EDISON

Viralytics

FY17 results

Looking towards pivotal Cavatak combo studies

Pharma & biotech

Viralytics continues to report impressive preliminary data for Cavatak in combination with immune checkpoint inhibitors (ICIs), whether administered intravenously (iv) or by intra-tumoural injection. Viralytics is currently recruiting additional patients in expansion cohorts in melanoma, lung and bladder cancers in order to obtain more robust estimates of tumour response rates. It has announced plans to initiate four Phase I studies in additional indications and has commenced planning for a potential pivotal study of Cavatak plus Yervoy in melanoma patients who had failed prior single-agent, anti-PD1 ICI therapy, a serious unmet medical need. Updates on MITCI, CAPRA and Keynote 200 are expected in Q218. We increase our valuation to A$469m or A$1.95/share (vs A$408m and A$1.70/share).

Year end	Revenue (A$m)	PBT* (A$m)	EPS* (c)	DPS* (c)	P/E (x)	Yield (%)
06/16	4.7	(8.0)	(3.8)	0.0	N/A	N/A
06/17	6.5	(11.3)	(4.7)	0.0	N/A	N/A
06/18e	5.9	(12.0)	(5.0)	0.0	N/A	N/A
06/19e	6.1	(12.5)	(5.2)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding exceptionals and share-based payments.

Cavatak/Yervoy responses where ICI therapy failed

Updated preliminary data presented at SITC in November for melanoma patients treated with Cavatak oncolytic virus in combination with Yervoy in the MITCI study included response rates of 29% in patients who had failed prior single-agent PD1 therapy, which compares to response rates of 11-14% reported for Yervoy alone. The Cavatak/Yervoy combo was very well tolerated. Planning has commenced for a pivotal study in this indication which could start in Q418, if the expanded MITCI study continues to deliver positive data.

iv Cavatak promising, further indication expansion

Preliminary tumour response rates from the Keynote-200 study of intravenous Cavatak plus Keytruda in lung and bladder cancer (30% and 28% respectively) were higher than reported for Keytruda monotherapy, which supports the efficacy of Cavatak when administered iv. The four new Phase I studies planned for FY18 (uveal melanoma, head and neck cancer, metastatic colorectal cancer and iv administration in melanoma) will generate considerable information about the potential breadth of application of Cavatak, which is also likely to be of considerable interest to potential partners.

Valuation: Increased to A$469m or A$1.95/share

Our valuation increases to A$469m or A$1.95/share (vs A$408m or A$1.70/share) as we add new indications for head and neck and colorectal cancer (replacing prostate), roll forward the DCF model and defer forecast deal timing to FY19. Viralytics had A$27.7m cash at 30 September 2017, sufficient to complete the ongoing Cavatak combination clinical trials (MITCI, CAPRA and STORM/Keynote 200), and the four planned Phase I studies. A pivotal trial of Cavatak plus Yervoy in melanoma would likely require additional funding (we model partner funding).

5 December 2017

Price	**A$0.72**
Market cap	**A$173m**
	US$0.76/A$
Net cash (A$m) at 30 September 2017	27.7
Shares in issue	240.3m
Free float	85%
Code	VLA
Primary exchange	ASX
Secondary exchange	OTCQX

Share price performance

%	1m	3m	12m
Abs	(8.9)	(20.6)	(37.8)
Rel (local)	(9.5)	(24.6)	(43.6)
52-week high/low		A$1.3	A$0.6

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

Initiate uveal melanoma Phase I	Q4 CY17
Initiate head and neck cancer Phase I	Q1 CY18
MITCI, CAPRA, Keynote 200 updates	Q2 CY18

Analysts

Dennis Hulme +61 (0)2 9258 1161

Juan Pedro Serrate +44 (0)20 3681 2534

healthcare@edisongroup.com

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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 57% 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$469m, or A$1.95 per share (undiluted)

We value Viralytics at A$469m, or A$1.95 per share (undiluted), using a risk-adjusted net present value method to discount future cash flows through to 2044 in metastatic melanoma, bladder cancer, non-small cell lung cancer, head and neck cancer and metastatic colorectal cancer (mCRC). We apply a 40% 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, a 10% probability in mCRC and 15% probability in other indications. Our approach assumes a partnering deal or out-licensing of Cavatak in FY19, with costs of subsequent clinical development borne by the partner/licensee.

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 Keynote 200 suggest that combining iv Cavatak with Keytruda leads to high response rates in lung and bladder cancer tumours following iv administration, but only a small number of patients have been evaluated so far. Further results from the Keynote 200 will be important pointers to utility beyond melanoma, although Cavatak can also be administered by ultrasound or CT-guided intralesional injections, as in the upcoming study in mCRC liver metastases.

Financials: Sufficient cash to initiate a pivotal trial

Viralytics reported cash of A$27.7m at 30 September 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 would 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. The emphasis of the programme is on combination immunotherapy and demonstrating that Cavatak is efficacious when administered intravenously. Exhibit 1 summarises the ongoing and completed Cavatak clinical trials.

Exhibit 1: Overview of ongoing and completed Cavatak clinical trials

Route	Indication	Stage	Development notes
Intralesional	Melanoma	Phase Ib	MITCI Phase Ib study in combination with Yervoy. Interim results include: ORR 29% (2/7) in patients who had failed prior single line anti-PD1/L1 ICI therapy; ORR 57% (8/14) in ICI-naive patients). Expansion cohort of ~44 patients who failed prior therapy with PD1/L1 ICI commenced recruitment Q117 (total n=60).
Intralesional	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 prostate cancer). Tumour biopsies suggest that Cavatak replicates in melanoma, lung and bladder tumours after iv administration.
Intravenous	Bladder, lung	Phase Ib	Phase Ib Keynote 200 (STORM Part B) trial of iv Cavatak plus Keytruda. Phase I dose escalation complete. Expansion cohorts are recruiting ~40 bladder and ~40 lung cancer patients. Preliminary efficacy included ORR on intention to treat basis of 3/10 (30%) and 5/18 (28%) for lung and bladder cancer, respectively.
Intralesional	Melanoma	Phase IIa	Phase II CALM study in melanoma (n=57, ORR 28%, durable response in 21% of patients). Monotherapy. Study complete.
Intralesional	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.
Intravesicular	Non-invasive bladder cancer	Phase I	Phase I CANON study. Intravesicular administration Cavatak as a single agent and with mitomycin C (n=16, 1 CR). Biopsies showed Cavatak increases immune cell infiltrates and PD-L1 expression vs untreated controls.

Source: Edison Investment Research. Note: ORR = overall response rate, PR = partial response, CR = complete response.

MITCI: Impressive Yervoy combo response rates

Viralytics presented an update at the Society for Immunotherapy of Cancer (SITC) meeting held in Washington DC on 7-11 November 2017 which showed that the MITCI study continues to deliver impressive response rates in patients with PD1-refractory melanoma. MITCI is a Phase Ib trial of intralesional Cavatak in combination with the anti-CTLA-4 ICI Yervoy in patients with advanced melanoma, many of whom had undergone prior ICI immunotherapy.

The preliminary best overall tumour response rate (BORR) in patients who have not undergone prior anti-PD1 therapy (PD1 naïve) was 57% (8/14, see Exhibits 2 and 4), while the response rate in patients who had failed prior single-line anti-PD1 therapy was 29% (2/7, Exhibits 3 and 5).

Exhibit 2: Best overall response for patients naïve to ICI therapy

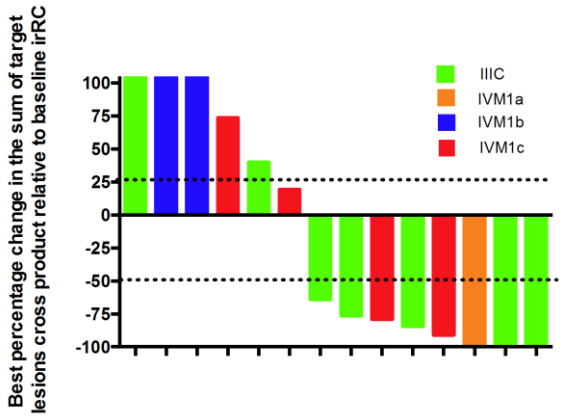
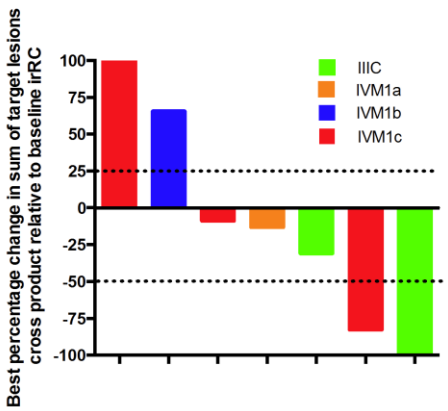


Exhibit 3: Best overall response for patients with prior single-line anti-PD1 therapy



Source: Viralytics corporate presentation November 2017

Exhibit 4: MITCI ICI therapy naïve responses

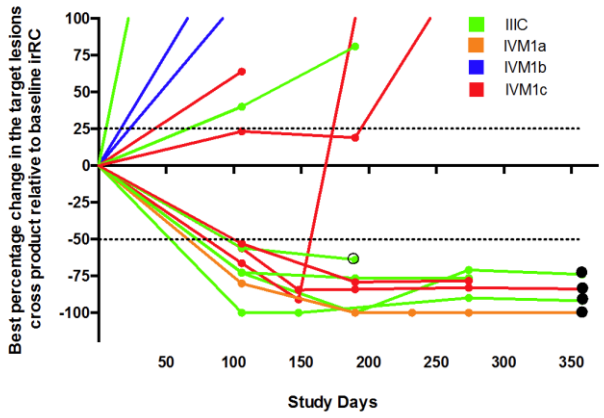
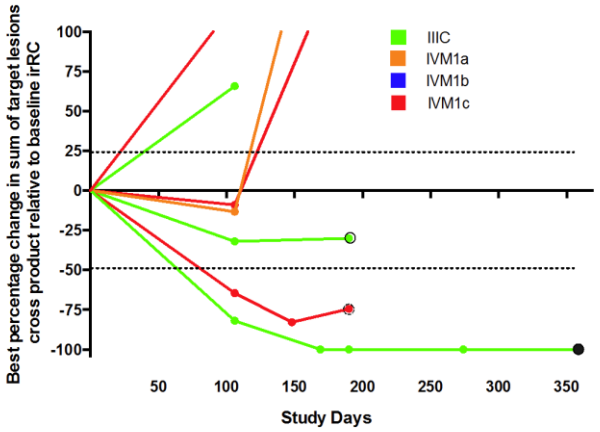


Exhibit 5: MITCI prior single-line anti-PD1 therapy



○ Subject on study; ● Subject completed study; ◌ No further response assessment due to index lesion excision

Source: Viralytics corporate presentation November 2017. Note: these so-called spider plots show the change in target lesions for each patient relative to baseline at each response assessment.

Cavatak outperforms other Yervoy combos

The preliminary response rates in patients who have failed prior PD1 therapy in the MITCI trial are very encouraging. Exhibit 6 compares response rates in the different patient subgroups in the MITCI trial to response rates reported for comparable populations of melanoma patients treated with Yervoy as a single agent or in combination with other oncolytic virus immunotherapies, with the oral IDO1 inhibitor epacadostat, or with the anti-PD1 ICI dug Opdivo.

The 29% response rate among patients who had failed prior anti-PD1 treatment but had not been previously treated with Yervoy compares favourably to a response rate of only 14% (14/97) when patients who had failed treatment with the PD-1 drug Keytruda were treated with Yervoy on its own, and 11% in Yervoy pivotal studies. Given that anti-PD1 drugs are becoming widely used in first line treatment of advanced melanoma, this class of patients represents a substantial potential market opportunity for Cavatak.

We also note that the 57% response rate in the MITCI trial in PD1 naïve patients is higher than that seen when other drugs were combined with Yervoy in PD1-naïve patients. This includes the 39% (39/98) response rate from a randomised Phase II trial of Yervoy combined with Amgen's approved oncolytic virotherapy, Imlygic (T-Vec) in which 98% of subjects were PD1 naïve (Chesney et al, ASCO 2017). We note that Amgen is focusing on combining Imlygic with PD1 inhibitors rather than Yervoy in its late-stage development programme.

Although the response rates for Cavatak plus Yervoy are higher than those reported for historical studies, the MITCI data so far includes response data on only 25 patients; the results will need to be further confirmed in the expanded study which will recruit 60 patients in total, with a focus on recruiting additional subjects who have failed prior anti-PD1 therapy.

While bearing in mind that the number of patients who have been assessed to date is small, and that response rates may change as additional patients are assessed, at this early stage it appears that Cavatak is more effective at inducing immune responses in melanoma patients in combination with Yervoy than any other therapy except PD1 inhibitors such as Opdivo, and the Yervoy/Opdivo combination is poorly tolerated by patients.

Exhibit 6: Tumour response rates for Cavatak/Yervoy vs other Yervoy combos in melanoma

	Cavatak/Yervoy		Imlygic/Yervoy		HF10/Yervoy		Epacadostat (IDO1)/ Yervoy		Yervoy	Opdivo/ Yervoy
Patient subgroup	**count**	**%**	**count**	**%**	**count**	**%**	**count**	**%**	**%**	**%**
Failed PD1* only	(2/7)	29%							14%	
PD1/L1 naïve	(8/14)	57%	(38/98)**	39%	(18/42)	43%	(9/30)	30%	10-19%#	58%
Grade 3/4 treatment related adverse events	(4/38)	11%		28%		37%		23%	20-27%	55%

Source: Edison Investment Research; Viralytics; Chesney et al ASCO 2017 abstract 9509 (Imlygic); Andtbacka et al ASCO 2017 abstract 9510 (HF10); Gibney et al Eur J Cancer.2015; 51: S106-7 (Epacadostat); Long et al SMR abstract 2016, Zimmer et al 2017, Bowyer et al 2016 (Yervoy alone); Larkin et al 2015 (Opdivo/Yervoy). Notes: *Includes anti-PD1 and anti PD-L1 therapies; **2/98 patients had prior PD1 therapy - separate breakdown not provided; #19% response rate as a first line treatment (Larkin et al 2015).

Low adverse event rate is a plus for Cavatak/Yervoy combo

No Cavatak-related grade 3 or higher adverse events have been reported in the MITCI study, and only four of the 38 patients (11%) who have commenced treatment have experienced Yervoy-related grade 3 or 4 adverse events (six grade 3/4 adverse events in these four patients - fatigue, elevated liver enzymes, pruritus, dehydration, hyperglycaemia).

The 11% treatment-related adverse event (TRAE) rate in the MITCI study is much lower than the 20-27% grade 3 TRAE rate reported for Yervoy on its own in advanced melanoma, and the 55% TRAE rate when Yervoy was combined with Opdivo. The results reported to date suggest that a Cavatak/Yervoy combination is much better tolerated than Opdivo/Yervoy, with similar efficacy. In this regard it is notable that there have been no cases of severe diarrhoea, colitis or pneumonitis, which are a common occurrence with other Yervoy treatment regimens. If the low adverse event rate for the Cavatak/Yervoy combo is confirmed in larger studies, it could give the combo a competitive advantage (if approved).

Potential for a pivotal study or even accelerated approval application if circumstances are right

Viralytics has commenced planning for a pivotal study of intralesional Cavatak plus Yervoy in melanoma patients who have failed treatment with a single PD1/L1 therapy. The trial could commence in Q418 if the combination therapy continues to display durable anti-tumour activity in the MITCI expansion cohort. Based on advice to date the company believes that a study in 200-220 patients randomised to Cavatak plus Yervoy vs Yervoy monotherapy would be appropriately sized. We estimate that cost of such a study would be in the order of US$20m, so it would be within the capacity of Viralytics to conduct this study on its own if it raised additional funding.

However, we believe that under certain circumstances there is the potential that the MITCI data could 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 event rates) as well as there continuing to be a significant unmet need for an effective treatment for this patient group (in this regard Amgen's Phase III Imlygic/Yervoy combo trial (NCT01740297) will be an important one to watch).

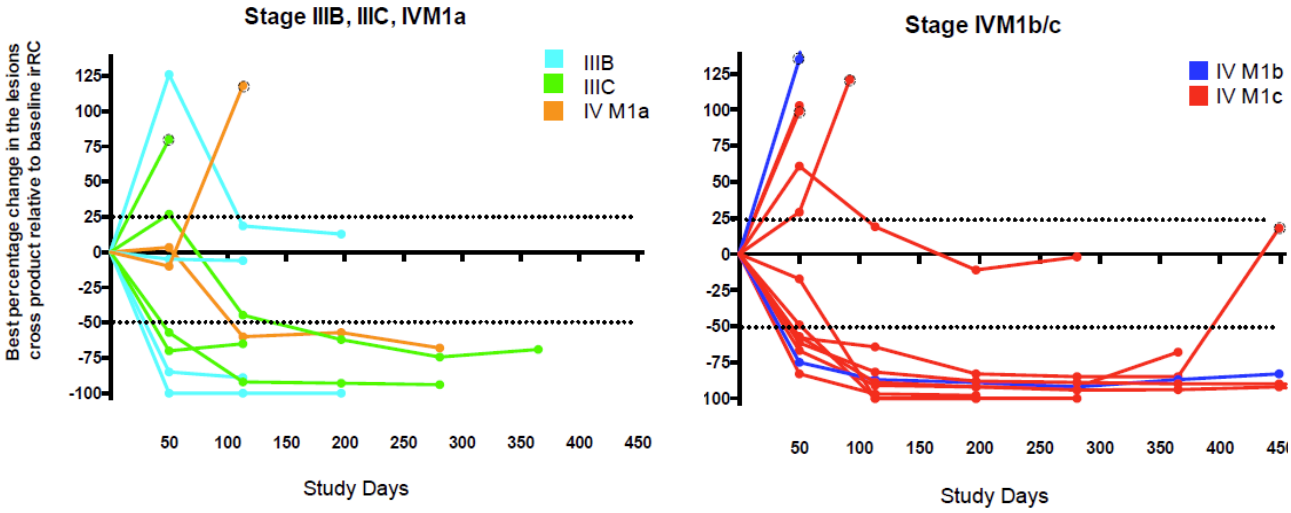
We note that the FDA approved Bavencio (avelumab) for metastatic Merkel cell carcinoma in March 2017 based on a 33% response rate in an 88-patient, single-arm trial. This data set is not much larger than the one Viralytics will have at the completion of the enlarged MITCI study.

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

CAPRA: Cavatak plus Keytruda is a potential first-line combo

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. Phase Ib data from the first 23 assessable patients which was presented at SITC in November showed an objective response rate of 61% (4/23), including responses in seven of 11 patients with the most advanced Stage IV M1c disease (Exhibit 9). Importantly, only three of 26 (12%) enrolled patients experienced grade 3/4 TRAEs were observed, all of which were Keytruda related. The trial had enrolled 26 of the target of 50 patients as of early November.

Exhibit 7: Spider plots of tumour responses from CAPRA, by disease stage



Source: Viralytics corporate presentation November 2017

The 61% preliminary response rate for Cavatak plus Keytruda in the CAPRA study is higher than the published rates for either agent used alone in late-stage melanoma: Cavatak 28% and Keytruda circa 33%. Exhibit 10 also shows that the CAPRA response rate is comparable to the 58% response rate in PD1-naïve patients for the approved Opdivo/Yervoy combination, and 57% and 58% for Keytruda combined with Imlygic and epacadostat, respectively, in preliminary studies. Exhibit 10 highlights that the tolerability of Cavatak plus Keytruda was much better than for the other combinations. In particular, Grade 3/4 TRAEs were reported for 55% of patients in the Phase III trial of the approved Opdivo/Yervoy combination, whereas they have only been reported for 12% of patients so far in the CAPRA study, none of which were Cavatak-related.

Epacadostat and Imlygic are both in Phase III studies in combination with Keytruda, with data expected in 2018.

Exhibit 8: Response and adverse event rates for select ICI combos in PD1 naïve melanoma

	Cavatak/ Keytruda	Imlygic/ Keytruda	Epacadostat/ Keytruda	Yervoy/ Opdivo
PD1/L1 naïve response rate	61%	57%	58%	58%
Grade 3/4 treatment related adverse events	8%	33%	19%	55%

Source: Edison Investment Research

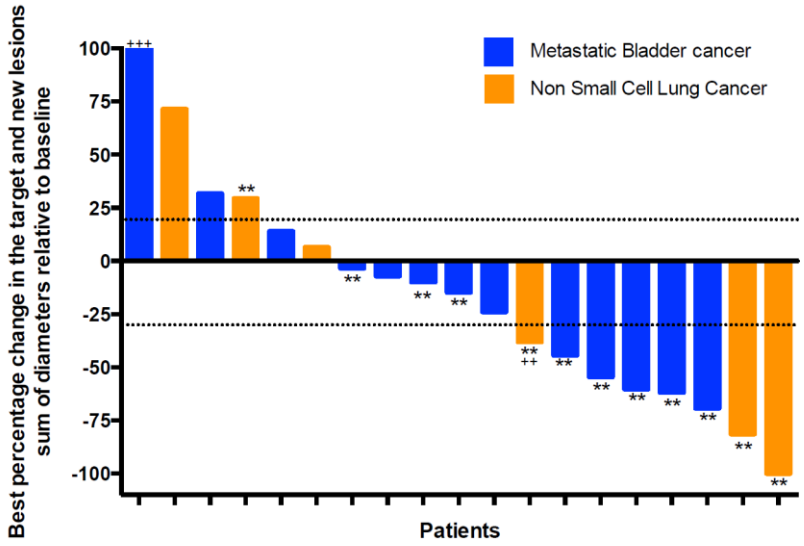
Keynote 200 - encouraging initial lung and bladder responses

Viralytics also presented initial data at SITC from the expansion cohorts of the Keynote 200 trial, which is being conducted in collaboration with Merck. The expansion cohorts of Keynote 200 are exploring whether viral replication in tumours following intravenous (iv) Cavatak administration can boost the efficacy of Keytruda in lung and bladder cancer patients.

Data was presented on the preliminary assessment of 28 checkpoint naïve patients. Nine of the 28 patients were not evaluable for target lesion response assessment due to early disease progression or study discontinuation. The early disease progression in part reflects the fact that this "all-comers" study is being conducted in a heavily pre-treated patient population, with 28% and 58% of the advanced bladder cancer and NSCLC patients, respectively, having received two or more prior therapies.

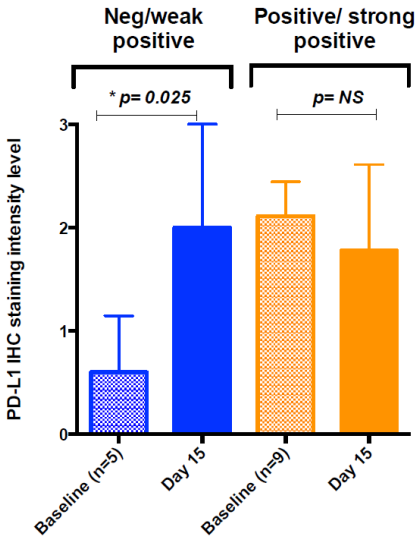
Exhibit 11 show that among the 19 evaluable patients responses were observed in three of six (50%) advanced small cell lung cancer (NSCLC) patients and five of 13 (38%) bladder cancer patients. On an intention to treat (ITT) basis, which includes the nine early withdrawals, the response rates were 3/10 (30%) and 5/18 (28%) for lung and bladder cancer, respectively.

Exhibit 9: Preliminary tumour responses in Keynote 200 assessable patients



Source: Viralytics investor presentation November 2017. Notes: ** patient currently on study; ++ day 176 response assessment; +++ day 43 response assessment. Response assessments based on irRECIST – dotted lines represent cut-offs for partial response or tumour progression.

Exhibit 10: Cavatak combo therapy boosts PD-L1 expression



Source: Viralytics. Note: IHC scoring 0=negative, 1=weak positive, 2=positive, 3=strong positive.

While bearing in mind the limitations of cross-trial comparisons and the fact that only a small number of patients have been evaluated to date, the preliminary ITT response rates for iv Cavatak plus Keytruda compare favourably to response rates to Keytruda monotherapy in second line (pre-treated) NSCLC (17-18%) and bladder cancer (21%) in pivotal studies, as shown in Exhibit 13.

Exhibit 11: Preliminary Keynote 200 response rates vs response rates in pre-treated patients in Keytruda pivotal studies

	NSLC		Bladder	
	count	%	count	%
Cavatak/ Keytruda evaluable patients	3/6	50%	5/13	38%
Cavatak/ Keytruda ITT	3/10	30%	5/18	28%
Keytruda monotherapy pivotal studies		17-18%		21%

Source: Viralytics, Keytruda prescribing information Table 19 (Keynote-010) and Table 22 (Keynote-045).

Exhibit 12 above shows that 15 days after the start of Cavatak therapy, there was a significant increase in the PD-L1 expression in tumours that were negative or only weakly positive for PD-L1 at the start of the study. The increased PD-L1 expression is a positive outcome because patients with high PD-L1 expression typically respond better to anti-PD1/L1 therapy. For example, in the Keynote-010 study of Keytruda in pre-treated NSLC patients, the response rate in patients with high PD-L1 tumour expression was ~30% vs ~10% for patients with low PD-L1 tumour expression.

So far 64 out of the target of 90 patients have been enrolled in Keynote 200 part B. A further clinical update on the study is expected in Q218.

Looking to target additional cancers and immunotherapy combinations

Viralytics has encountered strong interest in assessing Cavatak in combination with ICI drugs in additional settings and has announced plans to initiate 4 new Phase I trials by June 2018, as shown in Exhibit 14. We expect these studies to generate additional information about the potential breadth of applicability of Cavatak at a relatively low cost – likely around A$1-2m per study. We expect that this information to be of particular interest to potential partners who may be assessing how Cavatak would fit into their own product development pipeline.

Exhibit 12: Proposed timetable of studies in additional indications over coming year

Study	Planned start (CY)
CLEVER study of iv Cavatak plus Yervoy in uveal melanoma with liver metastases	Q417
ITCAHN study of intralesional Cavatak plus Keytruda in head and neck cancer	Q118
PaCKMAN study of iv Cavatak plus Keytruda in advanced melanoma.	Q118
Intralesional Cavatak plus an un-named checkpoint inhibitor in colorectal cancer metastatic to the liver	Q218

Source: Edison Investment Research, Viralytics

Our comments on the rationale for each of the studies include:

iv Cavatak plus Yervoy in uveal melanoma liver metastases

Liver metastases in uveal melanoma represent a serious unmet medical need for which there are no effective drug treatments. Uveal melanoma is rare form of melanoma occurring in the eye, representing ~5% of melanoma cases [1]. Following local resection of the primary tumour of the eye about half of people will suffer a recurrence, with 90% having liver metastases. Uveal melanomas behave differently to melanomas arising in the skin, and no prospective randomised trial has ever demonstrated an improvement in overall survival for metastatic uveal menanoma[1]. Response rates to single agent anti-PD1 therapy are only 3-4% in uveal melanoma[2]. If Cavatak plus the combo therapy can demonstrate efficacy in metastatic uveal melanoma it will be the only treatment to have done so.

Intralesional Cavatak plus Keytruda in head and neck cancer

This study will investigate whether intralesional Cavatak can increase the response rate to Keytruda, in a similar fashion to the improvements see in the CAPRA study in melanoma. Viralytics has previously treated four HNSCC patients with Cavatak in a Phase I study that ended in 2012. Keytruda is approved as a second line treatment for squamous cell carcinoma of the head and neck (HNSCC), based on a 16% ORR in a study of 174 patients with previously-treated disease.

We note that Amgen's Imlygic plus Keytruda combo is currently being investigated in the 40-patient Phase Ib component of a Phase Ib/III study in HNSCC[3].

iv Cavatak in melanoma

The majority of metastatic melanoma patients do not a have a readily accessible lesion for injection because the primary tumour in the skin has previously been excised. iv Cavatak could be a convenient way of treating these patients, and could potentially ensure that Cavatak is accessible for all metastatic melanoma patients.

1 Skin Cancer Foundation (US).

2 Melanoma Institute Australia

3 Harrington et al; Annals of Oncology, Volume 28, Issue suppl_5, 1 September 2017

Intralesional Cavatak plus un-named checkpoint inhibit in colorectal cancer liver metastases

Viralytics plans to test intralesional Cavatak plus an un-named checkpoint inhibit in patients with microsatellite-stable colorectal cancer (CRC) who have developed liver metastases.

Keytruda and Yervoy are approved for treating a small subset of metastatic colorectal cancer (mCRC) patients, with treatment limited to the 4-5% of mCRC[4] that have tumours with a high mutation burden identified as microsatellite instability high (MSI-H) and mismatch repair deficient (dMMR). PD1 ICI have not been shown to be effective in the other 95% of mCRC patients who have microsatellite-stable disease. In studies of PD-1 checkpoint inhibitors in mCRC patients there was only one responder among 33 patients, and that patient was MSI-H[5].

CRC is the third most common cancer in the US with 135,000 new cases and 50,260 deaths expected in the US in 2017; globally there were estimated to be 1.4m new cases and 700k deaths in 2012. About 20% of CRC patients eventually develop liver metastases[6], for which there are few effective treatments other than surgery. While this appears to be a higher-risk study, we expect that even a single responder would attract considerable commercial interest.

Separately, we note that there is continued interest by big pharma in investigating checkpoint inhibitor combinations in microsatellite stable mCRC, with Roche trialling Tecentriq in combination with its MEK inhibitor Cotellic in this patient group (clinicaltrials.gov NCT02788279).

Preclinical studies of additional immunotherapy combinations

Viralytics is also undertaking preclinical studies to assess Cavatak in combination with other immunotherapy agents such as LAG-3, TIM-3 and IDO. It has already shown that the triple combination of Cavatak plus an anti-PD1 antibody and an IDO inhibitor significantly reduced overall mouse tumour burden compared to anti-PD1/IDO inhibitor combination.

These studies could add value as Cavatak advances towards a potential licencing, partnering or sale transaction, by expanding its commercial opportunity across a range of disease indications and drug combinations.

Valuation

We lift our valuation of Viralytics to A$469m or A$1.95/share (undiluted) from A$408m or A$1.70/share. This reflects the following changes:

- following the announcement of plans for new Phase Ib Cavatak combination trials in additional indications, we have added risk-adjusted revenue streams in mCRC and HNSCC, and have removed the prostate cancer indication as the development of this indication appears to be a lower priority. For HNSCC we apply a 15% probability of success, in line with the other Phase I programs. For mCRC we apply a 10% probability of success because checkpoint inhibitors have not been shown to be effective as single agents in microsatellite stable disease, which makes this a higher-risk study in our view;
- we pushed back assumed Cavatak licence deal timing and melanoma launch date by 12 months to 2019 and 2022 respectively; and
- we have rolled forward the DCF model for the new financial year (2018).

4 Decision Resources Group, ESMO biomarker factsheet.

5 Le DT, et al. New England Journal of Medicine. 2015; 372:2509-2520

6 Manfredi et al Ann Surg. 2006 Aug; 244(2): 254–259.

Our valuation uses a risk-adjusted net present value (rNPV) method to discount future cash flows for the cancer indications shown in Exhibit 12 through to 2044, using a 12.5% discount rate. It assumes a partnering deal or out-licensing Cavatak in 2019 (previously 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 pivotal development.

Exhibit 13: 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	745.0	40%	298.0	1.24	Launch in 2022, with peak market penetration of 30% five years after launch. Peak global sales of US$1.0bn.
Cavatak in NSCLC	565.5	15%	84.8	0.35	Launch in 2023, with peak market penetration of 5% five years after launch. Peak global sales of US$950m.
Cavatak in metastatic bladder cancer	76.2	15%	11.4	0.05	Launch in 2023, with peak market penetration of 5% five years after launch. Peak global sales of US$130m.
Cavatak in mCRC liver metastases	403.5	10%	40.4	0.17	Launch in 2025, with peak market penetration of 10% five years after launch. Peak global sales of US$850m.
Cavatak in HNSCC	44.3	15%	6.6	0.03	Launch in 2025, with peak market penetration of 5% five years after launch. Peak global sales of US$50m.
Intravesical Cavatak in NMI bladder cancer	107.6	15%	16.1	0.07	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	281.1	50-35%	118.2	0.49	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)	(20.8)		(20.8)	(0.09)	
Admin	(43.2)	100-10%	(19.0)	(0.08)	
Tax	(408.8)		(101.4)	(0.42)	Australian corporate tax of 30%
Portfolio total	**1,750.6**		**434.4**	**1.81**	
Net cash (end FY17)			34.3	0.14	
Total			**468.7**	**1.95**	

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 2019 with all development costs borne by licensee and a 15% royalty on sales due to Viralytics.

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 loss of A$12.3m in FY16 (A$11.6m when foreign currency translation loss is excluded). R&D expenses for FY17 totalled A$13.5m vs A$8.6m in FY16, reflecting increased clinical development activities. A rebate of A$4.3m was received in Q317 under the Australian government's R&D incentive scheme, and A$6.5m is expected in FY18. We lift forecast R&D expenditure to A$13.5m in FY18, to match the increased expenditure in FY17. We do not include the foreign exchange translation gain or loss in our financial summary (Exhibit 13). Cash at 30 September of A$27.7m is sufficient to fund operations beyond the end of FY18 in our forecasts. We model a partner funding a significant proportion of R&D costs in FY19, but do not included any upfront or milestone payments from a potential licensing deal in FY19 in our financial forecasts.

Exhibit 14: Financial summary

A$'000s	2015	2016	2017	2018e	2019e
30-June	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS					
Revenue	2,454	4,655	6,480	5,873	6,090
R&D expenses	(5,925)	(8,604)	(13,493)	(13,500)	(14,000)
SG&A expenses	(2,568)	(4,515)	(4,729)	(4,729)	(4,729)
EBITDA	(6,040)	(8,464)	(11,742)	(12,357)	(12,639)
Operating Profit (before amort. and except.)	(6,074)	(8,501)	(11,794)	(12,453)	(12,760)
Intangible Amortisation	(390)	(390)	(390)	(390)	(390)
Exceptionals	0	0	0	0	0
Other	0	0	0	0	0
Operating Profit	(6,465)	(8,891)	(12,184)	(12,843)	(13,150)
Net Interest	527	508	543	411	280
Profit Before Tax (norm)	(5,547)	(7,993)	(11,250)	(12,042)	(12,480)
Profit Before Tax (FRS 3)	(5,938)	(8,383)	(11,641)	(12,432)	(12,870)
Tax	0	0	0	0	0
Profit After Tax (norm)	(5,547)	(7,993)	(11,250)	(12,042)	(12,480)
Profit After Tax (FRS 3)	(5,938)	(8,383)	(11,641)	(12,432)	(12,870)
Average Number of Shares Outstanding (m)	184.0	212.2	240.3	240.3	240.3
EPS - normalised (c)	(3.0)	(3.8)	(4.7)	(5.0)	(5.2)
EPS - normalised fully diluted (c)	(3.0)	(3.8)	(4.7)	(5.0)	(5.2)
EPS - (IFRS) (c)	(3.2)	(3.9)	(4.8)	(5.2)	(5.4)
Dividend per share (c)	0.0	0.0	0.0	0.0	0.0
BALANCE SHEET					
Fixed Assets	2,116	1,722	1,400	1,033	643
Intangible Assets	2,034	1,643	1,253	863	473
Tangible Assets	82	79	147	170	170
Investments	0	0	0	0	0
Current Assets	24,441	50,970	41,139	30,157	17,678
Stocks	0	0	0	0	0
Debtors	2,875	4,849	6,865	6,865	6,865
Cash	21,566	46,121	34,274	23,292	10,813
Other	0	0	0	0	0
Current Liabilities	(1,685)	(2,364)	(2,949)	(2,949)	(2,949)
Creditors	(1,685)	(2,364)	(2,949)	(2,949)	(2,949)
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	24,872	50,328	39,590	28,241	15,371
CASH FLOW					
Operating Cash Flow	(5,010)	(8,050)	(11,953)	(12,356)	(12,639)
Net Interest	544	508	543	411	280
Tax	0	0	0	0	0
Capex	(69)	(33)	(120)	(120)	(120)
Acquisitions/disposals	0	0	0	0	0
Financing	40	30,799	336	0	(0)
Dividends	0	0	0	0	0
Net Cash Flow	(4,495)	23,224	(11,194)	(12,065)	(12,479)
Opening net debt/(cash)	(24,336)	(21,566)	(46,121)	(34,274)	(23,292)
HP finance leases initiated	0	0	0	0	0
Other	1,725	1,331	(654)	1,083	0
Closing net debt/(cash)	(21,566)	(46,121)	(34,274)	(23,292)	(10,813)

Source: Company data, Edison Investment Research

Contact details	Revenue by geography
Suite 305, Level 3 66 Hunter Street Sydney 2000 Australia +61 2 9988 4000 www.viralytics.com/	N/A

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	8.3
Quest Asset Partners	6.4
Cormorant Global Healthcare Master Fund	6.2
The Capital Group Companies, Inc.	5.8
JCP Investment Partners	5.1

Companies named in this report

Merck, BMS, AstraZeneca, Roche, Amgen, Boehringer Ingelheim

Frankfurt +49 (0)69 78 8076 960
Schumannstrasse 34b
60325 Frankfurt
Germany

London +44 (0)20 3077 5700
280 High Holborn
London, WC1V 7EE
United Kingdom

New York +1 646 653 7026
295 Madison Avenue, 18th Floor
10017, New York
US

Sydney +61 (0)2 8249 8342
Level 12, Office 1205
95 Pitt Street, Sydney
NSW 2000, Australia