

## COMPANY NOTE

Initiating Coverage

USA | Healthcare | Biotechnology

August 29, 2013

# Jefferies

## Stemline Therapeutics (STML) Initiating at Buy with \$60 Target – Bet On Strong Single Cycle Efficacy

### Key Takeaway

**STML's lead drug, SL-401, is entering pivotal trials in 2014 in BPDCN, a rare lymphoma, and third-line acute myeloid leukemia. We are impressed by the robust response rates in both settings, including durable complete responses, after a single cycle of treatment, and we believe that even better efficacy could be achieved with multiple SL-401 cycles. We estimate SL-401 peak sales of \$500m+.**

**In May, Jefferies acted as a joint bookrunner in a public offering of STML common shares.**

**Highly Impressive SL-401 Efficacy After A Single Cycle.** SL-401 is IL-3 attached to diphtheria toxin, which is engineered to drop the toxin payload in cells that overexpress the IL-3 receptor. Robust activity has been observed after just a single cycle of SL-401 treatment in two settings. In BPDCN, a rare lymphoma affecting 500-1,000 patients in the U.S. each year, 5 of 6 patients have achieved an objective response, including four complete responses (CR) with one lasting more than nine months. In relapsed/refractory AML, there has been a 25% response rate (15/59) including two CRs.

**Next Steps: Pivotal Trials In 2014.** We believe the lead investigator of the Phase 1/2 study plans to retreat a BPDCN patient and may present data from this one patient at ASH in December. STML then plans to initiate pivotal trials of SL-401 using a multi-cycle regimen, first in single-agent, single-arm study in second-line BPDCN in 1H14 and then in a randomized, controlled study vs. physician's choice of chemotherapy in third-line AML in 2H14. We are optimistic that early response data in AML could lead to a positive survival outcome in the pivotal AML trial.

**Market Opportunity Could Be \$500m+.** We estimate third-line AML could represent \$500m+ in peak sales with BPDCN contributing \$70m+. The key risks to the STML thesis include translation of response rate data to a survival benefit in AML and the efficacy and safety of multiple cycles of SL-401. Upside to our model includes higher-than-expected pricing, expansion into earlier stages of therapy, new indications such as myelodysplastic syndrome or multiple myeloma, and a second pipeline drug, SL-701, a cancer vaccine for brain tumors where single agent objective responses have been observed in two studies.

### Valuation/Risks

We derive a price target of \$60 using a sum-of-the-parts DCF analysis (\$45 SL-401 + \$15 cash). Risks include clinical, regulatory, commercial.

USD	Prev.	2012A	Prev.	2013E	Prev.	2014E	Prev.	2015E
Rev. (MM)	--	0.0	--	0.0	--	0.0	--	0.0
<b>EPS</b>								
Mar	--	--	--	(0.90)A	--	--	--	--
Jun	--	--	--	(0.55)A	--	--	--	--
Sep	--	--	--	(0.44)	--	--	--	--
Dec	--	--	--	(0.49)	--	--	--	--
FY Dec	--	(1.82)	--	(2.20)	--	(2.98)	--	(2.92)
FY P/E		NM		NM		NM		NM

**BUY**

Price target \$60.00

Price \$33.88

### Financial Summary

Book Value (MM):	\$89.7
Book Value/Share:	\$7.23
Net Debt (MM):	(\$92.7)
Cash (MM):	\$92.7

### Market Data

52 Week Range:	\$39.18 - \$10.00
Total Entprs. Value (MM):	\$327.4
Market Cap. (MM):	\$420.1
Insider Ownership:	20.7%
Institutional Ownership:	70.1%
Shares Out. (MM):	12.4
Float (MM):	8.8
Avg. Daily Vol.:	189,351

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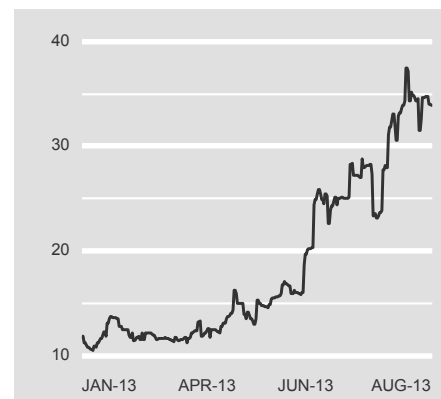
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### Price Performance



## Scenarios

## Target Investment Thesis

- We are encouraged by SL-401's single cycle response rates in the difficult-to-treat BPDCN and third-line AML settings
- Mechanism of action is sound, historical proxy (Ontak) has demonstrated safety over multiple cycles
- Upside from positive SL-401 mid-stage data in other indications (MDS, MM), and SL-701
- Target Price: \$60 = \$38 SL-401 AML indication + \$7 BPDCN + \$15 cash

## Upside Scenario

- Both BPDCN and AML show positive results in pivotal trials
- Upside from positive SL-401 mid-stage data in other indications (MDS, MM), and SL-701
- Target Price: \$106 = \$81 AML indication + \$10 BPDCN + \$15 cash

## Downside Scenario

- Failure in third-line AML indication
- BPDCN remains a viable program
- Additional indications for SL-401 are unsuccessful and SL-701 fails in pediatric/adult gliomas
- Target Price: \$22 = \$7 BPDCN indication + \$15 cash

## Long Term Analysis

## Revenue (millions)

N/A

## Long Term Financial Model Drivers

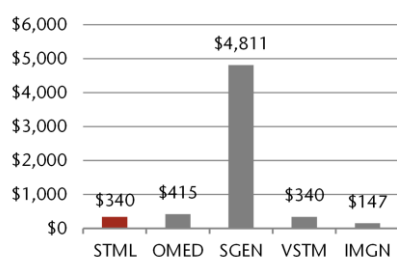
5-Year ('18-'23) Revenue CAGR **18%**

## Other Considerations

With several eagerly anticipated product launches, anemic pipelines at large cap biotech and pharma, and an increasingly conservative FDA stance, we believe mid- and small-cap biotech could lead sector performance in 2013. We see a premium placed on late-stage and marketed products. M&A interest could also factor into the performance of the sector, particularly among small-cap and mid-cap companies with later stage programs.

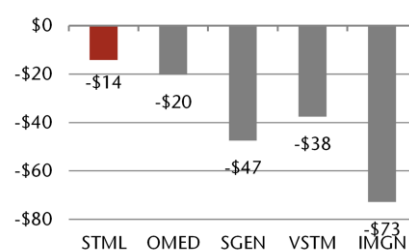
## Peer Group

## Group EVs



Source: FactSet

## Net Income



Source: Company data

## Recommendation / Price Target

Ticker	Recommendation	PT
STML	BUY	\$60
OMED	BUY	\$27
SGEN	BUY	\$45
VSTM	BUY	\$21
IMGN	BUY	\$21

## Catalysts

- 4Q13 – More from low-grade adult glioma trial at SNO
- 4Q13 – More SL-401 Phase 1/2 data and potential retreatment data in BPDCN at ASH
- 1Q14 – Decision from EMA on filing requirements for SL-401 in BPDCN and AML
- 2Q14 – Pivotal SL-401 BPDCN trial initiation
- 2H14 – Pivotal SL-401 3L AML trial initiation
- 2H14 – Initiation of Phase 2 SL-701 trials in adult GBM and pediatric glioma

## Company Description

Stemline Therapeutics, Inc. (STML) is a New York, NY-based clinical-stage biopharmaceutical company, specializing in the development of oncologic drugs that target cancer stem cells (CSCs) and tumor bulk. Cancer stem cells are thought to drive cancer progression, metastasis, and chemotherapy resistance. STML has two candidates in clinical trials, SL-401, humanized IL-3 linked to diphtheria toxin for third-line acute myeloid leukemia (AML) and for blastic plasmacytoid dendritic cell neoplasm (BPDCN). Pivotal trials are expected to begin for both indications in 2014. The company's other leading candidate is SL-701, a brain cancer vaccine consisting of synthetic peptides targeting IL-13Rα2 and EphA2. Phase 2b are expected to begin in 2014 in both pediatric glioma and adult second-line glioblastoma multiform (GBM).

## Company Overview

**Stemline Therapeutics Inc. (STML) is a New York City-based biotechnology company focused on developing therapeutics that target cancer stem cells (CSCs) and tumor bulk.** STML's lead product candidate, SL-401, is being developed for acute myeloid leukemia (AML) and blastic plasmacytoid dendritic cell neoplasm (BPDCN), a rare subtype of lymphoma. Based on early Phase 1/2 data showing meaningful clinical activity, we believe that SL-401 could be initially developed for the orphan relapsed/refractory BPDCN indication enabling SL-401 to reach market by early 2017 before applying for label expansion to address the broader AML indication later in 2017. Given the limited therapeutic options for BPDCN, we believe SL-401 could swiftly become the standard of care in this indication. We see third-line AML as a similarly compelling indication addressing a much larger market opportunity given the lack of salvage treatment options, especially if an overall survival benefit is demonstrated. There would also be the opportunity to further expand into earlier lines of therapy in both settings, in addition to pilot indications such as multiple myeloma and rare IL-3R+ cancers, where initial Phase 2 studies will be started in 3Q14, but these remain upside to our current valuation. STML is also developing SL-701 for pediatric malignant glioma and adult high-grade glioma. While we do not currently include SL-701 in our valuation, we believe it could be a meaningful source of upside to our estimates, and we note that single agent durable responses have been observed in multiple studies of SL-701.

## Valuation

We derive a \$60 valuation for STML solely on SL-401 prospects in BPDCN and third-line AML. We assume SL-401 will be launched for BPDCN in early 2017 with AML following later in 2017. We assume STML will retain U.S. rights to SL-401 but will seek a partner for ex-U.S. geographies during or following pivotal data with a partnership conservatively yielding \$50m upfront, \$25m in sales milestones, and tiered-royalties of 12-22%. We model peak penetration of 75% in BPDCN and 65% in AML, and pricing of \$150k in BDCN and \$75k in third-line AML, which would yield risk-adjusted sales of \$50+m and \$275+m in 2020, respectively. We apply a 75% probability of success for BPDCN and a 55% probability of success in AML to arrive at the risk-adjusted sales estimates shown in our model, and use a 12% weighted cost of capital and 20m fully diluted shares (including stock options and two future financings of 5m shares combined) to reach our price target of \$60. We do not currently assign value to SL-701 or label expansion opportunities for SL-401 in new indications.

## Risks

On the subsequent pages of our note, we review in detail the risks and controversies with the STML story. Key risks include clinical, regulatory and commercial risk. Chief among the clinical risks is the uncertain efficacy and safety of multiple cycles of SL-401. The Phase 2 data to date is based on a single cycle (5 daily doses) of SL-401. On safety, the dose-limiting toxicity has been capillary leak syndrome. Although experience with another diphtheria toxin conjugate, Ontak, would suggest that capillary leak syndrome may not worsen with multiple cycles of therapy, this still needs to be tested for SL-401. Separately, we assume that efficacy will become better (more responders, deeper responses, and/or more durable responses) with retreatment, but this also has not been confirmed yet. We also note that patients may have been previously vaccinated for diphtheria toxin and may have or develop antibodies against the toxin conjugate part of SL-401. Neutralizing antibodies could lead to safety and/or efficacy issues. We also note that the endpoint for the pivotal trial in third-line AML is overall survival. The Phase 2 trial was a single arm study with no control arm, primarily looking at response rates. While the overall survival of this Phase 2 cohort was favorable relative to historical controls by a significant margin, the Phase 2 population may have been skewed towards a healthier demographic than historical studies conducted in third-line AML.

## Controversies

**Will additional cycles of SL-401 lead to better efficacy?** The recent Phase 1/2 trial for SL-401 in advanced hematologic cancers involved only a single cycle of the drug, dosed as a daily 30-minute intravenous (IV) infusion for up to 5 consecutive days; however, cancer treatment typically involves dosing for repeated cycles until there are safety concerns or disease progression.

*No efficacy data to date on retreated patients.* The company is not aware of any data on retreatment of patients. We believe the lead investigator for the Phase 2 trial is currently contemplating whether to use his remaining manufactured SL-401 doses to treat additional patients or potentially retreat prior BPDCN responders. We expect more mature data from the Phase 1/2 trial and potentially new data on at least one retreated patient by the ASH meeting in December 2013.

*Response rate after a single cycle is very robust.* We note that durable responses were observed from a single cycle of SL-401. At ASCO 2013, STML presented updated results from 85 patients enrolled in the Phase 1/2 trial. In the AML part of the study, there were two complete responses (CRs) observed among the 70 patients treated, with the duration of response in these two responders of 8 and 25+ months (response was still ongoing prior to the patient being lost to followup). Among the 35 patients with third-line or later stage AML, an overall survival benefit of 3.6 months was observed (vs. historical OS rates in third-line AML of 1.5 months). In the BPDCN portion of the study, 83% of patients with relapsed/refractory BPDCN achieved an objective response to single cycle of SL-401 with a highly impressive four CRs and one PR. Although one CR lasted only a month, STML noted that three of the CRs were durable: new data since ASCO reveal that one lasted three months, one third-line patient experienced normalization of hepatic and splenic enlargement and achieved a 5-month CR, and one fourth line patient had resolution of associated malignant skin lesions and is currently at 11+ months with a CR with the response still ongoing. We are highly encouraged by the data from single agent, single cycle administration of SL-401. The observation of a high rate of objective responses, including complete responses, after a single cycle makes SL-401 one of the most effective cancer drugs among those we follow. Our expectation is that multiple cycles of therapy could lead to either a higher response rate, deeper responses (i.e., more CRs), and/or more durable responses (we believe that a clinically meaningful response would be over 3 months in this indication). Based on results from the Phase 1/2 trial, STML intends to advance SL-401 into a randomized Phase 2b trial in which third-line AML patients will be randomized to multiple cycles of SL-401 (the protocol will call for six cycles with the potential to extend dosing at the physician's discretion) or investigator choice from a list of third-line chemotherapy and best supportive care options, and in a single arm, pivotal Phase 2b trial in second-line BPDCN.

*Responses with Ontak got better with multiple cycles.* The closest comparable drug to SL-401 using the same basic technology is Ontak (denileukin diftitox), a conjugate of an interleukin targeting system linked to diphtheria toxin that was approved by the FDA for treatment of refractory cutaneous T-cell lymphoma (CTCL). In the Ontak pivotal trials, patients were allowed to receive up to 8 cycles of therapy, but the majority of patients did not get 8 cycles, a point that was made during the Advisory Committee meeting. Ligand argued that while time to first response was reported, it was not necessarily time to best response, as some patients who achieved a PR in early cycles eventually achieved CRs and of the 21 patients who responded, 19 had 8+ cycles and two had 6 cycles. It was noted that immunogenicity of Ontak led to a decreased average dosing beyond the first few cycles, complicating the codification of drug exposure in a regimen. Immune response was not predictive, as roughly 90% of patients developed similar levels of antibodies after two cycles. The advisory committee appeared to be somewhat conflicted about the appropriate duration of therapy, as the pivotal trials had not necessarily answered the

question of the optimal course of therapy. The FDA noted that most responders had responded by their third cycle and almost all had responded by their fourth cycle. They argued that it would be erroneous to draw a causal link between completion of the eight cycles and response, as the additional cycles (4-8) did not cause them to be responders. However, the FDA conceded that unlike with chemotherapy it would be difficult to assess patients after every few cycles to determine whether they were responding to therapy.

*Our Take: Retreatment should lead to better responses.* Based on the data for Ontak, the cytotoxic mechanism of action, and the wealth of data for chemotherapy and biologics showing that greater drug exposure generally leads to better efficacy, we believe that efficacy data could look even more robust with multiple cycles and look forward to potential preliminary data at the ASH meeting in Dec 2013 on retreatment of at least one BPDCN patient from the Phase 1/2 study.

**Will additional cycles of SL-401 be safe?** In the Phase 1/2 AML trial, STML evaluated two regimens: once daily every other day (q2d) SL-401 at doses of 4-12.5 mcg/kg for up to six doses or once every day (qd) SL-401 at doses of 7.1-22.1 mcg/kg for up to five doses.

*Focus toxicities include capillary leak syndrome and liver enzyme elevations.* STML did not identify a maximum tolerated dose (MTD) within its evaluated q2d dose range, but identified 16.6 mcg/kg/day qd as an MTD, as hypoalbuminemia and edema, both manifestations of capillary leak syndrome, were observed as the dose-limiting toxicity (DLT) at the 22.1 mcg/kg qd dose level. In the trial, transient transaminase elevation was the most commonly observed Grade 3 adverse event, but with no evidence of overt liver toxicity, and STML noted that there was no evidence of treatment-related bone marrow suppression.

*No data on retreatment yet – initial retreatment data may be generated by year-end 2013.* STML notes that, while they have no data on patients who have received a second cycle of therapy, we believe there may have been at least one AML complete responder who was being prepared to be retreated but was lost to follow up. The lead investigator for the Phase 1/2 study may use some remaining manufactured doses to retreat at least one BPDCN patient with a second cycle of therapy to explore safety and efficacy of multiple cycles. We believe early retreatment data in a patient may be available by the ASH meeting in Dec 2013. If positive, STML expects to begin Phase 2b trials of SL-401 in BPDCN with a goal of a 1H14 start in 40-50 previously-treated patients with BPDCN who will receive multiple cycles of SL-401 at 12 ug/kg for as long as there is a clinical benefit. STML expects to initiate its Phase 2b trial of SL-401 in 240 third-line AML patients in 2H14, which should also include the option of multiple cycles of treatment.

*Safety with Ontak did not appear to get worse over time.* The precautions taken against CLS in Ontak were also relatively straightforward – it was noted that CLS could be preventable or decreased by following Ontak infusions immediately with IV fluid boluses, to prevent Ontak-induced damage to the kidneys that caused protein loss into the urine and consequent hypoalbuminemia. Second, the presence of CLS and other SL-401 toxicities, if in proportions and severity in lesser degree or at most resembling those seen in Ontak toxicities, would not preclude successful approval of SL-401. At the Ontak ODAC meeting, an FDA consultant remarked that “the toxicities, as we are noting here, are very acceptable for this type of patient population in advanced stage,” which we believe would also apply to both the relapsed/refractory BPDCN and third-line AML settings. Separately, the Ontak label notes that infusion reactions were reported in 71% of patients across Phase 3 trials and serious infusion reactions were reported in 8% of patients; however, in patients receiving at least 4 cycles of Ontak, the incidence of infusion reactions was lower in cycles 3 and 4 compared to cycles 1 and 2. Ontak was also shown to cause constitutional symptoms in 91% of patients including fatigue, fever, chills, myalgias, or arthralgias, which were most common after the first cycle of therapy but

were often prevented in subsequent cycles by use of premedication (including Tylenol or antihistamines). That said, during the Ontak panel, it was noted that hypersensitivity-like reactions, characterized by symptoms such as dyspnea, back pain, chest pain, chest tightness, hypotension, rash and tachycardia that occurred during or within hours of the infusion, were more common during the earlier cycles, with 90% occurred after the first 2 cycles, but also reported during cycles 6 and 8. The incidence of hypotension, infection, pain, and rash were similar for early and late cycles. It was noted that the disproportionate incidence of adverse events during early cycles may have been influenced by the high dropout rate and frequent use of premedication. Overall, we are encouraged that multiple cycles of Ontak did not appear to lead to an accelerating rate of side effects, and if anything, the side effect profile appeared to improve with retreatment.

*Our Take: The Ontak experience and lower dosing of SL-401 lead us to believe that retreatment will likely be safe.* We do not expect that the rate of side effects (capillary leak syndrome or liver enzyme elevations) will become significantly worse upon multiple cycles, and in fact, the Ontak data and proper pretreatment of patients would suggest lower rates of CLS in subsequent cycles. We also note that Grade 3 CLS has not been observed at the 12.5 ug/kg/day dose being taken forward with SL-401, although many patients at this dose did experience mild-to-moderate symptoms of CLS which were generally self-resolving by the end of the five-day treatment period and required no special intervention.

**How treatment limiting will the capillary leak syndrome be?** In the Phase 1/2 study of SL-401, one particularly concerning class of adverse events was the emergence of signs of capillary leak syndrome (CLS), including hypoalbuminemia and edema, which were seen at the 16.6 ug/kg/day and 22.1 mcg/kg qd doses. CLS occurs when the endothelium lining the capillaries separate and allow fluid and protein to leak into interstitial tissues. The fluid loss causes hypotension and the fluid gain in the interstitium causes peripheral edema, pulmonary edema, and ascites, whereas the loss of protein, including serum albumin, further exacerbates these effects as decreased oncotic pressure causes more fluid to be lost to the vasculature. Treatment of CLS involves aggressive interventions such as intubation for airway protection and IV fluid and vasopressor therapy to prevent complications, major organ toxicity, and death. The main side effect of Ontak was CLS. Several mechanisms have been proposed to explain CLS: a direct drug effect that endogenous interleukins expressed on perivascular lymphocytes can serve as a target for interleukin-targeting therapies such as SL-401 or Ontak and implies a relationship between toxicity and dose, or a non-target phenomenon that identifies a proximal cause in inflammatory mediators such as leukotrienes and tumor necrosis factor that drive a “cytokine storm,” causing separation of endothelial cells. Although the latter theory appears to be the commonly accepted mechanism for the CLS based on our discussions with consultants and the company, which would suggest that both Ontak and SL-401 should have similar profiles, we also note data that there is also some IL-3 receptor expression seen on endothelial cells, which may contribute to enhanced CLS side effects with SL-401.

*Pretreatment and early intervention can reduce the rate and severity of CLS.* Given the potential severity of CLS, we believe it will be a high priority for STML to implement prophylactic measures and encourage the early detection of symptoms and appropriate treatment. We note that, in the Phase 1/2 trial, patients were premedicated with solumedrol, a corticosteroid, a class of drugs that is thought to reduce CLS symptoms, in addition to acetaminophen and diphenhydramine, similar to Ontak to prevent flu-like symptoms and infusion reactions, and ranitidine, which is known to have an antiemetic effect preoperatively. We note that hypoalbuminemia and edema, two symptoms of CLS, were observed as the dose-limiting toxicity (DLT) for SL-401 at the 22.1 mcg/kg/day dose. Although this DLT was observed at a dose-strength nearly double that being taken into Phase 2 trials, we note that mild-to-moderate symptoms of CLS were observed at the 12.5



ug/kg/day dose, and we believe that monitoring for early signs of CLS and aggressive intervention will be key to managing potential CLS issues. We note that, during a CLS episode, IV fluids and drugs such as adrenaline are administered to keep blood pressure at a level to maintain organ function and that these treatments may be followed by steroids. Diuretics can also be used to control edema. Albumin infusions can be administered to patients with low serum albumin. We note that in the Ontak pivotal trials, 7 patients stopped treatment due to CLS; however, these patients typically responded quickly to therapy. The precautions taken against CLS with Ontak were relatively straightforward – it was noted that CLS could be preventable or decreased by following Ontak infusions immediately with IV fluid boluses, to prevent Ontak-induced damage to the kidneys that caused protein loss into the urine and consequent hypoalbuminemia. We suspect that prophylaxis of patients with low baseline albumin and a diligent approach to monitoring should help moderate concerns over CLS with SL-401. To this end, although the company believes that SL-401 could eventually be administered on subsequent cycles as a monitored outpatient administration, the studies will employ inpatient hospitalization of patients for the five days of treatment per cycle.

*Ontak CLS findings were considered acceptable.* Given the close similarities between Ontak and SL-401, we believe the FDA's acceptance of a non-target phenomena explanation for Ontak's side effects and ultimate approval of the drug in 1998 will contribute to the acceptability of the CLS signs seen with high dose SL-401. We note that with the two Ontak dosing regimens under review at the time, signs of CLS were experienced by 24% of 143 patients, but only 8% reported 2 of the 3 CLS symptoms (hypotension, edema, and hypoalbuminemia), only 6% were hospitalized, and only 5% discontinued treatment. We see the ODAC's extensive discussion of the cause and significance of the CLS signs with Ontak and eventual 14-0 vote in favor of approval as positive signs of a manageable risk threshold for SL-401. We are encouraged by the relatively low frequency of these highly adverse variants of CLS parallels the outlier CLS event noted in the SL-401 phase 1/2 trial. At the Ontak ODAC meeting, a FDA consultant remarked that "the toxicities, as we are noting here, are very acceptable for this type of patient population in advanced stage." Given the similar average age of AML patients (60) at diagnosis compared to CTCL (55-60), the short life expectancy of relapsed/refractory BPDCN (less than 12 months) and third-line AML patients (1.5 months on average), and their likely presentation with similar comorbidities, we believe the generalization may also apply to the AML patient population for SL-401.

*SL-401 dosing will be lower than where CLS was observed and lower than the Ontak dose.* Concerns over toxicity are reduced if further trials with SL-401 show continued efficacy at sub-MTD levels, as the FDA will likely focus on the dosages for which the sponsor is seeking approval. Specifically, the company plans on moving forward the 12.5 ug/kg qd dose, where none of the 17 patients enrolled experienced Grade 3 CLS, although mild-to-moderate symptoms were observed at this dose. CLS was observed in 1 of 8 patients at the 16.6 ug/kg dose and 2 of 2 patients at the 22.12 ug/kg dose. Thus, the data to date suggest a much lower risk of CLS at the designated dose for future studies. Even if more severe CLS emerges at 12.5 ug/kg, we believe the presence of CLS and other SL-401 toxicities, if in proportions and severity in lesser degree or at most resembling those seen in Ontak toxicities, would not preclude successful approval of SL-401. Our consultants noted that they do not believe CLS would be an issue and would likely diminish from later trials as STML has become very good at training investigators on how to manage the side effect.

*Our Take: CLS will likely be acceptable.* While there may be a certain low rate of CLS, we note that the data to date suggest that it will be lower than that observed for Ontak (24%) and likely considered acceptable given the benefits of the drug and the unmet medical need in the two indications being pursued.

**Will anti-SL-401 antibodies negate the response to drug?** Because SL-401 is a foreign protein, patients may develop antibodies against the diphtheria portion, which have the potential to be neutralizing and make re-treatment difficult. Neutralizing antibodies can be associated with safety issues (anaphylactic reactions) and/or attenuated efficacy. Specifically, patients who have had a diphtheria vaccination have memory B-cells and the ability to create antibodies against diphtheria toxin.

*No correlation observed between antibodies and responses in BPDCN with SL-401.* We note that, of the five evaluable BPDCN patients presented at ASCO 2013, the three CRs demonstrated varying increases in antibody titers from baseline to day 15-30 of 6 to 34 ug/mL, 8 to 4,590 ug/mL, and 0.5 to 35 ug/mL (post-treatment immune response data were not available for the PRs). We note that a patient with the greatest immune response (8 to 4,590) was also the patient with the most durable response (9+ months). Thus, the preliminary data suggest no relationship between antibody response and efficacy.

*No correlation observed between antibodies and responses with Ontak.* Separately, we looked to the Ontak development program as a proxy, as the drug consisted of IL2 conjugated to a diphtheria toxin. In pivotal trials of Ontak, it was shown that roughly 38% of patients according to an ELISA assay had antibodies to diphtheria toxin prior to exposure in both the responder and non-responder cohorts (33% and 40% > 1.25 bl titre), a balance that suggests that baseline antibody presence did not materially impact response to treatment. Using a more sensitive cell-based bioassay, Ligand still found no difference in baseline antibody presence in responders and all comers, with roughly 50% in each group. After two cycles of treatment with Ontak, 90% of both responders and all-comers had antibodies, but they did not appear to predispose patients to side effects, including acute infusion-related events, and Ligand speculated that the antibodies may actually decrease concurrent side effects. A member of the FDA advisory committee noted, however, that high levels of neutralizing antibodies were detected by cycles 2 and 3, which were correlated with a decrease in constitutional signs, transaminitis and increased clearance, and as a result, the value of treatment beyond 3 courses was not apparent from the available data. However, it was noted that not only was patient response independent, but that patients experienced tachyphylaxis whether or not they had an antibody response. To further address the issue of antibodies, STML is developing and validating pharmacokinetic assays to measure serum drug levels and immunogenicity, a measure of antibodies produced in response to drug exposure. STML notes that it is developing these assays in parallel to its efforts to ramp up commercial grade manufacturing of SL-401, a step that has added a few months to the manufacturing scale-up, but which should enable them to avoid a bridging study.

*Our Take: We do not expect that antibodies will be an issue.* Given the preliminary data on antibodies to SL-401 in the BPDCN study and the experience with Ontak, we do not expect anti-SL-401 antibodies to be correlated to response. Initial efficacy data from the retreatment of BPDCN patients may help to address this question.

**Will SL-401 show an overall survival benefit in third-line AML?** At ASCO in 2013, STML presented updated results from the Phase 1/2 trial, in which two complete responses (CRs) out of 59 relapsed/refractory AML patients were observed with durations of 8 and 25+ months. There was an overall survival benefit of 3.6 months in the subgroup of patients with third-line or later AML. STML noted that these OS results compared to historical data showing 1.5 months of OS for third-line AML patients treated with standard of care; however, we believe that patient selection in the Phase 1/2 trial may have benefited average survival time. We spoke to one investigator who noted that healthier-than-average third-line patients were chosen to be involved in the Phase 1 trial, as they did not want patients to die right away, even if it is not evident from baseline demographics. The investigator commented that looking at the survival data from these patients and comparing them to data from a historical control population could be



misleading. In response, STML has noted the magnitude of the improvement in overall survival compared to historical controls is very large on a relative basis (more than a doubling of OS) and is much greater than the targeted 50% survival benefit in the pivotal trial, which helps to mitigate to some extent concerns on the comparability of the Phase 1/2 population to historical data, and of course, retreatment may improve the benefit seen on overall survival.

*Our Take: We have probability adjusted our AML sales for OS risk.* Given the risk in translating the response rate and OS data from the Phase 1/2 study to the pivotal trial, we have taken a conservative approach of applying a 55% probability of success to the AML indication in our valuation. That said, we are encouraged by the magnitude of the OS difference in the Phase 1/2 study and the potential for retreatment with multiple cycles to improve the efficacy benefit in AML.

**Will BPDCN duration of response improve with retreatment?** In a similar vein, for BPDCN, the endpoint for approval will likely be a combination of the overall response rate and the duration of response. While the overall response rate from the Phase 1/2 is robust and likely sufficient to convince the FDA and a panel of activity (we believe the bar for activity could be a 30-40% response rate vs. 83% observed in the Phase 1/2 trial), the durability of these responses has varied. Specifically, of the four complete responders in the Phase 1/2 study, CRs lasted for 1, 3, 5, and 11+ (ongoing) months. Therefore, only one patient has experienced a very long duration of response to therapy. We believe that a clinically meaningful duration of response would be 3 months in the second-line BPDCN setting, which would mean that 3 of 5 responders met these criteria. Once again, we believe that retreatment could help significantly in improving the durability of responses.

*Our Take: Retreatment should prolong duration of response.* We are confident that, as long as multiple cycles are safe, extending the dosing of SL-401 should improve upon the duration of response observed in BPDCN.

**Does IL-3 receptor expression affect response?** As SL-401 is a recombinant protein consisting of IL-3 linked to diphtheria toxin, which targets IL-3 receptor alpha (CD123), STML initially sought to treat IL-3R overexpressing cancers. IL-3 overexpression is known to occur in cancer stem cells (CSCs) and bulk tumor cells of hematological cancers including AML, MDS, CML, and BPDCN, which were enrolled in the Phase 1/2 trial, as well as ALL, Hodgkin's disease, and certain forms of NHL. Relative to normal stem cells, CSCs express more IL-3 receptor-alpha subunit, and it has served as a reliable marker of neoplastic stem cells, of which 99% express IL-3R relative to normal cells where only 1% will express IL-3R. We spoke to a researcher who had worked on the early development of SL-401 who suggested that there are particular receptor subunits, namely the alpha subunit or CD123, which may predict response to the drug. A preclinical paper also found that among 157 AML bone marrow biopsies, 40% of the AML patients exhibited CD123 immunohistochemical (IHC) expression, most frequently within the intermediate-risk group. Rather than target all patients with AML, our consultant suggested that an alternative approach would be to evaluate biomarkers in new Phase 2 studies in order to identify the subgroups of patients who may respond better to the drug (e.g., those patients with high IL-3 receptor overexpression).

*Feedback has been mixed on alpha vs. beta unit expression and correlation to response.* Although the Phase 1/2 investigators had not incorporated biomarker screening as they relate to SL-401 response, it is possible that doing so may help identify responders and improve SL-401 efficacy. Our consultant noted that SL-401 is targeted to the alpha subunit of the IL-3 receptor and determining expression levels of this subunit may help identify patients who are more likely to be favorable responders to the therapy. This is indirectly validated by the BPDCN population, in which the highest response rates were observed, where the highest levels of IL3 receptor expression of both the alpha and beta

subunits have been observed among the various target cancers. Although it has been reported that the alpha subunit expression is strictly correlated with the expression of the IL-3R beta chain subunit, our consultant also noted that identification of both IL-3R alpha and beta expression may help further tailor SL-401 treatment as some preclinical data exist to suggest that there is a stronger correlation between response and beta subunit expression in vitro.

*STML will collect but not prospectively screen patients for IL-3R expression in the pivotal trials.* The ongoing Phase 1/2 trial and the proposed pivotal trials do not use biomarkers to select for patient enrollment, but STML has commented that they are working to choose among several commercially available assays for determining IL-3R expression in an attempt to see retrospectively if there is any correlation between receptor expression and activity. STML notes that they intend to perform separate IL-3R assays for both cancer stem cells (CSCs) and bulk tumor cells, as they wish to conduct a pre-specified but retrospective analysis to determine whether there is a greater importance of IL-3R expression on SL-401 efficacy as measured by overall survival. To this end, the company notes that, with the caveat that there was no control arm in the Phase 1/2 study, there was a trend towards prolonged OS observed in those patients who experienced a partial response or blast cell reductions of 25% or more, although this historically has not been correlated with improved OS. STML has not ruled out looking at the expression levels of the beta subunit, if there is a convenient way to do so, but there is no commercially validated assay for the beta subunit at this time. As we await detail on the correlation between IL-3 receptor subunit expression level and efficacy, we remain confident in the overall success of the Phase 2 trials as note that SL-401 has been shown to effectively bind to IL-3 receptor alpha at picomolar concentrations and that the diphtheria toxin payload is so potent that only 1-2 molecules need to enter a cell to cause cell death.

*Ontak clinical experience suggests that level of receptor subunit expression may not be correlated with response.* To support the company's hypothesis, we note that in the Ontak pivotal trials, in which IL-2 expression was measured by screening the skin and peripheral blood for CD25, the IL-2 receptor alpha unit, it was difficult to identify a correlation between CD25 expression level and response to therapy. In the pivotal program, 58% of patients screened had greater than 20% CD25 positive cells, the entry criterion for the trial, of whom only 20% had 50+% CD25 expression. Ligand noted that their analysis of the 50+% subpopulation did not reveal a correlation with higher response rates. Separately, Ligand noted that, of the patients screened, 32 had multiple biopsies, of whom 14 had variable expression with one assay falling below the cutoff and the other above, 7 of whom were enrolled in the trial, and 3 of whom had documented responses. The 43% response rate among these patients with variable expression compared favorably to the 23-46% response rates observed in among the general population, suggesting that extent of receptor expression may not be predictive of response to receptor targeted therapies like Ontak or SL-401, where relatively low receptor expression could be sufficient for cell killing.

*Our Take: We would prefer to see IL-3 receptor expression used in the endpoints for AML, but the benefit could be strong enough in an unselected population to warrant approval and broad adoption.* We agree with the strategy of enrolling an all-comers population for the pivotal AML study, but we would prefer to see the company take an approach of testing all patients for IL-3 alpha subunit expression levels and looking at a subgroup of high IL-3R expression as a prospective co-primary endpoint, but we also accept that the efficacy benefit to date has been robust in an unselected population and that the Ontak experience suggests that receptor overexpression may not be correlated to response. In addition, the degree of receptor expression that defines a better response is unknown at this time. This finding has also been observed with another antibody-drug conjugate (Adcetris) where the degree of receptor overexpression has not been directly correlated to response (e.g., diffuse large B-cell lymphoma), and robust responses have been observed

in patients with very low CD30 expression. Ultimately, the powering of a study to incorporate co-primary endpoints may add an unnecessary delay to completion of enrollment in AML.

**How Will STML Price SL-401?** STML has been understandably guarded about pricing detail, but has acknowledged that they are initially targeting two serious, but very different indications. With respect to BPDCN, the company recognizes it as an ultra-orphan indication, which could enable aggressive pricing, in a model similar to that of Genzyme (Sanofi, SAN FP, €75, Buy); however, the company also acknowledges that third-line AML is a larger indication, and despite lacking many later-stage options, may be more price sensitive. However, third-line AML patients have, on average, a short expected survival time (<2mo), suggesting a high price per cycle may be achievable, especially if patients experience a significant survival benefit.

*Our Take: We have conservative pricing assumptions in our model. We have assumed a cost of therapy of \$25k per month of SL-401, resulting in an average cost per patient of \$150k in BPDCN and \$75k in third-line AML. We see there being the potential for upside to these assumptions depending on the efficacy benefit observed in Phase 3 trials.*

## Appendix

### SL-401

SL-401 is a biologic conjugate of IL-3 antibody attached to a diphtheria toxin payload using a Met-His linker. Unlike classic antibody-drug conjugates that are synthesized through a three-step process (antibody manufacturing using mammalian cells, linker manufacturer, and attachment of the linker and toxin to the antibody), SL-401 is manufactured as a single biologic through an E. coli bacterial fermentation process. The IL-3 SL-401 antibody targets the IL-3 receptor for delivery of the toxin to the cytosol of these cells, inhibiting protein synthesis and ideally avoiding damage to non-cancerous tissues. IL-3R is thought to be expressed specifically in hematological cancers, both bulk tumor cells and cancer stem cells (CSCs). These cancers include: acute myeloid leukemia (AML), blastic plasmacytoid dendritic cell neoplasia (BPDCN), myelodysplastic syndrome (MDS), chronic myeloid leukemia (CML), and non-Hodgkin's lymphoma (NHL). There was also preliminary activity shown in preclinical models of multiple myeloma. STML estimates that IL-3R is expressed in <1% of healthy hematopoietic stem cells, compared to expression in >99% of AML CSCs. Specifically, CSCs appear to overexpress the IL-3R alpha (CD123) subunit, where SL-401 binds. STML completed a single-agent, single-cycle Phase 1/2 trial in advanced hematologic cancer patients (n=86) across several indications, including BPDCN and AML. A small number of very advanced CML and high-risk MDS patients were also enrolled in this study. STML expects to begin two pivotal trials: a 40-50 patient, single arm, multi-cycle study in BPDCN to start in 2Q14 and a randomized trial in 240 patients comparing multi-cycle SL-401 to physician's choice of chemotherapy in third-line AML to start by year-end 2014. We expect data from BPDCN in 1H16 and data from AML in 2H16, with approval of each of these indications in 2017. SL-401 will also be studied in combination with chemotherapy in earlier lines of AML and as a single agent in other hematologic malignancies, with pilot studies in myeloma and rare tumors to start in mid-2014.

**BPDCN Background.** BPDCN is a cancer of the plasmacytoid dendritic cells found in skin, lymph nodes, marrow, and spleen. Because the disease was first described only in 1994, diagnosis is rare, but increasing. BPDCN accounts for roughly 0.44% of all hematologic malignancies. STML estimates that ~2,000 new cases are diagnosed annually across the US and Europe, with 700 in the U.S. and 1,300 in the EU. We are conservatively using a lower prevalence rate (~500 in the U.S.) based on our review of the epidemiological literature, but see upside from increasing physician awareness and data to suggest that BPDCN is potentially underdiagnosed due to rarity of the condition, the lack of treatment options, a change in the naming convention for the disease, and misdiagnosis as lymphoma, CTCL, PTCL, leukemia, or even melanoma. As expected, SL-401 was granted an Orphan Drug designation for the BPDCN indication by the FDA earlier this year. The course of disease is aggressive and often involves cutaneous lesions with subsequent or simultaneous malignancies in bone marrow and peripheral blood. Key antigens used to identify BPDCN are CD123 (95% of historical cases), TCL1 (89%), CD2AP (81%) and BDCA2/CD303 (75%). There are no approved drugs for any line of BPDCN therapy and the chemotherapy regimens used to treat AML or aggressive lymphoma have been ineffective after an initial response. Relapse is common and mean overall survival is only ~12 months.

**401 Phase 1/2 Study: BPDCN.** In the single arm trial, six patients with BPDCN have been enrolled to date: 5 treated with 5 daily doses (one cycle) of SL-401 at 12.5 µg/kg and 1 treated with 5 daily doses at 9.4 µg/kg, administered through IV for 15 minutes. One patient had de novo disease, one was first relapse, one was second relapse, and three were post-transplant. There were 5 responders among these 6 patients, with 4 CRs (duration: 11+ months ongoing, 5 months, 3 months, 1 month) and 1 PR (1 month). In the patient with 11+ month CR, antibody levels pre- and post-treatment were high at 8

and 4,590 µg/mL, respectively, while the patient with 5 month CR had lower levels of 6 and 34 µg/mL. There were no grade 3 toxicities, but grade 2 hypoalbuminemia was seen in all patients. This is a potential signal for capillary leak syndrome, but we consider this manageable. Grade 2 liver enzyme elevations and fever/chills were all seen in 4 of 5 patients each.

**AML Background.** AML is a disease in which immature non-lymphocytic white blood cells proliferate in the bone marrow, causing depletion of other cell lines. AML is the most common type of acute leukemia in adults and is estimated to account for 14,590 cases, or 30% of the 48,610 new cases of leukemia across adults and children in 2013, with an incidence rate of 3.7 per 100,000. However, AML is generally a disease of older adults, with a median age of 67 at diagnosis. As with BPDCN, CD123 (the alpha subunit of IL-3R) is strongly expressed in AML, with the literature pointing to 90%-95% of patients having CD123 expression, using flow cytometry. Standard treatment in first-line AML includes induction-maintenance chemotherapy (cytarabine, idarubicin, daunorubicin-mitoxantrone) and potentially stem cell transplant. There are no approved therapies in second- or third-line AML, although additional chemotherapy is often used in second-line. The one- and five-year survival rates for AML are 39% and 21%, respectively. In the third-line setting, STML estimates that overall survival is only 1.5 months.

**401 AHC Phase 1/2 Study: AML.** In the single-arm trial, there were 70 patients diagnosed with AML, including 11 first-line but chemotherapy-ineligible, 24 second-line, and 35 third-line or later patients. Patients were either dosed every second day (q2d) (Regimen A) at doses between 4.00 µg/kg to 12.50 µg/kg or every day (qd) (Regimen B) at doses between 7.07 µg/kg to 22.12 µg/kg. The maximum tolerated dose (MTD) was 16.60 µg/kg qd with activity seen in both the 12.50 and 9.40 µg/kg arms. In the third-line or later population, 23% saw experienced tumor shrinkages, with one complete response (25+ months ongoing in a fourth-line patient), and 20% had stable disease. One second-line patient also had a complete response (8 months). Median overall survival OS in the third-line setting was 3.6 months, compared to the STML's stated historical average of 1.5 months. STML also noted that in the 9.4, 12.5, and 16.6 µg/kg (therapeutically relevant) groups (n=16), the median OS was 5.6 months. We note that, at the 16.6 and 22.12 µg/kg doses, the three dose-limiting toxicities encountered were all associated with capillary leak syndrome. Other Grade 3 adverse events include elevated transaminases, although these were generally all self-resolving by the end of treatment. Overall, the most common adverse events include hypoalbuminemia, edema, fever, chills, and transaminitis. These Grade 1 and 2 AEs mostly did not warrant dose reduction and liver enzyme increases were nearly all transient.

**401 AHC Phase 1/2 Study: Other.** STML noted that the activity of CSCs cells decreased over time, down by an average of 79% on day 30 in 3 of 3 patients. Notably, two of these patients with ≥3 lines of therapy had OS of 7.2 months and 13.6 months. Last, the 401 AHC study also included 7 patients with high-risk, refractory myelodysplastic syndrome (MDS). Two of seven patients saw tumor shrinkage and an additional patient had stable disease. Three CML patients were also enrolled with no response observed, but the company notes that these were very sick, last-line patients, with plans to potentially explore earlier use of SL-401 in combination with standard of care.

**Next Steps For SL-401: Two Pivotal Trials, Two Pilot Studies In 2014.** In 2014, STML intends to initiate four trials: two pivotal trials in BPDCN in 1H14 (likely 2Q14) and AML in 2H14 (likely 4Q14), and two open-label pilot studies, multiple myeloma and other rare IL-3R+ cancers in mid-2014 (likely 3Q14). We expect the BPDCN trial to enroll roughly 40-50 patients and would expect a response rate of 30-40% to be viewed as a reasonable bar with the target of an average duration of response of at least 3 months. STML expects the trial to enroll in 18 months and about 24 months to file (1H16); we would expect a favorable outcome if data resemble those observed in the Phase 1/2 trial.

We note that if data are robust, SL-401 may be eligible to file for an expedited approval through the breakthrough pathway, a pathway for which we expect more detail from the company in 2014. We note that STML intends to enroll 240 patients in its AML trial in a 2:1 fashion between SL-401 vs. investigator choice of chemotherapy, which will be 90% powered to detect a 50% improvement in survival. In addition to a final analysis after 200 events that is expected after roughly 24 months, the trial will have interim looks at 90 and 140 events, which could lead to an earlier filing, if efficacy data look similar to the Phase 1/2 study. While the multiple myeloma opportunity appears to be clearly defined with roughly 22k and 28k patients in the U.S. and Europe, the other rare IL-3R+ cancer cohort is somewhat more loosely defined with roughly 4,000 and 5,000 patients in the U.S. and EU affected by relapsed/refractory hairy cell leukemia, mastocytosis, and basophilic and eosinophilic leukemias. Although we do not currently include them in our STML valuation, these pilot indications could potentially double the market opportunity for SL-401. Multiple myeloma specifically could be an interesting opportunity, as the mechanism of action of SL-401 is completely different from the current standard of care and may be complementary and represent a large market opportunity paralleling or exceeding AML. We note that STML has expressed an interest in potentially evaluating SL-401 in other IL-3R+ hematological cancers, including CML, but has noted that due to the aggressive course of the disease such trials may be better suited to SL-401 in combination with another agent in earlier stages of disease.

### SL-701

**SL-701 Vaccine Immunotherapy.** SL-701 is a subcutaneous injection of two analogue peptides (IL-13R $\alpha$ 2 and EphA2) for glioma (brain cancer)-associated antigen (GAA) epitopes. Both IL-13R $\alpha$ 2 and EphA2 are cell-surface receptors that are overexpressed in tumor bulk and cancer stem cells of certain high-grade gliomas. The IL-13R $\alpha$ 2 peptide being studied was modified to increase its affinity in HLA complexes. Specifically, these peptides only have affinity to human leukocyte antigen (HLA) type A2, which is found in roughly half of the general population. Following positive Phase 1/2 trials, STML expects to begin Phase 2b trials on SL-701 in mid-2014 in both pediatric malignant gliomas and second-line adult glioblastomas (GBM). Both indications fall under FDA orphan designation and both could be pivotal trials.

**SL-701 Formulation.** The formulation of SL-701 has evolved throughout the Phase 1 trials. For the Phase 2 trials, STML has settled upon a subcutaneous formulation of IL-13R $\alpha$ 2, EphA2, and a helper peptide (pan-DR), delivered in conjunction with an immunostimulant (poly-ICLC). Previously, the Phase 1 adult trial used a formulation of modified dendritic cells harvested through leukopheresis and loaded with IL-13R $\alpha$ 2, EphA2, gp100, and YKL-40 peptides. The formulation was then delivered by intranodal injections. In the Phase 1 pediatric trial, the formulation did not incorporate dendritic cells and contained 3 peptides: IL-13R $\alpha$ 2, EphA2 and survivin. STML believes that IL-13R $\alpha$ 2 and EphA2 are the active components and will advance to future trials without additional peptides. However, the company will continue to evaluate the benefit of adding other peptides. Last, STML expects to change the immunostimulant from poly-ICLC, which is not approved, to a more standard regimen of GM-CSF and imiquimod. STML believes this combination could potentially be more effective at boosting the immune system.

**Disease Prevalence.** Primary brain tumors account for ~2% of cancer in the US, or ~35,000 new cases annually. Of these, the most common form, glioblastoma multiforme (GBM), is also the most malignant (Grade 4). These cases have an incidence of ~2-3 per 100,000, or 12%-20% of brain tumors. The Grade 3 brain tumors, anaplastic gliomas (AG), have an incidence of ~0.5 per 100,000 and account for ~5% of adult brain tumors. STML estimates 10,000 US and 15,000-18,000 EU GBM cases annually. In children, brain and CNS tumors have an incidence rate of ~5 per 100,000, with malignant gliomas account for ~1 per 100,000. Brain stem tumors account for 10% of brain tumors. STML



estimates 1,600-2,000 US and ~3,400 EU pediatric high grade glioma cases annually. From a market opportunity standpoint, we note that the need for patients enrolled in the studies to be HLA-A2+ would reduce the target market to 40-50% of patients, although STML may also pursue studies in patients who are HLA-A2-.

**Disease Treatment.** There are limited options for treatment of glioma due to the high sensitivity of the surrounding healthy brain tissue. As resection must be conservative in the brain, it is usually followed by radiation and temozolomide (Temodar). STML estimates that relapse occurs in 85%-90% of patients. Second-line therapy often includes Avastin, but the drug could be falling out of favor given its relatively limited efficacy. Estimated median survival rate is ~15 months in first-line GBM, with a 5-yr rate of ~4%. Median overall survival in second-line patients is 8-9 months. Median survival is roughly 2-3 years for anaplastic astrocytomas and potentially ~5 years for anaplastic oligodendrogliomas. Tumors in the brain stem, which are most often in children, are often inoperable. In children aged 0-14, the glioblastoma and anaplastic astrocytoma 5-yr survival rates are 21% and 30%, respectively. However, STML notes that pediatric high grade glioma has a median OS of <1 year.

**Next Steps: Pediatric Phase 2 Study.** STML received funding approval from the National Cancer Institute to run the pediatric trial and is awaiting approval of the final protocol, which has been the limiting factor for trial initiation. STML hopes to begin the trial in mid-2014 with two 12-patient arms: one in patients in post-radiation brainstem gliomas and one in relapsed/refractory high grade gliomas. Following recruitment of the initial targeted 24 total pediatric patients, STML could accelerate additional recruitment by injecting its own funding. **Adult Phase 2:** STML will likely study standalone SL-701, rather than its previous guidance of a combination therapy with Avastin, as it believes Avastin in second-line therapy is falling out of favor following negative overall survival data in the first-line setting. The open-label trial would include <100 relapsed/refractory patients with GBM and could begin in mid-2014. This has the potential to be a study that could offer a rapid pathway to approval, based on the Avastin second-line example. **Low-Grade Adult:** Additional data from this ongoing Phase 1 trial (see below) could be presented at the Society for Neuro-Oncology meeting in San Francisco on Nov 21-24, 2013, which may include additional data on the correlation between immune responses and clinical responses, including data on time to onset for each.

**701 Pediatric Glioma Study (Phase 1/2).** The trial was initiated in 27 HLA-A2+ pediatric patients, 16 with newly diagnosed brainstem glioma, 5 with newly diagnosed non-brainstem high-grade glioma (HGG), 3 with recurrent non-brainstem HGG, and 3 with recurrent low-grade glioma (LGG). Patients were administered a subcutaneous injection as monotherapy in the arm every 3 weeks for up to 24 weeks with a concurrent injection of poly-ICLC. Patients with an objective response or stable disease after the 24-week treatment period had the option of receiving booster injections at 6-week intervals. Of the 22 evaluable patients, 15 patients had stable disease, 3 had partial responses (longest duration was 15 months), and 1 had persistent no evidence of disease following resection (20 months). There were also 4 cases of tumor pseudoprogression, which is a sign of anti-tumor activity. SL-701 was well tolerated (no Grade 3 toxicities), with side effects limited to fatigue, injection site reactions and low-grade fever. Of the 7 immunologically evaluable patients, 6 showed evidence of immune response (5 for IL-13R $\alpha$ 2, 3 for EphA3, 3 for survivin). The only correlation noted between immune response and clinical response was that the longest duration partial responder had a persistent IL13R response for 33+ weeks.

**701 Adult Recurrent High Grade Glioma Study (Phase 1/2).** The trial was initiated in 22 HLA-A2+ adult patients, 13 with recurrent GBM and 9 with recurrent AG. Patients underwent leukopheresis and peptides were loaded onto dendritic cells ex vivo. The formulation was then injected intra/perinodally every two weeks for 8 weeks, followed by monthly booster injections. Poly-ICLC was administered twice weekly. In

terms of efficacy, 6 of 13 patients with GBM and 7 of 9 patients with AG achieved an objective response or stable disease. This included 2 complete responses, one for 23+ months in a GBM patient with prior resection, radiation and Temodar, and one for 9 months in an AG patient. There were also 3 partial responses. In the GBM patients, median OS was 13 months (vs. historical 8-9 months) and AG patients also saw increased OS over historical. Of the 16 immunologically evaluable patients, 13 had at least 1 positive assay (IL-13R $\alpha$ 2, EphA2, gp100, YKL-40) and there was significant type-1 cytokine/chemokine up-regulation following the first injection, including significant increases in IFN $\alpha$ 1, CXCL10, TLR3, and CCL22). Investigators noted a correlation between higher IL-12 levels and longer time to progression.

**Ongoing Adult Low Grade Glioma Trial.** This trial was initiated in 24 HLA-A2+ adult patients, 14 with newly diagnosed high-risk low grade glioma and 10 with recurrent low grade glioma. So far, of the 17 patients who have completed all 8 courses of therapy (over 24 weeks), 10 have had stable disease.

**Licensing and IP.** STML has worldwide licenses on both peptides with the University of Pittsburgh, which ran both the adult/pediatric Phase 1 trials. The license for IL-13R $\alpha$ 2 is exclusive, whereas the license for EphA2 is not. STML notes in its 10-Q that there is a composition of matter patent in the US for IL-13R $\alpha$ 2, as it was modified to increase the immunostimulatory effects. In the EU, there are pending patent applications on method of use for IL-13R $\alpha$ 2, but no applications on the composition of matter, as STML does not believe that one can be issued. For EphA2, there are method of use patents issued in the US. STML believes that a composition of matter patent cannot be issued for EphA2. Much further down the road, we would note that the US composition of matter patent protecting the modified IL-13R $\alpha$ 2 (No. 7,612,162) could be reviewed following the Supreme Court ruling that gene sequences are not patentable. Further, the modification used to increase peptide affinity could potentially be obvious, given prior art on certain amino acid substitutions.

**Overall Take: Promising But Early.** We are encouraged by single agent activity that has been observed in two separate studies of SL-701 in a tough-to-treat indication, including durable objective responses, complete responses and encouraging trends on overall survival relative to historical data. We are also encouraged by the lack of side effects observed with SL-701. That said, the translation of these data into an overall survival benefit is risky, as was the case for Avastin (approved in recurrent glioblastoma after single-agent data showed a 20% objective response rate, but failed to improve overall survival when added to first-line chemoradiation for newly diagnosed glioblastoma). In addition, we note that the formulation of SL-701 was different for each of the Phase 1 trials and is changing again for subsequent Phase 2 trials relative to either formulation used in Phase 1. This increases the clinical risk associated with the program.

### Ontak

Ontak (denileukin diftitox) is also a conjugate of an interleukin targeting system linked to diphtheria toxin, which was FDA approved for treatment of refractory T-cell lymphoma (CTCL) in 1998, though it is no longer commercially available in the U.S. In the construction of Ontak, the C-terminal binding domain of the diphtheria toxin was replaced with the binding portion of human IL-2 antibody. With high-affinity IL-2 receptors expressed on lymphoma cells and lymphocytes, Ontak was found to have activity against a number of lymphomas, receiving FDA accelerated approval in 1999 for CTCL, which was converted to regular approval in 2008. The maximum tolerated dose in the early studies was 27 ug/kg/day. In the pivotal phase 3 trial for this indication, patients received 9 or 18 ug/kg/day IV drug for 5 days every 3 weeks for up to eight cycles. Associated side effects were both acute and chronic in nature, including complexes of fevers, chills, nausea, vomiting, myalgias, and arthralgias, CLS, and transient liver enzyme elevations.

## Management

**Ivan Bergstein, M.D. – Chief Executive Officer.** Dr. Bergstein is the founder of Stemline (August 2003) and has been Chief Executive Officer since the company's inception. Before Stemline, Dr. Bergstein was Medical Director of Access Oncology, Inc., a private clinical stage oncology-focused biotechnology company. Dr. Bergstein received a B.A. in mathematics from the University of Pennsylvania and an M.D. from the Mount Sinai Medical Center, where he completed a general surgery internship. He was a Jerome A. Urban post-doctoral fellow at Cornell University Medical College. Dr. Bergstein completed internal medicine residency and a clinical Fellowship in hematology-medical oncology at the New York Presbyterian Hospital-Weill Medical College of Cornell University, where he is currently a voluntary faculty member.

**Eric Rowinsky, M.D. – Chief Medical Officer, Head of Research and Development.** Dr. Rowinsky has been Chief Medical Officer and Head of Research and Development of Stemline since 2011. He was previously Executive Vice President and Chief Medical Officer for ImClone Systems, Inc., and Director of the Institute of Drug Development ("IDD") at the Cancer Therapy and Research Center. He also was the SBC Endowed Chair for Early Drug Development at the IDD and was a Clinical Professor of Medicine at the University of Texas Health Science Center at San Antonio. Dr. Rowinsky is an Adjunct Professor of Medicine at New York University School of Medicine. Dr. Rowinsky received his M.D. from Vanderbilt University School of Medicine and completed his internal medicine residency at the University of California, San Diego and his fellowship in medical oncology at Johns Hopkins Oncology Center.

**Kenneth Hoberman – Chief Operating Officer.** Kenneth Hoberman is Stemline's Chief Operating Officer. Prior to Stemline, Mr. Hoberman was Vice President of Corporate and Business Development of Keryx Biopharmaceuticals, Inc. and a Managing Director at Hawkins BioVentures, a healthcare advisory firm. Mr. Hoberman received a B.S.B.A. in finance from Boston University and completed post-baccalaureate studies at Columbia University.

**Stephen P. Hall – VP Finance and Chief Accounting Officer.** Mr. Hall is Stemline's Vice President of Finance and Chief Accounting Officer. Previously, Mr. Hall was founder and managing director of Deimos Consulting, LLC, a management consulting firm specializing in Life Sciences. He earned an A.B. degree from Harvard College and an MBA from the Stanford Graduate School of Business.

## Public Offering

In May, Jefferies acted as joint book-running manager in a follow-on public offering of 4.14m shares of STML common stock at a price of \$14.50 per share.

## Company Overview

Stemline Therapeutics, Inc. (STML) is a New York, NY-based clinical-stage biopharmaceutical company, specializing in the development of oncologic drugs that target cancer stem cells (CSCs) and tumor bulk. Cancer stem cells are thought to drive cancer progression, metastasis, and chemotherapy resistance. STML has two candidates in clinical trials, SL-401, humanized IL-3 linked to diphtheria toxin for third-line acute myeloid leukemia (AML) and for blastic plasmacytoid dendritic cell neoplasm (BPDCN). Pivotal trials are expected to begin for both indications in 2014. The company's other leading candidate is SL-701, a brain cancer vaccine consisting of synthetic peptides targeting IL-13R $\alpha$ 2 and EphA2. Phase 2b are expected to begin in 2014 in both pediatric glioma and adult second-line glioblastoma multiform (GBM). STML also has a portfolio of preclinical candidates targeting both solid and blood cancers. The company has a proprietary discovery platform targeting CSCs called StemScreen.

**STML: Historical and Projected Revenue and Earnings**

December 31 Fiscal Year (\$000s, except per share)	2012A	1Q13A	2Q13A	3Q13E	4Q13E	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E
U.S. 401 Sales	-	-	-	-	-	-	-	-	-	40,429	173,321	287,358	334,084
BPCDN	-	-	-	-	-	-	-	-	-	18,994	36,928	46,283	52,859
AML	-	-	-	-	-	-	-	-	-	21,435	136,393	241,075	281,226
Ex-U.S. 401 Sales	-	-	-	-	-	-	-	-	-	-	30,322	129,991	215,518
WW 401 Sales	-	-	-	-	-	-	-	-	-	40,429	203,643	417,349	549,603
Ex-U.S 401 Royalties	-	-	-	-	-	-	-	-	-	-	3,639	17,098	31,638
U.S. Milestones	-	-	-	-	-	-	-	-	-	-	50,000	10,000	5,000
Other Income	-	-	-	-	-	-	-	-	-	-	-	-	-
<b>Total Revenue</b>	-	-	-	-	-	-	-	-	-	<b>40,429</b>	<b>226,960</b>	<b>314,456</b>	<b>370,723</b>
Cost of Goods	-	-	-	-	-	-	-	-	-	6,064	25,998	43,104	50,113
Research and Development	2,964	1,797	3,662	3,845	4,037	13,341	20,012	25,015	26,265	27,579	30,337	36,404	45,505
Sales, General, and Administrative	2,942	1,247	917	927	936	4,026	12,500	15,000	25,000	60,000	65,500	71,550	76,874
<b>Total Operating Expenses</b>	<b>5,907</b>	<b>3,044</b>	<b>4,579</b>	<b>4,771</b>	<b>4,973</b>	<b>17,367</b>	<b>32,512</b>	<b>40,015</b>	<b>51,265</b>	<b>93,643</b>	<b>121,835</b>	<b>151,057</b>	<b>172,491</b>
Income (Loss) from Operations	(5,907)	(3,044)	(4,579)	(4,771)	(4,973)	(17,367)	(32,512)	(40,015)	(51,265)	(53,214)	105,125	163,399	198,231
Other Income	302	31	-	-	-	31	-	-	-	-	-	-	-
Other Expense	(0)	(125)	-	-	-	(125)	-	-	-	-	-	-	-
Interest Expense	(119)	(82)	(298)	(83)	(83)	(545)	(330)	(330)	-	-	-	-	-
Interest Income	10	-	3	334	311	647	836	1,329	2,267	2,414	2,538	3,321	4,448
Pre-tax Income	(5,714)	(3,220)	(4,874)	(4,520)	(4,745)	(17,359)	(32,006)	(39,016)	(48,999)	(50,801)	107,663	166,720	202,679
Tax Expense	-	-	-	-	-	-	-	-	-	-	39,835	61,686	74,991
Tax Rate	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	37%	37%	37%
<b>Net Income</b>	<b>(5,714)</b>	<b>(3,220)</b>	<b>(4,874)</b>	<b>(4,520)</b>	<b>(4,745)</b>	<b>(17,359)</b>	<b>(32,006)</b>	<b>(39,016)</b>	<b>(48,999)</b>	<b>(50,801)</b>	<b>67,828</b>	<b>105,034</b>	<b>127,688</b>
Diluted shares outstanding	3,442	6,148	9,837	12,589	12,689	10,316	12,968	16,210	18,476	18,769	19,091	19,445	19,835
Net Loss per share	\$ (1.66)	\$ (0.52)	\$ (0.50)	\$ (0.36)	\$ (0.37)	\$ (1.68)	\$ (2.47)	\$ (2.41)	\$ (2.65)	\$ (2.71)	\$ 3.55	\$ 5.40	\$ 6.44
Options Expense	561	2,285	577	1,000	1,500	5,362	6,703	8,378	10,473	13,091	16,364	20,454	25,568
EPS with Options Expense	\$ (1.82)	\$ (0.90)	\$ (0.55)	\$ (0.44)	\$ (0.49)	\$ (2.20)	\$ (2.98)	\$ (2.92)	\$ (3.22)	\$ (3.40)	\$ 2.70	\$ 4.35	\$ 5.15

Source: Company data, Jefferies Group LLC estimate  
August 28, 2013

**STML: Historical and Projected Changes in Financial Position**

December 31 Fiscal Years (\$000s)	2012A	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E
<b>Cash flows from operating activities</b>									
Net Income (Loss)	(5,714)	(17,359)	(32,006)	(39,016)	(48,999)	(50,801)	67,828	105,034	127,688
Adjustments to reconcile									
Non-cash interest expense	119								
Mark to market of put option liability	(69)								
Changes in operating assets and liabilities									
Accounts receivable, inventory					-	(3,369)	(18,655)	(34,420)	(25,276)
Prepaid expenses and other liabilities	(76)								
Other assets	(2,305)								
Accrued liabilities	3,918	1,910	2,524	1,250	1,875	6,052	1,376	2,020	2,404
Net cash used in operating activities	(4,127)	(15,449)	(29,482)	(37,765)	(47,123)	(48,117)	50,549	72,633	104,816
<b>Cash flows from investing activities</b>									
Purchase of marketable securities	-	-	-	-	-	-	-	-	-
Capital Expenditures	-	-	-	-	(10,000)	(10,000)	(10,000)	(10,000)	(10,000)
Redemption of marketable securities	-	-	-	-	-	-	-	-	-
Net cash provided by investing activities	-	-	-	-	(10,000)	(10,000)	(10,000)	(10,000)	(10,000)
<b>Cash flows from financing activities</b>									
Proceeds from issuance of preferred stock, net	-	-	-	-	-	-	-	-	-
Redemption of preferred stock	-	-	-	-	-	-	-	-	-
Proceeds from issuance of common stock	-	107,153	9,240	156,589	125,876	18,704	23,661	29,931	37,863
Proceeds from issuance of convertible notes	322	-	-	-	-	-	-	-	-
Net cash (used in) provided by financing activities	322	107,153	9,240	156,589	125,876	18,704	23,661	29,931	37,863
Net (decrease) increase in cash and cash equivalents	(3,805)	91,704	(20,242)	118,823	68,753	(39,413)	64,210	92,564	132,679
<b>Cash and cash equivalents at beginning of period</b>	<b>5,830</b>	<b>2,025</b>	<b>93,729</b>	<b>73,487</b>	<b>192,311</b>	<b>261,064</b>	<b>221,651</b>	<b>285,861</b>	<b>378,425</b>
<b>Cash and cash equivalents at end of period</b>	<b>2,025</b>	<b>93,729</b>	<b>73,487</b>	<b>#####</b>	<b>261,064</b>	<b>221,651</b>	<b>285,861</b>	<b>378,425</b>	<b>511,104</b>

Source: Company data, Jefferies Group LLC estimate

August 28, 2013

**STML: Historical Condensed Balance Sheets**

(\$000s)	12/31/12	3/31/13	6/30/13
<b>Current assets:</b>			
Cash and cash equivalents	2,025	30,736	92,686
Prepaid expenses and other current assets	299	680	1,162
Total current assets	2,324	31,416	93,848
Deferred financing fees	2,705	-	-
<b>Total assets</b>	<b>5,030</b>	<b>31,416</b>	<b>93,848</b>
<b>Current liabilities:</b>			
Accounts payable and accrued expenses	5,501	2,595	4,173
Total current liabilities	5,501	2,595	4,173
Convertible notes	2,007	590	-
Put option liability	30	-	-
<b>Total liabilities</b>	<b>7,538</b>	<b>3,186</b>	<b>4,173</b>
<b>Total stockholders' equity/(deficit)</b>	<b>(2,508)</b>	<b>28,230</b>	<b>89,675</b>
<b>Total liabilities and stockholders' equity/(deficit)</b>	<b>5,030</b>	<b>31,416</b>	<b>93,848</b>

Source: Company Reports, Jefferies Group LLC  
August 28, 2013

Source: Company data, Jefferies LLC estimates



## Company Description

Stemline Therapeutics, Inc. (STML) is a New York, NY-based clinical-stage biopharmaceutical company, specializing in the development of oncologic drugs that target cancer stem cells (CSCs) and tumor bulk. Cancer stem cells are thought to drive cancer progression, metastasis, and chemotherapy resistance. STML has two candidates in clinical trials, SL-401, humanized IL-3 linked to diphtheria toxin for third-line acute myeloid leukemia (AML) and for blastic plasmacytoid dendritic cell neoplasm (BPDCN). Phase 2b trials are expected to begin for both indications in 2014. The company's other leading candidate is SL-701, a brain cancer vaccine consisting of synthetic peptides targeting IL-13R $\alpha$ 2 and EphA2. Phase 2b are expected to begin in both pediatric glioma and adult second-line glioblastoma multiform (GBM). STML also has a portfolio of preclinical candidates targeting both solid and blood cancers. The company has a proprietary discovery platform targeting CSCs, StemScreen.

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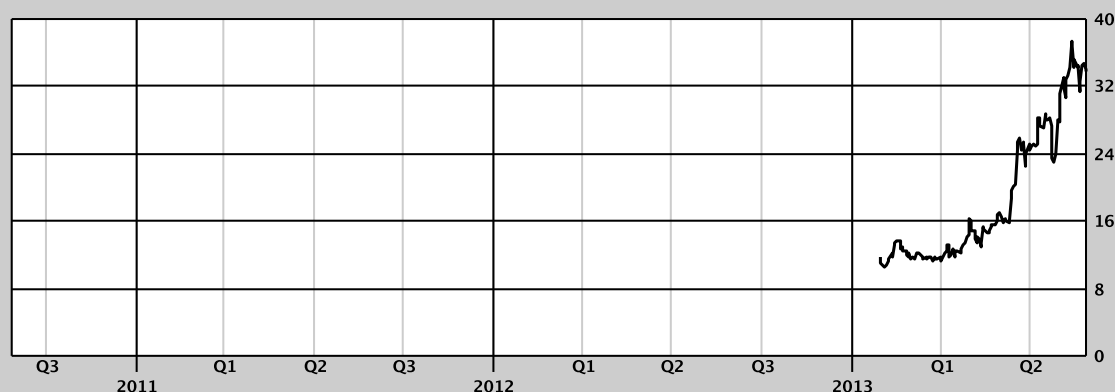
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- OncoMed Pharmaceuticals (OMED: \$16.94, BUY)
- Sanofi (SAN FP: €73.50, BUY)
- Seattle Genetics (SGEN: \$42.06, BUY)
- Verastem Inc. (VSTM: \$13.72, BUY)

Rating and Price Target History for: Stemline Therapeutics, Inc. (STML) as of 08-28-2013



## Distribution of Ratings

Rating	Count	Percent	IB Serv./Past 12 Mos.	
			Count	Percent
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HOLD	742	44.25%	119	16.04%
UNDERPERFORM	143	8.53%	1	0.70%

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