UBS

UBS Investment Research

Verastem

Global Equity Research

Americas

Biotechnology

12-month rating	**Buy**
	Prior: Not Rated
12m price target	**US$20.00**
	-
Price	**US$11.10**

RIC: VSTM.O BBG: VSTM US

7 March 2012

A New Approach to an Old Problem in Anticancer Therapy: Initiating with Buy

■ Initiating VSTM coverage with a Buy and $20 Price Target

Verastem is an early-stage biotechnology company that we view as uniquely positioned to leverage recent advances in cancer genetics and develop products that could overcome multidrug resistance to chemotherapy. We think at least one of its 3 late preclinical assets has the potential to reach proof of concept in "triple-negative" breast cancer, which would trigger significant valuation step-ups over 1-3 years.

■ Building value by targeting cancer stem cells (CSC's)

Key tenets of our thesis: [1] Verastem's technology and expertise confers a competitive advantage in targeting CSC's; [2] we assign a higher probability of success (30%) than the market; [3] comps suggest significant upside if ph1b/ph2 are successful; [4] there is significant strategic value in CSC-directed therapies.

■ Overcoming the limitations of chemotherapy of strategic importance

Multidrug resistance is the 'Achilles heel' of conventional anticancer therapies, and targeting CSC's is a highly rational approach. Although Verastem is initially focusing on a targeted population with limited treatment options (triple-negative breast cancer), establishing proof of concept that could be applied to other tumor types would represent an important therapeutic advance that we think would command significant strategic value (as a recent acquisition of a CSC company suggests).

■ Valuation: $20 Price Target by DCF and discounted multiple on sales

Our primary analysis is on DCF, but current / future comps are highly supportive.

Highlights (US$m)	12/09	12/10	12/11E	12/12E	12/13E
Revenues	-	0	0	0	0
EBIT (UBS)	-	(1)	(11)	(15)	(22)
Net Income (UBS)	-	(1)	(11)	(15)	(21)
EPS (UBS, US$)	-	(0.59)	(1.32)	(0.68)	(0.98)
Net DPS (UBS, US$)	-	0.00	0.00	0.00	0.00

Profitability & Valuation	5-yr hist av.	12/10	12/11E	12/12E	12/13E
EBIT margin %	-	-	-	-	-
ROIC (EBIT) %	-	-	>500	>500	>500
EV/EBITDA (core) x	-	-	-16.6	-8.8	-5.7
PE (UBS) x	-	-	NM	NM	NM
Net dividend yield %	-	-	0.0	0.0	0.0

Source: Company accounts, Thomson Reuters, UBS estimates. (UBS) valuations are stated before goodwill-related charges and other adjustments for abnormal and economic items at the analysts' judgement.
Valuations: based on an average share price that year, (E): based on a share price of US$11.10 on 06 Mar 2012 16:42 EST

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Trading data

52-wk range	US$11.70-10.86
Market cap.	US$0.21bn
Shares o/s	19.2m (COM)
Free float	29%
Avg. daily volume ('000)	51
Avg. daily value (m)	US$0.6

Balance sheet data 12/11E

Shareholders' equity	US$0.06bn
P/BV (UBS)	1.5x
Net Cash (debt)	US$0.06bn

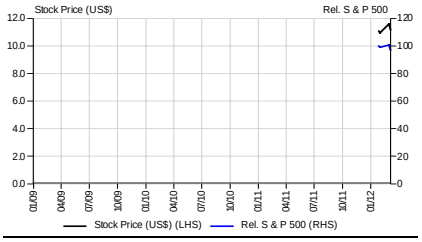
Forecast returns

Forecast price appreciation	+80.2%
Forecast dividend yield	0.0%
Forecast stock return	+80.2%
Market return assumption	5.3%
Forecast excess return	+74.9%

EPS (UBS, US$)

	12/11E From	12/11E To	12/11E Cons.	12/10 Actual
Q1	-	(0.37)	-	-
Q2	-	(0.44)	-	-
Q3	-	(0.50)	-	-
Q4E	-	(0.21)	-	(0.59)
12/11E	-	(1.32)	-	
12/12E	-	(0.68)	-	

Performance (US$)



Source: UBS

www.ubs.com/investmentresearch

Contents

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Overview

Portfolio manager's summary

We are initiating coverage of Verastem (VSTM) with a Buy rating and $20 price target. Verastem is an early-stage cancer-focused company that aims to create value by addressing an age-old limitation to standard cancer chemotherapy, namely tumor repopulation, resistance, and metastasis (which we call "the evil triad"). The company intends to leverage recent advances in our understanding of "cancer stem cells" (CSC's) that are thought to be responsible for seeding and repopulating tumors. Verastem's scientific founders were the pioneers in understanding CSC's, and its scientific advisory board is second to no biotechnology company, in our view. The clinical development program should serially de-risk at least 1 of Verastem's 3 assets over a 1-3 year period, driving significant upside to the current valuation.

We rate VSTM shares Buy with a $20 price target

The key tenets of our thesis:

(1) **Elegant CSC science appears highly translatable into a product.** Verastem seeks to leverage elegant CSC science produced by MIT Professor Robert Weinberg, a pioneer in tumor biology and CSC's. Central to our Buy thesis on VSTM, is that the science enabled the first opportunity to selectively target CSC's in triple-negative breast cancer (TNBC) as a practical adjunct to standard approaches, and hence should carry a higher than normal probability of success among pre-clinical biotech companies.

(2) **We assign a higher probability of success (30%) than the market.** Verastem has 3 assets that are expected be in clinical trials in 1H13e. We argue that the scientific rationale, targeted patient population, and use of key surrogate endpoints support a higher probability of success than the heavy discounting reflected in the current valuation.

(3) **Comps suggest significant upside potential with de-risking.** With shares currently trading at a market cap of ~$240m, we calculate that the current valuation reflects the discounting associated with the average early stage oncology program. In our view, phase-1b and -2 data will validate the CSC hypothesis and lower the discounting. We estimate that increasing the probability of success from 10-20% to 30% or higher will drive significant valuation step-ups, comparable to historical step-ups associated with proof of concept that support our $20 PT.

(4) **Track record of success for the founders, management, and advisors.** Verastem's scientific founders and the scientific advisory board are considered among the highest echelon of academic science. The executive management team is experienced and accomplished in delivering value to shareholders through several successful ventures in biotech, including the founding of 3 companies sold to larger biopharma companies, and 2 high-profile publicly traded companies.

Rating and Price Target Assumptions

On the basis of our proprietary due diligence we are initiating coverage on Verastem shares with a Buy rating $20 price target (Table 1 below). Our modelling of the metastatic triple negative breast cancer (TNBC) market suggests $1,339M in worldwide sales (un-risk-adjusted) of a Verastem compound are possible by 2025. Given the novel approach to targeting cancer stem cells, and the parallel development approach of a companion diagnostic, we forecast ~$63M in risk-adjusted 2018 sales, reflecting a low-60% penetration into the addressable patient population, with a 30% risk-weighting applied to sales. Our DCF is driven off the risk-adjusted sales estimates, with a 0% terminal growth rate, and 12.5% discount rate applied to the future cash flows.

Table 1: Verastem valuation by DCF and SOTP: We launch with a $20 PT

Valuation	DCF	SOTP	Average
NPV	$417m	$435m	$426m
Per Share	$19.53	$20.37	$19.95

Source: UBS research

Our price target is DCF-based but also supported by applying a multiple-based SOTP analysis, as well as a scenario analysis incorporating key sensitivities around risk-adjustment to peak sales in TNBC.

Risks to our thesis

We see several risks to our Buy rating on VSTM shares.

- **Clinical risk**: Clinical risk is the most significant near-term risk to our Buy rating. Failure of the 3 lead assets on efficacy and/or safety would represent a delay to commercialization, since Verastem would revert to back-up compounds in earlier stages of development.
- **Financing risk:** Verastem may need to access the capital markets to fund ongoing operations. We model an equity financing in 2014.
- **Regulatory risk**: If Verastem completes clinical trials and applies for marketing authorization in the US and EU, it would face risk that the regulatory agencies do not approve the drug candidates.
- **Competitive risks:** Verastem is not the only company developing agents targeting TNBC. While the Verastem approach is unique, it is not the only company developing compounds that could be effective in treating patients with TNBC. We note it is possible that other compounds could [1] have efficacy in killing CSCs, or [2] set a higher standard of care that could raise the clinical bar for improved safety or efficacy.
- **Patent risk:** If Verastem brings products to the market, generic competitors could challenge Verastem's patent estate.

Key pipeline assets and upcoming catalysts

Verastem has full worldwide commercial rights to three late preclinical assets: VS-507 (a Wnt pathway inhibitor); and VS-4718 and VS-5095, which are both FAK inhibitors. Verastem expects to have an IND from the FDA for VS-507 by YE12e and start clinical trials in 1Q13e. The FAK program would start clinical trials roughly a quarter later. Specific catalysts for the pipeline are listed in Table 2 below. Although we see a valuation step-up from phase-1b data (potentially late 2013), we expect phase-2 data (2014-15) would provide proof-of-concept for clinical assets, as well as the technology platform.

Table 2: Upcoming catalysts – Verastem

Pipeline Candidate	Target	Current Status	Phase I Timing	Phase II Timing
VS-507	Wnt	IND-tox	1H13	1H14
VS-4718/VS-5095	FAK	IND-tox	1H13	1H14
Companion Diagnostics	-	Marker selectin and validation	1H13 (Human trials)	-
NCE/Target 3	-	Lead selection	1H14	1H15

Source: Company reports, and UBS research

Environmental, social, and governance issues

The primary social issue we see affecting biotechnology is that of drug pricing and global access. While providing access to life-saving drugs is a priority for all of the companies, realities of the market are often balanced against perceived/intended social obligations. All of the companies we cover employ compassionate use programs that enable patients who benefit from therapies that are either too costly to afford or are still in clinical development, but provide tremendous benefit to the patient, often life-saving. Please refer to the drug pricing section of our sector initiation (Nov 15, 2010) for further discussion of issues around drug pricing and access.

An innovative approach to overcome and age-old problem

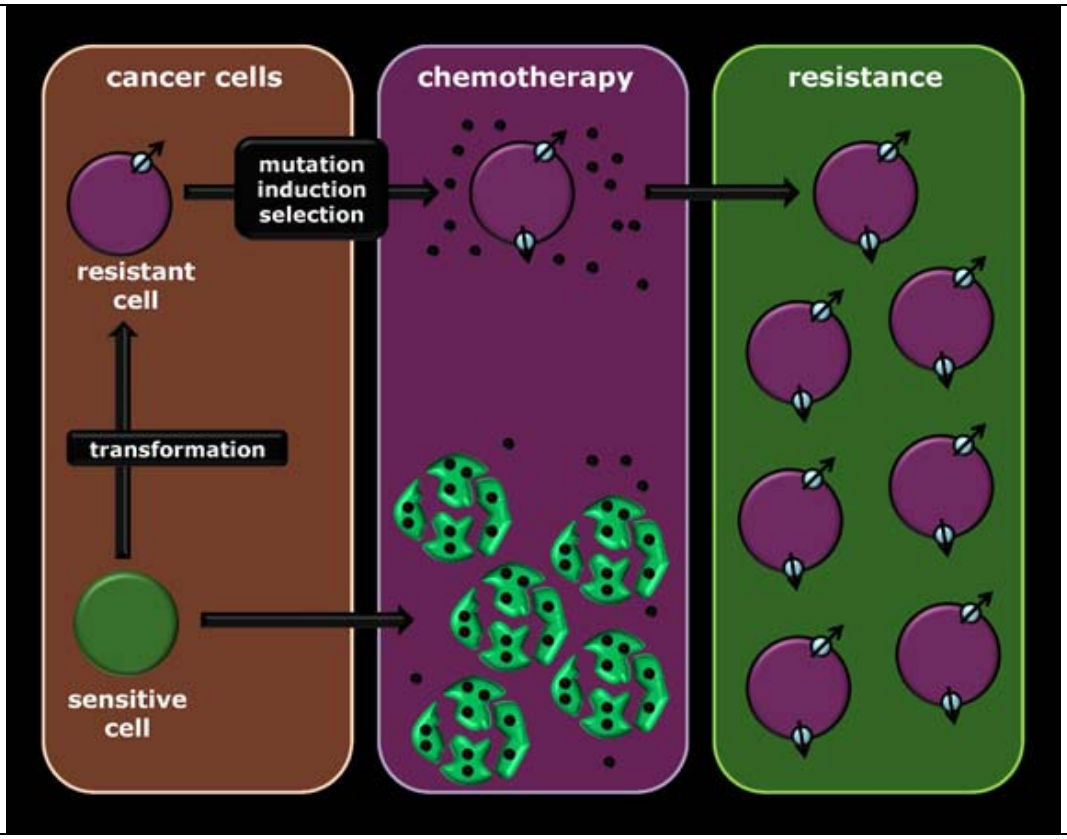
Verastem is aiming to solve a central problem in oncology, and is developing an innovative solution to conquering the "evil triad" in cancer – [1] repopulation, [2] resistance, and [3] metastases. This problem continues to evade advances in anticancer therapy and is ultimately responsible for cancer death. Below we outline one of the core problems with current anti-cancer therapy and how Verastem aims to solve it.

Tumors are good at evading therapy

There are many molecular principles or models available to explain the failure to control malignancies. Traditionally, cancer biologists have pointed to various mechanisms that cancer cells use to develop multidrug resistance to chemotherapy. These traditional views are reflected in Figure 1. Here, there is either pre-existing heterogeneity in the tumor cell population whereby some cells are sensitive to chemo and others aren't, or there are transformation events that occur that make sensitive cells resistant to chemo (left panel). Treating the tumor with chemotherapy results in significant debulking of the tumor (represented by the death of the sensitive cells in the lower middle panel).

However, the chemo-resistant cells are able to grow out and repopulate the tumor, and potentially spread to other sites.

Figure 1: The Traditional Model of Multidrug Resistance to Conventional Chemotherapy

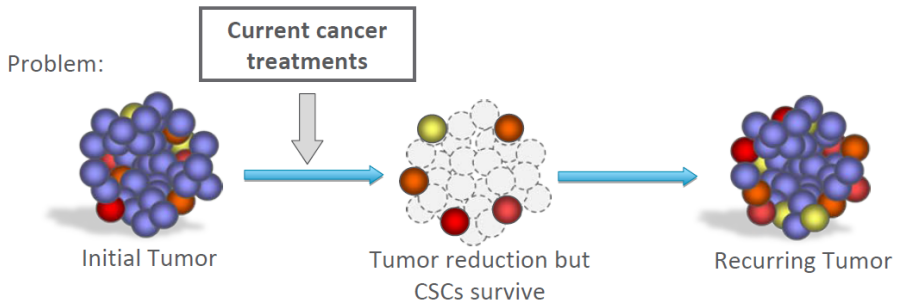


Source: http://www.mindupbioresearch.com/mdr.html

From EMT biology comes the bad actors: cancer stem cells (CSC's)

Professor Bob Weinberg and others pioneered a concept that elegantly describes the transformation of tumor cells into the "bad actors" in tumors. Based on years of cutting-edge molecular and cell biology, Weinberg and others have described how tumor cells can co-opt the epithelial-to-mesyechymal transition (EMT; a normal developmental program that plays an important role in embryonic development) to take on properties that confer greater metastatic potential, are resistant to chemotherapy, and repopulate tumors, thus furthering cancer pathogenesis (*see our section on EMT biology and Figure 2 below*).

Figure 2: The "Evil Triad" Results in Incomplete Eradication of Tumors

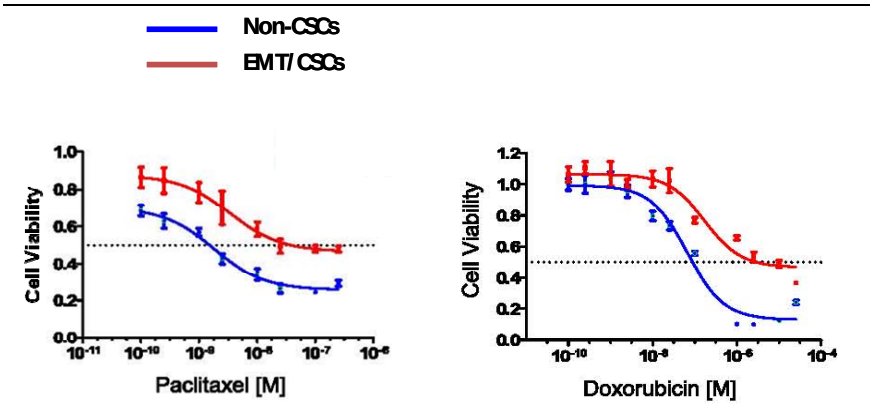


Source: Company reports and UBS research

What are CSC's responsible for? The "evil triad"

Conventional chemotherapy is quite effective in eradicating most cancer cells. However, CSCs, or cells that are thought to have undergone EMT (epithelial to mesenchymal transition) are considerably more resistant to anticancer drugs compared to cells that have not undergone EMT. The data below (Figure 3) illustrate that CSC's are resistant to chemotherapy relative to non-CSC tumor bulk, showing that at any given chemo dose, CSC's are more likely to be viable than the non-CSC's.

Figure 3: CSC's Are Less Sensitive to Chemo Than Non-CSC Breast Cancer Cells



Source: Company reports and UBS research – Adapted from Gupta et al Cell 2009

The Evil Triad

CSC's are thought to be the "bad actors" in tumors that are responsible for tumor recurrence.

[1] Tumor recurrence: The dandelion hypothesis

Tumor recurrence is thought to be driven by a subpopulation of cells (CSCs) with tumorigenic potential that is inherently resistant to traditionally used chemotherapy and radiation. In the literature, this is often referred to as the "dandelion hypothesis," which supposes that clinical activity and drug recurrence are analogous to cutting a dandelion (or other type of weed) off at ground level. While it may at first appear to kill the weed (tumor), only the

elimination of the root will prevent the dandelion from re-growing[1]. Therefore, a need for CSC-targeted therapies is apparent.

[2] Drug resistance: several mechanisms possible – Wnt (VS-507), FAK (VS-4718, VS5095) included

As outlined above, cancer recurrence may be driven by incomplete eradication of the tumor mass, largely because CSCs may be protected against widely used chemotherapeutic agents through mechanisms such as [1] increased proficiency in DNA damage repair, [2] high expression of ATP-binding drug transporters, and [3] activation of the PI3K/AKT and Wnt pathways[2]. The last method of resistance may indicate why one of Verastem's lead clinical candidates, VS-507, which targets the Wnt pathway, shows selective efficacy against CSCs in preclinical models. Importantly preclinical data suggest that the fraction of CSCs in the recurrent tumor is likely enriched after traditional chemotherapy, suggesting that after incomplete eradication of the entire tumor mass, the repopulated and recurrent tumor has become resistant to chemotherapy[3].

[3] Tumor metastasis: motility and invasiveness

While the relationship between resistance and tumor recurrence in CSCs (or CSC-like cells) is well-defined, their role in metastasis, and ultimately mortality is less well established (although evidence does clearly exist). Preclinical prostate cancer models have shown a clear relationship between a stem-cell-like subpopulation and metastases[4]. Also, CSCs have been found to be at the invasive front of pancreatic tumors where they may be primed for metastatic spread[5]. Given the inherent ability of CSCs to reproduce the parental tumor upon injection in immunocompromised mice, motile CSCs seem clear candidates for seeding distant metastatic sites[2]. Ultimately, given that EMT induction and CSC transition in cancer cells results in the cell acquiring invasive and metastatic properties, it is reasonable to ascribe a role to CSCs in tumor metastasis, and ultimately in cancer mortality.

Hence, targeting CSC's could be the answer

The "big idea" central to the Verastem approach is that if cancer stem cells are responsible for the initiation, metastasis, and recurrence of many cancers and may drive the ultimate failure of current therapies, then targeting cancer stem cells can achieve complete eradication of the tumor (Figure 4).

[1] Jones et al., JNCI 2004; 96: 583-5.

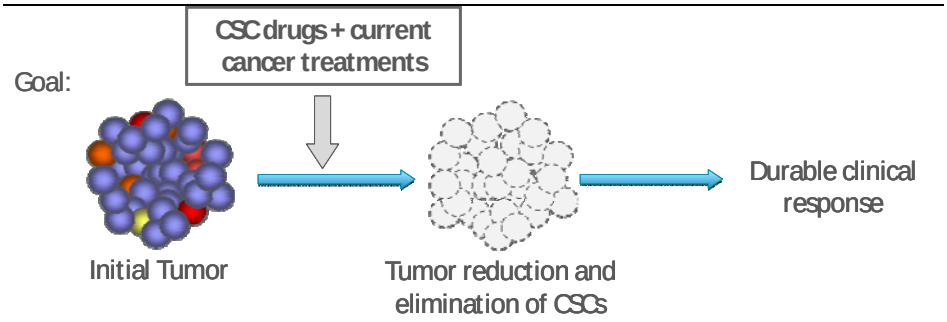
[2] Maugeri-Sacca et al., Clinical Cancer Research 2011; 17: 4942-7.

[3] Li et al., JNCI 2008; 100: 672-679.

[4] Mulholland et al., Cancer Res 2012: Epub ahead of print.

[5] Singh et al., Oncogene 2010; 29: 4741-4751.

Figure 4: Targeting CSC's May Prevent Recurrence, Resistance, and Metastasis



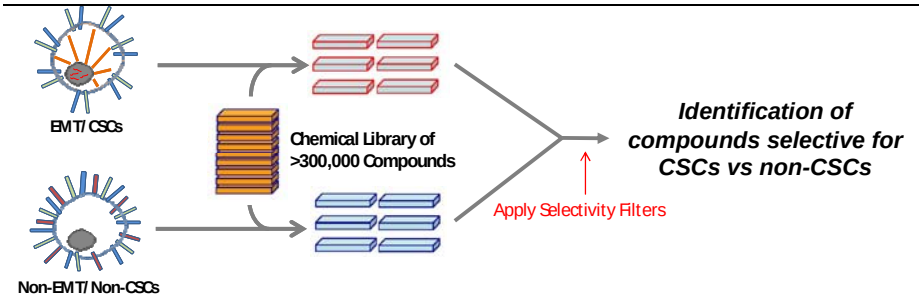
Source: Company reports and UBS research

Verastem is uniquely positioned to target CSC's

The Verastem cofounders are also the pioneers in the fields of CSC and EMT biology

The company utilizes proprietary technology developed by the pioneers of EMT biology, who are the Verastem scientific cofounders at the Whitehead Institute and the Broad Institute. As such, they are on the forefront of CSC and EMT biology, and integral to advances in the field. The approach is to screen compounds and identify drugs selectively targeting CSCs. The key step in this process was based on the seminal work by Weinberg *et al* who were able to solve the problem of identifying and harvesting a source of CSCs in sufficient size to assay[6]. Because CSCs exist *in vivo* in such a limited number, making harvesting from tissue samples untenable, the group instead developed technology (based on the link between the epithelial to mesenchymal transition (EMT) and the emergence of stem cells) that enables Verastem to screen compounds against a population of CSCs.

Figure 5: Proprietary assay allows for selection of anti-CSC compounds



Source: Company reports and UBS research

CSC selectivity is the secret ingredient

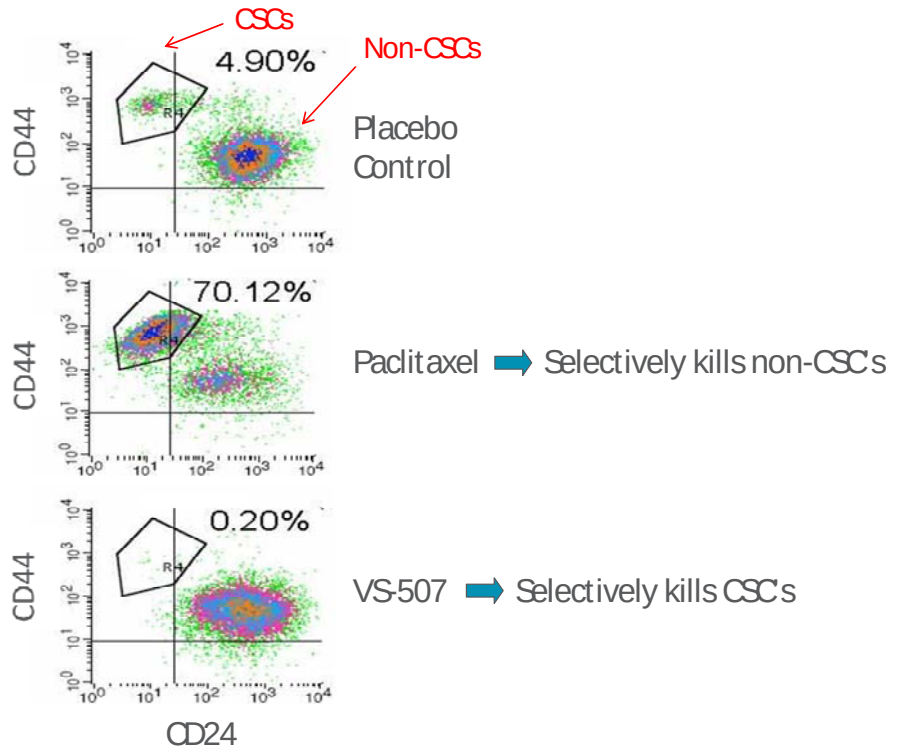
By virtue of Dr. Gupta's technological breakthrough that enables large volumes of CSC's to be made, the screening method allows for the characterization of a compound's ability to kill CSC's compared to their ability to kill cancer bulk cells, thereby identifying highly selective anti-CSC compounds. Indeed, results show that VS-507, which was identified in Dr. Gupta's screening, is highly selective in killing breast CSC's relative to common chemotherapies.

[6] Gupta et al., Cell 2009; 138: 1-15.

Figure 6 below illustrates the significant effect that paclitaxel can have on tumor bulk (see reduction in non-CSC breast cancer cells in the lower-right quadrant of the middle panel below, relative to the same quadrant in the top panel). However, the paclitaxel treatment leaves the CSC's (upper left quadrant) largely untouched.

In contrast, VS-507 treatment results in eradication of the CSC population without much effect on the non-CSC tumor cells, demonstrating its selectivity for CSC's. These data also highlight that anti-CSC therapies are expected to be used in combination with standard therapies in TNBC.

Figure 6: VS-507 Selectively Targets and Kills CSCs



Source: Adapted from Company presentations and Gupta et al., Cell 2009

Screening methodology useful for drug discovery, as well as assessing in-licensing candidates

Verastem has used its proprietary screening to identify lead compound VS-507, which has been shown to modulate the Wnt pathway, known to drive the EMT (*see EMT biology section below for details*). However, the screening platform has also been used to characterize the FAK program assets, which were purchased recently from a distressed seller (Poniard).

Verastem is developing drugs that target key CSC pathways

While VS-507 emerged out of the initial screens from the Gupta/Weinberg group, Verastem is also developing anti-cancer agents that target key pathways in CSC biology. Verastem's FAK program is being developed because the FAK pathway is associated with EMT, and its overexpression has been observed in CSCs, making it an ideal target as an anti-CSC therapy. Additionally, the

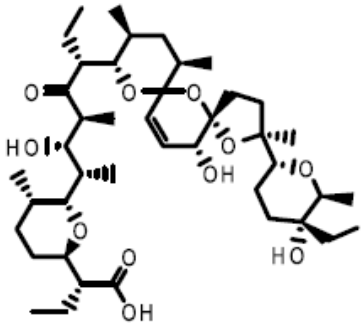
Verastem CSC screen shows the FAK compounds are highly selective for CSC's. We would not be surprised to see new targets emerging out of the Verastem pipeline that target other CSC-related pathways, including Notch and Hedgehog. Importantly, Verastem will look for genes overexpressed in CSC's, and then run selectivity screens to see which compounds perform best.

According to the company, pre-clinical toxicology studies are ongoing, with no untoward data that should preclude either FAK inhibitor from moving into phase I studies. Following the completion of phase Ib studies, Verastem will select either one FAK inhibitor and/or VS-507 to take into phase II. However, there are several back-up compounds coming through the preclinical pipeline (NCE target 3), should the clinical profile of the first three targeted candidates be sub-standard.

VS-507: Finger-lickin' good

VS-507 is a proprietary formulation of salinomycin, which was identified by Gupta *et al*. (2009) when screening for CSC-selective compounds. It is used as an additive to chicken feed, and is believed to have anticancer properties by virtue of its inhibition of the Wnt pathway.

Figure 7: VS-507 Chemical Structure

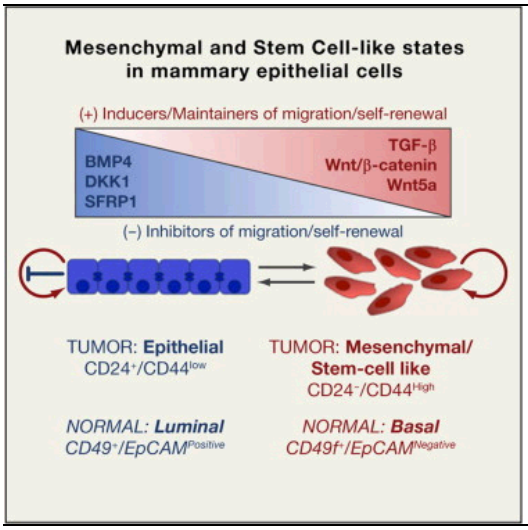


Source: Adapted from Gupta *et al., Cell* 2009

VS-507 targets CSCs through the Wnt pathway

Wnt has been shown to be activated upon entering a mesenchymal state[7]. Multiple players, including Wnt activation, E-cadherin inhibitors and TGF-β, are necessary to induce EMT, as demonstrated in normal and neoplastic human MECs (mammary epithelial cells). Further, Scheel et al showed that inhibiting autocrine signalling in the canonical and noncanonical Wnt pathways inhibits migration and self-renewal in primary MECs as well as lowering tumorigenicity and metastasis in derivative transformed cells. Verastem believes VS-507 targets CSCs through blocking Wnt signalling. In mouse models of breast cancer, VS-507 lowered CSC biomarkers (see below).

Figure 8: The Role of Wnt/β-catenin pathway in CSCs



Source: Scheel et al., Cell 2011; 145: 926-40

[7] Scheel et al., Cell 2011; 145: 926-940.

VS-507 treatment reduces expression of breast CSC genes

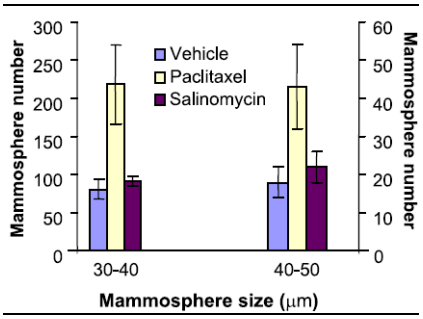
VS-507 treatment led to the loss of expression of CSC-associated genes that are correlated with tumors with poor prognosis

Assays were performed to measure gene expression associated with breast CSCs and normal mammary epithelial progenitor cells when treated with VS-507 (and paclitaxel). VS-507 effects on breast CSCs and progenitor genes as examined using previously published gene sets reduced several genes that were shown to be inversely correlated with metastasis-free survival and overall survival in different tumor types[8]. A subset of genes that are correlated with CSCs and shown to be downregulated in VS-507-treated cells will serve as the basis for potential biomarker analysis in clinical trials and further analysis.

VS-507 reduces tumor seeding ability and metastasis

In vitro, it has been demonstrated that VS-507 reduces the tumor-seeding ability of breast cancer CSCs (>100-fold decrease) relative to paclitaxel. In mouse models, VS-507 did not reduce the overall tumor size compared to paclitaxel; however, the number of CSCs in tumors from paclitaxel-treated mice was two-fold greater than VS-507-treated mice. Further, tumors in VS-507-treated mice exhibited greater necrosis and apoptosis (programmed cell death) compared to tumors in mice treated with placebo.

Figure 9: VS-507 Reduces Tumor Seeding Ability



Source: Adapted from Gupta *et al., Cell* 2009

Mice that were treated with VS-507 also expressed different tumor morphology than those treated with vehicle (placebo) or paclitaxel. Importantly, tumors in mice treated with VS-507 expressed E-cadherin protein (not normally expressed in the SUM159 cell line, which was injected into the mice), and cancer cells in these mice **displayed increased epithelial differentiation**.

VS-507 also reduces tumor metastasis in mice

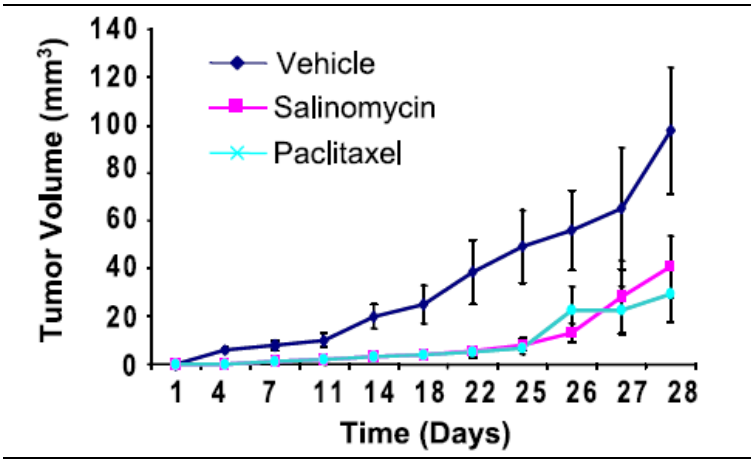
Regarding tumor metastasis, it is thought CSCs may play a role in the primary tumor spreading. To address this, VS-507-treated cancer cells (4T1) were put into the lungs of mice, and showed a four-fold reduction in metastasis compared to placebo treated cells, whereas paclitaxel-treated cells showed a two-fold increase vs. placebo. Lungs from these mice were then examined for markers of epithelial differentiation and EMT. **VS-507-treated cells showed increased epithelial differentiation (vs placebo and paclitaxel) and reduced EMT, whereas paclitaxel-treated cells showed increased EMT**. Overall, VS-507 and paclitaxel resulted in opposite effects on breast cancer cell differentiation, with VS-507 leading to increased epithelial differentiation and paclitaxel causing increased mesenchymal differentiation.

VS-507 reduces tumor burden in animal models of breast cancer

In our view, the strongest available preclinical data supporting VS-507's clinical potential is that treating animals with single-agent VS-507 results in the reduction of tumor burden through prevention of tumor growth (see Figure 10).

[8] Liu et al., NEJM 2007; 356:217-226.

Figure 10: VS-507 Has Antitumor Activity Comparable to Paclitaxel in an Animal Model of Breast Cancer



Source: Adapted from Gupta *et al.*, *Cell* 2009

VS-507 also effectively treats established tumors (according to Verastem; data not shown as it has been withheld for publication and presentation)

VS-4718 and VS-5095: Meet the FAKkers

In November 2011, Verastem acquired Poniard's FAK program and is focusing on two lead compounds, VS-4718 and VS-5095. Both compounds are nanomolar FAK (focal adhesion kinase) inhibitors.

FAK inhibition targets CSC survival

FAK has been implicated in cancer progression by activating MAPK, stimulating EMT and inducing tumor dissemination[9]. It was demonstrated FAK helps facilitate mammary tumor metastasis and chemotherapeutic targeting of FAK inhibits TGF-β-dependent metastasis. Verastem had identified FAK as a potential target through their proprietary screen, and then tested several FAK inhibitors.

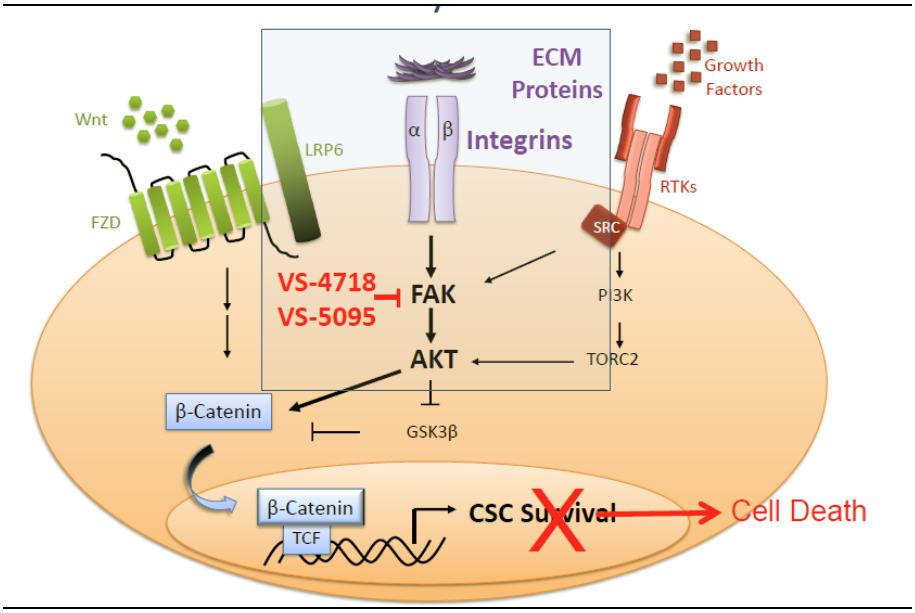
FAK is a non-receptor tyrosine kinase that is necessary for cell migration, proliferation and migration during embryogenesis

Using their proprietary technology, Verastem identified the CSC-targeting activity of VS-4718 and VS-5095 (the Poniard compounds were found to be the most selective (25x) of all of the compounds tested). Preclinically, these compounds demonstrated potent and selective inhibition of FAK, and also had good oral bioavailability and PK/PD. Importantly, both compounds showed marked reduction in primary tumor growth and metastatic burden.

Composition of matter IP for VS-4718 and VS-5095 expire in March, 2028, with related methods of use patents expiring in 2031

[9] Wendt and Schiemann, Breast Cancer Research 2009; 11:R68.

Figure 11: The Role of FAK in CSC Survival



Source: Company reports

FAK in breast cancer

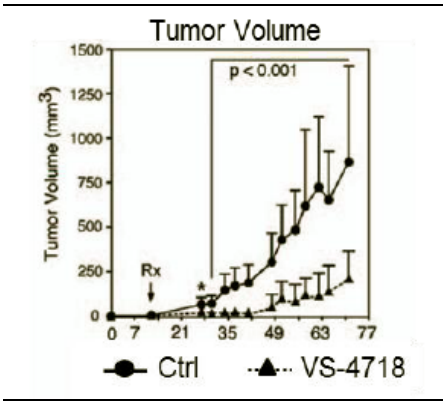
Increased FAK expression was found to be unfavorable in many cancer types, including breast cancer

In an *in vitro* breast cancer model (4T1 cells) it was shown that FAK is activated upon TGF-β-mediated induction of EMT which requires β3 integrin and Src (sarcoma proto-oncogene protein tyrosine kinase). In an examination of 393 invasive breast cancer tumors, tumors that were FAK FISH (fluorescence in situ hybridization) positive were associated with a higher histologic grade, higher T stage and a triple-negative phenotype. Moreover, survival analysis indicated that patients with FAK FISH positive tumors had a shorter overall and relapse-free survival[10].

In a mouse model of TNBC, VS-4718 inhibited primary tumor formation as well as inhibited tumor metastases, as shown below. Although preclinical, these data are suggestive that FAK inhibition can prevent both primary tumor formation as well as tumor metastases.

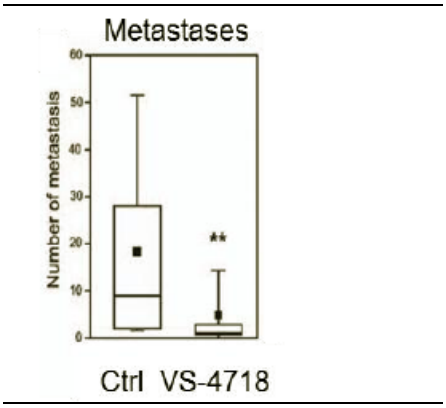
[10] Yom et al., Breast Cancer Res Treat 2011; 128: 647-55.

Figure 12: Inhibition of Primary Tumor



Source: Company reports

Figure 13: Inhibition of Metastases



Source: Company reports

Assessing the opportunity, and valuation implications

Given the lack of clinical data (phase I trials expected to start 2013), current valuations imply heavy risk-adjustment to reflect the early (pre-clinical) stage of development. However, our diligence suggests that the technical probability of success should justifiably be higher for the Verastem development program compared to its peers (pre-clinical oncology companies).

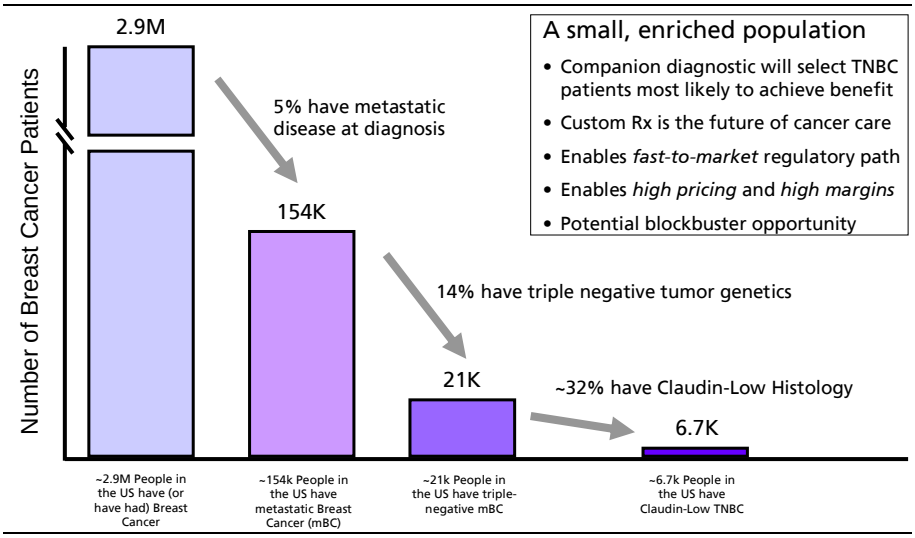
In the following section, we provide a framework around our $20 price target, and outline our view on the opportunity ahead as clinical data are reported and proof of principle on the Verastem CSC thesis is played out.

Setting the stage: Overview of market opportunity in metastatic TNBC

Although TNBC patients only represent 12-17% of breast cancer patients – assuming orphan drug pricing, a fully-penetrated market represents a blockbuster opportunity

By first targeting triple-negative breast cancer (TNBC), a tumor type that is known to be highly-enriched with cancer stem cells, the company is taking a rational and potentially fast-to-market approach to drug development. We note that while more than 2.9 million women are believed to have breast cancer, the TNBC population represents only a very small fraction of this population. Our diligence suggest that by the time a Verastem drug is approved to treat TNBC patients in 2017e, the addressable market in the US will be 7.4k patients (up from 6.7k today as demographics continue to shift). Given the small number of targeted patients, we believe the company can likely generate orphan-like oncology pricing, with an assumed launch price of >$100k annually. Under these assumptions, and in spite of the relatively small number of patients, a fully-penetrated market could generate blockbuster sales in the US alone.

Table 3: TNBC: Addressable Market Breakdown



Source: Company reports and UBS research

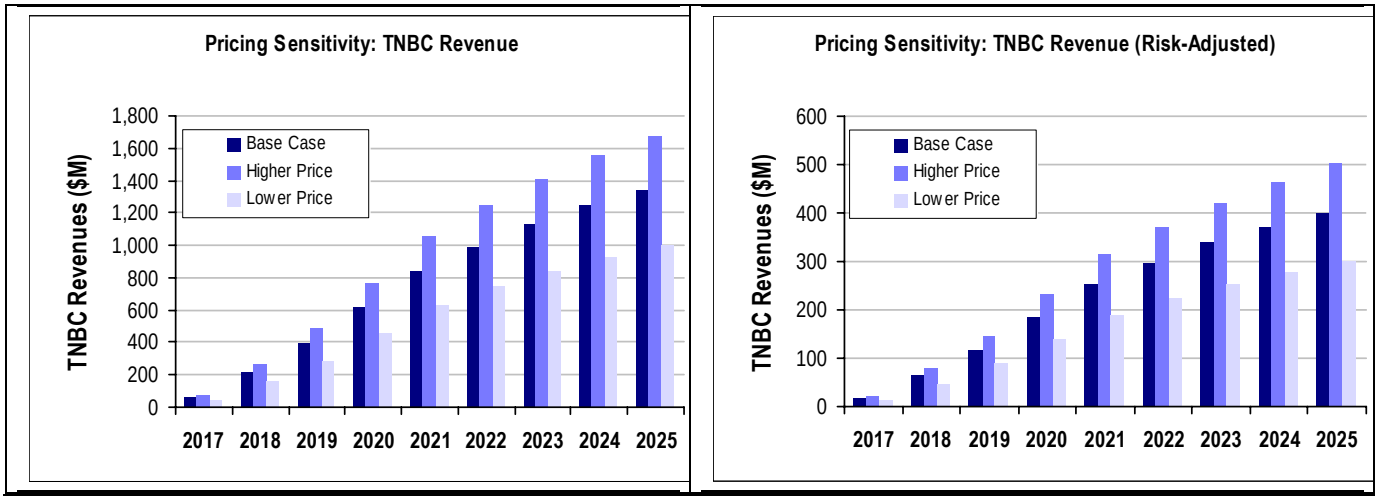
We looked to other targeted oncology markets as comps for our pricing assumptions, and our forecasts are based on a median of this range (Table 4). We note considerable sensitivity around potential pricing, and highlight the outsized impact on total revenue of a 25% change to our initial launch price assumption in the US (Chart 1).

Table 4: Targeted Oncology Pricing Comps

Drug	Manufacturer	Indication(s)	Assumed Annual Price
Folotyn (pralatrexate)	Allos Therapeutics	Relapsed / Refractory Peripheral T-cell Lymphoma (r/r PTCL)	$88,594
Inlyta (axitinib)	Pfizer	Renal Cell Carcinoma (RCC)	$105,840
Afinitor (everolimus)	Novartis	RCC	$89,841
Adcetris (bretuximab vedotin)	Seattle Genetics	Relapsed / Refractory Hodgkin Lymphoma, Anaplastic Large Cell Lymphoma	$81,000
Yervoy (ipilimumab)	Bristol-Myers Squibb	Melanoma	$120,000
Avastin (bevacizumab)	Genentech / Roche	mCRC, Non-Small Cell Lung Cancer (NSCLC), Glioblastoma Multiforme (GBM), RCC, mBC	$76,388
Revlimid (lenolidomide)	Celgene	Multiple Myeloma	$95,312
Jakafi (ruxolitinib)	Incyte	Myelofibrosis	$84,000
Provenge (sipuleucel-T)	Dendreon	Prostate Cancer	$93,000
Mean			**$92,664**
Median			**$89,841**

Source: Company reports and UBS research

Chart 1: UBS VSTM Valuation: Sensitivity to pricing changes (+/- 25% changes)



Source: Company reports and UBS research

Neoadjuvant setting could expand target population, but shorten duration

85% of newly diagnosed breast cancers patients are candidates for neoadjuvant therapy

While we expect the company to initially focus on the treatment refractory TNBC population, we believe a sound rationale exists for an anti-CSC agent to be used in the neoadjuvant setting as well. Given the role of CSCs in tumor initiation, the neoadjuvant setting would seemingly provide significant benefit to patients. Further, based on recent commentary from FDA leadership[11], the neoadjuvant setting could provide a fast to market strategy, as it may be one of the first areas where the FDA will formally accept surrogate biomarker data as an approvable endpoint (with a larger, confirmatory trial in the post-marketing setting). While the neoadjuvant TNBC setting is larger than the TNBC claudin low population (~27k vs. ~7k), the duration of therapy is markedly less, resulting in lower revenue per patient, but potentially a much larger market opportunity. We do not formally include sales from the neoadjuvant setting in our VSTM model as guidance from the FDA are still undefined, but believe it could add additional upside to our estimates.

Breast cancer expert thinks the Verastem approach will likely work in the neoadjuvant setting

We spoke with a leading breast cancer drug development expert, who has been the principal investigator on many trials over the years, and he believes targeting CSCs in the neoadjuvant setting should work, provided the right patient population is chosen and the right endpoints are used. The goal is to treat patients (who have large tumors) with upfront chemotherapy to shrink the tumor prior to surgical removal of the tumor. About 5-6 years ago, surrogate endpoints correlated with clinical benefit were being identified. For example, a pathologically disease-free state at the time of surgery is correlated with

[11] Esserman, et al., JAMA 2011; 306: 2608-2609.

progression-free survival (PFS) in Her2-positive breast cancer[12] (but not in estrogen receptor positive breast cancer patients).

The expert we spoke with does not believe pCR is registerable in the neoadjuvant setting, but provides a strong signal for clinical benefit (PFS)

Patients who are candidates for neoadjuvant therapy are newly diagnosed, stage II-III, with a tumor >2cm and operable (localized disease, potentially with minor metastasis) for whom there is curative intent via surgery. Our expert believes 85% of newly diagnosed breast cancer patients fit this description.

To further refine this population, biopsies can identify TNBC patients, the initial target population for Verastem compounds. Using pathologic complete response (pCR; more detail in the *Phase II Design: Proof-of-Concept and accelerated approval possible* section on page 25), a surrogate endpoint under review by the FDA as well as recently described in the NeoALTTO study, Verastem can gain early insight into the potential clinical benefit of their CSC-targeting compounds in the neoadjuvant setting. An improvement of just 15-20% over current pCR rates seen with taxanes (25-30% in TNBC) would be considered impressive. However, robust chemotherapy (taxanes + anthrocycline) lead to a pCR of 50%, but we note the tolerability and safety issues with anthrocyclines, leaving room for a better tolerated regimen that gives the same efficacy results.

In an analysis of clinical databases of breast cancer patients stages I-III, 22% of TNBC patients achieved a pCR vs. 11% non-TNBC patients[13]. If pCR was achieved, patients with TNBC and non-TNBC had similar survival. In another study done in Stage II-III TNBC patients, 6/18 patients (21%) achieved a pCR and 8 additional patients had significant pathologic partial responses with neoadjuvant single-agent cisplatin treatment[14]. pCR rates in TNBC patients range from 12% for single-agent taxane regimens to 27%-77% in multi-agent neoadjuvant trials[15,16,17], where the wide range in outcomes reflects differing treatment paradigms, patient selection, and sample sizes. Further, at the 2009 San Antonio Breast Cancer Symposium, a single center study of 46 triple negative breast cancer patients reported ~28% pCR rates when treated with anthrcyclines-based neoadjuvant therapy (87%), taxanes (9%), or other therapies (4%)[18]. The 77% pCR rate reported from the German group (Kern et al) at ASCO Breast in 2010 was from a small (13 patient trial), but represents a high efficacy bar in our view. The trial, which evaluated the efficacy of platinum and taxane-based combination therapy looks promising, but additional data from a larger study are needed to confirm.

[12] Gianni et al., The Lancet 2010; 375: 377-84.

[13] Liedtke et al., J Clin Onc 2008; 26: 1275-81

[14] Silver et al., J Clin Oncol 2010; 28: 1145-53.

[15] Liedtke et al., J Clin Onc 2008; 26: 1275-81

[16] Carey et al., Clin Cancer Res 2007; 13: 2329-34.

[17] Kern et al. 2010 ASCO Breast Cancer Symposium. Abstract nr 279

[18] Guiu et al. Cancer Research 2009; 69(24 Suppl): Abstract nr 1103

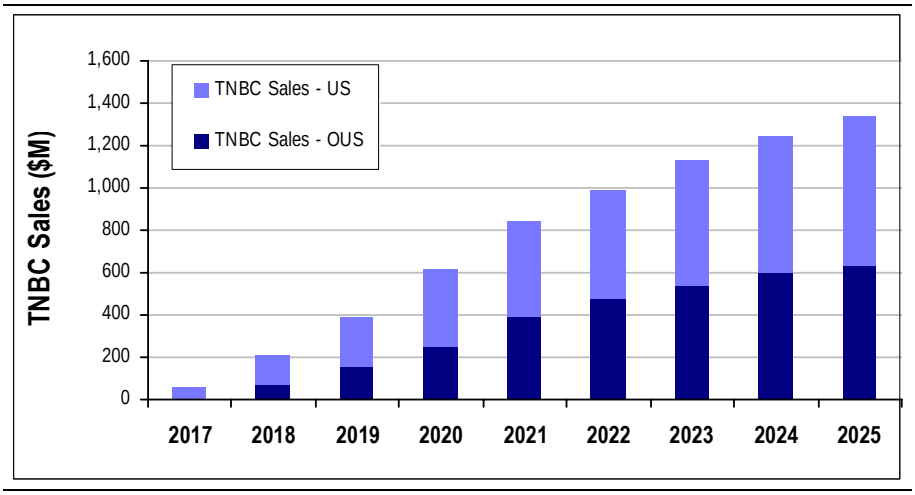
The Verastem approach should also have benefit in the metastatic setting, according to our expert, but more likely in earlier lines of therapy. Regarding approvable endpoints, robust PFS should be enough to get the drug over the goal post; our expert did not think OS was necessary for approval.

According to the expert we spoke with, a robust PFS benefit in the frontline setting is enough for regulatory approval

TNBC a sizeable opportunity; Extent of risk adjustment key to valuing VSTM

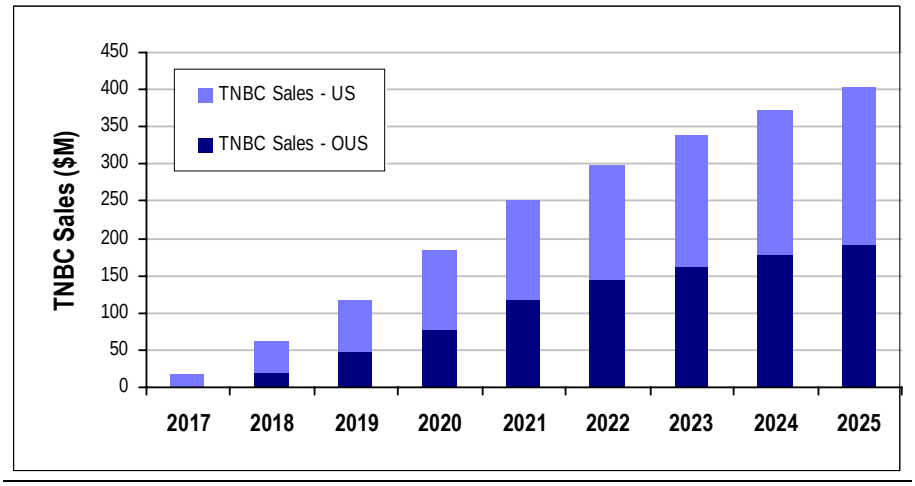
We forecast US sales in TNBC could reach $500M by 2022, assuming a modest 55% penetration into the ~8.2k addressable patient pool and ~$113k orphan drug pricing. We note however that on a risk-adjusted basis, sales are considerably lower, reflecting what we view as an appropriate 30% adjustment to reflect the early stage of development. We model $155M in risk-adjusted 2022 US sales, growing from $17.8M the first year of approval (2017e). While the US market targeting TNBC is sufficiently small such that Verastem can likely support a sales force, we believe the varying geographies and payors make a European commercialization plan more difficult. Therefore, our Verastem model assumes the company will establish an OUS partnership following the release of proof-of-concept phase II data in 2015/2016, further easing additional financing risk as the likely up-front payment could be used to help supplement additional development costs. Chart 2 (non-risk-adjusted) and Chart 3 (risk-adjusted) below outline our long-term sales expectations in the US, as well as royalty revenues for areas outside of the United States.

Chart 2: 2017-2025 TNBC Sales Estimates



Source: Company reports, UBS research

Chart 3: 2017-2025 TNBC Sales Estimates (Risk-Adjusted)



Source: Company reports, UBS research

Current valuation implies 80-90% risk adjustment

With shares trading at an implied enterprise value of ~$130M (~$247M market cap), the current valuation implies a heavily risk-adjusted technology outlook on the Verastem TNBC program (~10-12% under our valuation framework). While a 10-12% probability of success (POS; i.e., FDA approval) is generally in-line with similarly-staged oncology assets [19], we believe that the underlying technology, along with a sound lower-risk development plan (targeting a CSC-enriched disease population) as well as companion diagnostics, necessitate a higher POS than the market imply. Our $20 price target implies a ~30% probability of success (on both SOTP and by DCF), and reflects in our view a favorable outcome in the early clinical studies.

Table 5: POS Comparison: Current Valuation vs. UBS Price Target

	Current (as of 3/6/12)	UBSe 12-24mos PT
Price	$11.10	$20.00
UBSe 2020 Sales (Un-Risk-Adj.)	$826m	
Implied Prob. Of Success	12%	30%

Source: Company reports and UBS research

We assign a smaller risk adjustment (70%)

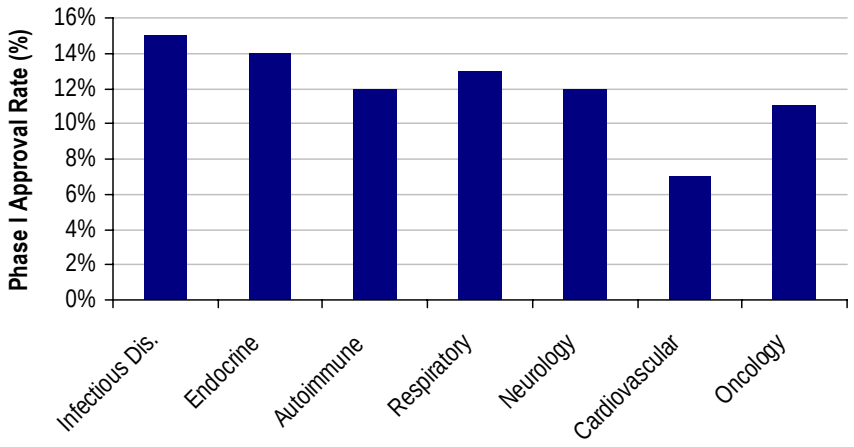
(1) **Available data show probability of success for phase I assets range between 8% - 19%**[8,20]. When establishing a point of comparison for POS for Verastem, we note the available literature is quite varied. While some

[19] Tufts Center for the Study of Drug Development. Sept/Oct 2007 Impact Report.

[20] Hay et al BIO / BioMedTracker Clinical Trial Success Rates Study. BIO CEO & Investor Conference Feb 2011.

sources place the approval rate for phase I oncology compounds as low as 8%, we note other data indicate that roughly 19% of phase I drugs are approved. Given that some cancers have proved quite difficult from a drug development standopoint, we are inclined to reference the BIO data which show that roughly 11% of phase I oncology drugs reach approval. These data generally correspond to the implied risk-weighting on VSTM shares (10-12% per our valuation framework)

Chart 4: Historic data indicate an 11% discount rate is a good comp for phl oncology



Source: UBS research: adapted from Hay et al BIO CEO & Investor Conference Feb 2011

(2) **Why VSTM is different: we think a higher POS is appropriate**. While we include a detailed breakdown of the Verastem technology platform and key issues starting on page 26, in brief we believe the key factors central to the story (*listed below*) warrant a lower risk-weighting, and reflect a higher probability of technical success of the TNBC development program.

- **TNBC is a targeted indication**. The lead development program for the CSC platform is in a tumor type that is highly enriched for cancer stem cells. Given the selective preclinical activity in CSCs compared to normal cancer tissue, we believe the CSC-targeted approach in the TNBC program should show increased activity in this population.
- **Companion diagnostic/biomarker analysis**. We note Verastem is developing a companion diagnostic in parallel with the therapeutics platform, to further guide patient selection for those who would have the best response to therapy. If successful, the diagnostic could help patient selection in both the clinical and commercial setting, increasing efficacy in those targeted patients, and lowering risk of clinical failure.
- **Recent approvals show validity in approach**. While the validation of the rational of targeted therapies was firmly established with the success of Genentech/Roche's HER2-targeting Herceptin, several recent approvals and clinical trials successes (Plexxicon's BRAF-targeting Zelboraf, Roche's Pertuzumab, T-DM1, etc.) continue to show that identifying and targeting the underlying driver of a tumor can yield significant clinical benefit.

- **Development plan offers several shots on goal**. With three CSC-targeting product candidates in development, even if the clinical profile (safety likely the biggest risk) is lacking in one of the candidates, two other compounds are still available. Further the company is utilizing a step-wise clinical development plan that leverages early biomarker data before a full trial is initiated.

(3) **Applying a higher POS yields significant upside from current levels**. Our $20PT implies 80+% upside from current levels, and in driven by a more favorable view on the technical outlook of the TNBC program than the market currently implies. While the current ~$130M enterprise value is consistent with similarly-staged oncology companies, we believe the CSC-targeting platform and rational development approach deserves a significant premium relative to its peers. Our new price target assumes a 30% POS, which reflects a positive outcome in the closest clinical catalyst, the expansion cohort in the planned phase Ib trial

The Verastem management team has a proven track record in creating value for shareholders and the scientific advisory board is comprised of the top leaders in the cancer stem cell field and EMT biology. We view the phase Ib data (late 2013/early 2014) in triple negative breast cancer as the key near-term value-creating event, with phase II data potentially providing proof-of-concept as early as 2015/2016.

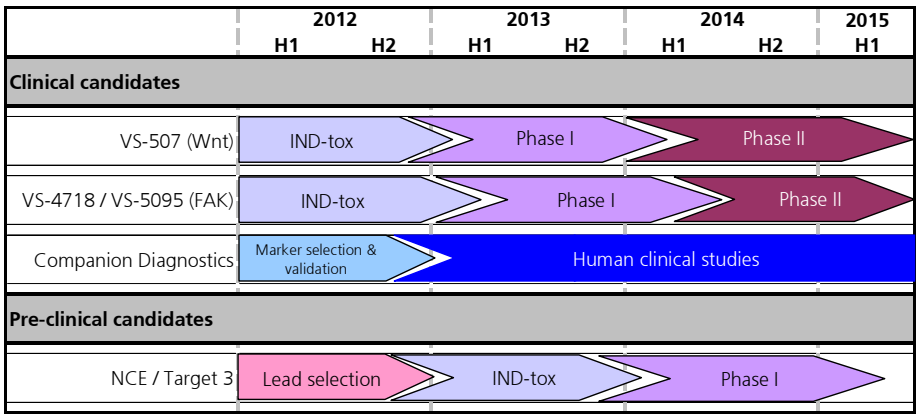
What are the catalysts? A look at the clinical development plan

We believe the clinical development path Verastem plans to undertake is sound, and appears lower-risk relative to other early-stage oncology programs. Specifically, by collecting biomarker data and gene signatures at all clinical stages starting with the phase I trial expected to start in early-2013, the company can screen and evaluate clinical response from patients and potentially enrich the study for those who are most likely to respond to therapy. Verastem has developed and continues to improve on a proprietary EMT signature for patient stratification and clinical development. In particular, mammosphere-specific gene expression was lost upon treatment with lead product candidate VS-507, whereas treatment with paclitaxel did not have an effect on this expression.

Tissue biopsies should aid in patient selection and biomarker analysis

While the development plan remains fluid at this point as the company finalizes its strategy both with its highly-regarded advisory board as well as the FDA, we view believe it [1] is lower-risk relative to other early-stage oncology programs, and [2] by incorporating biomarker analysis in the clinical plan, it offers potential for a fast-to-market strategy that could offer upside to our estimates. Of the three preclinical candidates in the pipeline, we expect Wnt pathway inhibitor VS-507 and one of the two FAK inhibitors (VS-4718/VS5095) to enter phase I clinical trials. An important aspect of the early clinical program is the use of biomarker data for each patient. This is aided by the fact that typically biopsies are taken for all breast cancer patients pre- and post-treatment, meaning that the company will have access to actual tissue to further define the patient population.

Figure 14: Verastem Development Plan – 2012 – 2015 Timelines



Source: Company research and UBS research

Valuation and Phase-1b data: A first peek at efficacy

Given the limitations of the phase I/Ib studies, we do not formally expect proof-of-concept of CSC-targeting in TNBC to be established once data are released. We do see the data as a value-creating event however, as safety and biomarker data will give the first signs of whether the clinical hypothesis of the Verastem technology is valid. We view the data as a risk-adjusting event, and believe that as clinical datapoints begin to emerge, investor interest, and market valuation will begin to grow.

[1] Phase I dose ranging safety study in solid tumors

While a small healthy subjects dosing trial is still a possibility (to accelerate the time needed to reach likely therapeutic doses in later studies), we believe the first informative data will come out of the phase I solid tumor trial. The company plans to enroll and dose roughly 40-60 patients with VS-507 and one of the two FAK inhibitors (20-30 patients each) with advanced solid tumors in a dose escalation trial, evaluating safety, tolerability, pK, biomarkers and clinical outcomes. The trial will utilize a standard 3+3 dose escalation trial design, and will initially focus on dosing and safety. Importantly, the trial will help guide the phase Ib expansion trial which will specifically focus on [1] patients who responded in the initial phase, [2] triple negative breast cancer (which is known to be enriched in CSCs), and possible [3] other tumors known to over express FAK (e.g. ovarian, colon, lung, and prostate).

Outside of safety data, we don't expect much in terms of efficacy data in this early trial. We note the patient population will likely be sicker (older patients, metastatic disease, etc.), so read-through on efficacy data (especially after a single dose) will likely be limited. Biomarker data may be more informative, as traditional efficacy endpoints may not show a considerable response, although it is possible that the early study results could give insights into target effect, surrogate markers of response, and ultimately patient selection for the expansion cohort.

[2] Phase Ib study in TNBC, other CSC-, FAK-enriched tumor types

Claudin-low tumors are enriched with cells that have stem cell properties and have features of the epithelial-to-mesenchymal transition (EMT)

Verastem will likely focus the phase Ib expansion trial on triple-negative claudin-low breast cancer patients. While we do not expect the trial to exclude other breast cancer subtypes, given a preference to enroll patients whose tumors are enriched with CSCs, we expect the majority of patients enrolled to be triple-negative claudin-low breast cancer patients. TNBC is characterized by a lack of estrogen receptor (ER), progesterone receptor (PR), and HER2 expression[21] and are thought to be enriched in CSCs as well as specific EMT biomarkers. This approach was focused on because it is a fast track development plan from EMT screening using an upfront diagnostic test. Approximately 12-17% of all breast cancer patients are triple-negative, which carries the burden of poor response to traditional therapy (chemotherapy and radiation) and cannot be treated with endocrine therapy. TNBC patients have a higher chance for disease recurrence than non-TNBC patients through the first 4 years after diagnosis.

We expect an informative phase-1b

The phase-1b trial will be primarily for the purpose of [1] finding appropriate doses in combination with taxol, and [2] correlating response with biomarkers. We do not expect definitive efficacy data to come out of the trial, because the dose-ranging implies suboptimal dosing without a dose-to-progression intent.

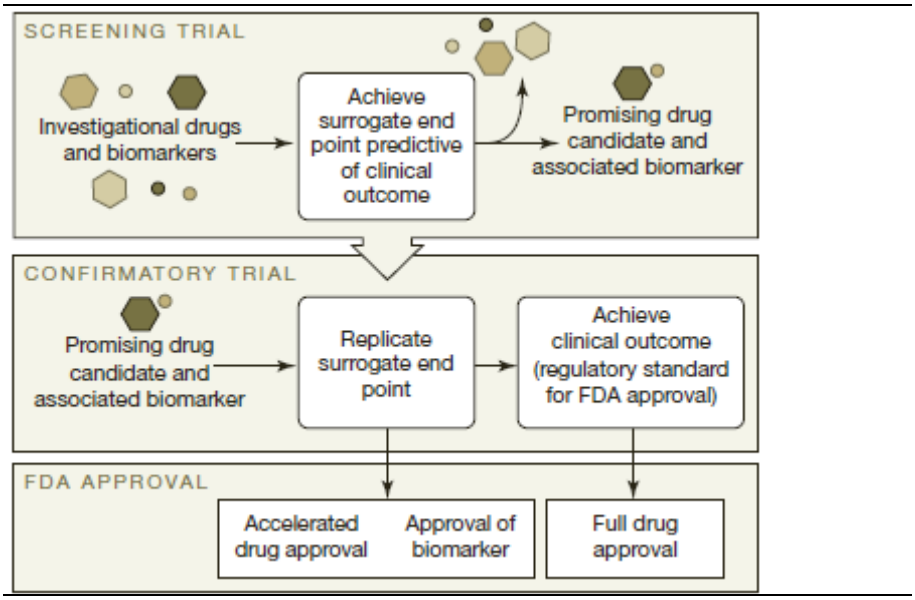
However, we believe that Verastem will look to maximize the safety information possible by leaving patients on drug unless they are progressing. **Therefore, we believe it is possible that the phase-1b could yield objective responses in a highly selected patient population, and thereby create a valuation step up if there are clear signs of efficacy.** Following the phase-1b, the company will select the best candidate to take into phase II combination studies (VS-507 and/or one of the FAK inhibitors).

Phase II Design: Proof-of-Concept and accelerated approval possible

While the phase I studies will be critical to establish the safety profile of the approach as well as detect early signs of efficacy, the phase II program will likely combine the anti-CSC agent (either Wnt or FAK) with standard chemotherapy (likely a taxane). Given the underlying hypothesis on the role of CSCs in tumor biology (Figure 15 below), the rationale for using a standard chemotherapy to de-bulk the tumor so that the anti-CSC agent can target the remaining population is sound in our view. Along those lines, we believe the company will likely pursue one of two phase II trial designs (potentially both). While a standard phase II efficacy trial in metastatic TNBC patients is likely, we believe the neoadjuvant setting could prove attractive as well. We point to a *Journal of American Medical Association* (JAMA) editorial from FDA director Dr. Janet Woodcock which suggests surrogate biomarker data could prove an approvable endpoint and be a fast-to-market strategy[11]. Below is an outline of a potential pathway for accelerated approval using pCR (Figure 15).

[21] Foulkes et al., NEJM 2010; 363:1938-48.

Figure 15: Potential Approval Pathway Using pCR



Source: Esserman, et al. JAMA 2011; 306: 2608-2609

We would expect the phase II program to incorporate both a standard phase II combination study (VS-anti-CSC + taxane vs. taxane in treatment failure patients), as well a more innovative strategy that could enable accelerated approval without the need for a comprehensive pivotal phase III program (prior to commercialization). Specifically in the neoadjuvant setting Verastem may utilize a biomarker-based analysis, similar to the I-SPY2-TRIAL[11], which uses pathologic complete response (pCR) as a predictor of recurrence-free survival (RFS), the current regulatory standard for approval in breast cancer by the FDA. Specifically, drugs that are considered successful when they complete the trial are predicted to have an 85% likelihood of success in a confirmatory randomized neoadjuvant trial of 300 patients with tumor that have the drug's newly identified biomarker signature.

Dr. Woodcock went on to note that while formal guidance from the FDA is expected this year, for drugs that significantly increase the rate of pCR within the I-SPY2 screening program, an expedited drug development program using pCR for accelerated approval could be established. Following the initial phase II study, a broader-scale randomized confirmatory trial could be initiated that would accrue enough participants to follow up on RFS in the post-commercialization setting. Ultimately, while specifics have yet to be announced (we expect FDA guidance to be announced prior to the start of the phase II trial), we believe if a significant result is found for pCR and toxicnities are reasonable, the drug could be approved (generally as part of a regimen) under accelerated approval, with the requirement to follow up women for recurrence for a minimum of 3 years.

Recent phase III data from the NeoALTTO study[22] demonstrated that two anti-HER2 agents given in combination with taxanes gave a higher pCR rate than either single agent (plus taxane) alone. Pathological complete response rate was 51% when Tykerb and Herceptin were added to neoadjuvant chemotherapy. This compares to Tykerb plus chemotherapy (25%) and Herceptin plus chemotherapy (30%).

Table 6: pCR Rates Seen in NeoALTTO (in combination with paclitaxel)

	Tykerb	Herceptin	Tykerb + Herceptin
pCR	25%	30%	51%

Source: Baselga, J et al., Lancet 2012; 379: 633-40

Although the bar of pCR in HER-2+ patients has been set at the ~50% level, we note that TNBC patients have very limited treatment options, so the bar for Verastem's approach is significantly lower, since our expert believes conventional approaches alone have shown only a ~25-30% pCR.

Phase II combination data could deliver true proof of concept

Although we cautiously will look for signs of efficacy in the phase-1b study, a more robust view on efficacy could emerge from the phase II trial in combination with taxanes. We view these data as a financeable event and likely the biggest value-creating event for the company. If positive, this could establish proof-of-concept on an efficacy basis, and, depending on trial design, could lead to accelerated approval. We have compiled a comparable company analysis for oncology companies across several stages of development, and note the largest step-up in valuation occurs once proof-of-concept has been established (Table 7 below). Of the companies included in our analysis, establishing POC has yielded a >250% return relative to development-stage oncology companies.

Table 7: Comparable Companies Analysis: Valuation Step-Up Biggest on POC

Tier	Median Market Cap ($M)	Step-Up from Prev. Tier	Total Step-Up
Commercial Smid Oncology	2,117	46%	815%
Post-Phase 3	1,449	115%	na
Proof of Concept	674	191%	na
Development-Stage Smid Oncology	231	na	na

Source: UBS research, FactSet

Significant strategic value in CSC targeting

The Verastem approach offers strategic value for potential partners, with a unique drug screening platform and innovative approach to anti-cancer therapy. We note recent transactions from other companies targeting CSCs highlight the

[22] Baselga, et al., Lancet 2012; 379: 633-40.

growing interest in the field. Specifically, Dainippon Sumitomo Pharma announced last week that it was acquiring Boston Biomedical (BBI), a small private clinical-stage biotech company targeting CSCs (specific target/pathway has yet to be announced). The potentially $2.3B deal ($200M upfront, $540M in development milestones, and up to $1.89B in sales milestone payments) was born out of a pre-existing development agreement which was signed in April of 2011 (~1-year after lead compound BBI608 entered clinical studies). While the mechanism or target for BBI have not yet been released, we believe interest in the sector bodes well for Verastem given its thought-leading scientific founders and compelling (and patent-protected) platform technology.

Further, given the potential role of CSCs across several tumor types, we would expect most companies (including those with pre-existing development work in CSCs) to be interested in a potential partnership. Another early-stage CSC-targeting company has also partnered with a large Japanese pharmaceutical company (Prism BioLab partnered its phase I Wnt inhibitor with Eisai in early 2011). Details of the $300M deal were not announced, but we note that at the time of the agreement, no data had been reported (phase Ia/Ib trials currently ongoing).

CSC, EMT? Here's a science backgrounder

Cancer stem cells (CSCs)

The notion of CSCs is not new and has been a topic of both debate and interest in the academic and clinical oncology community since the 1990's. It is hypothesized that CSCs have increased seeding potential and are resistant to conventional (chemotherapy, radiation, etc) therapy. The foundation of this hypothesis is that over time, the CSCs not destroyed by traditional therapy become enriched, comprising a larger total composition of the tumor mass. Given that stem cells are self-renewing, and that this population is being selected for through the eradication of therapy-responsive cells, over time the bulk of the tumor will be made up of CSCs, making treatment much more difficult. Further, it has been demonstrated that CSCs can proliferate and differentiate to form different tumor types when transplanted[23].

The exact mechanism of CSC resistance to therapy remains unclear

The first evidence of CSCs came in 1997, when $CD34^{+}/CD38^{-}$ (progenitor/stem cells) leukemic cells were transplanted into NOD/SCID mice, giving rise to leukemic cells in the recipient animal[24]. Years later, CSCs have been associated with therapeutic resistance in breast[25] and brain[26] cancer. It is possible the reason recurring tumors are more aggressive is because there is a higher proportion of CSCs residing in the tumor, thus conferring therapeutic resistance.

Older stem cells accumulate mutations (genetic and epigenetic) and may down regulate DNA repair pathways, which may confer resistance to chemotherapy-

[23] Casara et al., Journal of Oncology 2008; 12 pages.

[24] Bonnet et al., Nature Medicine 1997; 3: 730-37.

[25] Li et al., Journal of NCI 2008; 100: 672-79.

[26] Bao et al., Nature 2006; 444: 756-760.

induced cell death. Another theory is the chemotherapy-resistant phenotype of CSCs may be sustained by IL-4, which then acts against the cytotoxic effects[27].

In addition, a proportion of CSCs (and stem cells) are quiescent, ie, not cycling. It is during this quiescent state that non-cycling cells avoid the toxic effects of chemotherapy, and are therefore able to reconstitute the tumor[28]. The tumor microenvironment also plays a role, and the hypoxic conditions are thought to lead to a higher expression of stemness markers in cancer cells growing in these conditions[29].

The origin of CSCs, whether they arise from existing stem cells or from acquiring oncogenic properties from terminally differentiated cells, leading to dedifferentiation to a stem cell state, is still poorly understood. Data from the leukemic cells transplanted into NOD/SCID mice suggests CSCs arise from normal stem cells, since CSCs are also $CD34^{+}/CD38^{-24}$. But, differentiated cells can be artificially induced into a pluripotent state[30]. Induced stem cells are known to be tumorgenic, forming teratomoas in immunocompromised mice.

The loss of tumor suppressor function and gain of oncogenic activity lead to dedifferentiation; therefore, CSCs may be borne out of the acquisition of faulty genetics. This is exemplified by the oncogenic fusion protein MLL-AF9, which can transform hematopoietic progenitor cells into leukemic stem cells[31].

The clinical importance of CSCs is still largely unknown, but new evidence suggests the limited durability of tumor responses to anticancer therapies is rooted in resistant CSCs. While the molecular mechanisms underlying CSCs (breast CSCs in particular) have yet to be fully elucidated, the literature suggests that several key pathways are likely involved. Activation of the PI3K/Akt pathway (through PTEN knockdown) can lead to enrichment of mammary stem cells[32]. It is through this process that the canonical Wnt/β -catenin pathway is thought to play a role in breast CSC biology as well (Figure 16 below). Importantly, both pathways have been implicated in breast cancer progression and poor prognosis, making the Wnt pathway a potentially attractive target. In addition to PI3K/Akt, Notch and Hedgehog have also been suggested as playing a central role in CSC generation. We note CSCs often show aberrant signalling in each of these pathways, implying they are central to CSC generation and survival. Further, given the role the pathways play in early development, similarities to CSC are unsurprising.

It is thought the emergence of CSCs is in part a result of the EMT, which we describe in detail below.

[27] Todaro et al., Cancer Res 2006; 66: 1491-99.

[28] Dekaney et al., Am J Physiol Gastrointest Liver Physiol 2009; 297: 461-70.

[29] Heddleston et al., Cell Cycle 2009; 8: 3274-84.

[30] Takahashi and Yamanaka, Cell 2006; 126: 663-76.

[31] Krivtsov et al., Nature 2006; 442: 818-32.

[32] Patel et al., Breast Cancer 2010; 2: 1-11.

EMT biology

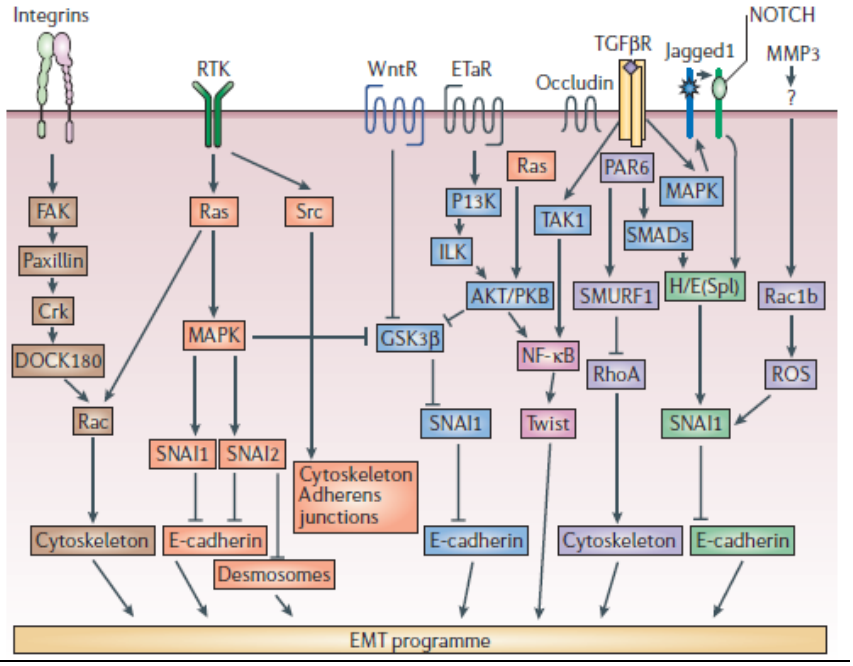
Epithelial-mesenchymal transition (EMT) is when epithelial cells detach from the epithelial sheet and acquire a mesenchymal phenotype[33]. EMT is important in many biological processes, including embryogenesis and wound healing. The EMT process is mediated by different transcription factors, including Twist, Snail and Slug, which then upregulate the expression of other genes including vimentin and downregulate E-cadherin in epithelial cells (mesenchymal cells do not express E-cadherin)[34].

EMT is related to CSC biology through the notion that cancer is a disease of abnormal wound healing, whereby EMT in adults is involved in wound healing and tissue repair

E-cadherin repression is a main target of EMT, since E-cadherin is associated with an epithelial phenotype. There is cross-talk between cadherins and integrins that facilitates the switch to integrin-mediated adhesion during EMT[35]. A switch in cadherin type (from type I to type II) is often observed during EMT, which culminates in the formation of migratory mesenchymal cells[36]. In combination with Wnt-mediated signalling, β-catenin promotes gene expression changes though a transcriptional complex. The canonical EMT program is characterized by alterations in gene expression[37]. A detailed illustration of EMT regulation can be found in Figure 16.

It is also possible that cancer cells may only undergo partial EMT, retaining some epithelial qualities

Figure 16:EMT Regulation



The reversal, MET, has also been reported and may be necessary for metastasis

Source: Thiery and Sleeman, Nature Reviews Molecular Cell Biology 2006

[33] Biddle and I Mackenzie, Cancer Metastasis Rev. 2012: 31

[34] Thiery, Current Opinion in Cell Biology 2003; 15: 740-46.

[35] Thiery and Seelman, Natured Reviews Molecular Cell Biology 2006; 7:131-142.

[36] Chu et al., J. Biol. Chem 2005; 281: 2901-10.

[37] Singh and Settleman, Oncogene 2010; 29:4741-51.

EMT is important to metastasis

Approximately 90% of tumors are epithelial in origin, so it is unlikely that they could metastasize given they are largely immobile. In tumors, EMT is associated with motility, invasiveness and self-renewal properties. One proposed idea is that maybe all tumor cells have the ability to undergo EMT, but only CSCs can undergo EMT and subsequently grow and repopulate in distant sites[53].

Metastatic cancer cells, which have undergone EMT, exhibit a CSC-like phenotype. Specifically, disseminated breast cancer cells that have migrated to pleural effusions, are enriched for a $CD44^{high}/CD24^{low}$ CSC-like population[38]. $CD133^{+}$ mesenchymal-like cells in pancreatic tumors express CXCR4, a chemokine receptor, which is often found at the invasive front of tumors where they are primed for metastasis[39]. Along those lines, *CD44* is a β-catenin/TCF-4 target gene, which illustrates a potential connection between the EMT-associated Wnt pathway and CSC maintenance[40].

TGF-β is associated with metastasis in breast cancer. $CD44^{high}/CD24^{low}$ CSCs highly express a TGF-β pathway quality and transition into a more epithelial-like phenotype after TGF-β inhibition, suggesting TGF-β may be driving breast cancer EMT, thereby promoting CSC maintenance[41].

Breast cancer

During metastasis, tumor cells acquire mesenchymal gene-expression patterns and properties, which allows for establishing a tumor at a second site

EMT appears to play an important role in tumor seeding and metastasis as well as tumor resistance to chemotherapy and adjuvant therapies. $CD44^{high}/CD24^{low}$ mammary tissue cells express EMT markers, which raises the question between normal tissue and stem-likeness. However, this is further complicated by the fact that not all stem cells express an EMT phenotype (ie, skin stem cells only have an epithelial phenotype)[42]. The induction of an EMT in normal or neoplastic mammary epithelial cell populations has been shown to result in the enrichment of cells with stem-like properties[43].

In tumors, CSCs that have undergone an EMT are more invasive because they are able to seed themselves. However, it is yet to be determined whether EMT is necessary for metastasis. Overall, the **EMT gives rise to metastatic and invasive properties, a stem cell-like phenotype with self-renewal properties and resistance to conventional cancer therapies**.

Colorectal cancer

In colorectal cancer (CRC), there are changes in gene expression patterns that are characteristic of EMT. Specifically, claudin-1, a component of the tight-junction, has been found to be upregulated in CRC, which is associated with phenotype changes seen in EMT. Upregulation of claudin-1 also promotes

[38] Al-Hajj et al., PNAS 2003; 100: 3983-88.

[39] Hermann et al., Cell Stem Cell 2007; 1: 313-323.

[40] Wielenga et al., Am J Pathol 1999; 154: 515-523.

[41] Shipitsin et al., Cancer Cell 2007; 11: 259-273

[42] Barrandon et al., PNAS 1987; 84: 2302-06.

[43] Mani et al., Cell 2008; 133: 704-715.

metastasis[44]. CRC cells have also been shown to express mesenchymal markers at the leading edge of the tumor.

Lung cancer

The role of EMT in lung cancer has also been studied and offers yet another target for Verastem's approach. It has been hypothesized that cigarette smoke may play a role in TGF-B-mediated EMT based on increased epithelial cell proliferation. Several regulators of EMT have been linked to cigarette smoke[45].

OSI demonstrated that lung cancer patients who expressed EMT epithelial biomarkers responded better to erlotinib + chemotherapy vs. those who only received chemotherapy[46]. It is thought that during EMT, mesenchymal cells appear to have acquired abnormal EGFR-independent survival signals, thus evading apoptosis, and are also able to migrate. This seems to be the case during EMT for non-small cell lung cancer, colorectal and pancreatic carcinoma.

Like anything in science; there are detractors

CSC controversy

While the concept of CSCs appears to be a promising target for cancer therapy, there is controversy around the CSC model, largely rooted in two key areas: [1] what type of cells CSCs can give rise to and [2] whether CSC precursors are in fact stem cells[47]. It is poorly understood whether CSCs can differentiate and become different cell types. There does not appear to be a clear way to classify CSCs either. For instance, CSCs maybe be a function of cell type of origin, stromal microenvironment, acquired mutations and stage of malignant progression[48]. Also, in some tumors, the proportion of CSCs may be equal to that of non-CSCs[49].

Another factor that complicates matters is that of the tumor environment. It is thought that the host biology impacts cancer cell engraftment, and thereby various cancer models and different animal models are directly comparable. Therefore, the number/proposition of CSCs should be stated on a relative basis, not absolute, since the tumor microenvironment and overall health of the host may likely impact CSC representation[47].

Further complicating matters is the potential intercovertability of CSCs to non-CSCs, and the rate at which this happens. However, it has been shown that this flux likely happens through normal cell cycle dynamics, ie, is detectable, and that CSCs are capable of sustaining themselves indefinitely[50]. However, if non-CSCs can give rise to CSCs, this would confound attempts to target CSCs to eradicate the tumor mass, since non-CSCs could repopulate the tumor and confer therapeutic resistance.

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[44] Dhawan et al., J Clin Invest 2005; 115: 1765-1776.

[45] Dasari et al., Am J Respiratory Cell and Molecular Biology 2006; 35:3-9.

[46] TRIBUTE study

[47] Gupta et al., Nature Medicine 2009; 15: 1010-1012.

[48] Quintana et al., Nature 2008; 456: 593-98.

[49] Honeth et al., Breast Cancer Research 2008; 10: R53.

[50] Clarkson and Strife Leuk. Lymphoma 1997; 11: 101-107.

The molecular mechanisms underlying the generation of CSCs point to different signalling pathways that are involved in both stem cells and cancer. Specifically, the PI3K/Akt and Wnt/β-catenin pathways are involved in breast cancer progression and associated with poor progression. Notch signalling helps control cell survival and division, and can lead to self-renewal of mammary stem cells[51]. Moreover, $CD44^{high}/CD24^{low}$ cells have dysregulated Hedgehog signalling[52]. All of these pathways are associated in some degree with breast CSC generation, so targeted therapy may be inherently challenging. Given the suggested role of each pathway in breast CSCs, it is possible that targeting only one of the three pathways may not be fully effective, as inhibiting one (Wnt for example) could lead to over-expression of the others to maintain similar biological activity. We note similar examples are quite common in anti-cancer therapy, although we note that data so far show that the Verastem compounds are quite effective in killing CSCs, and so-far do not suggest an over-compensation from other mechanisms.

EMT controversy

A main source of controversy around the EMT theory is that of the MET, or mesenchymal to epithelial transition, which suggests EMT is transient and reversible. This thinking may help explain why metastasized tumors (carcinomas) retain an epithelial phenotype. Another source of debate is that EMT has only been observed *in vitro* and *in vivo* in animal (transgenic) models, but yet to be confirmed in humans[53].

Four main arguments sceptics make against EMT are: [1] pathologists haven't seen EMT in human tumor samples; [2] there is no convincing evidence of EMT in live animal models with cancer; [3] EMT studies are not specific for mesenchymal cells; and [4] markers are unreliable because tumors are genetically unstable

It has also been asserted that the majority of pathologists are skeptical of the EMT theory based on [1] lack of EMT evidence in tumors and [2] that EMT is an artifact of *in vitro* culture conditions[54]. However, the latter can be refuted on the basis that EMT requires an intricate combination of several (transcription) factors, not just one. Another cause for refute among pathologists is that of the epithelial nature of tumor metastasis, not the mesenchymal properties that have been seen *in vitro*. This phenomenon highlights the possible MET needed for full metastases, which has yet to be characterized in humans. However, some EMT proponents note that it is hard to distinguish cancer cells that have not yet undergone EMT from mesenchymal cells in surrounding connective tissue, making it hard for pathologists to distinguish the two.

It has yet to be reported that EMT occurs through specific stimulation and pathways, not just random chance. Also, the frequency of EMT occurance needs to be determined, and that it is a "planned" transition in tumorgenesis. Going further, it has been suggested that the acquisition of mesenchymal markers and phenotype in progressing tumors is the result of genomic instability, and that EMT does not occur in tumors[55].

[51] Dontu et al., Breast Cancer Res 2004; 6: R605-15.

[52] Lui et al., Cancer Res 2006; 12: 6063-71.

[53] Garber, Journal National Cancer Institute 2008; 100:232-34.

[54] Bastid, Cancer Metastasis Rev 2012; pages 1-7.

[55] Tarin et al., Cancer Research 2005; 65:5996-6000.

Regarding biomarkers, there is no specific marker for a mesenchymal cells that is derived from a cancer cell vs. an innate mesenchymal cell[53]. However, as a part of their ongoing research to identify biomarkers associated with CSCs, Verastem is looking to characterize specific markers associated with mesenchymal cells that have undergone an EMT. They are currently doing work on a panel of genetic and protein-based markers in animal models, which will then be tested in humans for validation.

Connecting the dots: Why the Verastem approach makes sense

As outlined above, discoveries made by the scientific co-founders of Verastem were leveraged to identify its CSC-specific lead product candidate VS-507. Here we outline the rationale on why we believe the Verastem approach makes sense, and why preclinical VS-507 activity should translate into successful human data.

Identifying CSC-targeted therapies

In preclinical assays, breast cancer cells forced into EMT had an increased resistance to chemotherapeutic drugs paclitaxel and doxorubicin[6]. Based on these results, cell populations induced into an EMT were not distinguishable from CSC-enriched populations (identified using cell-surface markers). In additional experiments, it was demonstrated that a non-tumorigenic epithelial cell line treated with paclitaxel had similar treatment responses in the same cell line that had been neoplastically transformed. Therefore, agents that selectively target non-transformed calls may also be toxic to CSCs. This observation was the basis for identifying agents that selectively target mesenchemically transdifferentiated breast epithelial cells.

VS-507 appears to have a higher selective toxicity for CD44^{high}/CD24^{low} CSC-enriched populations

Verastem screened over 16,000 compounds, 32 of which exhibited selective toxicity, and 8 of which were chosen for further testing[6]. Four of these eight were shown to have selective inhibition in a human breast epithelial cell line (HMLE^{shEcad}) that had undergone EMT. One compound in particular, salinomycin (VS-507), was shown to have a higher level of selectivity to the transformed cell line as compared to the control cell line, and was therefore chosen for further investigation.

Competition: Not the only ones in the game

Competition in CSC- and EMT-targeted therapies

Verastem is not the only biotechnology company looking to target CSCs and the EMT. OSI Pharmaceuticals is partnered with Aveo Pharmaceuticals to develop new therapies to block EMT initiation or destroy CSCs that have undergone EMT. Like Verastem, their approach aims to develop proprietary datasets to identify biomarkers that support OSI's therapeutic pipeline. Under the collaboration, cancer targets are being identified using Aveo's translation research platform HRP (Human Response Platform). HRP is predicated on using genetically-defined mouse models of human cancers in which each model contains signature genetic mutations found in human disease. We summarize the CSC competitive landscape in Table 8 below.

Table 8: CSC-targeted Compounds in Development

Drug	Company	Pathway	Indication	Phase
LGK974	Novartis	Wnt	Melanoma, breast, lobular carcinomas	I
PRI-724	Prism Lab Corp	Wnt	Advanced solid tumors	I
PF-04449913	Pfizer	HH	Solid tumors, CML, other hematopoietic malignancies	
LEQ506	Novartis	HH	Advanced solid tumors, recurrent/refractory medulloblastoma	I
IPI-926	Infinity	HH	Metastatic pancreatic cancer, recurrent head and neck cancer	I
GDC-0449	Roche Genentech	HH	MM, various indications	I
PF-04554878	Pfizer	FAK	Various solid tumors	I
GSK2256098	GlaxoSmithKline	FAK	Various solid tumors	I
OMP-21M18	OncoMed	DLL4	Pancreatic cancer	I
BBI608	Boston Biomedical	-	CRC	III
BBI503	Boston Biomedical	-	Various solid tumors	I

Source: Adapted from Dela Cruz, R et al., Am J Blood Res 2011; 1: 135-145; clinicaltrials.gov, UBS research

There are several players looking to target CSCs through inhibiting various pathways or targeted molecules thought to be involved in the self-renewal process. The most advanced is Boston Biomedical's **BBI608**, which is set to begin phase II trials in colorectal cancer (CRC). Phase I data (presented in 2010) showed 6/9 evaluable patients achieved stable disease (SD) for at least 8 weeks at the 400mg/day dose. Extended SD was seen in 2 CRC patients (54+ and 20+ weeks) and one with head and neck cancer (17 weeks)[56]. The most common AEs were grade 1-2 diarrhea and nausea.

BBI503 is in phase Ib trials for multiple solid tumors. While the target has not been disclosed for either compound, they are said to inhibit "cancer stemness", and were identified using BBI's proprietary drug discovery platform, focused on cancer stemness and CSCs.

LGK974 (Novartis) is currently in phase 1 development in patients with melanoma and lobular breast cancer. LGK974 is a selective, orally bioavailable Porcupine inhibitor of the Wnt pathway. The phase I dose-escalation study is enrolling 50 patients for whom no effective standard treatment is available. Data is possible YE2013.

Prism BioLab is also developing a Wnt-pathway targeting agent that is currently in phase Ia/Ib trials. The drug, **PRI-724**, is partnered with Eisai Pharmaceuticals, and is an inhibitor for CBP/β-catenin complex formation, which modulates the B-catenin dependent pathway of Wnt-signaling. Similar to the rationale for Wnt-targeting for VS-507, activation of the Wnt pathway is thought to play a central role in cancer stem cell biology, primarily around the maintenance and homeostasis of normal tissues. The literature show Wnt signalling is required for development of mammary tissue, and dysregulation of the pathway has been implicated in breast and colon cancers. Given the similarities between normal adult stem cells and cancer stem cells suggest that the same signaling pathways (including Wnt, Hedgehog, and Notch) are implicated in both, and are likely

[56] Langlebon et al., ASCO 2010; Abstract LB-171.

involved in CSC regulation[57]. Furthermore, lobular breast cancer commonly shows reduced expression of E-cadherin that can lead to release of membrane-bound c-catenin into the cytoplasm and potentially increase Wnt signalling in the presence of Wnt ligand. The drug is currently in an ongoing trial evaluating PRI-724 in subjects with advanced solid tumors. The 64-patient study was initiated in February 2011, with data expected in early 2013. The study will first evaluate the safety and determine the maximum tolerated dose, and provide biomarker data to inform the second part of the study which will enrich for colorectal and pancreatic cancer.

There are several FAK inhibitors in development as well

While Verastem is not the first to take a FAK inhibitor into the clinic, they believe their clinical candidates (VS-4718 and VS-5095) are more potent

Both Pfizer and GlaxoSmithKline have FAK inhibitors in clinical development. At ASCO last year, Pfizer presented phase I data for **PF-04554878**, a potent inhibitor of both FAK and Pyk2. Dose-ranging data in patients with solid tumors (CRC (15), pancreatic (4), ovarian (3), bile duct (3), breast (2) and other (9)) found that 425mg BID is the dose that will be studied in phase II. Stable disease (SD) was seen in 33% of patients after 2 cycles, but only 6% of patients had SD for ≥ 9 cycles. Dose-limiting toxicity (DLT) was found to be Grade 3 headache and unconjugated hyperbilirubinemia, all reversible upon stopping drug. The most common adverse events (AE) were nausea, vomiting and unconjugated hyperbilirubinemia. While some early efficacy data has been reported, what would likely be of more interest is changes in biomarkers associated with CSCs.

GSK is currently recruiting an open-label dose escalation study of their FAK inhibitor, **GSK2256098**, in patients with solid tumors.

[57] Takahashi-Yanaga, et al., Cancer Res 2010; 16: 3153-62.

Appendix: Verastem Fast Facts

Company description

Verastem is an early-stage biotechnology company focused on discovering and developing novel small molecule drugs targeting cancer stem cells, accompanied with a companion diagnostic. The EMT platform, used to identify CSC-targeting anti-cancer molecules is licensed from the Whitehead Institute and the Broad Institute. Using this technology, Verastem has created a library of CSCs to screen against potential CSC-targeted agents to treat cancers. VS-507 will be the first compound to enter phase I clinical trials, and was discovered using this proprietary screening method. VS-507 targets the Wnt pathway, which has been implicated in the generation of CSCs.

In November, 2011, Verastem acquired Poniard's FAK program. FAK has been shown to be overexpressed in several solid tumors, including breast, pancreatic and brain cancer, and targets CSCs. Particularly, VS-4718 and VS-5095 and being studied in preclinical assays and one will be examined in phase I trials in parallel with VS-507.

Verastem is headquartered in Cambridge, Massachusetts.

Executive management with a track record of success

Verastem is headed up by co-founder, Chairman and Chief Executive Officer **Christoph Westphal, MD, PhD**, who has significant executive experience in the biotechnology arena. Most recently, he was a co-founder and CEO of Sirtris Pharmaceuticals (SIRT), which was acquired by GlaxoSmithKline in 2008 at a significant premium to the IPO price. He also co-founded and was CEO of two high-profile publicly-traded companies: Alnylam Pharmaceuticals (ALNY) and Momenta Pharmaceuticals (MNTA). Dr. Westphal also co-founded Alnara Pharmaceuticals, which was acquired by Eli Lilly in 2010.

Robert Forrester, Chief Operating Officer, has several years of management experience across a breadth of roles, including Chief Executive Officer, Chief Operating Officer and Chief Financial Officer. His experience includes management roles at CombinatoRx Pharmaceuticals (now Zalicus Pharmaceuticals), Forma Pharmaceuticals and Coley Pharmaceuticals, which was acquired by Pfizer in 2007.

Jonathan Pachter, PhD, is Vice President and Head of Research and Development at Verastem. Before joining Verastem, Dr. Pachter was the Senior Director of Cancer Biology at OSI Pharmaceuticals, which was acquired by Astellas Pharma Inc. in 2010. He has over 20 years of experience in small molecule drug development in the field of oncology.

World class Scientific Advisory Board

Verastem's Scientific Advisory Board (SAB) is comprised of a who's who in the field of CSCs and EMT biology. Verastem co-founder **Robert Weinberg, PhD**, is a founding member of the Whitehead Institute and Professor of Biology at MIT, and is a pioneer in the field of cancer genetics. He discovered the first tumor suppressor gene, the first oncogene and a protein known to bind to HER2,

Dr's Weinberg, Lander and Gupta are co-founders of Verastem

which is implicated in the formation of CSCs. Notably, Dr. Weinberg gave the keynote address at the world's largest cancer meeting, ASCO, in 2011 on EMT biology.

Piyush Gupta, PhD, is a Verastem co-founder and a member of the Whitehead Institute and an Assistant Professor of Biology at MIT. Together with Dr. Lander and Dr. Weinberg, Dr. Gupta co-developed proprietary EMT screening assays to identify drugs targeting CSCs and a genetic expression signature, useful in identifying biomarkers in CSCs treated with CSC-targeting drugs.

Eric Lander, PhD, is a Verastem co-founder, and a founder of the Broad Institute and Professor of Biology at MIT and Systems Biology at Harvard Medical School. He is well-known for playing an integral role in the Human Genome Project and as an advisor at the highest levels of government.

Rounding out the SAB are the following:

- **Julian Adams, PhD**, former Senior vice President of Development and Millennium Pharmaceuticals and a developer of Velcade
- **Jose Baselga, MD, PhD**, Chief of Hematology and Oncology at Massachusetts General Hospital and Professor of Medicine at Harvard
- **George Dailey, MD, PhD**, Professor of Hematology and Oncology and Director of Stem Cell Transplantation Program at Children's Hospital and Professor of Biological Chemistry and Molecular Pharmacology at Harvard Medical School
- **Peter Elliott, PhD**, former Senior Vice President and Head of Research and Development at Sirtris, co-developer of Velcade at Millennium
- **Daniel Haber, MD, PhD**, Director of Massachusetts General Hospital Cancer Center and Professor of Medicine at Harvard Medical School
- **Joseph Schlessinger, PhD**, Chairman and Professor of Pharmacology at Yale School of Medicine
- **Phillip Sharp, PhD**, recipient of the 1993 Nobel Prize in Medicine
- **Roger Tung, PhD**, President and Chief Executive Officer of Concert Pharmaceuticals and former Vice President of Drug Discovery at Vertex, and co-inventor of Lexiva and Agenerase
- **Christopher Walsh, PhD**, Hamilton Kuhn Professor in the Department of Biological Chemistry and Molecular Pharmacology at Harvard Meical School
- **Eric Weiner, MD**, Director of the Breast oncology Center at the Dana Farber Cancer Institute and Professor of Medicine at Harvard Medical School

Discounted Cash Flow Analysis

Figure 17: VSTM DCF Valuation

	2011	2012E	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E
Total Revenues	-	-	-	-	15,000	15,000	32,835	82,288	95,592	141,899	183,785	211,084	238,125	259,393	280,093	302,131	325,586
growth	*na*	*na*	*na*	*na*	*na*	*0%*	*119%*	*151%*	*16%*	*48%*	*30%*	*15%*	*13%*	*9%*	*8%*	*8%*	*8%*

	2011	2012E	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E
Net Income	(10,898)	(15,005)	(21,505)	(29,599)	(28,538)	(35,895)	(28,637)	8,493	12,465	47,330	79,249	77,394	92,010	103,632	115,520	132,048	142,076
growth	*na*	38%	43%	38%	-4%	26%	-20%	-130%	47%	280%	67%	-2%	19%	13%	11%	14%	8%

	2011	2012E	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E
Operating Free Cash Flow	(9,956)	(14,882)	(21,080)	(28,860)	48,653	(50,000)	(42,354)	(4,868)	(1,838)	33,221	79,435	77,589	92,216	103,848	115,747	132,286	142,326
growth	*na*	*na*	*na*	*na*	*na*	-203%	-15%	-89%	-62%	-1907%	139%	-2%	19%	13%	11%	14%	8%

Net Present Value Analysis	
Discount Rate	12.5%
Terminal Growth Rate	0.0%
Terminal Value (total)	158,818
Net Enterprise Value	317,509
Net Cash and Equivalents	99,612
Market Value	417,121
Shares Outstanding	21,359
NPV (per-share)	**$20**

Source: UBS estimates

Sum-of-the-Parts Analysis (Discounted Peak Sales Multiple)

Figure 18: VSTM Discounted Multiple on Sales

Product	Risk-Adj. Revenue ($000's)	Peak sales year	Multiple	Discount Rate	NPV ($000s)	NPV (Per Share)
TNBC - US Sales	210,675	2025	6.0	12.5%	273,389	$13
TNBC - Ex-US Royalty	47,770	2025	6.0	12.5%	61,991	$3
Net cash					99,612	$5
Total					434,991	$20
Total shares (000s)						21,359
Per share value ($)						**$20**

Source: UBS estimates

Financials: Income Statement, Balance Sheet, and Statement of Cash Flows

Figure 19: VSTM Income Statement (2010 – 2016e)

(in thousands, except for EPS)	2010	2011	1Q12E	2Q12E	3Q12E	4Q12E	2012E	2013E	2014E	2015E	2016E
Revenues											
Risk-adj TNBC sales - US	-	-	-	-	-	-	-	-	-	-	-
Royalties on risk-adj TNBC OUS sales	-	-	-	-	-	-	-	-	-	-	-
Total TNBC revenues	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Other Revenue (incl. Milestone Payments)	-	-					-	-	-	15,000	15,000
Total revenues	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**15,000**	**15,000**
Operating Expenses											
Cost of Goods Sold	-	-	-	-	-	-	-	-	-	-	-
Research & Development	400	7,883	2,600	2,750	2,850	2,900	11,100	16,428	22,999	34,959	38,455
General & Administrative	384	3,015	890	950	1,000	1,065	3,905	5,077	6,599	8,579	12,440
Total Operating Expenses	**784**	**10,898**	**3,490**	**3,700**	**3,850**	**3,965**	**15,005**	**21,505**	**29,599**	**43,538**	**50,895**
Operating Income	**(784)**	**(10,898)**	**(3,490)**	**(3,700)**	**(3,850)**	**(3,965)**	**(15,005)**	**(21,505)**	**(29,599)**	**(28,538)**	**(35,895)**
Investment Income	-	-	125	125	125	125	498	403	666	1,303	991
Interest Expense	-	-	-	-	-	-	-	-	-	-	-
Pretax Income (Loss)	**(784)**	**(10,898)**	**(3,365)**	**(3,575)**	**(3,725)**	**(3,840)**	**(14,507)**	**(21,101)**	**(28,933)**	**(27,235)**	**(34,903)**
Income tax provision	-	-	-	-	-	-	-	-	-	-	-
Net Income (Loss)	(784)	(10,898)	(3,365)	(3,575)	(3,725)	(3,840)	(14,507)	(21,101)	(28,933)	(27,235)	(34,903)
Reedemable preferred stock accretion	(2)	(22)									
Net Income (Loss) for EPS	**(786)**	**(10,876)**	**(3,365)**	**(3,575)**	**(3,725)**	**(3,840)**	**(14,507)**	**(21,101)**	**(28,933)**	**(27,235)**	**(34,903)**
EPS basic	($0.59)	($1.52)	($0.16)	($0.17)	($0.17)	($0.18)	($0.68)	($0.98)	($1.14)	($1.07)	($1.35)
EPS diluted	**($0.59)**	**($1.52)**	**($0.16)**	**($0.17)**	**($0.17)**	**($0.18)**	**($0.68)**	**($0.98)**	**($1.14)**	**($1.07)**	**($1.35)**
Shares Outstanding (Basic)	1,325	8,277	21,059	21,259	21,459	21,659	21,359	21,573	25,288	25,541	25,797
Shares Outstanding (Diluted)	1,325	8,277	21,059	21,259	21,459	21,659	21,359	21,573	25,288	25,541	25,797

Source: Company reports and UBS research

Figure 20: VSTM Balance Sheet

(in 000's)	2010	2011	2012E	2013E	2014E	2015E	2016E
ASSETS							
Cash and equivalents	3,584	61,824	99,612	80,516	132,967	261,170	199,112
Other Current Assets	12	6	8	12	16	24	28
Total current assets	**3,596**	**61,830**	**99,620**	**80,528**	**132,983**	**261,194**	**199,140**
Property and equipment, net	8	719	1,519	2,319	3,219	4,119	5,119
Other assets	0	132	182	260	359	527	616
Restricted cash	0	86	86	86	86	86	86
Total Assets	**3,604**	**62,767**	**101,407**	**83,193**	**136,647**	**265,926**	**204,961**
LIABILITIES AND STOCKHOLDER'S EQUITY							
Accounts payable	279	1,246	1,716	2,459	3,384	4,978	5,819
Accrued expenses	89	762	1,049	1,504	2,070	3,044	3,559
Deferred rent	0	86	355	355	154	154	0
Deferred revenue	0	0	0	0	0	0	0
Total current liabilities	**368**	**2,094**	**3,120**	**4,317**	**5,608**	**8,176**	**9,378**
Deferred rent	0	1,104	1,018	663	308	154	0
Deffered revenue	0	0	0	0	0	75,000	60,000
Liability for shares subject to repurchase	0	81	81	81	81	81	81
Long-term debt, net	0	0	0	0	0	0	0
Total liabilities	**368**	**3,279**	**4,219**	**5,061**	**5,997**	**83,411**	**69,459**
Total stockholders' equity	**3,236**	**59,488**	**97,188**	**78,132**	**130,650**	**182,515**	**135,503**
Total liabilities and shareholders' equity	**3,604**	**62,767**	**101,407**	**83,193**	**136,647**	**265,926**	**204,961**

Source: Company reports and UBS research

Figure 21: VSTM Statement of Cash Flows

(in 000s)	2010	2011	2012E	2013E	2014E	2015E	2016E
Net income (loss)	(784)	(10,898)	(14,507)	(21,101)	(28,933)	(27,235)	(34,903)
Adjustments used to reconcile operating activities							
Depreciation and Amortization	0	101	200	300	400	500	600
Stock-Based Compensation Expense	52	742	742	742	742	742	742
Common Stock Used In Exchange for License	46	0	0	0	0	0	0
Change in Operating Assets and Liabilities	**356**	**1,595**	**723**	**925**	**1,239**	**77,591**	**(13,705)**
Prepaid expenses and other current assets	(12)	6	2	4	4	8	4
Other Assets	0	(132)	50	79	98	169	89
Accounts Payable	279	967	470	743	925	1,594	841
Deferred Revenue	0	0	0	0	0	75,000	(15,000)
Accrued expenses and deferred rent	89	754	201	99	211	821	360
Net cash used in operating activities	**(330)**	**(6,865)**	**(12,119)**	**(18,210)**	**(25,313)**	**129,189**	**(60,972)**
Cash flows from investing activities							
Purchases of property and equipment	(8)	(754)	(800)	(800)	(900)	(900)	(1,000)
Investing Activities	0	(86)	(86)	(86)	(86)	(86)	(86)
Net cash (used in) provided by investing activities	**(8)**	**(840)**	**(886)**	**(886)**	**(986)**	**(986)**	**(1,086)**
Cash flows from financing activities							
Proceeds from issuance of redeemable conv. pref. stoc	3,921	60,000	0	0	0	0	0
Proceeds from issuances of common stock	1	38	56,700	0	78,750	0	0
Net cash provided by financing activities	**3,922**	**60,038**	**56,700**	**0**	**78,750**	**0**	**0**
Net increase in cash and cash equivalents	**3,584**	**52,333**	**43,695**	**(19,096)**	**52,451**	**128,203**	**(62,058)**
Cash and cash equivalents - Beginning of period	0	3,584	55,917	99,612	80,516	132,967	261,170
Cash and cash equivalents - End of period	3,584	55,917	99,612	80,516	132,967	261,170	199,112

Source: Company reports and UBS research

Verastem

Income statement (US$m)	-	-	-	12/09	12/10	12/11E	% ch	12/12E	% ch	12/13E	% ch
Revenues	-	-	-	-	0	0	-	0	-	0	-
Operating expenses (ex depn)	-	-	-	-	-	-	-	-	-	-	-
EBITDA (UBS)	-	-	-	-	(1)	(11)	1290.1	(15)	37.7	(22)	43.3
Depreciation	-	-	-	-	0	0	-	0	-	0	-
Operating income (EBIT, UBS)	-	-	-	-	(1)	(11)	1290.1	(15)	37.7	(22)	43.3
Other income & associates	-	-	-	-	0	0	-	0	-	0	-
Net interest	-	-	-	-	0	0	-	0	498158.9	0	-19.1
Abnormal items (pre-tax)	-	-	-	-	0	0	-	0	-	0	-
Profit before tax	-	-	-	-	(1)	(11)	1290.0	(15)	33.1	(21)	45.5
Tax	-	-	-	-	0	0	-	0	-	0	-
Profit after tax	-	-	-	-	(1)	(11)	1290.0	(15)	33.1	(21)	45.5
Abnormal items (post-tax)	-	-	-	-	0	0	-	0	-	0	-
Minorities / pref dividends	-	-	-	-	0	0	-	0	-	0	-
Net income (local GAAP)	-	-	-	-	(1)	(11)	1290.0	(15)	33.1	(21)	45.5
Net Income (UBS)	-	-	-	-	(1)	(11)	1290.0	(15)	33.1	(21)	45.5
Tax rate (%)	-	-	-	-	0	0	-	0	-	0	-
Pre-abnormal tax rate (%)	-	-	-	-	0	0	-	0	-	0	-

Per share (US$)	-	-	-	12/09	12/10	12/11E	% ch	12/12E	% ch	12/13E	% ch
EPS (local GAAP)	-	-	-	-	(0.59)	(1.32)	122.5	(0.68)	-48.4	(0.98)	44.0
EPS (UBS)	-	-	-	-	(0.59)	(1.32)	122.5	(0.68)	-48.4	(0.98)	44.0
Net DPS	-	-	-	-	0.00	0.00	-	0.00	-	0.00	-
Cash EPS	-	-	-	-	(0.59)	(1.32)	122.5	(0.68)	-48.4	(0.98)	44.0
BVPS	-	-	-	-	2.44	7.19	194.3	4.55	-36.7	3.62	-20.4

Balance sheet (US$m)	-	-	-	12/09	12/10	12/11E	% ch	12/12E	% ch	12/13E	% ch
Cash and equivalents	-	-	-	-	4	62	1625.0	100	61.1	81	-19.2
Other current assets	-	-	-	-	0	0	-50.0	0	37.7	0	43.3
Total current assets	-	-	-	-	4	62	1619.4	100	61.1	81	-19.2
Net tangible fixed assets	-	-	-	-	0	1	8887.5	2	111.3	2	52.7
Net intangible fixed assets	-	-	-	-	0	0	-	0	-	0	-
Investments / other assets	-	-	-	0	0	0	-	0	22.8	0	29.4
Total assets	-	-	-	-	4	63	1641.6	101	61.6	83	-18.0
Trade payables & other ST liabilities	-	-	-	-	0	2	469.0	3	49.0	4	38.4
Short term debt	-	-	-	-	0	0	-	0	-	0	-
Total current liabilities	-	-	-	-	0	2	469.0	3	49.0	4	38.4
Long term debt	-	-	-	-	0	0	-	0	-	0	-
Other long term liabilities	-	-	-	-	0	1	-	1	-7.3	1	-32.3
Total liabilities	-	-	-	-	0	3	791.1	4	28.7	5	20.0
Equity & minority interests	-	-	-	-	3	59	1738.3	97	63.4	78	-19.6
Total liabilities & equity	-	-	-	-	4	63	1641.6	101	61.6	83	-18.0

Cash flow (US$m)	-	-	-	12/09	12/10	12/11E	% ch	12/12E	% ch	12/13E	% ch
Net income	-	-	-	-	(1)	(11)	1290.0	(15)	33.1	(21)	45.5
Depreciation	-	-	-	-	0	0	-	0	-	0	-
Net change in working capital	-	-	-	-	0	2	348.0	1	-54.7	1	28.0
Other (operating)	-	-	-	-	0	1	657.1	1	0.0	1	0.0
Net cash from operations	-	-	-	-	0	(9)	2494.2	(13)	52.3	(19)	49.0
Capital expenditure	-	-	-	-	0	(1)	9325.0	(1)	6.1	(1)	0.0
Net (acquisitions) / disposals	-	-	-	-	0	0	-	0	-	0	-
Other changes in investments	-	-	-	-	0	0	-	0	-	0	-
Cash from investing activities	-	-	-	-	0	(1)	10400.0	(1)	5.5	(1)	0.0
Increase/(decrease) in debt	-	-	-	-	4	60	-	0	-	0	-
Share issues / (repurchases)	-	-	-	-	0	0	-	57	-	0	-
Dividends paid	-	-	-	-	0	0	-	0	-	0	-
Other cash from financing	-	-	-	-	0	0	-	0	-	0	-
Cash from financing activities	-	-	-	-	4	60	1430.8	57	-5.6	0	-
Cash flow chge in cash & equivalents	-	-	-	-	4	51	-	43	-	(20)	-
FX / non cash items	-	-	-	-	-	8	-	(5)	-	1	-
Bal sheet chge in cash & equivalents	-	-	-	-	-	58	-	38	-	(19)	-
Core EBITDA	-	-	-	-	(1)	(11)	1290.1	(15)	37.7	(22)	43.3
Maintenance capital expenditure	-	-	-	-	0	(1)	-	(1)	6.1	(1)	0.0
Maintenance net working capital	-	-	-	-	0	0	-	0	-	0	-
Operating free cash flow, pre-tax	-	-	-	-	(1)	(12)	1386.2	(16)	35.6	(22)	41.1

Source: Company accounts, UBS estimates. (UBS) valuations are stated before goodwill-related charges and other adjustments for abnormal and economic items at the analysts' judgement. Note: For some companies, the data represents an extract of the full company accounts.

Verastem

12-month rating **Buy**

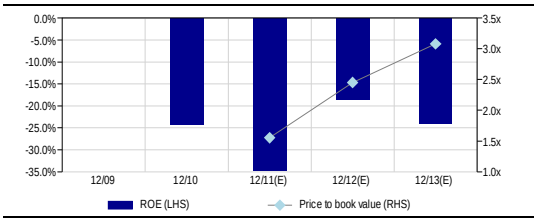
12m price target **US$20.00**

Company profile

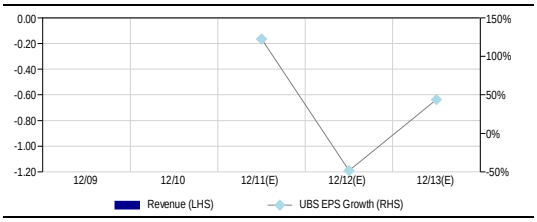
Verastem is a Cambridge, Massachusetts-based early-stage biotechnology company focused on the discovery and development of novel small molecule drugs and companion diagnostics targeting cancer stem cells. The proprietary EMT screening platform, licensed from the Whitehead Institute at MIT, has helped select and identify the company's 3 leading candidates (VS-507, a Wnt inhibitor, and two FAK inhibitors VS-4718 and VS-5095). The company plans to begin human trials over the next 12-15 months for VS-507 and one of the two FAK inhibitors, and could be in phase II trials as early as 2015.

Profitability

ROE v Price to book value



Growth (UBS EPS)



Valuation (x)	5Yr Avg	12/09	12/10	12/11E	12/12E	12/13E
P/E (local GAAP)	-	-	-	NM	NM	NM
P/E (UBS)	-	-	-	NM	NM	NM
P/CEPS	-	-	-	NM	NM	NM
Net dividend yield (%)	-	-	-	0.0	0.0	0.0
P/BV	-	-	-	1.5	2.4	3.1
EV/revenue (core)	-	-	-	-	-	-
EV/EBITDA (core)	-	-	-	-16.6	-8.8	-5.7
EV/EBIT (core)	-	-	-	NM	NM	NM
EV/OpFCF (core)	-	-	-	NM	NM	NM
EV/op. invested capital	-	-	-	NM	NM	NM

Enterprise value (US$m)		12/09	12/10	12/11E	12/12E	12/13E
Average market cap		-	-	213	213	213
+ minority interests		-	0	0	0	0
+ average net debt (cash)		-	(4)	(33)	(81)	(90)
+ pension obligations and other		-	0	0	0	0
- non-core asset value		-	0	0	0	0
Core enterprise value		-	-	181	133	123

Growth (%)	5Yr Avg	12/09	12/10	12/11E	12/12E	12/13E
Revenue	-	-	-	-	-	-
EBITDA (UBS)	-	-	-	NM	37.7	43.3
EBIT (UBS)	-	-	-	NM	37.7	43.3
EPS (UBS)	-	-	-	122.5	-48.4	44.0
Cash EPS	-	-	-	122.5	-48.4	44.0
Net DPS	-	-	-	-	-	-
BVPS	-	-	-	194.3	-36.7	-20.4

Margins (%)	5Yr Avg	12/09	12/10	12/11E	12/12E	12/13E
EBITDA / revenue	-	-	-	-	-	-
EBIT / revenue	-	-	-	-	-	-
Net profit (UBS) / revenue	-	-	-	-	-	-

Return on capital (%)	5Yr Avg	12/09	12/10	12/11E	12/12E	12/13E
EBIT ROIC (UBS)	-	-	-	NM	NM	NM
ROIC post tax	-	-	-	NM	NM	NM
Net ROE	-	-	(24.2)	(34.7)	(18.5)	(24.1)

Coverage ratios (x)	5Yr Avg	12/09	12/10	12/11E	12/12E	12/13E
EBIT / net interest	-	-	-	-	-	-
Dividend cover (UBS EPS)	-	-	-	-	-	-
Div. payout ratio (%, UBS EPS)	-	-	-	-	-	-
Net debt / EBITDA	-	-	4.6	5.7	6.6	3.7

Efficiency ratios (x)	5Yr Avg	12/09	12/10	12/11E	12/12E	12/13E
Revenue / op. invested capital	-	-	-	0.0	0.0	0.0
Revenue / fixed assets	-	-	-	0.0	0.0	0.0
Revenue / net working capital	-	-	-	0.0	0.0	0.0

Investment ratios (x)	5Yr Avg	12/09	12/10	12/11E	12/12E	12/13E
OpFCF / EBIT	-	-	1.0	1.1	1.1	1.0
Capex / revenue (%)	-	-	-	-	-	-
Capex / depreciation	-	-	-	-	-	-

Capital structure (%)	5Yr Avg	12/09	12/10	12/11E	12/12E	12/13E
Net debt / total equity	-	-	NM	NM	NM	NM
Net debt / (net debt + equity)	-	-	NM	NM	NM	NM
Net debt (core) / EV	-	-	-	(18.1)	(60.9)	(73.0)

Source: Company accounts, UBS estimates. (UBS) valuations are stated before goodwill-related charges and other adjustments for abnormal and economic items at the analysts' judgement.
Valuations: based on an average share price that year, (E): based on a share price of US$11.10 on 06 Mar 2012 16:42 EST Market cap(E) may include forecast share issues/buybacks.

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Verastem

Verastem is a Cambridge, Massachusetts-based early-stage biotechnology company focused on the discovery and development of novel small molecule drugs and companion diagnostics targeting cancer stem cells. The proprietary EMT screening platform, licensed from the Whitehead Institute at MIT, has helped select and identify the company's 3 leading candidates (VS-507, a Wnt inhibitor, and two FAK inhibitors VS-4718 and VS-5095). The company plans to begin human trials over the next 12-15 months for VS-507 and one of the two FAK inhibitors, and could be in phase II trials as early as 2015.

Statement of Risk

We see several risks to our Buy rating on VSTM shares. We see risk to our Buy rating if VS-705, VS-4718 and/or VS-5095 have unforeseen safety, tolerability or toxicity signals or fail to yield positive phase 1b clinical results. We also see downside risk if the companion diagnostic fails to identify the appropriate population or biomarkers to better quantify benefit/risk. Finally, we see further downside risk if competition shows better data with CSC-targeting therapies, which would potentially lessen the strategic value of Verastem's assets.

Analyst Certification

Each research analyst primarily responsible for the content of this research report, in whole or in part, certifies that with respect to each security or issuer that the analyst covered in this report: (1) all of the views expressed accurately reflect his or her personal views about those securities or issuers and were prepared in an independent manner, including with respect to UBS, and (2) no part of his or her compensation was, is, or will be, directly or indirectly, related to the specific recommendations or views expressed by that research analyst in the research report.

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UBS Investment Research: Global Equity Rating Allocations

UBS 12-Month Rating	Rating Category	Coverage[1]	IB Services[2]
Buy	**Buy**	57%	36%
Neutral	**Hold/Neutral**	37%	35%
Sell	**Sell**	7%	17%
UBS Short-Term Rating	**Rating Category**	**Coverage[3]**	**IB Services[4]**
Buy	**Buy**	less than 1%	0%
Sell	**Sell**	less than 1%	12%

1:Percentage of companies under coverage globally within the 12-month rating category.
2:Percentage of companies within the 12-month rating category for which investment banking (IB) services were provided within the past 12 months.
3:Percentage of companies under coverage globally within the Short-Term rating category.
4:Percentage of companies within the Short-Term rating category for which investment banking (IB) services were provided within the past 12 months.

Source: UBS. Rating allocations are as of 31 December 2011.

UBS Investment Research: Global Equity Rating Definitions

UBS 12-Month Rating	Definition
Buy	FSR is > 6% above the MRA.
Neutral	FSR is between -6% and 6% of the MRA.
Sell	FSR is > 6% below the MRA.
UBS Short-Term Rating	**Definition**
Buy	Buy: Stock price expected to rise within three months from the time the rating was assigned because of a specific catalyst or event.
Sell	Sell: Stock price expected to fall within three months from the time the rating was assigned because of a specific catalyst or event.

KEY DEFINITIONS

Forecast Stock Return (FSR) is defined as expected percentage price appreciation plus gross dividend yield over the next 12 months.

Market Return Assumption (MRA) is defined as the one-year local market interest rate plus 5% (a proxy for, and not a forecast of, the equity risk premium).

Under Review (UR) Stocks may be flagged as UR by the analyst, indicating that the stock's price target and/or rating are subject to possible change in the near term, usually in response to an event that may affect the investment case or valuation.

Short-Term Ratings reflect the expected near-term (up to three months) performance of the stock and do not reflect any change in the fundamental view or investment case.

Equity Price Targets have an investment horizon of 12 months.

EXCEPTIONS AND SPECIAL CASES

UK and European Investment Fund ratings and definitions are: Buy: Positive on factors such as structure, management, performance record, discount; Neutral: Neutral on factors such as structure, management, performance record, discount; Sell: Negative on factors such as structure, management, performance record, discount.

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Company Name	Reuters	12-mo rating	Short-term rating	Price	Price date
Verastem[2, 4, 5, 6, 16]	VSTM.O	Buy	N/A	US$11.10	06 Mar 2012

Source: UBS. All prices as of local market close.
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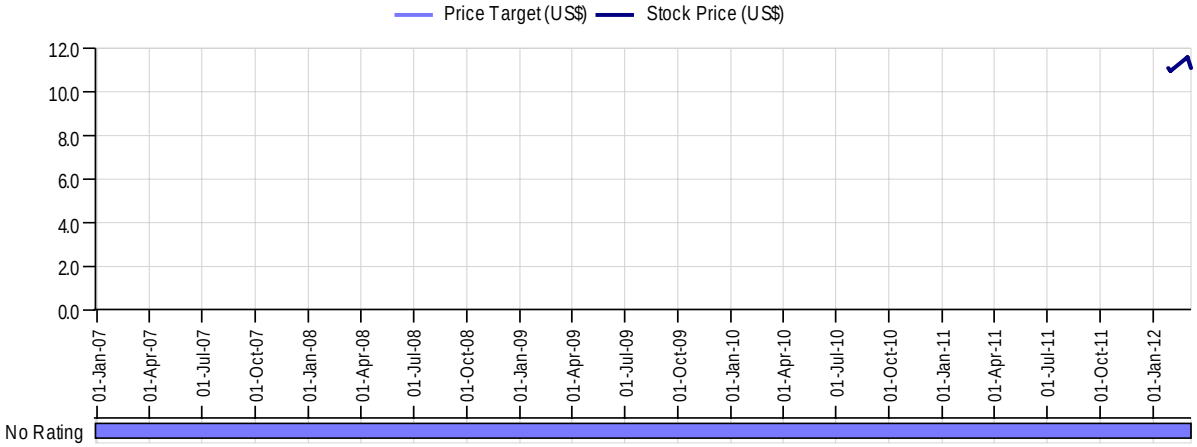
Verastem (US$)



Source: UBS; as of 06 Mar 2012

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