses a risk-adjusted net present value (rNPV) method to discount future cash flows of the cancer indications shown in Exhibit 11 through to 2033, using a 12.5% discount rate. It assumes a partnering deal or out-licensing Cavatak in 2018, with the costs of subsequent clinical development borne by the partner/licensee.

Our model includes risk-adjusted upfront payments and clinical, regulatory and sales milestones from a potential licensing deal, based on average Phase II deal metrics from BioCentury (US$25m upfront payment, US$240m total milestones) and our own assessment of the development stage of Cavatak. There is a broad range of value for deals in the oncolytic virus field; from the US$236m Boehringer Ingelheim/Vira Therapeutics deal for a drug that is still in preclinical development and the December 2016 licence deal between Bristol-Myers Squibb and the unlisted British biotech PsiOxus for its preclinical armed oncolytic virus NG-348 (US$50m upfront, and up to $886m in development, regulatory and sales-based milestones), to $1bn ($425m cash upfront and $575m earnout) of the Amgen/BioVex deal for Phase III asset, T-Vec. We maintain our previous assumption that milestone payments for a Cavatak licence deal will total US$355m as the product

is generating favourable clinical data, and advancing towards mid-stage development. With the increased probability of success, the risk-adjusted value of the milestones increases to A$162m from A$145m.

Exhibit 11: Viralytics rNPV valuation

Value driver	Unrisked NPV (A$m)	Probability of success	rNPV (A$m)	rNPV per share (A$)	Key assumptions	
Cavatak in metastatic melanoma	721.6	40%	288.6	1.20	Launch in 2021, with peak market penetration of 30% five years after launch. Peak global sales of US$1.0bn.	Assumes simultaneous product launches in US, Europe and RoW; average price of drug US$75k in US and US$45k elsewhere. One cycle of treatment per patient. Out-licensing in 2016 with all development costs borne by licensee and a 15% royalty on sales due to Viralytics.
Cavatak in NSCLC	504.5	15%	75.7	0.31	Launch in 2023, with peak market penetration of 5% five years after launch. Peak global sales of US$950m.	
Cavatak in CRPC	152.0	15%	22.8	0.09	Launch in 2023, with peak market penetration of 2% five years after launch. Peak global sales of US$285m.	
Cavatak in metastatic bladder cancer	68.0	15%	10.2	0.04	Launch in 2023, with peak market penetration of 5% five years after launch. Peak global sales of US$130m.	
Intravesical Cavatak in NMI bladder cancer	96.0	15%	14.4	0.06	Launch in 2024, with peak market penetration of 10% five years after launch. Peak global sales of US$185m, assuming average price of drug US$10k in US market, and global sales 2x US sales. 15% royalty on sales due to Viralytics.	
Milestones	271.5	50-40%	114.3	0.48	US$35m upfront payment (50% risk adjustment); US$20m milestones on Phase III start, US$40m filing, US$120m on approval and US$175m sales related milestones (40% risk adjusted).	
R&D expenses (net of rebate)	(14.3)		(14.3)	(0.06)		
Admin	(37.7)	100-10%	(16.4)	(0.07)		
Tax	(428.1)		(120.4)	(0.50)	Australian corporate tax of 30%	
Portfolio total	1,333.4		375.0	1.56		
Net cash (end FY17e)			34.9	0.15		
Total			408.3	1.70		

Source: Edison Investment Research

Sensitivities: Trial results and partnering key risks

Viralytics is subject to typical biotech company development risks, including the unpredictable outcome of trials, regulatory decisions, success of competitors, financing and commercial risks. In particular, it has a very high single-product risk, with its entire value residing in Cavatak. The investment case hinges on the outcome of clinical trials and the company's ability to secure a partnership (or further capital) to advance Cavatak into late-stage trials. Ideally, a partner would have the resources to evaluate Cavatak in multiple cancer indications. The greatest commercial opportunity for Cavatak is likely to be in combination with checkpoint inhibitors or other targeted agents – outcomes of ongoing Phase Ib combination trials could be critical to future clinical and commercial success.

Financials

Viralytics reported a total loss of A$9.1m in FY16 (A$8.4m when foreign currency translation loss is excluded) and a loss of A$7.1m in H117 (six months ending 31 December 2016). R&D expenses for H117 totalled A$6.0m vs A$4.5m in H116, reflecting increased clinical development activities. A rebate of A$4.3m was received in Q317 under the Australian government's R&D incentive scheme, so we reduce forecast revenue in FY17 by A$0.1m to match that figure. We lift forecast R&D expenditure by A$1.0m to A$12.0m in FY17 and by A$4.0m to A$12.0m in FY18, in line with the increased expenditure in H117. We have reduced forecast net interest revenue by A$0.4m in FY17 and A$0.3m in FY18 to match the rate earned in H117. We do not include the foreign exchange translation gain or loss in our financial summary (Exhibit 12). Cash at 31 March of A$39m is sufficient to fund operations beyond the end of FY18 in our forecasts.

Exhibit 12: Financial summary

A$'000s	2014	2015	2016	2017e	2018e
30-June	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS					
Revenue	2,508	2,454	4,655	4,296	4,800
R&D expenses	(4,998)	(5,925)	(8,604)	(12,000)	(12,000)
SG&A expenses	(2,438)	(2,568)	(4,515)	(4,515)	(4,515)
EBITDA	(4,928)	(6,040)	(8,464)	(12,219)	(11,715)
Operating Profit (before amort. and except.)	(4,956)	(6,074)	(8,501)	(12,274)	(11,771)
Intangible Amortisation	(390)	(390)	(390)	(390)	(390)
Exceptionals	0	0	0	0	0
Other	0	0	0	0	0
Operating Profit	(5,346)	(6,465)	(8,891)	(12,664)	(12,161)
Net Interest	296	527	508	553	418
Profit Before Tax (norm)	(4,660)	(5,547)	(7,993)	(11,720)	(11,353)
Profit Before Tax (FRS 3)	(5,050)	(5,938)	(8,383)	(12,110)	(11,743)
Tax	0	0	0	0	0
Profit After Tax (norm)	(4,660)	(5,547)	(7,993)	(11,720)	(11,353)
Profit After Tax (FRS 3)	(5,050)	(5,938)	(8,383)	(12,110)	(11,743)
Average Number of Shares Outstanding (m)	119.2	184.0	212.2	240.3	240.3
EPS - normalised (c)	(3.9)	(3.0)	(3.8)	(4.9)	(4.7)
EPS - normalised fully diluted (c)	(3.9)	(3.0)	(3.8)	(4.9)	(4.7)
EPS - (IFRS) (c)	(4.2)	(3.2)	(3.9)	(5.0)	(4.9)
Dividend per share (c)	0.0	0.0	0.0	0.0	0.0
BALANCE SHEET					
Fixed Assets	2,523	2,116	1,722	1,310	896
Intangible Assets	2,475	2,034	1,643	1,253	863
Tangible Assets	48	82	79	57	33
Investments	0	0	0	0	0
Current Assets	27,120	24,441	50,970	39,702	28,373
Stocks	0	0	0	0	0
Debtors	2,784	2,875	4,849	4,849	4,849
Cash	24,336	21,566	46,121	34,853	23,524
Other	0	0	0	0	0
Current Liabilities	(767)	(1,685)	(2,364)	(2,364)	(2,364)
Creditors	(767)	(1,685)	(2,364)	(2,364)	(2,364)
Short term borrowings	0	0	0	0	0
Long Term Liabilities	0	0	0	0	0
Long term borrowings	0	0	0	0	0
Other long term liabilities	0	0	0	0	0
Net Assets	28,877	24,872	50,328	38,647	26,904
CASH FLOW					
Operating Cash Flow	(5,486)	(5,010)	(8,050)	(12,218)	(11,714)
Net Interest	0	544	508	553	418
Tax	0	0	0	0	0
Capex	(8)	(69)	(33)	(33)	(33)
Acquisitions/disposals	0	0	0	0	0
Financing	25,180	40	30,799	0	0
Dividends	0	0	0	0	0
Net Cash Flow	19,686	(4,495)	23,224	(11,698)	(11,329)
Opening net debt/(cash)	(5,079)	(24,336)	(21,566)	(46,121)	(34,853)
HP finance leases initiated	0	0	0	0	0
Other	(429)	1,725	1,331	429	0
Closing net debt/(cash)	(24,336)	(21,566)	(46,121)	(34,853)	(23,524)

Source: Company data, Edison Investment Research

Contact details	Revenue by geography
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Management team	
CEO: Dr Malcolm McColl	CSO: Professor Darren Shafren
Dr McColl has been CEO since January 2013. He was previously VP business development at Starpharma and responsible for partnering activities and programmes. Other roles include director of business development for Hospira (formerly Mayne Pharma) and CSL, where he was global VP of business development for the Animal Health division.	Dr Shafren is associate professor of virology in the faculty of health, University of Newcastle, and the inventor of the technology acquired by Viralytics. He is responsible for research, development and intellectual property management.
CFO: Robert Vickery	Director – Regulatory Affairs: Dr Jennifer Rosenthal
Mr Vickery is a chartered accountant with over 20 years' experience in industry and professional practice. During the past decade he has held senior finance roles with several biotech and innovation-based businesses.	Dr Rosenthal has more than 20 years' experience in the biotechnology sector where she has successfully managed teams and projects in the areas of clinical programme management and regulatory affairs. Prior to joining Viralytics in 2015 she was director of clinical and regulatory affairs at Alchemia where she was responsible for the management of the company's HyACT platform, including a Phase III trial of lead oncology product HA-Irinotecan.

Principal shareholders	(%)
BVF Partners	13.6
Cormorant Global Healthcare Master Fund	9.1
Quest Asset Partners	7.5
JCP Investment Partners	5.1
Orbimed	5.0

Companies named in this report
Merck, BMS, AstraZeneca, Roche, Amgen, Boehringer Ingelheim

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