EDISON

Verastem

Mesothelioma trial disclosed

Adaptive VS-6063 Phase II design

Pharma & biotech

Verastem's investor update at ASCO 2013 disclosed the detailed design of its Phase II trial of its lead product, VS-6063, in mesothelioma, which should shortly start enrolling patients. The 350-patient adaptive study will focus on VS-6063's efficacy as first-line maintenance therapy. In our opinion, the approach will allow Verastem to demonstrate activity quickly in this highly intractable indication and could potentially support a registration with a relatively low clinical efficacy bar. We see upside in the stock as Verastem approaches the first significant clinical data from the study, possibly in late-2014.

Year end	Revenue ($m)	PBT* ($m)	EPS* ($)	DPS ($)	P/E (x)	Yield (%)
12/11	0.0	(13.68)	(10.6)	0.0	N/A	N/A
12/12	0.0	(31.98)	(1.58)	0.0	N/A	N/A
12/13e	0.0	(36.56)	(1.59)	0.0	N/A	N/A
12/14e	0.0	(37.69)	(1.70)	0.0	N/A	N/A

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

Well-designed Phase II for VS-6063

The Phase II trial will examine VS-6063 vs placebo in c 350 mesothelioma patients who achieved stable disease or better (excluding patients with complete response, CR) after ≥4 cycles of platinum + pemetrexed. With an adaptive design, the study will evaluate VS-6063's efficacy (OS, PFS and quality of life) relative to expression of the Merlin biomarker (Merlin-High or Merlin-Low) and, based on an interim analysis, there will be a decision whether to continue to enrol all comers or a subgroup (likely to be low Merlin). The trial could become pivotal, and thus used as the basis for an approval, if sufficiently robust efficacy data are produced.

Mesothelioma is a unique opportunity for VS-6063

Mesothelioma receives relatively little investor attention, perhaps because of its low (and plateauing) incidence in the US. There are an estimated 12,000 cases worldwide in the major markets, which would support a c $500m market with conservative price assumptions. However, actual incidence rates are likely to be much higher, and given the long gestation period for the disease and the fact that asbestos usage continues in many emerging countries, such as China, India, Russia and Brazil, it is likely to grow fast in the developing world.

Valuation: Moving towards inflection

We have adjusted our valuation to reflect Q1 net cash, but otherwise this remains unchanged. Thus we value Verastem at $287m, or $12.90 a share, based on a risk-adjusted NPV. We highlight that Verastem's EV of c $115m is relatively low, given it will shortly have a drug candidate in a potential pivotal study. This perhaps reflects the focus on cancer stem cell therapy, which is an interesting but as yet unproven concept. Proof-of-concept data from the Phase II mesothelioma trial could therefore be a catalyst for value inflection.

12 June 2013

Price	**US$9.34**
Market cap	**US$199m**
	$1.55/£
Net cash ($m) at end Q113	84.4
Shares in issue	21.2m
Free float	61%
Code	VSTM
Primary exchange	NASDAQ
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	(4.2)	0.0	(7.6)
Rel (local)	(4.8)	(5.6)	(25.5)
52-week high/low	US$11.17		US$6.47

Business description

Verastem is a biopharmaceutical company focused on discovering and developing novel drugs that selectively target cancer stem cells (CSCs). Its lead drug is VS-6063, a FAK inhibitor, currently in Phase II testing. Its pipeline also includes VS-4718, another FAK inhibitor and VS-5584, a PI3K/mTOR inhibitor, both entering Phase I testing this year.

Next events

Initiation of VS-6063 Phase II	Mid-2013
Completion of VS-6063/paclitaxel dosing portion of Phase I	H213
VS-4718 Phase I start	H113
VS-5584 Phase I start	H213

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VS-6063 ready to go to key Phase II study

Verastem shortly expects to enrol its first patients into its Phase II trial of its lead product, the focal adhesion kinase inhibitor VS-6063, in mesothelioma. This will bring the company a step closer to producing proof-of-concept clinical data, a key driver for the investment thesis. In our view, Verastem has developed a well thought out Phase II trial design for VS-6063 that incorporates both data from a competitor drug with the same mechanism and Verastem's understanding of cancer stem cell biology. This study could yield the first clinical proof-of-concept data for any cancer stem cell-directed therapy and usher in a new class of cancer drugs.

Adaptive Phase II trial design: Multiple looks and shots on goal

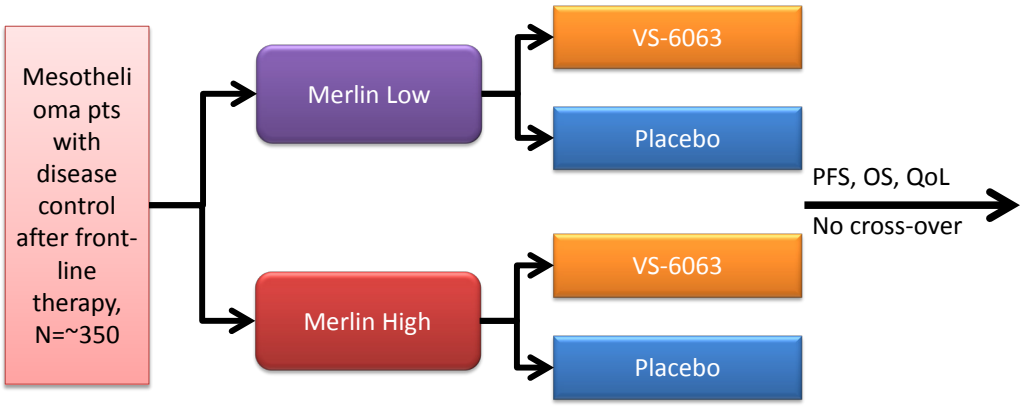
The Phase II trial has an adaptive design in which c 350 mesothelioma patients who have achieved a stable disease (SD) or better (SD and partial response, PR) to first-line treatment (a platinum agent and pemetrexed) will be given VS-6063 (400 mg BID) or placebo as maintenance therapy until progression. The trial thus excludes patients who have achieved a complete response (CR), although in practice very few do so in this condition. Enrolled patients will be divided into two groups, Merlin High and Merlin Low, so that clinical efficacy, including overall survival (OS), progression-free survival (PFS) and quality of life (QoL) can be analysed based on their expression of the biomarker Merlin (high/low) as well as in all patients.

At the interim analysis, which is to be performed at approximately half of the events for the planned final analysis, PFS will be analysed for the two subgroups. This allows the study to test the hypothesis that the FAK inhibitor may be more (or only) effective in the low Merlin subgroup. Thus, if one subgroup (i.e. Merlin High) is not showing activity, further enrolment will only continue in the other. Simultaneously, based on the interim analysis, the study may be resized if needed. If efficacy for one subgroup (e.g. Merlin low) or both is robust, the company intends to engage with regulatory agencies and seek for the trial to be designated pivotal, so that final data could be used as basis for approval.

The design has OS and PFS as co-primary end points, a practice that is used by other drug developers, particularly for maintenance trials. If PFS benefit is shown to be robust at the interim analysis, it could serve as the end point for accelerated approval, with OS confirmed for full approval.

The design is underpinned by Verastem's work on the association of focal adhesion kinase inhibition and Merlin expression and, in our view, provides a clear path for approval, with clinical efficacy more easily proven with a smaller sample size. Regulatory agencies, particularly the FDA, are amenable to approving cancer drugs where strong efficacy can be shown, even based on surrogate markers such as response rate of PFS, in well-defined sub-populations. If the same activity shown in preclinical studies is shown in the Phase II trial, we would expect to see a dramatic PFS difference in the Merlin Low sub-group. Such a robust efficacy would give the drug a better and speedier chance of approval than if based on efficacy in the entire population. The adaptive and multi-group trial design gives Verastem the chance to realise this possibility at interim analysis. We estimate that the drug could be approved in 2016 as a best scenario, just three years after it entered clinical trials.

Exhibit 1: Schema of Verastem's Phase II trial of VS-6063 in mesothelioma



Source: Verastem

Mesothelioma: Rare but increasing

Mesothelioma is unusual among cancers in that there is a long-established and causal relationship with exposure to asbestos. As asbestos use is banned in most developed countries, the perception is that the disease incidence rates are likely plateauing or declining. However, while this may be true in some countries (such as the US), it is not so in many other developed countries and is growing in emerging nations such as in China, India, Russia and Brazil. While asbestos exposure is clearly the primary risk factor, the disease also has a long latency period, often more than 20 years. Thus people may now be developing the disease based on exposure to the material 20 years ago. Japan only instituted a ban on the material in 2006 and the new incidences there jumped threefold from 2005 to 2012, illustrating a trend that may continue in many developed countries. In many other countries asbestos is either not officially banned or only partially banned.

According to Asbestos.com, there are about 3,000 new cases of mesothelioma identified annually in the US. In 2012, there were 1,278 new cases identified in Japan. It is estimated that there are about 24,000 new cases of mesothelioma annually worldwide and the incidence will increase until 2020. However, with countries such as China, Indian, Russia and Brazil currently probably underestimated, the real incidences may continue to increase even after 2020.

We estimate that there are c 8,300 new cases of mesothelioma diagnosed each year in the US, the top five EU countries and Japan. As 50-60% of these patients are expected to achieved disease control after first line therapy, there are c 4,980 VS6063 addressable patients in the key markets. Assuming a per patient treatment cost of $50,000, a conservative assumption compared to many of the current cancer drugs, the market would be c $249m. However, if the drug could eventually reach the estimated c 12,000 patients addressable worldwide, and assuming half the cost of treatment in countries outside of the US, top-five EU and Japan, the total market could approach $500m. In a scenario in which VS-6063's efficacy is found to be robust only in Merlin Low patients, which is about half of the population of the total mesothelioma patients, the market size could be still close to c $500m, because the duration of treatment would be expected to be longer in the subpopulation and, as a biomarker-targeted drug, it would be in position to command higher pricing.

Competing studies in the mesothelioma are listed in Exhibit 2.

Exhibit 2: Ongoing clinical trials in mesothelioma

Compound/technology	Company	Trial
NGR-hTNF/hTNF- CNGRCG peptide conjugate NGR-hTNF	MolMed	390-pt Phase III trial (NGR015) of NGR-hTNF plus BIC (doxorubicin, gemcitabine, or vinorelbine]) vs placebo plus BIC in second-line (**results: Dec 2013**). Results of 57-patient Phase II study presented at ASCO 2010.
		100-pt Phase II study of NGR-hTNF vs pbo as maintenance in pts treated with Alimta/cisplatin (**results: Jun 2013**).
Avastin/VEGF mab	Roche/IFCT	445-pt Phase II/III study of pemetrexed/cisplatin ± Avastin in first-line (**result: Dec 2014**).
Alimta	Lilly/NCI	96-pt Phase II of Alimta vs observation as maintenance in pts treated with Alimta/cisplatin (**result: Dec 2015**).
Amatuximab/mesothelin mab	Morphotek	86-pt Phase II, single-arm study in first-line (**results: Feb 2014**).
Recentin (cedirinib)/VEGFR inhibitor	AstraZeneca/NCI	NCI-sponsored 116-pt Phase I/II study of pemetrexed/cisplatin ± cedirinib in first-line (**results: Jun 2014**).
CBP501/G2 checkpoint inh.	CanBas	72-pt Phase I/II study of pemetrexed/cisplatin ± CBP501 in first-line (**results: Apr 2012**; no report yet).
Affinitor (everolimus)/mTOR inh.	Novartis/MSK	55-pt Phase II study in second-line (**results: Jun 2013**); 9-pt Phase II study in second- or third-line patients with Merlin/NF2 loss (complete).
Cixutumumab/IGFR mab	Lilly/NCI	20-pt Phase II, single-arm study in second-line (**results: Jul 2013**).
Erbitux/EGFR mab	Lilly/NCI	18-pt Phase II, single-arm study in first-line (**results: Sept 2013**).
ADI-PEG 20/peg-arginine deiminase	Polaris/Canver UK	66-pt Phase II study in ASS-negative, second-line (**results: Jan 2014**).
HSV1716/oncolytic virus	Virttu Biologics	12-pt Phase II study (**results: Apr 2014**).
Fresolimumab/TGF-β mab	Sanofi	20-pt Phase II study in second-line (**results: due Oct 2012; complete, but no data reported**).
CRS-207/vaccine	Aduro BioTech	16-pt Phase Ib study in combination with pemetrexed/cisplatin in first-line (**result: Jun 2014**).
Oshadi D and R/unknown	Oshadi	17-pt Phase IIa study (**results: Dec 2015**).
Tremelimumab/CTLA-4 mab	AstraZeneca/ Azienda	29-pt Phase II, single arm study in second-line (**results: Jan 2015**).
TroVax/Vaccine	Oxford BioMedica/ Wales Cancer Trials	26-pt Phase II, single arm study in first-line (**results: Dec 2014**).
PF-03446962/ALK1 mab	Pfizer/NCIC	26-pt Phase II, single-arm study in second-line (**results: Jun 2014**).
Oncolytic measles/vaccine	Mayo Clinic	36-pt Phase I study in first-line (**results: Nov 2013**).

Source: Edison Investment Research

Sensitivities

Verastem is subject to the risks typically associated with biotech company drug development, including the possibility of unfavourable or ambiguous outcomes in clinical trials, the success of competitors and commercial decisions by partners or potential partners. Verastem may carry higher risks than peers because: 1) the CSC theory is new and unproven – no drugs specifically targeting CSCs have yet been shown to be effective in clinical trials; 2) Verastem's drug candidates are in the early stage of development and early stage drugs not only have lower clinical success rates, but also face more development challenges as treatment standards change; and 3) Verastem's cash may only support its operation by 2015 and it needs to raise additional funds before then.

Specifically, Verastem shares may be sensitive to VS-6063's clinical progress in mesothelioma, including the speed at which the company can enrol patients and the robustness of the efficacy in the trial. Furthermore, the outcome of other drugs in development for this disease, in particular Roche's Avastin (which is being examined in first line) and, to a lesser extent, MolMed's NGR-hTNF, could affect's VS-6063's market potential as a maintenance therapy for mesothelioma.

In addition, future decisions by GSK in relation to the development of GSK2256098, another FAK inhibitor, could affect Verastem. The product has completed two Phase I studies and if GSK were to decide to move aggressively into mesothelioma, it could be a setback for Verastem given GSK's substantially stronger financial capability.

Valuation

We have updated our valuation to reflect the Q113 cash, marketable securities and long-term investments at $84.4m, which yields a total valuation of $287m, or $12.9 per share (fully diluted). The product pipeline value contribution remains unchanged from that previously published at $203m, which is based on a risk-adjusted NPV using a standard discount rate of 12.5%. For

product pipeline valuation, we have estimated peak sales of $829m for VS-6063 in mesothelioma and ovarian cancer and peak sales of $346m for VS-4718 and VS-5584. In both cases, there are also conservative, in our view, as indications have not been determined for these two drugs. We apply probabilities of clinical success rates of 15% for VS4718 and VS-5584, 25% for VS-6063 in ovarian cancer and 35% in mesothelioma. The calculation reflects the royalty pay-outs to licensors of each compound, including Pfizer, Poniard/Scrippts and S*Bio.

We apply a probability of clinical success of 35%, higher than the average, for VS-6063 in the Phase II maintenance setting of mesothelioma. This is based on our view that VS-6063 could generate GSK2256098-like efficacy in the disease: doubling and tripling of PFS comparing to historical standard in ITT and merlin-negative patients, respectively. In addition, the Phase II trial could be designated pivotal, therefore justifying a higher success date.

Exhibit 3: Verastem valuation

($m except for per share data)	rNPV ($m)	rNPV/ share ($)	Prob. Of success	Launch	Peak sales	Royalty	Patent expiry	Key assumptions
VS-6063, 2nd-line mesothelioma	$73.8	$3.31	35%	2016	$297	-10%	2029	US treatable pts: 2,250 annually; full course treatment cost: $37,500 in 2016
VS-6063, 2nd-line ovarian cancer	$76.8	$3.45	25%	2018	$532	-10%	2029	US treatable pts: 8,912 annually; full course treatment cost: $31,210 in 2018
VS-4178, cancer	$26.5	$1.19	15%	2019	$346	-3.5%	2029	
VS-5584, cancer	$26.0	$1.17	15%	2019	$346	-5.5%	2029	
Total pipeline value	$203	$9.12						
Net cash by year end of Q113	$84	$3.79						
Total firm value	$287							
Total diluted shares (m)	22.3							
Value per share ($)	$12.9							

Source: Edison Investment Research

Financials

Verastem reported a loss of $9.0m, or $0.44 per share in Q113, while net cash used in operating activities was $6.3m. Cash and equivalents at the end of Q113 amounted to $84.4m. We expect the company's cash and cash equivalents, marketable securities and long-term investments at the end of 2013 to be $65.5m. Based on our projection of cash burn, we estimate that this cash should support the company's operations into Q415, at which time (or preferably earlier) the company would need to raise additional funds, either from the capital market or from strategic players, to continue its development efforts. As per Edison's policy, no revenue from potential future licensing agreements is assumed in the financial model.

Exhibit 4: Financial summary

$'000s	2010	2011	2012	2013e	2014e
Year end 31 December					
PROFIT & LOSS					
Revenue	0	0	0	0	0
Cost of Sales	0	0	0	0	0
Gross Profit	0	0	0	0	0
EBITDA	(784)	(13,698)	(32,230)	(36,714)	(37,754)
Operating Profit (before amort. and except.)	(784)	(13,698)	(32,230)	(36,714)	(37,754)
Intangible Amortisation	0	0	0	0	0
Exceptionals	(2)	(32)	(6)	0	0
Other	0	0	0	0	0
Operating Profit	(786)	(13,730)	(32,236)	(36,714)	(37,754)
Net Interest	0	15	246	146	66
Profit Before Tax (norm)	(784)	(13,683)	(31,984)	(36,568)	(37,688)
Profit Before Tax (FRS 3)	(786)	(13,715)	(31,990)	(36,568)	(37,688)
Tax	0	0	0	0	0
Profit After Tax (norm)	(784)	(13,683)	(31,984)	(36,568)	(37,688)
Profit After Tax (FRS 3)	(786)	(13,715)	(31,990)	(36,568)	(37,688)
Average Number of Shares Outstanding (m)	0.9	1.3	18.8	21.5	22.1
EPS - normalised and fully diluted (c)	(0.9)	(10.6)	(1.6)	(1.6)	(1.7)
EPS - (IFRS) (c)	(0.9)	(10.6)	(1.7)	(1.7)	(1.7)
Dividend per share (c)	0.0	0.0	0.0	0.0	0.0
Gross Margin (%)	N/A	N/A	N/A	N/A	N/A
EBITDA Margin (%)	N/A	N/A	N/A	N/A	N/A
Operating Margin (before GW and except.) (%)	N/A	N/A	N/A	N/A	N/A
BALANCE SHEET					
Fixed Assets	8	11,096	35,841	9,272	1,000
Long-term investment	0	8,994	34,944	8,000	0
Property Plant & Equipment	8	709	811	800	1,000
Other	0	1,393	86	472	0
Current Assets	3,596	47,941	57,058	58,545	44,731
Cash and cash equivalents	3,584	20,954	10,096	19,006	43,570
Marketable securities-short term	0	26,857	46,456	38,478	0
Prepaid expenses and other current assets	12	130	506	1,061	1,161
Other	0	0	0	0	0
Current Liabilities	(368)	(3,146)	(2,399)	(4,414)	(5,814)
Creditors	(368)	(3,146)	(2,399)	(4,414)	(5,814)
Short term borrowings	0	0	0	0	0
Long Term Liabilities	0	(516)	(58)	0	0
Long term borrowings	0	0	0	0	0
Other long term liabilities	0	(516)	(58)	0	0
Net Assets	3,236	55,375	90,442	63,403	39,917
CASH FLOW					
Operating Cash Flow	(330)	(10,147)	(22,847)	(25,368)	(26,302)
Net Interest	0	15	246	146	66
Tax	0	0	0	0	0
Capex	(8)	(785)	(310)	(45)	(200)
Acquisitions/disposals	0	0	0	0	0
Financing	3,922	64,224	57,602	(765)	0
Dividends	0	0	0	0	0
Net Cash Flow	3,584	53,307	34,691	(26,032)	(26,436)
Opening net debt/(cash)	0	(3,584)	(56,805)	(91,496)	(65,484)
HP finance leases initiated	0	0	0	0	0
Other	0	(86)	0	0	0
Closing net debt/(cash)	(3,584)	(56,805)	(91,496)	(65,464)	(39,048)

Source: Edison Investment Research, Verastem accounts

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